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Encyclopedia of Psycho-pharmacology

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Encyclopedia of Psychopharmacology

Ian P. Stolerman (Ed.)

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Volume 1

A–K

With 206 Figures and 129 Tables

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Volume 2

L–Z

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Preface

Psychopharmacology is the study of the effects of psychoactive drugs on the functioning of the central nervous system at all levels of analysis, thus embracing cognition, behaviour, psychological states, neurophysiology, neurochemistry, gene expression and molecular biology. It includes, as integral parts of its domain, the medicinal and social uses of the substances, the interaction of environmental and genetic factors with the actions of psychoactive drugs, their use for probing the functionality of the central nervous system, and drug dependence and abuse.

The modern science of psychopharmacology was developed in the second half of the 20th century as a consequence of innovative "blue-skies" laboratory research, and the parallel recognition of the specific therapeutic effects of a new generation of drugs that brought about the so-called "psychopharmacological revolution". This Encyclopedia of Psychopharmacology attempts to bring together much of this knowledge that has been acquired in the last fifty years in a format that makes it accessible to a diverse range of non-specialists and students. It facilitates the dissemination of what has been learned to a broader population of researchers, clinicians and advanced students. The level of the entries is typically mid-way between articles for informed laypeople and reviews for specialised biomedical experts. The diversity of disciplinary areas of which psychopharmacology is comprised means that it is a useful educational resource when specialists need to extend their role into areas beyond their primary fields of expertise. People in related fields, students, teachers, and laypeople will benefit from the information on the most recent developments of psychopharmacology.

The scope of the product is defined by the definition above and by the scope of the journal Psychopharmacology, a premier peer-review journal for publication of original research and expert reviews. The aim is to provide detailed information on psychopharmacology and its sub-disciplines, such as clinical psychopharmacology, molecular neuropsychopharmacology, behavioural pharmacology in laboratory animals, and human experimental psychopharmacology. Nevertheless, the interdisciplinary nature of the field has engendered very different ideas about the meaning of the word "psychopharmacology", and there is probably no definition that could meet with universal and permanent acclaim. It is like the proverbial story of the blind men and the elephant. Some see psychopharmacology primarily as the scientific study of the psychological and behavioural effects of substances in normal subjects. Others regard it as mainly concerned with the development and evaluation of pharmacotherapies for psychiatric states. Yet a further important group of scientists have been engaged in defining the actions of psychoactive drugs across the huge range of disciplines of which neuroscience is composed including, among others, neurochemistry, neurophysiology and molecular biology. It is hoped that the project will help to shed light on the interconnections between the different parts of the elephant, showing how the effects of drugs within the intact conscious, behaving organism are related to their properties at the levels of molecules, cells and neural systems.

The wide-ranging entries in the Encyclopedia of Psychopharmacology are written by leading experts, including basic and clinical scientists in academia and industry. The entries fall into several main categories. Target essays include descriptions of fundamental psychological and biological processes that are influenced by psychoactive drugs; here the emphasis is at the behavioural and psychological level, although important functions in the neuropharmacological and psychosocial domains are included. Targets at the molecular and cellular levels constitute the primary domain of the Encyclopedia of Molecular Pharmacology (Offermanns and Rosenthal, Eds. Springer 2008) that may be seen as a parallel endeavour. Those entries named according to psychiatric disorders describe the role of pharmacotherapy in treatment, with reference to differential therapies for subclasses of a disorder, with cross-references to essays on the drugs used. Conditions where drug treatment is not normally used are excluded except for substance use disorders, where the main characteristics of all the disorders are pertinent even though there is no pharmacotherapy for some of them. Drugs are the stock-in-trade of psychopharmacologists and therefore many entries are named according to drugs or drug classes. These essays review their general pharmacology, with an emphasis on psychotropic and other central nervous system effects; their neuropharmacological mechanisms of action are described in relation to receptor or enzymatic targets, key events that occur downstream from the receptor, and brain regions, with cross-references to the psychiatric states in which the drugs are used most often. Other essays focus upon the key methods used in the field, describing the main

features of the techniques and outlining their roles in psychopharmacology, the types of information obtained and why they are needed; the advantages and limitations of a technique may also be summarised.

The essays are complemented by more than 1,150 short definitions; essays and definitions cross-reference each other and other relevant entries. Entries appear in an alphabetical sequence that makes the printed encyclopedia easy to use. Users of the online version benefit from hyperlinks that correspond to the cross-references in the printed version.

I thank the many members of the publisher's staff who have participated in this project and have supported it so ably. Throughout the enterprise I have also enjoyed the support of an outstanding team of Field Editors, all of whom have sustained internationally recognized records of scholarly activity in psychopharmacology. The team includes individuals based in pharmaceutical industry as well as in academia, reflecting the frequent and often essential collaborations between these sectors. It would not have been possible to produce the Encyclopedia of Psychopharmacology without their guidance on its content and their assistance with the selection of authors and reviews of the submitted entries. I also thank the hundreds of individual authors whose exceptional work forms the substance of the product and who have given so generously of their time and expertise.

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A

ABC Transporters

Definition

Adenosine triphosphate (ATP)-binding cassette (ABC) transporters constitute a superfamily of primary active transport systems that are present from prokaryotes to humans. ABC transporters hydrolyze ATP to transport various substrates across cellular membranes. 48 ABC transporters are present in humans and are classified in seven subfamilies. The human ABCB1 or P-glycoprotein is responsible for multiple drug resistance (MDR) in pumping chemotherapeutic drugs out of the cell. A few ABCC members, also known as MRP (multiple drug resistance associated protein), and ABCG2 or BCRP (breast cancer resistance protein) are like, P-gp, expressed at the BBB where they play a protective role for the brain against xenobiotics.

Abeta

► Amyloid-Beta

Abridged Somatization

► Somatoform and Body Dysmorphic Disorders

Absorption

Definition

Absorption is the process of a drug entering the general circulation.

Cross-References

► Distribution
► Excretion
► Liberation
► Metabolism
► Pharmacokinetics

Abstinence

Definition

The act or practice of refraining from indulging in appetitive behaviors, typically relating to substance use.

Abstinence Syndrome

► Withdrawal Syndromes

Abuse

Definition

Abuse of something is the use of it in a wrong way or for a bad purpose.

Abuse Liability

Synonyms

Abuse potential

Definition

Abuse liability is a term used to denote properties of a drug that would lead to abuse and dependence in humans if it were to become available as a prescription medication or through illicit routes. It is assessed primarily from the ability of a drug to produce positive outcomes in laboratory tests predictive of abuse and dependence in humans. Clinical and epidemiological data are also taken into account when available. Abuse liability also depends upon other factors such as the formulations in which the drug becomes available, its cost, and the ease of synthesizing it.

Cross-References

► Drug Discrimination
► Drug Self-Administration
► Withdrawal Syndromes

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Abuse Liability Evaluation

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Synonyms

Abuse potential

Definition

The abuse liability of a drug or a class of drugs is their propensity to be abused and produce adverse public health consequences. Although much of what constitutes abuse liability of a drug arises from the pharmacological properties of the drug itself (i.e., its ability to produce psychoactive effects associated with risk for abuse and/or addiction, also known as abuse potential), it can also be affected by social and cultural factors and may change from time to time as one drug or class of drug gain popularity in a particular culture. Individual products, even those containing the same generic drug, can differ in abuse liability, which may be determined by the specific formulation, the indication for which it is used and such things as its market penetration.

Current Concepts and State of Knowledge

Background

One of the principal strategies for drug abuse prevention is to place regulatory controls on the manufacture, distribution, sales, and possession of drugs with abuse liability. This strategy is embodied in international treaties and in the drug abuse control laws of individual countries. The simplest level of control for medications is to require a physician prescription for their use. Drug abuse control treaties and laws place additional requirements on drugs that have demonstrated abuse liability. Consequently, it is essential for the function of this drug abuse prevention strategy that there be a means of establishing which drugs have abuse liability and should be subjected to such regulations. In addition, the existing regulations call for differential restrictions on drugs based on differences in their abuse liability; therefore, it is also necessary to have a means of ranking this propensity.

At the international level, drug abuse control resides in two treaties, the Single Convention on Narcotic Drugs and the Convention on Psychotropic Substances (http://www.unodc.org/unodc/en/treaties/index.html). The United Nations has been given the authority to implement these treaties. Most countries are signatory to these treaties and among their obligations are to control manufacture, distribution, sale and possession of drugs at least as strictly as called for in the treaties. The drug abuse control laws differ somewhat among countries, so to illustrate how abuse liability impacts on drug abuse control, we will use as an example the ▶ Controlled Substances Act (CSA) in the US (http://www.usdoj.gov/dea/pubs/csa.html).

Under the CSA, drugs with abuse liability are placed in one of the five schedules (I-V), with Schedule I having the most restrictions and Schedule V the least. The intent is for the drugs with the greatest abuse liability and potentially causing the greatest public health concerns to be in Schedule I, with successively lower Schedules used for progressively less dangerous drugs. There is controversy about whether or not the existing classifications of drugs are consistent with this intent.

The remainder of this article will focus on how abuse liability is measured scientifically. The CSA specifies eight factors which should be assessed in determining abuse liability, but these factors do not easily translate into specific scientific assessments, so we will use a more scientifically based analysis. In this regard, it is important to distinguish between the assessment of abuse liability of drugs which are widely available to the public already and new drugs or medications, where data on actual abuse are not available but assessments of their abuse potential need to be made prior to their approval or a scheduling decision. In the former, methods from epidemiology are of paramount importance in assessing the actual abuse of the drugs. For new products, data from laboratory and clinical testing are usually the main source of information on abuse liability. Several regulatory agencies and scientific organizations have proposed strategies for abuse liability assessment (Balster and Bigelow 2003), which include chemical properties, animal test procedures (Negus and Fantegrossi 2008), human laboratory testing (Preston and Walsh 1998), and information that can be obtained from clinical efficacy trials.

Chemical Properties and Formulation

New medications that are based on analogs of existing drugs of abuse are often presumed to have abuse liability. Knowledge of structure-activity relationships can also be used to predict sites of action in the brain that might mediate abuse-related effects of drugs. Medications that are metabolized to known drugs of abuse or that can be

easily converted to an abusable drug can be considered to have abuse potential. Water soluble drugs and formulations are at increased risk for injection use. In some cases, it is possible to formulate drugs in ways that reduce their abuse liability and that are relatively tamper proof. Delayed or sustained formulations may have less abuse liability than their immediate release counterparts.

Animal Laboratory Testing of Abuse Liability

Knowledge of the pharmacological properties of a novel medication is an important first step in predicting their abuse potential. Indeed, binding assays and other means of determining a drug's cellular sites of action in the brain are typically used to assess if the drug acts on receptor systems or neural circuitry known to mediate the abuse-related effects of known drugs of abuse.

In general, the more similar a new drug is to known drugs of abuse the more likely it is to have abuse liability. The concept has often been referred to as pharmacoequivalence, and standard pharmacological tests of the properties of drugs can be used to establish pharmacoequivalence. For example, opioids, depressants, amphetamine-like stimulants, hallucinogens, and other classes of abused drugs can produce typical, class-specific profiles of pharmacological properties in animal tests. Often, developers of new medications are attempting to retain therapeutic properties (e.g., analgesia, sedation, etc), while reducing abuse potential.

► Drug discrimination testing in animals is a useful means of assessing pharmacoequivalence particularly because the discriminative stimulus effects of drugs are related to the nature of their acute subjective effects (Holtzman 1990). For abuse liability testing, novel drugs are typically tested in animals that have been trained to discriminate one or more known drugs of abuse from placebo. For example, animals trained to discriminate morphine from vehicle could be used to test a novel analgesic for morphine-like discriminative stimulus effects employing ► stimulus generalization procedures. With the use of appropriate training drugs, it is possible to characterize discriminative stimulus effects with high specificity. For example, mu and kappa opioids can be distinguished from one another, as can the various subtypes of GABA agonists.

Drug ► self-administration is also widely used for abuse liability assessment in laboratory animals. This procedure directly measures the reinforcing effects of drugs using standardized procedures, and has been used in rodents and nonhuman primates. One commonly used form of self-administration is the drug substitution procedure in which animals are trained to self-administer a known drug of abuse under limited access conditions, typically using fixed-ratio schedules of reinforcement and the intravenous route of drug administration. When rates of self-administration become reliable from day to day, a test drug is substituted to determine if animals will maintain responding. It is essential to test a range of doses of the test drug. More advanced self-administration procedures have also been used to measure reinforcement efficacy to compare the relative abuse liability of various drugs. For example, in progressive ratio procedures animals are required to make more lever presses for subsequent injections, and the maximal number of presses they make is used as the measure of reinforcement efficacy.

Testing for the development of a ► physical dependence syndrome can also be done in animals (Aceto 1990). Physical dependence is a feature of many, but not all, drugs of abuse. It is related to abuse potential because it may increase the likelihood of further drug-taking as well as being an adverse consequence of drug use. Physical dependence testing is used predominantly for opioids and depressants because the withdrawal syndromes are most pronounced with these classes of drugs. Cross-dependence can also be used to determine the extent to which a novel drug resembles a known drug of abuse. There are two primary models. One, which is often referred to as single dose suppression, utilizes animals that have already been made dependent on a known drug of abuse, such as morphine or pentobarbital, and then a test drug is administered during withdrawal to see if it suppresses the withdrawal signs that would normally emerge. If a test drug exhibits ► cross dependence in this procedure, it is very likely to produce dependence by itself. For example, a drug that suppresses withdrawal signs in morphine-withdrawn animals will probably produce dependence of the opiate type. The other common methodology is the assessment of primary physical dependence in which the test drug is administered repeatedly (or continuously by infusion) for a week or more. During treatment, animals can be injected with an antagonist (e.g., naloxone) to determine if precipitated withdrawal occurs or the drug administration can be discontinued and animals observed for spontaneous withdrawal signs.

Other animal test procedures that have been used for abuse liability assessment include the assessment of ► tolerance or ► cross tolerance, ► conditioned place preference, and altered thresholds for electrical self-stimulation of the brain.

Human Laboratory Testing of Abuse Liability

Abuse liability assessment studies conducted with humans typically occur prior to approval and marketing of a novel compound and/or new formulation of an existing

compound, but only after comprehensive safety evaluations of the new agent have been conducted in nonhumans and humans (Phase 1). Whether specific abuse liability testing in humans is needed depends on existing knowledge of the abuse potential for the test compound and pharmacologically related compounds, and the outcomes of animal abuse liability screening.

Standardized laboratory-based procedures have been developed to assess abuse potential in humans (Preston and Walsh 1998). Typically these studies are conducted using paid volunteers who are experienced with the class of drug under evaluation. Experienced drugs users provide a sensitive indicator of the positive mood effects of their drug of choice. When appropriate, abuse liability studies are sometimes conducted in normal (i.e., nondrug using individuals) and patient populations. Participants in these studies are screened for physical and mental health, cognitive ability to provide consent and answer questionnaires, and for recent drug use that would interfere with testing.

The most widely used approach for human abuse liability testing is the controlled assessment of the subjective experience of drug effects through structured and unstructured questionnaires (i.e., subjective effect reports). Key design elements for these studies include (1) testing a broad range of doses of the study agent in a controlled environment, (2) inclusion of a placebo control, (3) testing multiple doses of a positive control drug (i.e., a known drug from the same class with well characterized abuse potential), and (4) randomized dosing and double-blind procedures. Questionnaires are presented before and at regular intervals after the drug is administered (typically as an acute dose) in order to capture the onset, magnitude, and duration of drug action. The procedure produces a dose-effect of subject-reported responses associated with the test drug relative to a drug with known abuse potential.

Several standardized self-report measures are used to assess abuse liability. One measure is the visual analog scale, which allows subjects to rate their state in relation to specific questions or descriptors on a line labeled "not at all" and "extremely." Typical questions are for example, "How much do you like the drug?" "How strong is the drug?" or "Do you feel nauseous?" Other measures are adjective-rating scales, which employ a Likert-rating (e.g., ratings on a 0–10 scale), such as an opioid rating scale with effects such as nodding and itchy. The Single Dose Questionnaire (Fraser et al. 1961) is an opioid-specific questionnaire originally developed at the ►Addiction Research Center located at the ►U.S. Narcotics Prison Farm in Lexington, Kentucky where much of the seminal work in this research area was originally developed. Another widely used questionnaire (also developed at the Addiction Research Center) was a large empirically-derived battery known as the ►Addiction Research Center Inventory (ARCI; Haertzen 1966). This battery was derived after administration of drugs from a wide array of pharmacological classes, including ►opioids, ►alcohol, ►sedatives, ►psychostimulants, and ►hallucinogens. The original version has 550 true–false items subdivided into numerous subscales, with each sensitive to a specific drug-induced subjective state (e.g., the Morphine–Benzedrine Group scale (MBG) is used as a proxy for the euphoric effects produced by opioids and amphetamines; the Weak Opioid Withdrawal scale is sensitive to withdrawal symptomatology). A shortened version with only 49 items of the ARCI is most commonly employed in contemporary studies (Martin et al. 1971). Numerous other validated or locally developed questionnaires are also used.

Observer-rated measures yield additional information on observable signs of drug intoxication of which the subject may be unaware and are free of the potential bias/experimental noise that can result from drug intoxication. Cognitive and psychomotor test procedures may also be used to evaluate the impairing effects of the study drugs. These tests may include simple assessments such as balance, reaction time, and standard sobriety tests or more sophisticated cognitive measures which capture direct effects on cognitive processing and memory.

Drug discrimination and self-administration procedures have been adapted from the animal laboratory for use in humans. While these procedures are not typically used for abuse liability screening, they may provide additional relevant information. Human drug discrimination outcomes are generally concordant with those from the animal studies. Drug self-administration procedures are used most commonly with marketed agents to compare abuse liability among drugs or to evaluate potential pharmacotherapies for drug abuse treatment (Comer et al. 2008).

Evaluation of physical dependence capacity in humans was historically conducted using direct addiction studies. In early studies, subjects were exposed to repeated dosing with the test drug and then tested for signs of a withdrawal syndrome. However, these direct addiction studies are no longer conducted for ethical reasons. Instead, physical dependence is studied in currently dependent humans using substitution and withdrawal suppression procedures. For example, methadone-maintained subjects may be enrolled to examine the ability of another opioid to substitute for their maintenance dose or marijuana-dependent individuals may be maintained experimentally on equivalent oral THC doses during study participation.

Abuse Liability Assessment in Clinical Trials

Abuse liability is not typically assessed in clinical trials, which are usually designed to assess efficacy on a specified therapeutic outcome. Nevertheless, ► Phase I trials can produce information about the nature of the intoxication after administration of high doses (Brady et al. 2003). The adverse events in ► Phase II and ► Phase III trials can be a source of information about drug liking or other abuse-related phenomena, and escalation of use, or missing test medication might indicate a propensity for diversion.

Cross-References

► Addiction Research Center
► Addiction Research Center Inventory
► Conditioned Place Preference and Aversion
► Controlled Substances Act
► Cross Dependence
► Cross Tolerance
► Drug Discrimination
► Phase I, II and III Clinical Trials
► Physical Dependence
► Self-administration of Drugs
► Stimulus Generalization
► Tolerance
► US Narcotics Prison Farm

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Abuse Potential

► Abuse Liability
► Abuse Liability Evaluation

Acamprosate

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Synonyms

Calcium acetylhomotaurinate; Campral

Definition

Acamprosate, marketed under the brand name Campral, is an orally administered drug approved in the USA and throughout much of the world for treating ► alcohol abuse and dependence.

Pharmacological Properties

History

Alcohol-use disorders, which include both alcohol abuse and dependence, make up one of the most prevalent categories of substance use disorders in the USA, affecting almost 18 million Americans. The Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV; APA 1994) characterizes alcohol dependence as a maladaptive pattern of drinking leading to clinically significant impairment, as manifested by a compulsion to drink, a lack of control over the amount of alcohol consumed and continued drinking, despite a realization of the problems associated with it. Physiological symptoms of tolerance and withdrawal may also be present. One of the most challenging aspects of recovering from alcohol dependence is maintaining abstinence after acute withdrawal and avoiding

subsequent relapse to drinking (Koob and Le Moal 2006). The goal of maintaining abstinence can be undermined by acute stressors like anger, loneliness, or hunger or by more chronic conditions such as cognitive impairment, polysubstance abuse, and mood and sleep disturbances. Supplementing counseling approaches with medications targeted to treat the biological aspects of drinking behavior can help in the maintenance of abstinence.

Three medications are currently approved for the treatment of alcohol dependence – ► disulfiram, ► naltrexone (oral and injectable extended release), and acamprosate (Koob and Le Moal 2006). A number of other therapeutic agents are under investigation; these include serotonergic agents, anticonvulsants, GABA receptor agonists, cannabinoid receptor antagonists, and corticotrophin-releasing factor antagonists. Disulfiram has been available for decades; however, high rates (up to 80%) of nonadherence to this aversive medication have contributed to its decreased use by the treatment community. Naltrexone has been available since 1994; however, it has not been readily adopted by practitioners to treat alcohol dependence. The recent Food and Drug Administration (FDA) approvals of acamprosate (2004) and an injectable extended formulation of naltrexone (2006) offer new pharmacologic options for treating this disorder.

Acamprosate is a safe and well-tolerated pharmacotherapy that has been studied in numerous clinical trials worldwide. It has been used successfully for over 15 years in 28 countries and has been prescribed for more than 1.5 million alcohol-dependent patients. Clinical trials have consistently shown that acamprosate is effective in maintaining abstinence in recently detoxified patients, especially when patients are motivated to be abstinent (Mason and Crean 2007). Current research also indicates that acamprosate has a unique mechanism of action, which may have implications for its therapeutic use (De Witte et al. 2005). In contrast to disulfiram, which causes aversive behavior through negative physical effects, or naltrexone, which tempers the pleasurable effects of alcohol, acamprosate acts to normalize dysregulation in neurochemical systems that have been implicated in the biological mechanisms of alcohol dependence.

Mechanism of Action

Acamprosate is an analog of amino acid neurotransmitters such as taurine and homocysteic acid and it has been demonstrated that acamprosate binds to a specific spermidine-sensitive site that modulates the NMDA receptor in a complex way. The NMDA receptor is one of the ► glutamate receptor subtypes. This work suggests that acamprosate acts as a "partial co-agonist" at the NMDA receptor, such that low concentrations enhance activation when receptor activity is low, and high concentrations inhibit activation when receptor activity is high. This may be particularly relevant to the success of acamprosate as a pharmacotherapy given that chronic exposure to ethanol results in an upregulation of ► NMDA receptors and an upregulation in the density of ► voltage-dependent calcium channels (Littleton 2007). Thus, sudden alcohol abstinence causes the excessive numbers of NMDA receptors to be more active than normal, and to produce the symptoms associated with acute ► alcohol withdrawal, such as ► delirium tremens and seizures and with the more persisting symptoms associated with early abstinence, such as craving and disturbances in sleep and mood (Tsai and Coyle 1998). Withdrawal from alcohol induces a surge of excitatory neurotransmitters like glutamate, which in turn activates the NMDA receptors (Tsai and Coyle 1998). Conversely, acamprosate promotes the release of taurine in the brain (Dahchour and De Witte 2000). Taurine is a major inhibitory neuromodulator/neurotransmitter and an increase in taurine availability would also contribute to a decrease in hyperexcitability. Thus, each of these changes produced by acamprosate may contribute to a decrease in the neuronal hyperexcitability commonly observed following acute alcohol withdrawal and that may underlie symptoms associated with relapse, like craving, negative affect and insomnia. Therefore, it has been hypothesized that acamprosate may promote abstinence by minimizing or normalizing some of the physiological changes produced by chronic heavy ethanol exposure.

Animal Models

Acamprosate has been shown to reduce ethanol consumption in rodents that have an extended history of ethanol exposure or are ethanol-dependent (Spanagel et al. 1996). It also has been shown to reduce the increased ethanol consumption associated with a period of enforced abstinence from ethanol (the alcohol deprivation effect) in rats (Heyser et al. 1998; Spanagel et al. 1996). In contrast, acamprosate appears to have less of an effect on alcohol consumption in alcohol naïve and nondependent rats (Heyser et al. 1998). Acamprosate also has been reported to attenuate some of the behavioral and neurochemical events associated with ethanol withdrawal (Dahchour and De Witte 2000). For example, acamprosate reduces the hyperactivity and elevated glutamate levels observed during the first 12 h of ethanol withdrawal. However, not all aspects of withdrawal are reduced by acamprosate, such as withdrawal-induced hypothermia. In addition to the direct effects on ethanol consumption, acamprosate

has been shown to inhibit cue-induced ► reinstatement of alcohol-seeking behavior in an operant conditioning model (Bachteler et al. 2005). Taken together, these results provide support for the use of acamprosate specifically as an anti-relapse medication following acute alcohol withdrawal.

Pharmacokinetics

The recommended dosage of acamprosate is two 333-mg tablets taken three times daily, with no dose adjustment required for body weight or gender (Campral package insert, 2005). Acamprosate is absorbed via the gastrointestinal tract, with pharmacokinetic linearity in terms of dose and time. Absolute bioavailability of acamprosate under fasting conditions is approximately 11%; after food intake, bioavailability decreases by approximately 20%, but this decrease lacks clinical significance (Wilde and Wagstaff 1997). Plasma protein binding is negligible. Importantly, acamprosate is not metabolized in the liver and approximately 90% of the drug is excreted unchanged in the urine (Wilde and Wagstaff 1997). Therefore, the pharmacokinetics of acamprosate are not altered in patients with mild to moderate hepatic impairment and no dose adjustment is required in such patients. Since there is a risk of accumulation of acamprosate with prolonged administration of therapeutic doses in renally impaired patients, the use of acamprosate is contraindicated in patients with severe renal impairment. The pharmacokinetics of acamprosate have not been evaluated in pediatric or geriatric populations.

Because acamprosate is not metabolized by the liver, it is unlikely to cause drug–drug interactions via cytochrome P450 inhibition. Its pharmacokinetics are not altered by co-administration with ► diazepam, ► disulfiram, ► antidepressants, or ► alcohol – substances that are often taken by patients with alcohol dependence. In pharmacokinetic studies with human subjects, co-administration with naltrexone increased the rate and extent of acamprosate absorption. These results suggest that combination therapy may improve the ► bioavailability of acamprosate without compromising its tolerability (Mason and Crean 2007).

Efficacy

Acamprosate was initially studied in Europe, and more recently, in Brazil, Korea, Australia, and the USA. The acamprosate double-blind, placebo-controlled clinical trial database included over 6500 outpatients from 15 countries and is reported in 23 published studies (Mason and Crean 2007). Nineteen of these trials used relatively equivalent methodology in terms of entry criteria, treatment, handling of drop-outs, outcome measures, and assessment of compliance. Patients received the psychosocial intervention typical of their treatment setting. Treatment duration ranged from 2 to 12 months with 13 trials 6 months or longer in duration. Patients were generally recently detoxified and typically had been abstinent for about 5 days at entry into the trials. In these studies, the principal ► efficacy measure was abstinence, which was assessed as the rate of patients completing the trial with no consumption of alcohol at all, the cumulative proportion of the study duration when the patients remained abstinent, and/or the time to first drink.

The results have been consistent in the majority of published studies, and generally show a significant beneficial effect of acamprosate on abstinence outcomes relative to placebo. A factor of 2 in the difference in the proportion of patients achieving stable abstinence was observed in approximately one-third of studies. A beneficial effect on the time to first drink was also frequently observed.

Overall, the published placebo-controlled studies demonstrate the efficacy of acamprosate for supporting abstinence over a broad range of patients in association with a variety of different psychosocial interventions. A number of these studies assessed the persistence of a treatment benefit after the study medication was stopped, and found acamprosate efficacy was maintained for up to 12 months post-treatment relative to placebo. In addition, the result of a recent multi-center, ► double-blind, ► placebo-controlled clinical trial of acamprosate conducted in the United States showed that the benefits of acamprosate were optimized in patients who had a clearly identified goal of abstinence at the start of treatment (Mason and Crean 2007).

Safety and Tolerability

The safety profile of acamprosate appears favorable. The only adverse event consistently reported across trials more frequently in acamprosate-treated patients with respect to placebo-treated patients was mild and transient diarrhea. Across clinical trials, the rate of early terminations due to drug-related adverse events did not differ between acamprosate and placebo-treated patients. Pharmacovigilance subsequent to the commercialization of acamprosate in 1989 has not identified any health risk associated with acamprosate use in over 1.5 million patients. Clinical investigations show no evidence of ► tolerance, ► dependence, or the emergence of a ► withdrawal syndrome or rebound drinking when treatment is ceased (Mason and Crean 2007). Comprehensive safety guidelines may be reviewed in the package insert for acamprosate (Forest Pharmaceuticals, Inc. 2005).

Conclusion

Acamprosate appears to be useful in the treatment of alcohol dependence above and beyond the effects of counseling alone. Acamprosate appears to work by normalizing the dysregulation of NMDA-mediated glutamatergic neurotransmission that occurs during chronic alcohol consumption and withdrawal, and thus attenuates one of the physiological mechanisms that may prompt relapse. Acamprosate requires around a week to reach steady-state levels in the nervous system and its effects on drinking behavior typically persist after the treatment is completed.

Studies into the efficacy of acamprosate in alcohol-dependent patients are generally favorable. Clinical studies and post-marketing experience indicate that acamprosate is typically safe when used as approved by the FDA in alcohol-dependent patients, including those dually diagnosed with psychiatric disorders. The majority of randomized controlled trials of acamprosate given in conjunction with counseling show significantly improved alcoholism treatment outcome relative to counseling administered with placebo. This evidence base suggests that acamprosate should be routinely considered by medical professionals for patients entering alcoholism treatment, taking into account the patient's treatment goals and preferences as well as the safety considerations outlined above.

Cross-References

- ► Alcohol Dependence
- ► Alcohol Withdrawal
- ► Disulfiram
- ► Glutamate Receptors
- ► Naltrexone
- ► Voltage-Gated Calcium Channels (VDCC)

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Acetaldehyde

Synonyms

ADH; Ethanal

Definition

Acetaldehyde is an intermediate by-product in normal carbohydrate metabolism. It is known to psychopharmacologists as the first metabolite of alcohol that is eliminated primarily through oxidation by the enzyme alcohol dehydrogenase in the liver. Acetaldehyde, in turn, is converted to acetate by aldehyde dehydrogenase. Acetaldehyde has pharmacological effects on the cardiovascular system, the liver, monoamine neurotransmitter metabolism, brain function, and behavior. At high levels, it can be toxic, causing headache, facial flushing, nausea and vomiting, tachycardia, headache, sweating, dizziness, and confusion.

Acetylcholine

Definition

A neurotransmitter in the brain and peripheral nervous system involved in the mediation of motor and autonomic functions, and in the mechanisms of cognitive events such as memory functions.

Acetylcholinesterase and Cognitive Enhancement

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Synonyms

Anti-Cholinesterases

Definition

Acetylcholinesterase inhibitors are molecules that inhibit the acetylcholinesterase enzyme from metabolizing (hydrolyzing) acetylcholine, thus increasing both the level and duration of action of the neurotransmitter acetylcholine.

Pharmacological Properties

Cholinergic System Effects on Cognitive Functioning

Several decades of research support the critical role of CNS cholinergic systems in cognition in humans, particularly in learning and memory formation and attention. Beginning with studies by Drachman (1977), temporary blockade of ▶ muscarinic receptors produced impairments of learning and memory that resembled changes associated with normal aging and was proposed as a model of the cognitive deficits in ▶ Alzheimer's disease (AD). Such findings were supported by animal studies showing that cognitive performance of younger animals after the administration of ▶ scopolamine was similar to older untreated animals (Bartus et al. 1982). These studies were extended by Newhouse et al. (1988) who showed that when elderly normals and depressed patients were given scopolamine, their performance declined to a level similar to AD patients. There is thus an age- and disease-related functional decline in muscarinic cholinergic system resources that matches the decline in cell number and other cholinergic markers seen in autopsy studies. Investigations of CNS nicotinic cholinergic receptors have shown qualitatively similar findings. Newhouse et al. (1994) have shown that blocking CNS ▶ nicotinic receptors with the antagonist ▶ mecamylamine in humans produces measurable cognitive impairment with a similar age- and disease-related increase in sensitivity. These studies showed that cognitive impairment followed the blockade of central nicotinic receptors, which partially modeled cognitive impairment that occurs with aging and degenerative disorders (e.g., AD). Studies of both nicotinic agonists and antagonists (Newhouse et al. 2004) have helped to establish the importance of CNS nicotinic receptors in human cognitive functioning and justified efforts to develop therapeutic agents aimed at these receptors. Thus, the effects of acetylcholinesterase inhibitors on cognitive functioning must be contextualized with an appreciation of effects on both cholinergic receptor systems (muscarinic and nicotinic).

In humans, the cholinergic system has been implicated in many aspects of cognition, including the partitioning of attentional resources, ▶ working memory, inhibition of irrelevant information, and improved performance on effortful tasks. Warburton and Rusted (1993) have proposed that the cholinergic system modulates processes that are supported by a limited capacity central executive and that the cholinergic system influences information processing during tasks that engage the control processes for the allocation of attentional resources. Cholinergic system manipulation appears to affect performance on resource demanding tasks as well as during the allocation of attention.

More recently, advances in basic animal research, cognitive pharmacology, and functional imaging have allowed a reformulation of the cholinergic hypothesis of cognitive functioning. Sarter et al. (2005) proposed that the cholinergic system modulates attentional functioning in two ways: first it serves to optimize bottom-up, signal-driven detection processes. Second, the cholinergic system also optimizes top-down, knowledge-based detection of signals, and the filtering of irrelevant information. Thus, the cholinergic system will be involved whenever a task is difficult or relevant and/or irrelevant information is difficult to discriminate, requires partitioning of attentional resources, inhibition of irrelevant information, or increased cognitive effort.

Human functional brain imaging studies have shown that cholinergic stimulation increases cortical activity in extrastriate and intra-parietal sensory areas during encoding and facilitates visual attention-associated activity in extrastriate cortex. Nicotinic cholinergic stimulation enhances reorienting of attention and alters parietal lobe activity associated with this process (Thiel et al. 2005) and may enhance the activity of a distributed neural network. Nicotinic cholinergic stimulation also specifically improves inhibitional attentional functioning (Potter and Newhouse 2004). By contrast, muscarinic cholinergic blockade reduces learning-related activity in the hippocampus (Sperling et al. 2002) and alters prefrontal and perirhinal cortical activity specifically associated with novelty. Studies have shown that muscarinic and nicotinic receptor-specific antagonists cause task-related alterations in activation in frontal and parietal areas during working memory tasks (Dumas et al. 2008).

These data support the concept that cholinergic system activation is phasic rather than tonic and serves to interrupt ongoing activity in the cortex in the context of an attentional requirement (top-down) or a signal requiring reorienting (bottom-up). A hypothesis suggested by

prior neuroimaging studies suggests that nicotinic and muscarinic systems may be responsible for different aspects of task performance; e.g., nicotinic stimulation may affect attentional modulation, rather than simply acting as a general signal gain enhancing system, whereas muscarinic effects may be more tied to stimulus processing or encoding (Thiel et al. 2005).

Studies of ► acetylcholinesterase inhibitors support these hypotheses regarding cholinergic functioning. Studies have shown that during the attentionally demanding N-back task, subjects with ► mild cognitive impairment (MCI) had increases in frontal activation after donepezil treatment relative to control subjects without MCI. In these patients with MCI, frontal regions were recruited during this task with the aid of the pro-cholinergic drug. Other pharmacological functional magnetic resonance imaging (fMRI) studies investigating the treatment of MCI with galantamine have found increased recruitment of task-related brain areas, including bilateral frontal areas and the hippocampus during semantic association, attention, and spatial navigation tasks following treatment. Donepezil treatment in AD subjects improved performance on an attention task of target cancelation while showing no effects on memory tasks (Foldi et al. 2005). Studies of the acetylcholinesterase inhibitor physostigmine have shown increased cortical activity after physostigmine compared to placebo while performing a working memory task in extrastriate and intraparietal areas during encoding but not during retrieval. Physostigmine administration also facilitates visual attention by increasing activity in the extrastriate cortex during a repetition priming task.

Thus, experimental studies using acetylcholinesterase inhibitors suggests that cholinergic system activity modulates stimulus-specific processing of sensory information in selected cortical areas. In addition, the activity of brain regions involved in memory processing such as the hippocampus and frontal lobe may be modulated by cholinergic system activity. The effects of acetylcholinesterase inhibitors on sensory areas may reflect the role of the cholinergic system in modulating attentional processes, and effects on memory-related processing areas similarly suggest effects of cholinergic modification of encoding-related activity for long-term storage.

Neuroimaging methods such as ► functional magnetic resonance imaging (fMRI) have increasingly been used by investigators as a tool to study neural processes involved in human cognitive function. Several functional imaging studies using healthy volunteers have found that enhancing acetylcholine activity via acetylcholinesterases can enhance the effect of selective attention within the extrastriate visual cortex, but not all stimulus processing regions or stimulus types are affected in a similar fashion. Based on the findings that brain activity related to both selective attention and emotional processing can be independently enhanced with physostigmine in the fusiform gyrus, and that physostigmine decreases differential activation due to attention in the posterolateral occipital cortex, cholinergic projections may modulate attention-related and emotion-related activity in distinct parts of the extrastriate and frontoparietal cortices. It has been found that physostigmine effects stimulus-selectivity and attention-related brain activation differently in patients with AD compared to healthy controls. Physostigmine partially reversed impaired stimulus activity in extrastriate visual cortices in AD patients, but negatively affected face-selectivity in the right fusiform cortex in both patients and controls. In contrast to physostigmine's reversal of impairment seen in the Alzheimer's patients, it was found to impair stimulus-related and task-related activity in controls. This finding may reflect a region-specific loss of functional cholinergic inputs in AD and/or regional variations in cortical AD neuropathology. Patients classified as cholinesterase inhibitor (ChEI) responders (based on changes in Clinical Interview Based Impression of Change and Mini Mental State Exam scores) showed a restoration of regional brain function using fMRI in the same areas used by elderly controls while performing semantic association and working memory tasks following 20 weeks of ChEI treatment (Vanneri et al. 2009). In those patients classified as nonresponders, activation patterns appeared less like the elderly controls and there was a reduction in task-related activation. Thus, recent studies tend to suggest that cholinergic stimulation with ChEI agents appears to increase task-related activation and decrease activity in areas of cortex that are unrelated to normal task activity.

Current Acetylcholinesterases

Cholinesterase inhibitors can be described as being either reversible (tacrine, ► donepezil, huperzine, and ► physostigmine), pseudoirreversible (► rivastigmine, metrifonate), or irreversible (soman, sarin, and VX). The latter class has not generally been found to have clinical applications, and are primarily toxic nerve agents or used as pesticides. Four cholinesterase inhibitors have been approved for the symptomatic treatment of AD (see Table 1): tacrine (an aminoacridine), donepezil (a benzylpiperidine), rivastigmine (a carbamate), and ► galantamine (a tertiary alkaloid). Physostigmine was the cholinesterase inhibitor most studied in the early phases of antidementia drug development, but is now generally used only as an investigational tool and for the treatment of glaucoma and myasthenia gravis. Another inhibitor of clinical

Acetylcholinesterase and Cognitive Enhancement. Table 1. Pharmacologic characteristics of cholinesterase Inhibitors.

Name	Class	Reversibility	Inhibition	Elimination half-life (h)
Tacrine	Acridine	Reversible	Noncompetitive	2–4
Donepezil	Piperidine	Reversible	Mixed	73
Rivastigmine	Carbamate	Pseudo-irreversible	Noncompetitive	5
Physostigmine	Carbamate	Reversible	Competitive	0.5
Galantamine	Phenathrene alkaloid	Reversible	Competitive	4.4–5.7
Huperzine A	Lykopodium alkaloid	Reversible	Mixed	4.8

importance is huperzine, a lykopodium alkaloid isolated from the Chinese herb Huperiza serrata.

Tacrine was the first reversible acetylcholinesterase inhibitor to be studied and approved for the treatment of AD, and is about four times more potent in its action on butyrylcholinesterase than on acetylcholinesterase. The therapeutic effects of tacrine do not seem to be correlated closely with its anticholinesterase activity, so it is thought that other neurochemical actions of the drug may be contributing to its behavioral activity. Tacrine is also known to produce problematic side effects in many patients, including hepatotoxicity.

Physostigmine is an alkaloid isolated from the seed of a perennial plant of West Africa (the Caliber bean), and is classified as a carbamate acetylcholinesterase and reversible inhibitor (Giacobini 2000). Physostigmine is the most potent of the carbamate derivatives, which also includes rivastigmine. Both of these agents are more selective for butyrylcholinesterase than for acetylcholinesterase.

Rivastigmine is a pseudo-irreversible cholinesterase inhibitor, and is found to specifically inhibit the acetylcholinesterase subtype found primarily in the hypothalamus and cortex. This particular subtype is implicated in the accumulation and maturation of amyloid plaque.

Donepezil was approved as a treatment for AD in 1996, and is known to be more selective for acetylcholinesterase versus butyrylcholinesterase (Giacobini 2000). Donepezil is a reversible inhibitor but due to its long pharmacokinetic half-life (about 100 h), it produces long lasting inhibition. The rate of onset of pharmacodynamic activity, however, is slow because the drug is relatively slowly absorbed.

Galantamine is a reversible acetylcholinesterase and competitive inhibitor, but unlike other agents, can also act on nicotinic receptors by allosteric modulation. As it is a weak cholinesterase inhibitor, this allosteric modulation of nicotinic receptors has been postulated to be a significant contributor to the activity of the drug. It has been proposed that modulation as opposed to agonism may protect against down regulation of post-synaptic receptors and thus allow the drug to have a more sustained action.

Huperzine is a potent, highly specific, reversible inhibitor of acetylcholinesterase. It has been found that the potency of Huperzine A is similar or superior to other inhibitors currently being used in the treatment of AD, based on in vitro and in vivo comparison studies.

Behavioral Effects of Acetylcholinesterase Inhibitors

Due to the extensive distribution of cholinergic pathways in the brain, anticholinesterase activity affects a wide range of behavior in animals and in humans. Although acetylcholine was not identified as a brain transmitter until 1914, physostigmine was isolated as a natural product and used as clinical therapy as early as 1877 (Giacobini 2000). The most recent neuropharmacological application of these agents has been as antidementia drugs. Tacrine was the first drug approved for the treatment of AD and was shown to improve memory, language, praxis, and activities of daily living.

In patients with AD, it is thought that cholinergic deficits in limbic and paralimbic structures contribute to the development of abnormal behavior, and human pharmacology data support the concept that stabilization of cholinergic function could improve both behavioral symptoms and cognitive deficits (Giacobini 2000). Most clinical trials have shown that acetylcholinesterase inhibitors improve scores on cognitive subscales of the AD Assessment Scale, the Mini-Mental State examination, and global scales such as the Clinical Interview-Based Impression of Change (CIBIC). For noncognitve domains, scales such as the AD Assessment Scale (ADAS-noncog) and the Neuropsychiatric Inventory (NPI) scale have most consistently demonstrated the ability of AChEIs to improve noncognitive behavioral problems including apathy, disinhibition, abberant motor behaviors, and anxiety. These agents temporarily improve, stabilize, or reduce the rate of decline in memory and other intellectual functions relative to placebo.

Comparison Between Acetylcholinesterase Inhibitors

In a meta-analysis done by Hansen et al. the affects of three major acetylcholinesterase inhibitors on behavior and cognition in 26 different studies were reviewed. Two trials directly comparing donepezil and galantamine showed conflicting results; the longer 52-week, fixed dosed trial found no significant differences between the agents in cognition for treated patients, while the shorter 12-week trial using flexible doses of drug showed significant differences in cognition and function favoring donepezil. In a 2-year double blinded randomized trial comparing flexible doses of donepezil and rivastigmine, treated patients had similar favorable changes in cognition and behavior as measured by Severe Impairment Battery (SIB) and Neuropsychiatric Inventory (NPI). Patients treated with rivastigmine had significantly better functional and global assessment outcomes. In a shorter, 12-week open label trial comparing flexible doses of donepezil and rivastigmine, no statistically significant differences were seen in cognition. For donepezil, rivastigmine, and galantamine, Hansen et al. concluded that the meta-analyses of placebo-controlled data support modest overall benefits for stabilizing or slowing decline in cognition, function, behavior, and clinical global change (Hansen et al. 2008). In another review of 24 trials, it was found that donepezil improved cognition and global functioning for patients with AD and ► vascular dementia. In 10 studies investigating galantamine versus placebo, there was consistent evidence that patients being treated with galantamine showed a positive effect on cognition and global assessment. There is less consistent evidence for a significant difference in cognition for tacrine versus placebo.

Treatment with cholinergic agents may also show beneficial behavioral and cognitive responses in other disorders with cortical cholinergic abnormalities such as ► Lewy body dementia, Parkinson's disease with dementia, olivopontocerebellar atrophy, vascular dementia, Down's syndrome, and traumatic brain injury. It has also been hypothesized that the cognitive deficits seen in ► schizophrenia could be in part secondary to dysfunction within the cholinergic system. Although findings have been negative, this concept is under investigation with the use of cholinergic agents, e.g., nicotinic agonists, as possible treatments.

Cholinesterase inhibitors have also been reported to prevent and/or reduce common behavioral disturbances seen in patients with AD, including apathy, agitation, and ► psychosis (hallucinations and delusions). Visual hallucinations and apathy are the most commonly reduced symptoms. Anxiety, disinhibition, agitation, depression, delusions, and aberrant motor behavior are also found to improve in some studies but not all.

Factors that may Affect Acetylcholinesterase Effect

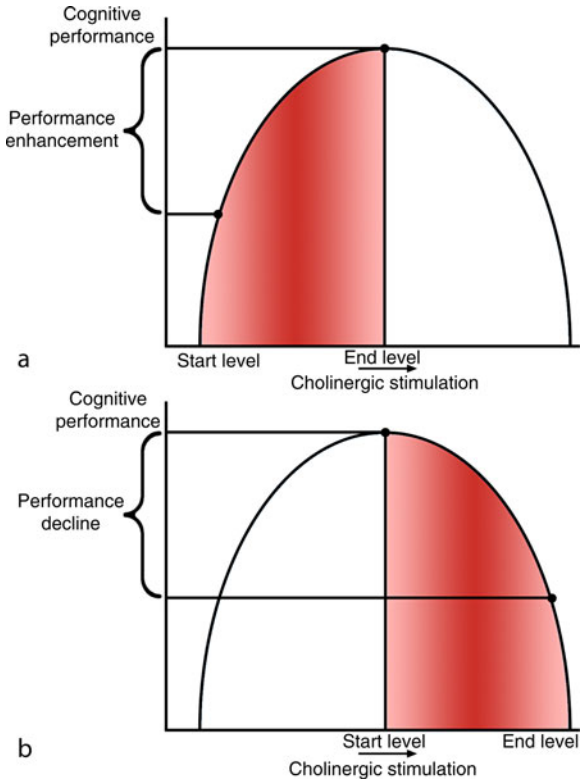
For procholinergic drugs, as the dose is increased, efficacy increases. However, side effects may become a limiting factor more rapidly than loss of efficacy, with an upside down U-shaped curve describing the relationship between cholinergic stimulation and cognitive benefit. Also, due to the phasic properties of cortical acetylcholine function, it is often difficult for increased acetylcholine in the synaptic cleft to result in stimulation of post-synaptic receptors independently from pre-synaptic activity. The ability of pre-synaptic neurons to respond to signaling may also be reduced by excessive autoreceptor stimulation. A wide range of response to treatment is seen, and may be due to variations in cholinergic deficit between patients. There may be a potential role for the ► apolipoprotein E4 genotype, as its presence is linked with late-onset AD, though the effect of this allele on the degree of Alzheimer neuropathology is not clearly understood. These individuals have less brain ► choline acetyltransferase and nicotinic receptor binding, which may contribute to developing cognitive dysfunction from cholinergic deterioration. It is clear that differences in age, disease severity, and genotype may all influence ► cholinergic deficits, and thus, the response to acetylcholinesterase therapy will vary between individuals.

Contradictions Regarding Effects of Acetylcholinesterase Inhibitors on Human Cognitive Functioning

A review of the effects of acetylcholinesterase inhibitors on cognitive functioning and performance in humans demonstrates both performance enhancement and impairment. A careful look at the nature of these disparate studies reveals clues to understanding the seemingly contradictory nature of research in this area.

Studies which tend to show impairment generally use normal unimpaired subjects. These studies tend to conclude that blocking acetylcholinesterase does not improve cognitive functioning and may impair it. By contrast, studies which tend to show improvement generally utilize clinical populations or normal subjects who have been artificially impaired. These studies generally demonstrate and/or conclude that acetylcholinesterase inhibitors have cognitive-enhancing effects. These disparate results can be resolved by considering that the findings reflect the differing populations utilized for the experiments. These populations can be expected to show quite different responses to nicotine based on principles of rate dependency or

baseline effects of cholinergic agents (e.g., the Yerkes-Dodson principal) (Fig. 1). Cognitive performance can be envisioned as a parabolic function related to cholinergic stimulation with intermediate levels of stimulation producing optimal performance and either low or high levels of stimulation impairing performance. If an individual subject who is performing suboptimally due to a disease state or impairment (e.g., AD), his performance will be enhanced by increased cholinergic stimulation via acetylcholinesterase inhibition (Fig. 1a). However, if an individual subject is already performing at or near their optimal level of performance, increasing cholinergic stimulation following acetylcholinesterase inhibitor administration will produce deterioration in cognitive functioning (Fig. 1b). The same analysis may apply if the individual is normal but the task demands are severe.



Acetylcholinesterase and Cognitive Enhancement. Fig. 1. Effects of cholinergic stimulation through acetylcholinesterase blockade are dependent on baseline performance and are subject to nonlinear effects. (**a**) Baseline performance is low and cholinergic augmentation through produces improvement in performance. (**b**) Baseline performance is normal/high and cholinergic augmentation impairs performance.

If the task is demanding enough in terms of attention, especially over a period of time, then the individual may move back to the left in terms of the performance curve and optimal performance may require enhanced cholinergic stimulation.

Studies of normal volunteers are thus unlikely to show cognitive improvement with cholinergic stimulation due to the fact that these individuals are likely to be operating at or near their optimal level of performance, particularly in the setting of experimental paradigms with pre-training for cognitive tasks, financial incentives, etc.

The preponderance of evidence is that stimulation of cholinergic receptors is most easily detected by effects on attentional systems and to some extent psychomotor speed. The most well-documented effect of cholinergic augmentation is on intensifying or sustaining attention to stimuli or tasks over a prolonged period of time. In addition, there is evidence from studies of individuals with disorders such as schizophrenia and ADHD that nicotinic cholinergic stimulation enhances selective attention, sensory detection, and inhibitional processes in attention. Positive effects of nicotinic stimulation, via acetylcholinesterase inhibitors on learning in memory may be mediated by effects on attentional functioning. Learning and memory require acquisition, encoding, storage, and retrieval. However, attention is the "front end" of this process, and adequate attentional functioning is a primary requirement for higher order processing.

Attention and related processes may be thought of as an endophenotype for cholinergic stimulation and consequently drug development. Attention, central processing impairment, and executive dysfunction may be orthogonal to the underlying neuropsychiatric diagnoses and should be considered as an independent target for drug development across diagnostic categories. Particular attentional deficits in different diagnoses may still respond to cholinergic stimulation with acetylcholinesterase inhibitors, however, the parameters for assessing improvement may be quite different between disease states and will require careful attention to particular specific agents, dosing regimens, and outcome measures for experimental studies. Paying careful attention to the issue of baseline dependency in treatment response will be vital to ensuring appropriate interpretation of experimental results, both for studies of normals and individuals with disease states. Targeting specific populations that are already impaired is much more likely to reveal potential benefits of cholinergic stimulation. Studies of normal or unimpaired individuals with acetylcholinesterase inhibitors are unlikely to show cognitive benefits except under extreme task demands.

Cross-References

► Cognitive Enhancers: Role of the Glutamate System
► Dementias and other Amnestic Disorders
► Mild Cognitive Impairment
► Muscarinic Agonists and Antagonists
► Nicotinic Agonists and Antagonists

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Acetylcholinesterase Inhibitors

Definition

These drugs prevent the breakdown of acetylcholine by inhibiting the action of the enzyme acetylcholinesterase. Their action therefore leads to an increase in the concentration of acetylcholine at the synapse.

Cross-References

► Acetylcholinesterase and Cognitive Enhancement

N-Acetylcysteine

Definition

It is the *N*-acetyl derivative of the amino acid L-cysteine, and is a precursor in the formation of the antioxidant glutathione in the body. Furthermore, it is used as a mucolytic agent and in the management of acetaminophen overdose. *N*-acetylcysteine increases cystine–glutamate exchange activity and thereby restores inhibitory tone on presynaptic metabotropic glutamate receptors. Clinically, it has reduced both cocaine use and the desire for cocaine.

Acquired Tolerance

► Tolerance

Action Inhibition

► Behavioral Inhibition

Action Potentials

Synonyms

Nerve impulse; Nerve spikes

Definition

Action potentials are pulse-like waves traveling along excitable membranes. Action potential initiation occurs when the voltage of the membrane increases sufficiently (depolarizes), thus activating (opening) voltage-gated sodium channels. Since the concentration of sodium channels outside the cell is much larger than the inside, sodium ions rush into the cell and represent the fast upstroke portion of the action potential wave. The Na channels close as the voltage peaks, and potassium channels then open allowing potassium ions to flow out of the cell since the concentration of potassium ions is much larger on the inside of the cell than the outside. This represents the falling phase of the action potential

waveform, and thus repolarizes the membrane ready for the next action potential.

Activation

Definition

The stimulation of a receptor by a ligand that stabilizes the receptor in the open conformation.

Activational Effects of Hormones

Definition

Immediate (temporary) effects of hormones that "come and go" with the presence and absence of the hormone.

Cross-References

► Sex Differences in Drug Effects

Active Avoidance

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Synonyms

Conditioned avoidance response; two-/one-way active avoidance

Definition

Active avoidance refers to experimental behavioral paradigms where subjects (mainly rodents) are trained to, following the onset of a conditioned stimulus (CS), move from a starting position to another position in the testing apparatus within a fixed amount of time (avoidance). Failure to move within the given time frame, results in the onset of a negative reinforcer, usually a weak electric shock in a grid floor, until a correct move is performed (escape). In animals performing at a high level of correct response following training, drugs that are effective as antipsychotics, but not other classes of drugs, show a unique ability to selectively suppress the avoidance behavior, within a clinically relevant dose range, while leaving escape behavior intact. Because of this robust marker for the prediction of antipsychotic activity, the active avoidance test is primarily used, and considered an important screening tool, for the detection of novel potentially ► antipsychotic drugs.

Principles and Role in Psychopharmacology

Background

It was found early that antipsychotic drugs for the treatment of ► schizophrenia had the ability to produce a selective suppression of active avoidance/conditioned avoidance behavior in rats (Cook and Weidley 1957). Later, as more antipsychotic drugs came on the market, it was found that this was a unique property among antipsychotics that was not shared by other classes of pharmacological agents, and that the selective suppression of conditioned avoidance response (CAR) produced by the antipsychotic drugs correlated with their main therapeutic mechanism of action namely brain dopamine D2 receptor blockade (Arnt 1982).

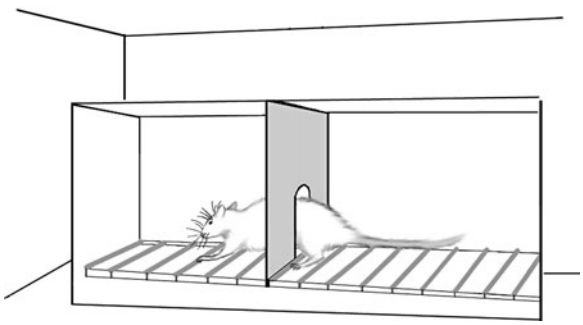
History and Procedures

The active avoidance procedure has connections back to classical conditioning (as first presented by I.P. Pavlov in 1927) (► Classical (Pavlovian) conditioning). The concept was further developed by the experimental psychologist B.F. Skinner. Skinner showed that a certain behavior could be maintained by the consequences it produced, and called this type of behavior operant behavior (► Operant behavior in animals). Thus, operant behavior (such as active avoidance response) can be defined as behavior that is maintained by its consequences.

The basic principle of active avoidance is that an animal (usually rodent) is trained (conditioned) to make a specific response within a fixed time interval when presented with an auditory, or visual, stimulus (CS). During training, incorrect responses (i.e., late responses) will trigger a negative reinforcer (unconditioned stimulus; UCS), usually a weak electric footshock presented in a grid floor, that will be active together with the CS until a correct response occurs. Thus, the animal terminates the negative reinforcer (together with the CS) by making the appropriate response. If the response, expected to be performed by the animal, is to move from one place to another upon presentation of the CS, the procedure is said to be using the active avoidance paradigm. Active avoidance procedures using a negative reinforcer typically record three dependent variables: avoidance (correct move within stipulated time frame), escape (correct, but late, move following onset of negative reinforcer), and escape failure (failure to perform a correct move despite the onset of negative reinforcer within a certain cut-off time) (see e.g., Wadenberg et al. 2007).

The active avoidance paradigm can be carried out mainly in two different ways: (1) one-way active avoidance; (2) two-way active avoidance. The one-way active avoidance procedure has the experimenter placing the animal in a chamber with a metal grid floor (for the electric shock, UCS), and upon presentation of the CS, the animal is required to move from the starting chamber into another (safe) compartment of the experimental box or jump onto a wooden pole hanging down from the ceiling of the box. The experimenter then has to move the animal back into the starting chamber for the next trial. In the two-way active avoidance procedure on the other hand, the animal moves back and forth (shuttles) between two compartments of equal size and appearance in the box via an opening in the partition dividing the box into the two compartments (shuttle-box) (Fig. 1). Here, the animal has to learn that upon presentation of the CS, it is always supposed to cross over to the other empty compartment in the box. Training and experimental sessions typically consist of a fixed number of trials over a certain time interval. The two-way active avoidance procedure has over time become the most commonly used procedure, most likely in part because this procedure can be set up as a computer-assisted apparatus with several boxes run simultaneously by one computer, thus saving time and money.

The training phase (typically needing three to four consecutive training days) in the active avoidance paradigm can be considered an acquisition phase (i.e., acquisition of avoidance performance), while, following training, animals that perform well show retention (over time) of the acquired avoidance performing ability. Screening for novel, potentially antipsychotic drugs uses well-trained, high avoidance performing animals. The marker for potential antipsychotic activity thus is the ability of an acutely administered drug to selectively, and temporarily, suppress the retention of avoidance performance in the animals.



Active Avoidance. Fig. 1. The figure shows a conventional two-way active avoidance apparatus (schematic drawing by Sofia I Wadenberg).

Evaluation and Use of the Active Avoidance Test

Animal behavioral tests (so-called animal models), used in the development of novel drugs for pharmacological treatment of diseases, are typically evaluated and rated for their fulfillment of validity criteria such as (1) predictive, construct and face validity; (2) their reliability; and (3) how they fare in terms of producing false positives or negatives. The active avoidance test is commonly considered to have high predictive validity, since all clinically effective antipsychotics, but not other classes of drugs, show the ability to selectively suppress avoidance behavior with a positive correlation between doses needed for the selective suppression of avoidance and their clinical potency for the effective treatment of schizophrenia (Seeman et al. 1976). More recently it was also found that antipsychotics produce selective suppression of avoidance in doses that result in a brain striatal dopamine D2 receptor occupancy around 65–75% in the rat (Wadenberg et al. 2001), which is also the percentage of dopamine D2 receptor occupancy usually needed for therapeutic response to occur in schizophrenic individuals following antipsychotic treatment. In other words, the active avoidance test identifies potential antipsychotic activity of new drugs tested with high predictive certainty. The active avoidance test has also been shown to have some construct validity (i.e., selective suppression of avoidance may mimic a blockade of some pathophysiological mechanisms in schizophrenia). Thus, the local application of an antipsychotic-related dopamine D2 receptor blocking agent, (-)sulpiride, into various brain areas in the rat, produced selective suppression of avoidance only when injected into the nucleus accumbens/ventral striatum (Wadenberg et al. 1990), a brain area that has a prominent role in the dopamine mesolimbic pathway that is commonly thought to be involved in the psychotic symptoms in schizophrenia (Laruelle et al. 1996) (► Aminergic hypotheses for schizophrenia). The active avoidance test has, however, no face validity, as it does not mimic any behavioral core symptoms of schizophrenia. The active avoidance test also shows high reliability, as there is a high degree of agreement between laboratories as to which compounds produce antipsychotic-like effects and in what dose range that occurs. Finally, to the best of the Author's knowledge, the active avoidance test produces few, if any, false positives or negatives. Thus, there is no antipsychotic, known to be clinically effective, that does not produce a selective suppression of active avoidance within a clinically relevant dose range. In addition, drugs

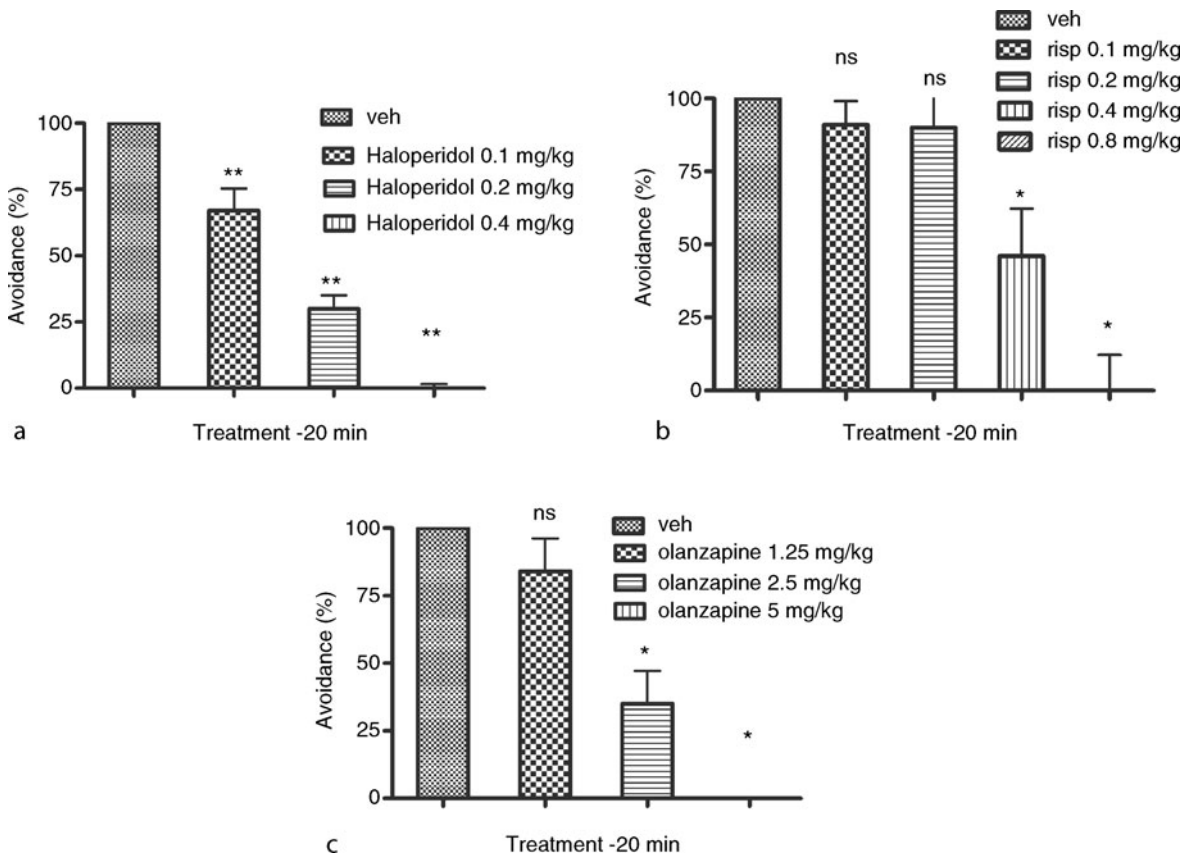
that have failed in clinical trials, or studies, for antipsychotic activity (such as for example, selective serotonin2A antagonists, selective dopamine D1 or D4 receptor antagonists) also, either showed no effect on active avoidance, or failed to produce a dose dependent suppression of avoidance without concomitant inhibition also of the escape variable (i.e., producing failures).

Based on the properties listed above, the active avoidance test falls into the category of so-called screening tests. A screening test is used by drug companies to evaluate synthesized molecules for a specific therapeutic property. When the screening test is an animal behavioral test, drug companies usually label the procedure in vivo pharmacology. Effects in these tests should occur following an acute administration of test drug, and only molecules that are effective against a particular disease should produce the specific effect that constitutes the marker for clinical activity – in this case selective suppression of avoidance within a clinically relevant dose range is produced.

The Active Avoidance Test and Identification of Drug Pharmacological Properties

There is no doubt that active avoidance behavior is strongly associated with brain dopamine neural transmission, and that the suppression of avoidance performance correlates significantly with the degree of striatal dopamine D2 receptor occupancy produced by D2 receptor blocking antipsychotic drugs. However, the active avoidance test not only identifies traditional, mainly dopamine D2 blocking antipsychotics such as haloperidol (Fig. 2a), but is also equally sensitive in detecting the antipsychotic activity of the newer, so-called atypical, antipsychotics with a different mechanism of action such as combined lower dopamine D2/high serotonin2 receptor blockade (e.g., olanzapine, risperidone) (Fig. 2b,c), or being partial agonists at dopamine D2 receptors rather than pure D2 antagonists (i.e., aripiprazole).

In addition, data from clinical studies (Litman et al. 1996; Schubert et al. 2006) are in line with, and support,



Active Avoidance. Fig. 2. Shown are typical dose-response effects on active avoidance response (selective suppression of avoidance) by the typical antipsychotic haloperidol (**a**), and the atypical antipsychotics risperidone (**b**), and olanzapine (**c**) in rats. Data are presented as medians ± semi-interquartile range (n=6–9).

experimental data showing that the active avoidance test also reliably detects sufficient antipsychotic activity obtained by adjunct treatment with some non-D2 blocking agents (such as alpha2 adrenoceptor antagonists or acetylcholinesterase inhibitors) to a low dose of an antipsychotic not giving sufficient dopamine D2 occupancy alone to produce antipsychotic activity (Wadenberg and Karlsson 2007; Wadenberg et al. 2007). Thus, the ability of the active avoidance test to detect antipsychotic activity does not seem to be solely limited to the detection of drugs with direct dopamine D2 receptor blocking properties. This certainly increases the value of this test as a screening tool in further development of new antipsychotic drugs, since many current development strategies, in order to minimize side effects and improve therapeutic efficacy, aim at moving away from molecules with mainly strong dopamine D2 receptor blocking properties.

Alternative Use of the Active Avoidance Test

The active avoidance test is primarily a test for detecting antipsychotic activity, that is, the ability of tested compounds to counteract psychotic symptoms in patients. However, since there is an element of training and learning (acquisition) associated with this test, there have been attempts to investigate if the test may be used also as a model for the detection of compounds that will enhance learning (effects on acquisition) or memory (effects on retention). Such attempts have overall not produced any consistent data. In fact, drugs that normally would impair memory (such as for example, drugs blocking brain neural transmission of acetylcholine) do not suppress avoidance behavior. Furthermore, the administration of a dopamine D2 receptor blocking antipsychotic to the animals during the training/acquisition phase does not impair the final outcome of avoidance performance in the absence of drug. This would suggest that suppressive effects on avoidance performance are not related to the impairment of memory, but rather to a temporary attenuation of the conditioned reflex, or urge, to hurry over to the other side in order to avoid getting a footshock. Indeed, gross observations of the behavior in animals given an antipsychotic drug strongly indicate that upon presentation of the CS, these animals still remember exactly what they are supposed to do; they just do not care enough to move within the time frame. Another way of explaining this phenomenon, although somewhat speculative, could be that the reason why active avoidance does not seem to work as a memory test, is because the acquisition and retention performance of active avoidance seem to primarily involve the brain subcortical mesolimbic system in general considered to be mediating behavior associated with basic reward and survival factors (i.e., survival reflexes), rather than recruiting higher order brain structures, such as for example, the prefrontal cortex, that are involved in memory processes of higher order events (Wadenberg et al. 1990).

Advantages and Limitations of the Active Avoidance Test

The active avoidance test has proven to be a unique and very useful screening test for the detection of drugs with antipsychotic activity with high predictive validity as well as excellent reliability. However, individuals suffering from schizophrenia do not only present with psychotic symptoms, but also have features of social withdrawal and cognitive impairment. These symptoms have a crucial impact on the quality of life for these individuals, and unfortunately, many of the currently used antipsychotics do not adequately improve these symptoms. Therefore, novel compounds showing antipsychotic-like effects in the active avoidance test, need to be tested also in an animal model of cognition as a complementary investigation of their potential cognitive enhancing activity compared with currently used antipsychotics. A major improvement in the field would be the development of an animal behavioral screening test that identifies both antipsychotic and cognitive enhancing activity of tested drugs.

Cross-References

- ▶ Aminergic Hypotheses for Schizophrenia
- ▶ Animal Models for Psychiatric States
- ▶ Antipsychotic Drugs
- ▶ Classical (Pavlovian) Conditioning
- ▶ Operant Behavior in Animals

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Active Immunization

► Vaccination

Activities of Daily Living

Definition

The activities of daily living (ADLs) are a defined set of activities necessary for normal self-care. The activities are movement in bed, transfers, locomotion, dressing, personal hygiene, and feeding. These six activities are defined as follows:

1. Movement in bed (sitting in, rising from, and moving around in bed)
2. Transfers (moving from one seat to another, changing position from sitting to standing, and transferring to and from the toilet and bed)
3. Locomotion (walking on the level, on gentle slopes, and downstairs)
4. Dressing (putting on socks, stockings, and shoes, as well as clothing the upper and lower trunk)
5. Personal hygiene (grooming, and washing of face, trunk, extremities and perineum)
6. Feeding (eating and drinking, but not the preparation of food)

Activities of Living Scales

► Impairment of Functioning; Measurement Scales

Acute Brain Failure

► Delirium

Acute Brain Syndrome

► Delirium

Acute Confusional State

► Delirium

Acute Disappointment Reaction

Definition

A syndrome involving lowered or dysphoric mood, which occurs in response to a perceived unpleasant experience such as a loss, rejection, or insult to one's self-concept or self-esteem. The person having the acute disappointment reaction may or may not be fully aware of, or fully able to explain, the issue to which the reaction is in response. Acute disappointment reactions are usually relatively brief – generally lasting at most a week or two – unless the insult to which the response is attached is of a repetitive or continuing nature.

Cross-References

► Depressive Disorder of Schizophrenia

Acute Tolerance

Definition

Acute tolerance is a diminution of effect either during a single drug-taking episode such that the drug produces greater effects as blood concentration increases compared to when blood concentration decreases, or if the effect is less on the second time that the drug is taken.

Acute Tyrosine/Phenylalanine Depletion

► Phenylalanine and Tyrosine Depletion

AD-5423

► Blonanserin

Adaptability

► Behavioral Flexibility: Attentional Shifting, Rule Switching and Response Reversal

Add on Therapy

► Drug Interactions

Addiction

Definition

The condition of a human or an animal where a drug is sought after and taken in spite of negative consequences to the individual. It is a state of obsession and compulsion in which the body depends on a substance for normal functioning, characterized by a loss of control over its consumption. The use of the term is usually restricted to the most serious and severe forms of drug abuse.

Addiction Research Center

Synonyms

ARC; NIDA IRP

Definition

The Addiction Research Center (ARC) began as the research component of the U.S. Narcotics Prison Farm located in Lexington, Kentucky. It was a very important site for early clinical pharmacology studies of opioids and other drugs of abuse. Methods for assessing the physiological and subjective effects of drugs of abuse were refined here, and include such instruments as the Addiction Research Center Inventory and the Single Dose Questionnaire. The ARC eventually became the intramural research unit of the National Institute on Drug Abuse and moved to Baltimore, Maryland.

Cross-References

► Abuse Liability Evaluation
► Addiction Research Center Inventory
► U.S. Narcotics Prison Farm

Addiction Research Center Inventory

Synonyms

ARCI

Definition

A true/false questionnaire developed at the Addiction Research Center used to assess the subjective effects of various drugs of abuse. Items include such statements as:

I have a pleasant feeling in my stomach.
I am sweating more than usual.
I have a floating feeling.
My movements seem slower than normal.

The original version had 550 such statements, but newer and shorter versions have been developed and validated as well. The most widely used version today includes only 49 items. Responses on the ARCI yield scores on various scales (five for the short form) that were empirically derived by administering known drugs of abuse and establishing the pattern of responses. For example, the Morphine-Benzedrine Group scale (MBG) is used as a proxy for the euphoric effects produced by opioids and amphetamines.

Cross-References

► Abuse Liability Evaluation
► Addiction Research Center
► Opioids

Addiction Stroop Test

► Attentional Bias to Drug Cues

Addictive Disorder: Animal Models

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Synonyms

Experimental drug dependence

Definition

Animal model: Experimental preparation developed for studying a given phenomenon found in humans. It is at the basis of experimental medicine, with its two sides: physiology and pathology.

Individual differences: Refer to the concept of differential psychology, personality, and temperament. Each individual is unique in terms of genetic and environmental backgrounds, and of life events and history.

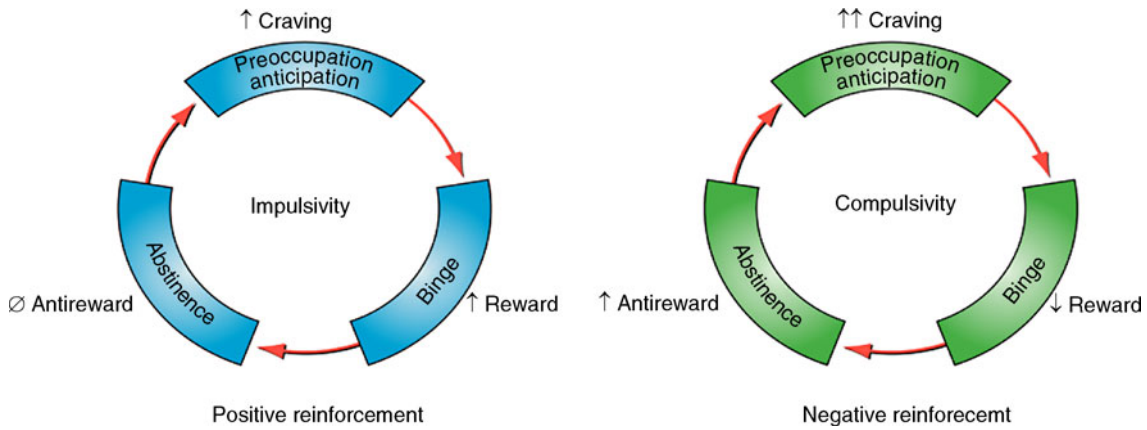
Vulnerability or frailty: A construct inherent to medical practice, for genetic or environmental reasons. It represents a biological state at the limits of homeostasis.

Current Concepts and State of Knowledge

Introduction: A Model of What?

In behavioral pathology and comparative psychiatry a precondition for an animal model is to be informed about what will be modeled. The poor awareness of the complexity of such human conditions is the origin of misunderstanding between clinicians and neurobiologists. This is particularly true in the field of drug abuse. Drug ► addiction, also known as substance dependence, is characterized by (1) compulsion to seek and take the drug, (2) loss of control in limiting intake, and (3) emergence of a negative emotional state (e.g., dysphoria, anxiety, irritability) when access to the drug is prevented (Koob and Le Moal 1997). The terms addiction and substance dependence (as currently defined by the American Psychiatric Association (1994)) are used interchangeably and refer to a final stage of a misusage process that moves from drug use to a chronic relapsing disorder. This point is critical. It is referred here to a brain pathology from which a recovery is questionable. In other words, the occasional but limited or controlled use of a drug with a potential for abuse or dependence is distinct from the emergence of a chronic drug-dependent state. An important goal of current neurobiological research is to understand the molecular and neuropharmacological neuroadaptations within specific neurocircuits that mediate the transition from occasional, controlled drug use to the loss of behavioral control over drug seeking and drug taking. A key element of the addiction process is the underactivation of natural motivational systems such that the reward system becomes compromised and that an antireward system becomes recruited to provide the powerful motivation for drug seeking associated with compulsive use (Koob and Le Moal 2008).

The process of drug addiction involves elements of both ► impulsivity and compulsivity (Fig. 1), where impulsivity can be defined by an increasing sense of tension or arousal before committing an impulsive act and by a sense of pleasure, gratification, or relief at the time of



Addictive Disorder: Animal Models. Fig. 1. "The addiction cycle." Diagram describing the addiction cycle that is conceptualized as having three major components: preoccupation/anticipation ("craving"), binge/intoxication, and withdrawal/negative affect. Note that as the individual moves from the impulsivity stage to the compulsivity stage, there is a shift from positive reinforcement associated with the binge/intoxication component to negative reinforcement associated with the withdrawal/negative affect component. Craving is hypothesized to increase in the compulsivity stage because of an increase in the need state for the drug that is driven not only by loss of the positive reinforcing effects of the drugs (tolerance), but also by generation of an antireward state that supports negative reinforcement. (Reproduced with permission from Koob and Le Moal 2008.)

committing the act. Compulsivity can be defined by anxiety and stress before committing a compulsive repetitive behavior and relief from the stress by performing the compulsive behavior. Collapsing the cycles of impulsivity and compulsivity yields a composite addiction cycle comprised of three stages: preoccupation/anticipation, binge/intoxication, and withdrawal/negative effect, where impulsivity often dominates at the early stages and compulsivity dominates at terminal stages. As an individual moves from impulsivity to compulsivity, a shift occurs from positive reinforcement driving the motivated behavior to negative reinforcement driving the motivated behavior. These three stages interact with each other, becoming more intense, and ultimately leading to the *final pathological state*: addiction. Here it is important to realize that the main symptoms correspond to different structural–functional entities including large systems in the brain.

Classic Validation of Animal Models of Drug Addiction

- General typology of animal models

Animal models are critical for understanding the neuropharmacological mechanisms involved in the development of addiction. While there are no complete animal models of addiction, animal models may exist for elements of the syndrome. An animal model can be viewed as an experimental preparation developed for studying a given phenomenon found in humans (McKinney 1988; Geyer and Markou 2002). The most relevant conceptualization of validity for animal models of addiction is the concept of *construct validity*. Construct validity refers to the interpretability, "meaningfulness," or explanatory power of each animal model and incorporates most other measures of validity where multiple measures or dimensions are associated with conditions known to affect the construct. An alternative conceptualization of construct validity is the requirement that models meet the construct of functional equivalence, defined as assessing how controlling variables influence outcome in the model and the target disorders and the most efficient process for evaluating functional equivalence has been argued to be through common experimental manipulations, which should have similar effects in the animal model and the target disorder (Katz and Higgins 2003). This process is very similar to the broad use of the construct of *predictive validity*. *Face validity* often is the starting point in animal models where animal syndromes are produced, which resemble those found in humans in order to study selected parts of the human syndrome but is limited by necessity. *Reliability* refers to the stability and consistency with which the variable of interest can be measured and is achieved when, following objective repeated measurement of the variable, small within- and between-subject variability is noted, and the phenomenon is readily reproduced under similar circumstances. The construct of *predictive validity* refers to the model's ability to lead to accurate predictions about the human phenomenon based on the response of the model system. Predictive validity is used most often in the narrow sense in animal models of psychiatric disorders to refer to the ability of the model to identify pharmacological agents with potential therapeutic value in humans. However, when predictive validity is more broadly extended to understanding the physiological mechanism of action of psychiatric disorders, it incorporates other types of validity (i.e., etiological, convergent or concurrent, discriminant) considered important for animal models, and approaches the concept of construct validity. Some animal models have been shown to be reliable and to have construct validity for various stages of the addictive process will be described.

- Animal models and the stages of the addiction cycle

Table 1 summarizes the models used in most laboratories according to the stages of the addiction cycle.

1. Animals models for the Binge/Intoxication Stage

According to the evolution of the process defined above (Fig. 1), the individual moves from impulsivity to compulsivity with the development of preoccupation-anticipation and when he or she is in abstinence, negative effect and withdrawal symptoms progressively appear as signature of addiction. The procedures used have proven reliability and to have predictive validity in their ability to understand the neurobiological basis of the acute reinforcing effects of drugs. If one could reasonably argue that drug addiction mainly involves counteradaptive mechanisms that go far beyond the acute reinforcing actions of drugs, understanding the neurobiological mechanisms for positive reinforcing actions of drugs of abuse also provides a framework for understanding the motivational effects of counteradaptive mechanisms. Many of the operant measures used as models for the reinforcing effects of drugs of abuse lend themselves to within-subjects designs, limiting the number of subjects required. Indeed, once an animal is trained, full dose-effect functions can be generated for different drugs, and the animal can be tested for weeks and months. Pharmacological manipulations can be conducted with standard reference compounds to validate any effect. In addition, a rich literature on the experimental analysis of behavior is available for exploring the

Addictive Disorder: Animal Models. Table 1. Stages of the addiction cycle and models.

Stage	Source of reinforcement	Animal models
Binge/ intoxication	Positive reinforcement	Conditioned place preference
		Drug self-administration
		Decreased reward thresholds
		Intracranial self-stimulation
Withdrawal/ negative affect	Negative reinforcement	Conditioned place aversion
		Increased self-administration in dependence
		Increased reward thresholds
		Intracranial self-stimulation
Preoccupation/ anticipation	Conditioned positive and negative reinforcement	Drug-induced reinstatement
		Cue-induced reinstatement
		Stress-induced reinstatement
		Protracted abstinence

hypothetical constructs of drug action as well as for modifying drug reinforcement by changing the history and contingencies of reinforcement. The advantage of the intracranial self-stimulation (ICSS) paradigm as a model of drug effects on motivation and reward is that the behavioral threshold measure provided by ICSS is easily quantifiable. ICSS threshold estimates are very stable over periods of several months. Another considerable advantage of the ICSS technique is the high reliability with which it predicts the abuse liability of drugs. For example, there has never been a false positive with the classic discrete trials threshold technique. The advantages of place conditioning as a model for evaluating drugs of abuse include its high sensitivity to low doses of drugs, its potential utility in studying both positive and negative reinforcing events, the fact that testing for drug reward is done under drug-free conditions, and its allowance for precise control over the interaction of environmental cues with drug administration.

2. Animal Models for the Preoccupation/Anticipation Stage

Each of the models outlined above has face validity to the human condition and ideally heuristic value for understanding the neurobiological bases for different aspects of the craving stage of the addiction cycle. The DSM-IV criteria that apply to the craving stage and loss of control over drug intake include any unsuccessful effort or persistent desire to cut down or control substance use. The extinction paradigm has predictive validity, and with the reinstatement procedure, it can be a reliable indicator of the ability of conditioned stimuli to reinitiate drug-seeking behavior. The conditioned-reinforcement paradigm has the advantage of assessing the motivational value of a drug infusion in the absence of acute effects of the self-administered drug that could influence performance or other processes that interfere with motivational functions. For example, nonspecific effects of manipulations administered before the stimulus drug pairings, do not directly affect the assessment of the motivational value of the stimuli because the critical test can be conducted several days after the stimulus drug pairings. Also, the paradigm contains a built-in control for nonspecific motor effects of a manipulation by its assessment of the number of responses on an inactive lever.

The animal models for the conditioned negative reinforcing effects of drugs are reliable measures and have good face validity. Work in this area, however, has largely been restricted to the opiate field where competitive antagonists precipitate a withdrawal syndrome. There is consensus that the animal reinstatement models have face validity. However, predictive validity remains to be established. To date, there is some predictive validity for the stimuli that elicit reinstatement in the animal models, but little evidence of predictive validity from studies of the pharmacological treatments for drug relapse. Very few clinical trials have tested medications that are effective in the reinstatement model, and very few anti-relapse medications have been tested in the animal models of reinstatement. From the perspective of functional equivalence or construct validity there is some evidence of functional commonalities. For example, drug re-exposure or priming, stressors, and cues paired with drugs all produce reinstatement in animal models and promote relapse in humans.

3. Animal Models for the Withdrawal/Negative Affect Stage

It has been proposed by some authors that the motivational measures of drug withdrawal have much the

same value for the study of the neurobiological mechanisms of addiction as procedures used to study the positive reinforcing effects of drugs. ICSS threshold procedures have high predictive validity for changes in reward valence. The disruption of operant responding during drug abstinence is very sensitive. Place aversion is hypothesized to reflect an aversive unconditioned stimulus. Drug discrimination allows a powerful and sensitive comparison to other drug states. The use of multiple dependent variables for the study of the motivational effects of withdrawal may provide a powerful means of assessing overlapping neurobiological substrates and to lay a heuristic framework for the counteradaptive mechanisms hypothesized to drive addiction.

Individual differences, the concept of vulnerabilities and animal models

(a) Individual differences: a central problem in addiction medicine

For all the paradigms presented above and in consequence for these animal models used, all the subjects (rodents) are equal. The data are presented by means with their standard errors. In clinical practice, huge individual differences exist for the proneness to take drugs, for their perceived reinforcing effects and above all for the propensity to continue to misuse them and enter in a spiral of addiction. In other words, one of the most important problems in drug addiction today is to understand why an enormous amount of people take drugs according to the various circumstances of social life whereas only a small percentage of them will become addicted. Some individuals can stop their misusage without noticeable withdrawal syndrome. It is also reported that some get hooked with the first usage. Some individuals are vulnerable, other not. Vulnerability refers to a construct that covers all the fields of medicine. After a period devoted to the description of symptoms and diagnostic, then to identify the pathophysiological bases of the disease, then to find the causes, then to cure, predictive medicine will be the next step, i.e., to discover markers and prodromic states of vulnerabilities. Some vulnerabilities are specific for a given class of diseases, other are, in the state of knowledge, nonspecific. It is a strange phenomenon that while the problem of vulnerability in addiction medicine is abundantly discussed in clinical literature, it is almost completely absent in experimental and animal research.

Needless to say, drugs also have their own pharmacological effects that depend on intrinsic and differential dangerousness of the products. However, a drug is addictive because a specific individual in a given social environment uses it. Moreover, a vulnerable phenotype and vulnerability are revealed a-posteriori.

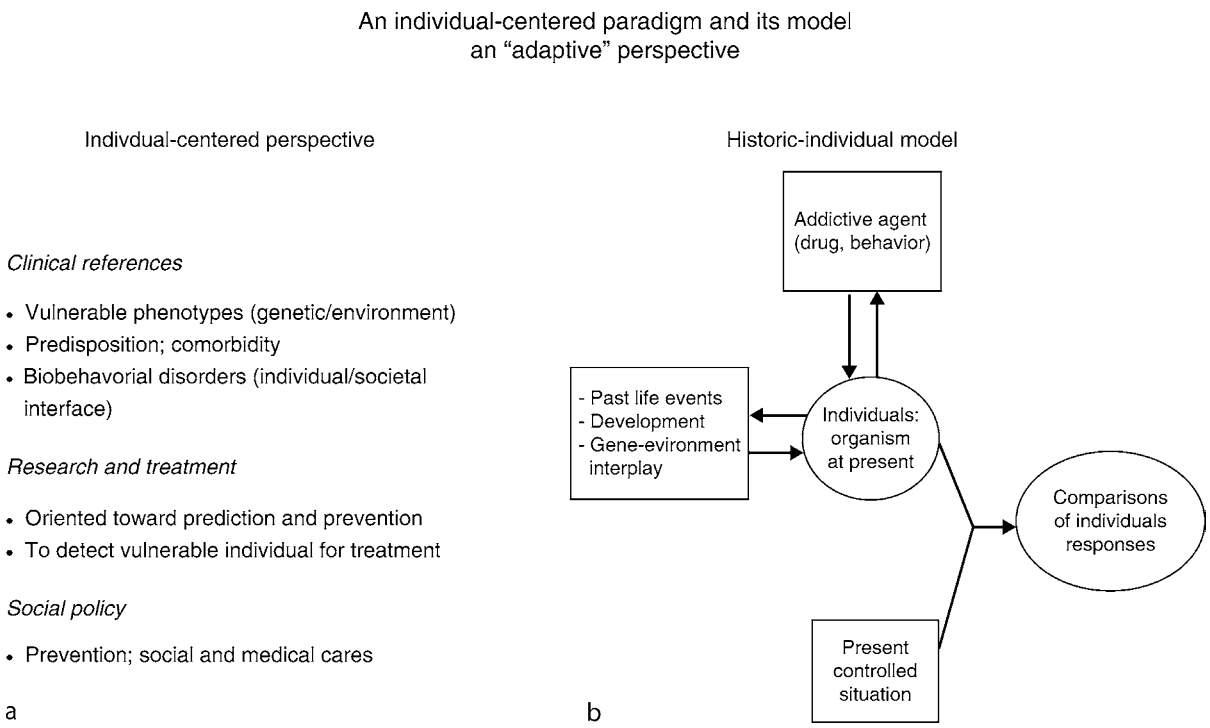
The origins of vulnerability are numerous and interacting: genetic, environmental, aversive life events and stress, age and gender. All these factors have left traces in the organism. Vulnerability participates to psychopathological syndromes and to comorbid factors diagnosed in most of the psychiatric disorders. Each individual has his own history that participates in a unique way to the entrance in addiction process. These factors, each or associated, contribute to psychobiological traits. However, such a view, based on clinical observations and studies is at variance with most of the experimental investigations and raised methodological considerations about animal and biological models and the neuroscience of addiction in general.

(b) Vulnerability and transition to addiction: two opposite views

The first one, adaptive or individual-centered, places the subject with his own characteristics at the center of research and interest. The adaptive perspective (Fig. 2) is based on a predisposition, on the fact that explains why subjects are at risk and why their intrinsic predisposed state determines the neuroplasticity induced by drugs.

To detect the sources of vulnerability would lead to predictive medicine and toward psychosocial interventions. A translation from the real world and from clinical psychiatry to the laboratory must discover and develop models that will present (1) gradual individual differences from the resilient to the most vulnerable phenotypes, (2) a transition from use to misuse for some animals prone to enter in the disease spiral and, (3) the main symptoms of the disease as defined by the DSM IV at the end of the process. An individual-centered approach is basically a historic approach. Patients and animals are considered different and more or less vulnerable because of their past, of developmental characteristics or genetic background. The sequences of the process are represented in Fig. 3.

This paradigm opposes classic pharmacological approaches, i.e., drug-centered, or exposure model, based on drug-induced neuroplasticity and on acquired vulnerability. Here, drug abuse is a iatrogenic disorder and both research and therapeutics are oriented toward understanding drug pharmacological properties and toxicological actions on brain substrates, and toward counteracting these effects by other pharmacological means. This paradigm is largely dominant in laboratory research; animals are considered not in relation with their past (a-historic models) but with the amount of drug taken (Fig. 4).



Addictive Disorder: Animal Models. Fig. 2. "An individual-centered research paradigm (**a**) for an historic-individual animal model (**b**)." Individuals are considered as different from the point of view of their past life events, developmental characteristics, and genetic background. Individual comparisons require nonparametric statistics. (Reproduced with permission from Le Moal (2009) Drug abuse: vulnerability and transition to addiction. Pharmacopsychiatry 42:S42–S55, © Georg Thieme Verlag Stuttgart, New York.)

Individual differences are hidden under statistical standard errors or considered as protocol artifacts.

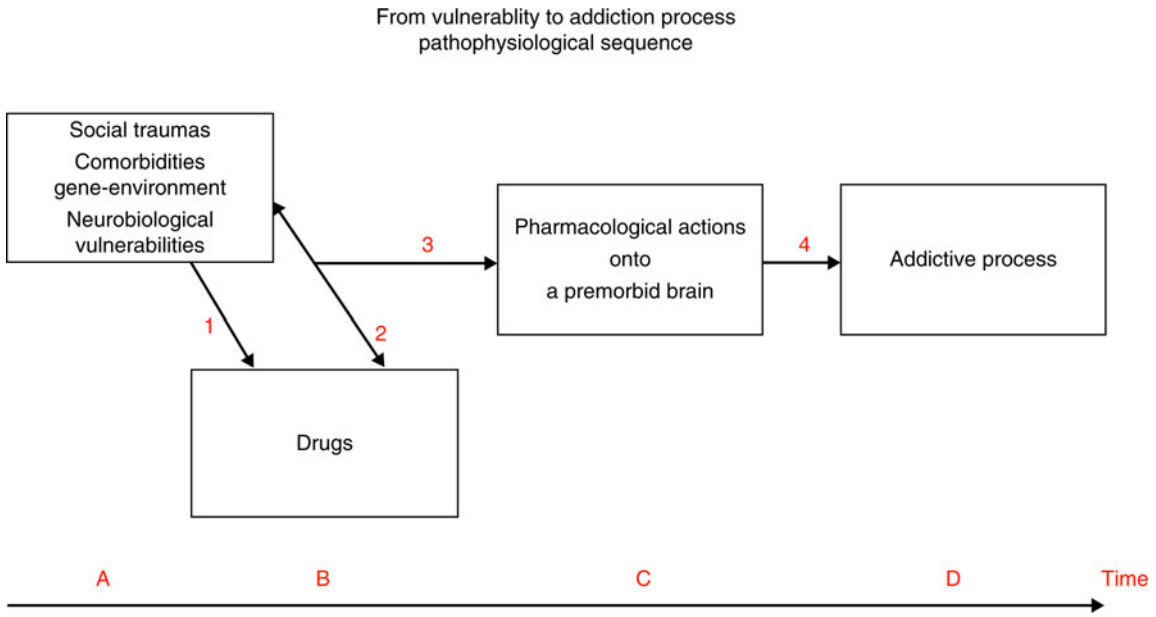
These two different research interests and practices have their own logic and necessities and are sometimes complementary. It is important to discover the neurotoxic damages and neuroplasticities induced by drugs. These neurobiological changes explain the transition from impulsive to compulsive behaviors and loss of control. Drugs of abuse have different addictive properties. It is a trivial observation that frequent usage of a drug, or the repetition of specific behaviors, combined with the intrinsic dangerous state of each drug (gambling, eating, sex...) are dangerous by themselves and lead progressively to loss of control.

(c) Two recent models: drug-centered versus individual centered

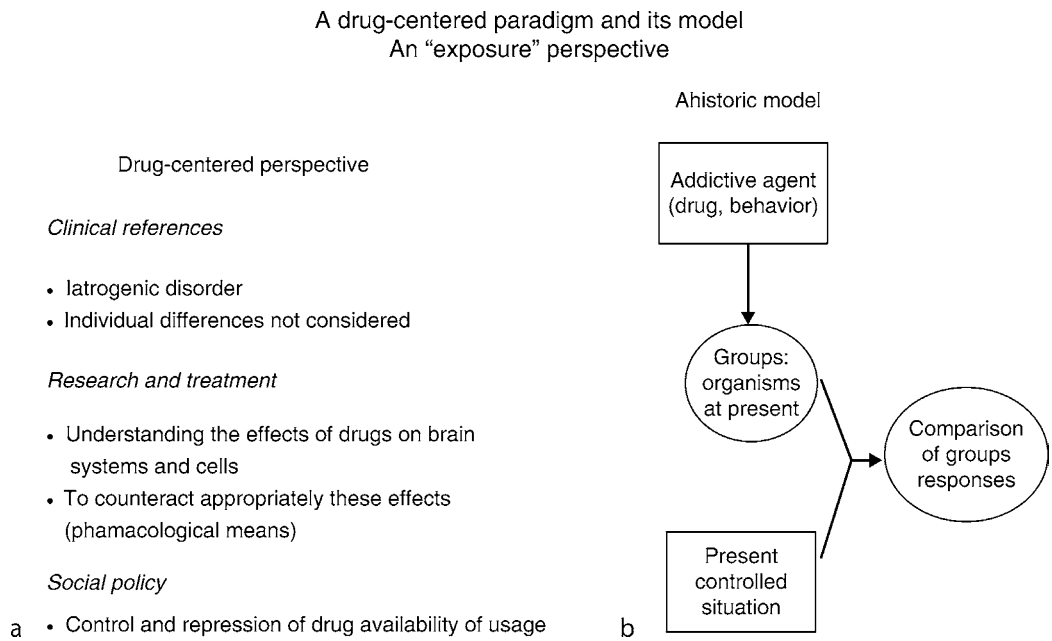
A conceptual framework upon which animal models can be directly related to the compulsive behavior and loss of control over intake, that is the hallmark of addiction, is to specifically relate a given animal model to a specific symptom of the DSM-IV criteria for addiction. Recent studies have emphasized animal models that contribute to specific elements of the DSM-IV criteria with strong face validity, and at the same time may represent specific endophenotypes of the compulsive nature of the addiction process.

1. Ahistoric model: escalation in drug self-administration with prolonged access

A progressive increase in the frequency and intensity of drug use is a behavioral phenomena often characterizing the development of addiction and has face validity with the DSM-IV criteria. A framework with which to model the transition from drug use to drug addiction is found in a recent animal model of prolonged access to intravenous cocaine self-administration. Historically, animal models of cocaine self-administration involved the establishment of stable behavior from day to day to allow the reliable interpretation of data provided by within-subject designs aimed at exploring the neuropharmacological and neurobiological bases of the reinforcing effects



Addictive Disorder: Animal Models. Fig. 3. "Vulnerability to addiction process." A given drug or behavior (e.g., eating, gambling, sex) is "addictive" because of its exposure to a vulnerable individual (1) who will be prone to repeat the drug use (2). Drug use then will induce neuropharmacological and neurotoxicological effects and profound neuronal changes (3) and then addiction (4). A, B, C, D: Process sequence. (Reproduced with permission from Le Moal (2009) Drug abuse: vulnerability and transition to addiction. Pharmacopsychiatry 42:S42–S55, © Georg Thieme Verlag Stuttgart, New York.)



Addictive Disorder: Animal Models. Fig. 4. "A drug-centered research paradigm (**a**) for a ahistoric animal model (**b**)." Group comparisons require parametric statistics. The subjects are not considered from their individual characteristics – they are considered equal or similar. (Reproduced with permission from Le Moal (2009) Drug abuse: vulnerability and transition to addiction. Pharmacopsychiatry 42:S42–S55, © Georg Thieme Verlag Stuttgart, New York.)

of acute cocaine. Typically, after the acquisition of self-administration, rats allowed access to cocaine for 3 h or less per day establish highly stable levels of intake and patterns of responding between daily sessions. These models do not fit with the concept of addiction.

To explore the possibility that differential access to intravenous cocaine self-administration in rats may produce different patterns of drug intake, rats were allowed access to the intravenous self-administration of cocaine for 1 or 6 h per day. One hour access (short access or ShA) to intravenous cocaine per session produced low and stable intake as observed previously. In contrast, with 6 h access (long access or LgA) to cocaine, drug intake gradually escalated over days (Ahmed and Koob 1998). It is observed in the escalation group, there was increased intake during the first hour of the session as well as sustained intake over the entire session and an upward shift in the dose-effect function, suggesting an increase in hedonic set point. When animals were allowed access to different doses of cocaine, both the LgA and ShA animals titrated their cocaine intake, but the LgA rats consistently self-administered almost twice as much cocaine at any dose tested, further suggesting an upward shift in the set point for cocaine reward in the escalated animals. Escalation also is associated with an increase in break point for cocaine in a progressive-ratio schedule, suggesting an enhanced motivation to seek cocaine or an enhanced efficacy of cocaine reward.

This model fits with the drug-centered paradigm. It is a-historic: the subjects are not considered from their individual characteristics but considered at the beginning of the experiment equal or similar. Only the drug parameters (amount taken) change.

2. Historic model: differential vulnerability for a transition to addiction

A second model considers that each individual has different characteristics and vulnerabilities to the pharmacological aspects of drugs. Such differential vulnerabilities had been demonstrated for the propensity to like drugs. A first paper published demonstrated that it was possible to evidence in rats (1) marked individual differences in the development of psychostimulant self administration; (2) that a differential propensity to drug taking was predicted by individual reactivity to novelty, a robust permanent trait; (3) a significant positive correlation between the magnitude of the reactivity and the amount of the drug self-administered during an acquisition session (Piazza et al. 1989). In a recent study explored further the behavioral effects of drug-taking in animals with access to cocaine for 3 months and a number of behavioral tests were administered that were hypothesized to capture DSM-IV criteria of addiction (Deroche-Gamonet et al. 2004). Unsuccessful effort or a persistent desire to cut down or control substance use was linked to the persistence of cocaine seeking during a period of signaled non-availability. A great deal of time spent in activities necessary to obtain the substance was linked to performance on a progressive-ratio schedule, and continued substance use despite knowledge of having a persistent physical or psychological problem was linked to the persistence in responding for drug by animals when drug delivery was associated with punishment. Rats were trained to self-administer cocaine intravenously and then separated by groups based on a test for reinstatement to small doses of cocaine administered after 5 days of extinction. The animals with the high tendency to show reinstatement showed progressively increased responding during signaled nondrug periods, higher break points on the progressive-ratio test, and higher responding after punishment (Deroche-Gamonet et al. 2004). Further study of rats subjected to all three tests above revealed that the animals that met all three positive criteria represented 17% of the entire population, a percentage noted by the authors to be similar to the number of human cocaine users meeting the DSM-IV criteria for addiction while 41% of the rats were resilient (0 criterion). This model highlights the importance of differential vulnerability to addiction. It demonstrates huge individual differences for the propensity to enter in the addiction cycle. It is typically anindividual-centered model and corresponds to what is met in addiction medicine.

Conclusion

Animal models for addiction have progressed from simple drug reinforcement models to sophisticated models with solid face validity. Escalation in drug intake with extended access has been observed in numerous laboratories with all the drugs of abuse. This drug-centered model do not discriminate animals according to potential previous vulnerabilities; here the transition to addiction is linked to compulsivity. More recently, animal models for criteria of addiction that reflect the channeling toward drug seeking at the expense of other environmental contingencies (Deroche-Gamonet et al. 2004; Vanderschuren and Everitt 2004) have been developed and linked to the compulsive loss of control over intake. The model described above may prove particularly sensitive to the transition to addiction in otherwise vulnerable individuals.

Acknowledgments

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Cross-References

- ► Animal Models for Psychiatric States
- ► Cocaine
- ► Personality: Neurobehavioural Foundation and Pharmacological Protocols
- ► Pharmacokinetics
- ► Phenotyping of Behavioral Characteristics
- ► Psychostimulant Addiction
- ► Sedative, Hypnotic and Anxiolytic Dependence
- ► Self-Administration of Drugs
- ► Stress: Influence on Drug Action
- ► Withdrawal Syndrome

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Add-on Therapy

Definition

Strategy to enhance a therapeutic effect by an additional drug.

Adenine-9-β-D-Ribofuranoside

► Adenosine

Adenine Riboside

► Adenosine

Adenosine

Synonyms

(2R,3R,4R,5R)-2-(6-aminopurin-9-yl)-5-(hydroxymethyl) oxolane-3,4-diol; 9-β-D-ribofuranosyladenine; Adenine-9-β-D-ribofuranoside; Adenine riboside

Definition

Endogenous nucleoside made up of the purinic base adenine and the pentose carbohydrate ribose linked through an N-9 bound. Adenosine is present in all mammalian tissues at both the intra- and extracellular level, and takes part in important physiopathological phenomena (e.g., modulation of inflammation, regulation of heart rhythm). At the level of the central nervous system, adenosine promotes a generalized inhibition of neuronal functionality, a reason why it is often referred to as "endogenous neurodepressant."

Cross-References

- ► Caffeine

Adenosine A_1 Receptors

Definition

Protein G-coupled receptors whose stimulation inhibits the signal cascade mediated by adenylyl cyclase. A_1 receptors have a widespread distribution in the brain, being enriched at significant levels in almost every cerebral area. A_1 receptors are mostly located at the presynaptic level, where they inhibit the release of ► neurotransmitters. Postsynaptic A_1 receptors have also been described on medium-sized spiny neurons projecting from the caudate nucleus to the substantia nigra. These receptors may co-localize with D_1 receptors at the neuronal level, and opposite functional interactions between these receptors

exist (e.g., stimulation of A_1 receptors depresses D_1 receptors-mediated effects).

Cross-References
► Caffeine

Adenosine A_{2A} Receptors

Definition
Protein G-coupled receptors whose stimulation activates adenylyl cyclase-mediated signal cascade. The large majority of A_{2A} receptors (about the 95%) are enriched in the caudate-putamen, where they are located at the postsynaptic level on medium-sized spiny neurons projecting to the globus pallidus. Presynaptic A_{2A} receptors have been detected, in the cortex, basal ganglia, and hippocampus, which participate in the regulation of neurotransmitter release. A_{2A} receptors usually co-localize at the neuronal level with D_2 receptors and opposite functional interactions between these receptors have been described (e.g., stimulation of A_{2A} receptors attenuates D_2 receptors-induced effects). A_{2A} receptors also display a similar modulatory activity on the function of D_1 receptors that is exerted through cross-talk mechanisms involving the basal ganglia network.

Cross-References
► Caffeine

ADH

► Acetaldehyde
► Alcohol Dehydrogenase
► Arginine-Vasopressin

ADHD

► Attention Deficit Hyperactivity Disorder

Adherence

Definition
Adherence refers to taking a drug in the way it has been prescribed, related to both dose and length of time.

Cross-References
► Agoraphobia

Adjunctive Behavior

► Schedule-Induced Polydipsia

Adjunctive Drinking

► Schedule-Induced Polydipsia

Adjustability

► Elasticity

Adjustment Disorders

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Synonyms
Anxiety or mixed states; Reactive depressions; Stress-related mood disorders; Subthreshold diagnoses

Definition
In DSM-IV, the adjustment disorders comprise a distinct group of subthreshold states that emanate from a known stressor that is not of an unusual or catastrophic type, and that can result in maladaptation at work, at school, or at the social level (e.g., interpersonal functioning), all within 3 months of the stressor (in the ICD-10, onset must occur within 1 month of exposure to an identifiable stressor). They can be further defined by the accompanying mood state, e.g., depressed, anxious, or mixed; by the presence of a disturbance of conduct; or by the absence of these predominating features, in which case they are considered unspecified. They can be acute (less than 6 months) or chronic (lasting 6 months or more). The criteria for diagnosing adjustment disorders are compromised in that there is no *specification of*, or *symptom checklist for*, (1) the stressor(s), (2) the maladaptation, or (3) the

accompanying behavior, mood state, or symptoms – the three components in the algorithm for this diagnosis. This characteristic of the adjustment disorder diagnosis means that its classification is more subjective than that of most of the other psychiatric disorders, thereby raising issues of validity and reliability. In addition, adjustment disorders need to be differentiated from normal dysphoric states, acute stress disorders, bereavement, and other problems that may be the focus of the mental health worker's attention. They are not solely the result of a psychosocial problem requiring medical attention, e.g., noncompliance, phase of life problem, etc. Although the upper threshold for diagnosing adjustment disorders is established by the specific criteria for the minor and major psychiatric disorders, the entry threshold between the adjustment disorders and psychosocial problems or normality is not sufficiently demarcated by operational criteria. This lack of specificity and questionable reliability and validity are the hallmarks of interface disorders and subthreshold phenomena, whether they are in diabetes mellitus, hypertension, or depression. Maercker et al conceptualize adjustment disorders as a stress response syndrome in which intrusions, avoidance of reminders, and failure to adapt are the central processes and symptoms. Empirical investigations have shown that the symptom profiles of adjustment disorders are very different in children and adolescents when compared with adults. The future evolution of this and other psychiatric diagnoses will need to consider the effect of developmental epochs, gender, and medical comorbidity on symptom profiles.

The subthreshold disorders present major taxonomical and diagnostic dilemmas, since they are poorly defined, overlap with other diagnostic groupings, and have indefinite symptomatology. However, the advantage of the "indefiniteness" of these subthreshold disorders is that they permit the classification of early or prodromal states when the clinical picture is vague and indistinct, and yet the morbid state is in excess of that expected in a normal reaction, and treatment at this stage is indicated.

Role of Pharmacotherapy

Clinical Features, Etiology, and Pathogenesis

Adjustment disorder with depressed mood: Predominant symptoms are depressed mood, tearfulness, or feelings of hopelessness.

Adjustment disorder with anxious mood: Predominant symptoms are nervousness, worry, or jitteriness or, in children, fears of separation from major attachment figures.

Adjustment disorder with mixed anxiety and depressed mood: Manifestations of depression and anxiety.

Adjustment disorder with disturbance of conduct: Predominant manifestation is a disturbance in conduct, in which there is violation of the rights of others or of major age-appropriate societal norms and rules (e.g., truancy, vandalism, reckless driving, fighting, and defaulting on legal responsibilities).

Adjustment disorder with mixed disturbance of emotions and conduct: When the predominant manifestations are both emotional symptoms (e.g., depression, anxiety) and a disturbance of conduct (see earlier subtype).

Adjustment disorder unspecified: Maladaptive reactions (e.g., physical complaints, social withdrawal, or work or academic inhibition) to psychosocial stressors that are not classifiable as one of the specific subtypes of adjustment disorder.

Etiology

As stated earlier, the adjustment disorders are a product of stressor(s) in a person's life, that is, the precipitating event for this psychiatric disorder is one or more exogenous stressor. It is one of those psychiatric disorders for which an etiology is known. It is assumed that once the stressor is terminated or the patient adjusts to the stressor, the adjustment disorder symptoms, e.g., disturbance of mood or conduct, will also terminate. However, some stressors do not abate, e.g., chronic medical illness, joblessness, financial distress, etc., and the patient may continue to have an adjustment disorder in excess of 6 months. Thus, adjustment disorders join that group of disorders that also have exogenous stressors as the key etiological agent, e.g., acute stress disorder and posttraumatic stress disorder. These stress-related disorders, the organic mental disorders and the substance abuse disorders, for all of which an etiology can be identified, are thus differentiated from the majority of psychiatric disorders in the primary psychiatric taxonomy, the DSM-IV, for which definitive etiologies are not known. Furthermore, since the stressor and symptom profiles in adjustment disorders have not been specified and therefore cannot be measured in a reliable and valid way, these disorders remain a subjective diagnosis.

This also means the adjustment disorders are difficult to study to ascertain their actual frequency in various populations. For similar reasons, it is difficult to study cohorts receiving various interventions in randomized controlled trials: it is uncertain whether one has comparable patient groups when attempts are made to observe outcomes. Adjustment disorders have been diagnosed in over 60% of burn patients, greater than 20% of patients with multiple sclerosis, and over 40% of poststroke

patients. This is the most common psychiatric diagnosis in medically ill inpatients in acute care general hospitals referred for consultation, with rates ranging from 11.5% to 21.5%. Fabrega et al, at the University of Pittsburgh, observed that 2.3% of patients in a walk-in clinic had adjustment disorder only, while in those with other psychiatric or personality disorder comorbidity, the rate was 20%. Mezzich et al, from the same institution, observed that 29% of the patients in the adjustment disorder group had a positive response on indicators for suicide risk, whereas such indicators were seen in 9% of the normal (no illness) group. This emphasizes that a subthreshold diagnosis may be associated with serious symptomatology and mortality as an outcome. Obviously, suicidality is not subthreshold. Adjustment disorder patients with suicidality had lower platelet monoamine oxidase (MAO) activity, higher activity of the norepinephrine metabolite 3-methoxy-4-hydroxyphenylethylene glycol (MHPG), and higher cortisol levels than controls. Although these findings differ from the lower MHPG and cortisol levels found in some studies of patients with major depressive disorder and suicidality, they are similar to findings in other major stress-related conditions.

One must always be on the alert for the symptom profile seen in a patient with an adjustment disorder evolving over time to that of a minor or major depressive disorder, or to a generalized anxiety disorder; the maturation of symptoms over time can easily reach the criteria for these major psychiatric entities.

Treatment

The use of psychopharmacological interventions for adjustment disorders has not been agreed upon, and guidelines usually recommend that talking therapies be applied initially – psychotherapy or counseling. The Cochrane Database reveals only two randomized controlled trials of psychotherapeutic treatment for this condition. Gonzales-Jaimes and Turnbull-Plaza demonstrated that "mirror psychotherapy" for adjustment disorders with depressed mood secondary to a myocardial infarction was both an efficient and effective treatment. Mirror therapy is described as a type of therapy with psychocorporal, cognitive, and neurolinguistic components, with a holistic focus. Mirror therapy was compared to Gestalt psychotherapy or medical conversation in addition to a control group. An "activating intervention" (emphasizing the acquisition of coping skills and the regaining of control) was employed specifically for patients with adjustment disorder associated with occupational dysfunction. In comparison with the control group, the activating intervention decreased sick leave and shortened absenteeism. In a mixed study group of minor depression and adjustment disorders, brief psychodynamic therapy demonstrated greater improvement than brief supportive therapy in a 6-month follow-up. In an unpublished study of eye movement desensitization and reprocessing (EMDR), patients with adjustment disorder and anxious or mixed features, but not those with depressed mood, had significant improvement.

If talking therapy has not been successful in relieving symptoms, then a trial with a selective serotonin reuptake inhibitor (SSRI) (for adjustment disorder, depressed type) or benzodiazepine (for adjustment disorder, anxious type) is warranted. In a retrospective chart review, it appeared that adjustment disorder patients were twice as likely to respond to typical antidepressant therapy in contrast to depressive patients. In another study, the efficacy of etifoxine, a non-benzodiazepine anxiolytic drug, and lorazepam were compared in a primary care setting. Those on etifoxine had less rebound after stopping the medication.

Research is not conclusive on the use of psychopharmacological agents in patients with adjustment disorder. It would be preferred that cautious psychotropic drug administration is employed to avoid subjecting the patient to the risk of unfavorable medical drug-psychotropic drug adverse interactions. Psychotropic medication will not be necessary if the adjustment disorder resolves. If it evolves into a minor or major psychiatric disorder, then appropriate psychopharmacological agents should be employed. If the adjustment disorder does not respond to psychotherapy or the symptoms are significantly uncomfortable or disabling, then small doses of antidepressants and/or anxiolytics may be appropriate. This is especially true for patients with severe life stress(es) and an unrelenting depressed or anxious mood. Tricyclic antidepressants or buspirone are recommended in place of benzodiazepines for adjustment disorder patients with current or past excessive alcohol use, because of the greater risk in these patients of abuse of, or dependence on, the prescribed medications. The use of antidepressants is important for those patients with debilitating maladaptation and in whom the mood is pervasive, especially if a trial of psychotherapy has been shown to be ineffective. Psychopharmacological interventions can be started concurrently with psychotherapies in severe cases of adjustment disorders.

Cross-References

- ▶ Acute Stress Disorder
- ▶ Anxiety
- ▶ Benzodiazepines

▶ Depression and Related Compounds
▶ SSRIs
▶ Stress Disorders
▶ Subthreshold Diagnoses

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Adolescence and Responses to Drugs

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Synonyms

Adolescent neurodevelopmental vulnerability; Peri-adolescent psychopharmacology

Definition

Adolescence is a major developmental phase in which the body, brain, mind, and behavior of the child progress to those of an adult. Although it has long been known that mental functioning and behavior differ significantly between children and adults, an emerging body of evidence indicates that these changes are driven by changes in brain architecture and function. To the extent that these changes are the most robust in, or exclusive to, adolescence, this phase may also represent a context in which drugs impacting the central nervous system produce especially potent and long-lasting alterations.

Current Concepts and State of Knowledge

Adolescent Neurodevelopment

Adolescence encompasses the growth and alteration of many neural and somatic systems and spheres of function that evolve with differing developmental timelines both within and between individuals (Cicchetti and Cohen 2006). Given this complexity, precise definitions of its start and end are elusive. Adolescence is a phase of continuous change within a lifespan of continuous change, while cultural–legal demarcations of the onset of adulthood vary widely. Behavioral neuroscience assumes a general concept of peri-adolescence as the passage of the individual from characteristics of mind, brain, and behavior specific to, and shared among, children of different ages (i.e., from birth to ages 10–15), to characteristics shared among healthy adults (i.e., from age 18–25 and older) (Erickson and Chambers 2006; Romer and Walker 2007). Fundamentally, children are the recipients of teaching and caretaking; their role is to learn about their environment through instruction and play while inviting and acquiescing to caretaking. Adults are the providers of teaching and caretaking; their role is to manipulate, and work within, the environment in the service of caretaking. Between these age ranges (from approximately 13–23 years), adolescent neurodevelopment revises the brain from a design best adapted to play, learning, experimentation, and receiving care, to one best adapted to acting on what has been learned and delivering care.

Changes in Mind and Behavior

Adolescent neurodevelopment involves changes spanning multiple spheres of higher order central nervous system function and anatomy, including those that subserve cognition, emotion, and motivation (Romer and Walker 2007). Cognition in childhood, initially dependent on concrete interpretations of the physical world, and yet prone to fantasy and make-believe, becomes increasingly efficient and accurate with respect to classifying and predicting complex contingencies. Emotions are used less unidimensionally for engendering caretaking or exploring relationships with specific caregivers. They become more complex,

and at times volatile, both for asserting independence from caregivers, and for experimenting with and learning effective emotional conduct across a potentially large variety of peer and other social relationships spanning diverse personal and occupational domains (Nelson et al. 2004). Motivation becomes extremely sensitive to novelty and social competition, especially with respect to stimuli or situations that characterize adult social, sexual or occupational roles, and skill sets (Chambers et al. 2003). Reflecting a desire to achieve adult abilities, and even adult levels of power, the adolescent is motivated to act as an adult, even though prior experience has been largely limited to imaginative play and verbal or role-modeled instruction. Instead of playing with toy cars, the adolescent is suddenly motivated to drive real ones.

Changes in Brain Form and Function

Profound changes involving multiple brain regions underlie the adolescent transformation. Those changes occurring in the ► prefrontal cortex (PFC) are currently the best characterized (Erickson and Chambers 2006; Romer and Walker 2007). The PFC functions as the brain's closest analogue to the central processing unit of a computer; it governs decision making and regulates cognitive working memory, attention, and emotional awareness. Its central functional role and high degree of connectivity with a diversity of cortical and subcortical brain regions, which are more directly specialized in memory formation, emotion, and motivation, probably relate to its keystone position as the last cortical structure to undergo significant micro- and macrostructural revision prior to adulthood. Within the PFC, both excitatory and inhibitory neurons undergo shifts in patterns of connectivity, in which many short-range connections are eliminated (e.g., ► synaptic pruning), and long-range (e.g., transcortical) connections undergo final stages of ► myelination, rendering them more efficient for transferring information. Macrostructurally, these changes correspond to overall declines in PFC energy demands and PFC gray matter thickness. In totality, these changes correspond to the development of greater computational efficiency, adult cognitive styles, and the ability of PFC cognitive processes to intervene in or regulate complex emotional and motivational processes.

While research on developmental changes within subcortical regions primarily involved in memory formation (e.g., ► hippocampus), emotion (e.g., ► amygdala), and motivation (e.g., ► nucleus accumbens/mesolimbic ► dopamine system) is itself in an early developmental stage, growing evidence indicates that, like the PFC, all of these regions undergo peri-adolescent developmental revision (Cicchetti and Cohen 2006; Nelson et al. 2004). Changes spanning these areas include alterations in intrinsic and extrinsic neural connectivities involving multiple neurotransmitter, neuropeptide and neurohormonal systems that collectively change the way these regions process information and communicate with each other and the PFC. For example, parameters of dopamine neurotransmission into the PFC and nucleus accumbens undergo peri-adolescent maturational changes implicated in the particularly robust aspects of adolescent motivation, such as behavioral sensitivity to novel stimuli (Romer and Walker 2007). While both the hippocampus and the amygdala are richly endowed with neurohormonal receptors related to stress responsivity (e.g., corticosteroids) and sexuality (e.g., estrogens and androgens), peri-adolescent changes in the levels and regulation of these hormones can have profound effects on cellular and local circuit functions (Chambers et al. 2003; Nelson et al. 2004). These changes in turn contribute to adolescent-age alterations in emotional, social, and sexual behavior and related motivational programming, as mediated in part via the connectivity of the hippocampus and the amygdala with the nucleus accumbens and prefrontal cortex.

An important aspect shared among these modulatory neurotransmitters and neurohormonal factors is that they are powerful inducers and facilitators of ► neuroplasticity. While the information-processing and learning and memory functions of neurons and local neural connections throughout the central nervous system are most directly carried by changes in the way excitatory and inhibitory transmitters (e.g., ► glutamate and ► GABA) send signals between individual neurons, these modulatory factors (e.g., dopamine and corticosteroids) can produce more broadly distributed influences on the manner, scope, quality, and depth of local neuroplastic changes. These effects are observable on the molecular, cellular, and physiological as changes in cellular mechanisms that govern glutamatergic/GABA transmission, neural firing properties, dendritic arborizations of individual neurons, birth of new neurons, and stimuli-induced activation patterns spanning whole neural networks. Thus, by hierarchically influencing mechanisms of local plasticity in a way that is broadly distributed throughout multiple brain regions in a coordinated fashion, these modulatory systems likely play a key role in the global theme of structural revision in adolescent neurodevelopment. Understanding how these neuromodulatory factors are themselves changed during adolescence, as a result of developmentally timed and environmentally triggered changes in gene expression, will increasingly form the focus of future research on adolescent neurodevelopment.

Impact of Drugs During Peri-Adolescent Neurodevelopment

Peri-adolescent changes in neural systems function, architecture, and plasticity, unparalleled by neural events in middle childhood or adulthood, may reflect a transition that relates to the flexibility–stability dilemma, a fundamental concept of theoretical neuroscience. In this concept, neural systems are thought to operate optimally in the service of one of two goals: learning new information (flexibility) vs. acting on what has been learned (stability) (Liljenstrom 2003). Importantly, while the brain is capable of serving both of these goals to some extent, it cannot serve them both to the highest degree possible simultaneously. The vast yet limited biological resources of the brain, and physical rules of ▶ neuroinformatics, would require that the brain operate in a way that optimizes one goal at the expense of the other. By developmental design, flexibility is favored in childhood, while stability is most adaptive in adulthood. In adolescent neurodevelopment, the brain must undergo a considerable revision of architecture and function to shift the brain toward the stability goal. During this phase, the artificial (e.g., pharmacological) perturbation of neural processes and systems, particularly those that impact the neuroplasticity of cognitive, motivational, and emotional substrates, could produce effects that are thereafter "locked-in," in a semipermanent way, as the brain shifts its design toward the stability goal.

Impact of Drug Exposure on Motivation and Addiction Vulnerability

The most clear and broad-based evidence for such a pharmacological effect is the heightened capacity of addictive drug exposure during adolescence for determining future motivational programming with respect to the acquisition of addictive disorders (Chambers et al. 2003). The vast majority of adult-age addictions begin in adolescence (ages 15–25). Greater accumulated dose of drug exposure, earlier exposure, and the extent of multidrug experimentation during adolescence are all risk factors for adult addictions.

The advancement in our understanding of this developmental age vulnerability to addictions has been informed in part by research on ▶ dual diagnosis in mental illnesses such as ▶ schizophrenia, which involve both peri-adolescent developmental onset and high rates of addiction comorbidity. Adolescence is a normative period of heightened novelty seeking, behavioral disinhibition, and risk taking, all serving as component manifestations of the more general construct of impulsivity (Erickson and Chambers 2006). ▶ Impulsivity, whether occurring in normative adolescence or as an abnormal feature of adult mental illness, is a general trait-marker of addiction vulnerability (Erickson and Chambers 2006; Redish et al. 2008). Moreover, it is often a manifestation of those immature or dysfunctional PFC substrates that are responsible for decision making and response inhibition. As reviewed earlier, during adolescence the PFC is normally immature and thus incapable of adult levels of decision making and behavioral control. At the same time, subcortical motivational systems (e.g., the nucleus accumbens/dopamine system) are operating in a particularly robust manner. This not only allows motivational programming to be relatively sensitive to novel or other reinforcing stimuli that promote dopamine transmission. By virtue of the capability of dopamine itself to regulate neuroplastic events in the PFC and nucleus accumbens, this robustness of function may also facilitate changes governing maturational plasticity underlying the installment of stable, long-lasting, motivational repertoires (Chambers et al. 2003, 2007). In adolescence, this scenario may be viewed simplistically as a car acquiring an accelerator before it acquires adequate brakes. Of course, only the accelerator can make the car go, and give the driver cause for needing, and learning how and when, to apply the brakes. In normative adolescent neurodevelopment, this developmental plan, in which the PFC matures under conditions of robust motivational function, is thought to be a necessary aspect of initiating experiential-action learning, with all of its hazards (Chambers et al. 2003). With addictive drug exposure, and by virtue of the shared pharmacological effect of addictive drugs to further augment dopamine transmission and exert neuroplastic effects, motivational–behavioral repertoires (and underlying neural systems) are potently and more semipermanently sculpted to include drug-seeking and – taking as frequent behavioral options (Chambers et al. 2007).

Impact of Drug Exposure on Cognition and Emotion

The centrality of dopamine in both natural motivation and in the reinforcing properties of drugs with diverse psychoactive and pharmacological profiles (e.g., nicotine, alcohol, cocaine, amphetamine, cannabinoids, and opiates) has rendered progress in our understanding of the responsiveness of adolescents to the motivational properties of drugs a relatively straightforward process. Expanding outward from this core of knowledge, research is beginning to explore the more complex task of understanding how adolescent neurodevelopmental change involving spheres of function other than motivation, and encompassing other neurotransmitter systems and brain regions, may make adolescents particularly vulnerable to long-lasting cognitive and emotional effects of drug

exposure. In essence, this exploration is a contemporary variant of the long-pursued notion that drug use can cause or predispose to permanent acquisition of psychiatric illness or illness features. For many recreational drugs frequently used in the general population, this thesis has not proven easy to support with firm clinical and epidemiological data. However, new evidence detailing the unique and profound neurodevelopmental revision of the brain during adolescence, along with the recognition of the capacity of drugs to modulate cognitive and emotional functions during this developmental period, has renewed interest in this area. For instance, new findings indicate that peri-adolescent ► nicotine exposure can have an enduring impact on acetylcholine neurotransmission in the brain, while producing long-lasting cognitive and emotional dysfunction potentially consistent with features of mental illness (Slotkin 2008). Similarly, ► alcohol as a drug active at glutamatergic and GABAergic synapses, and in a host of other neurotransmitter systems, may produce semipermanent cognitive and emotional changes (Clark et al. 2008). Since endogenous ► cannabinoids are robustly active in PFC and hippocampal networks as modulators of glutamatergic and GABAergic transmission and plasticity, marijuana smoking in adolescence could have particularly profound and long-lasting effects toward changing thresholds for developing mental disorders that involve these regions, including ► schizophrenia and ► depression.

Conclusion

As research on adolescent drug effects continues to evolve, it is expected that animal modeling, involving developmentally timed drug exposures in peri-adolescence, will play an especially crucial role in advancing understanding in this field, given the ethical boundaries, time and cost expenses, and lack of environmental control inherent to longitudinal prospective human studies. Examining adolescent developmental effects of recreational drugs is also expected to inform and inspire investigations that may reveal properties of therapeutic agents that may semipermanently ameliorate or abort illness trajectories for varieties of mental disorders of peri-adolescent onset or worsening.

Cross-References

► Alcohol
► Attention
► Cannabinoids
► Cocaine
► Excitatory Amino Acids and Their Antagonists
► Glutamate
► Impulsivity
► Inhibitory Amino Acids and Their Receptor Ligands
► Long-Term Potentiation and Memory
► Neurogenesis
► Neurosteroids
► Nicotine
► Protein Synthesis and Memory
► Schizophrenia
► Synaptic Plasticity (paired with neuroplasticity)

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Adolescent Neurodevelopmental Vulnerability

► Adolescence and Responses to Drugs

Adrenocorticotropic Hormone

Definition

ACTH or corticotrophin is released from the anterior pituitary corticotrophs into the circulation for stimulating adrenal glucocorticoid synthesis and secretion. It is derived from the pro-opiomelanocortin (POMC) precursor.

Adult Neurogenesis

► Neurogenesis

Adventuresome

► Risk Taking

Adverse Effect

Synonyms
Adverse reaction; Adverse side effect

Definition
An adverse event is a harmful effect that is the result of a medication or intervention.

Adverse Reaction

► Adverse Effect

Adverse Side Effect

► Adverse Effect

AEA

► N-arachidonylethanolamine

Affect

► Emotion and Mood

Affective Disorders

► Mood Disorders

Affective Dominant

Definition
Type of schizoaffective disorder dominated by depressive or manic symptomatology.

Affective State

Synonyms
Current mood; Emotional state

Definition
Moods, emotions, and feelings elicited by stimuli in the environment, including interactions with conspecifics. The transient nature of these experiences results in these affective responses being finite, though their duration can range from seconds to weeks.

Cross-References
► Emotion and Mood

Affinity

Synonyms
K_D^{-1}

Definition
A property of drugs that bind to receptors that reflects the attractiveness of the drug to the receptor, or the likelihood that the drug will bind to the receptor when it is in close proximity. Both receptor agonists and antagonists have affinity for receptors. It is equal to the ratio of the concentration of the bound complex to the product of the reactant concentrations at equilibrium, [LR]/([L], and is usually described in terms of its reciprocal, the equilibrium dissociation constant.

Aggression

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Synonyms

Aggressiveness; Aggressive behavior; Agonistic behavior; Violence

Definition

In most general terms, aggression refers to behavior that is harmful to others or expresses the intention to do so.

Impact of Psychoactive Drugs

Types of Aggression

Aggressive acts are shaped by social experiences via action on molecular events in discrete ascending aminergic pathways from the mesencephalon to the limbic and cortical targets, and the cascade of these intracellular events is increasingly understood. Aggressive behavior is an important behavioral adaptation in all phyla of living creatures, mainly serving reproductive purposes. In addition, maladaptive types of aggressive behavior are the focus of human and veterinary medicine and also of the criminal justice system. Types of aggression differ in terms of their ontogenetic and phylogenetic origins, motivations, and functions, and all indications are in their neurobiological mechanisms. Clinicians distinguish between those types of aggression that include hostile, affective, impulsive, and reactive features from those that are characterized by proactive, premeditated, instrumental, controlled, and also predatory elements. Behavioral researchers, by contrast, focus on adaptive types of aggressive behavior, mostly as part of reproductive strategies such as aggression during the formation and maintenance of dominance hierarchies or territories. Animal species that disperse during the reproductively active lifespan as well as those that live cohesively, engage in aggressive behavior in order to secure the resources for reproduction or to protect the offspring.

The classic ethological thesis that ritualized displays are the major means to maintain a dominance hierarchy has been challenged by rare, but repeatedly documented episodes of intensely injurious aggression in chimpanzees that pursue neighboring groups in order to kill them. The significance of lethal raiding parties in hominids constitutes problems, not the least of which for the typology of aggressive behavior, since it focuses on rare events that are carefully planned and coordinated and, at the same time, involve intense autonomic and behavioral excitement. The adaptive purpose of these lethal raids eludes the traditional theoretical framework. Conventionally, once the frequency, duration, and intensity of aggressive behavior escalate beyond the species-typical levels, it is considered maladaptive and may constitute a behavioral pathology in need of intervention.

Much pharmacological, neurochemical, and molecular biology research on aggressive behavior uses laboratory mice, often recombinant inbred strains and transgenic lines. These animals are housed in same-sex groups, preventing the species-typical formation of demes ("breeding units"), and only a small proportion of these mice actually engage in territorial aggressive behavior that is characteristic of this pugnacious species. Under captive laboratory conditions, group-housed animals may develop a despotic social organization, with one male dominating all other group members.

Neurotransmitters

More than any other neurochemical system, brain ▶ serotonin remains the focus for neurobiological studies of mechanisms mediating impulsive, hostile, and intensely violent outbursts as well as predatory-like aggression. Only detectable in trace amounts in mammalian brain, this phylogenetically old transmitter, arising from cells along the center of the neuroaxis and acting in mammals on at least 14 different receptor subtypes, has a significant role in aggression ranging from invertebrates to humans. Several neurotransmitters comprising amines, acids, ▶ neuropeptides, and ▶ neurosteroids interact with serotonin (5-hydroxytryptamine, 5-HT).

Glutamate

▶ Glutamate and ▶ GABA are the extensively distributed excitatory and inhibitory transmitters, and they modulate the cellular and behavioral effects of serotonin at several levels of the ascending mesocorticolimbic pathways. Early research has established an excitatory role of glutamate in violent outbursts during seizures, although the precise role of glutamate activity during ictal and inter-ictal events remains to be defined. Sparse evidence shows how pharmacological manipulations of glutamate receptor subtypes affect aggressive behavior and also suggests a potential role of ▶ NMDA receptors in escalated aggressive behavior. Low-affinity channel blockers such as ▶ memantine or partial agonists to the glycine-binding site on the NMDA receptor may offer potential options in the pharmacotherapeutic management of escalated aggressive behavior due to their favorable side-effect profile. Regulatory changes in NMDA receptor systems occur also in individuals who are repeatedly victimized by aggressors as revealed by prevention of their sensitized response to psychomotor stimulants with protective administration of NMDA receptor antagonists. It will be of considerable interest to learn how glutamate modulates the ascending monoaminergic, especially dopaminergic and serotonergic projections to limbic and cortical target areas. Several

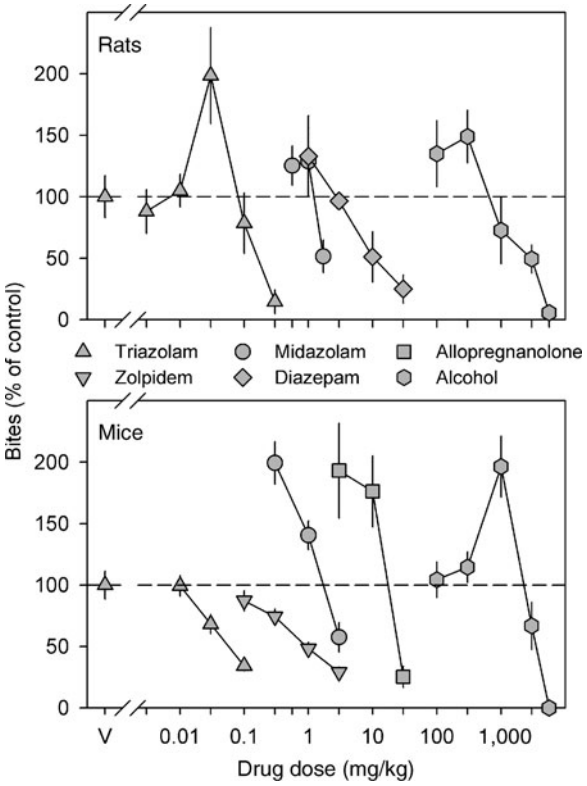
metabotropic glutamate receptors appear to be promising pharmacotherapeutic targets in the management of escalated aggressive behavior.

GABA

By distinction from glutamate, GABA and particularly, the $GABA_A$ receptor complex have been consistently implicated in the neural control of several types of aggressive behavior. Especially positive ► allosteric modulators of the $GABA_A$ receptors such as benzodiazepines, barbiturates, ethanol, and progestin-derived neurosteroids can increase aggressive behavior after low acute doses or after tolerance to the sedative doses has developed (Fig. 1). At moderate and higher doses, the antiaggressive effects of these substances are accompanied by sedation and motor impairment. The bidirectional effects of allosteric positive modulators of the $GABA_A$ receptors depend not only on the dose, but also on the context and the prior experience with aggressive behavior. When social consequences lower the rate of aggressive behavior, benzodiazepines and ethanol are more likely to increase its occurrence. In spite of the consistent epidemiological evidence linking alcohol to two thirds of all violent crimes, the neurobiological mechanism of action for these alcohol effects remains elusive. The current challenge is to understand how an individual's prior experiences with aggressive behavior modify the $GABA_A$ receptor complex so that proaggressive effects of $GABA_A$ positive modulators emerge. The prevalent current hypothesis attributes the divergent effects of $GABA_A$ positive modulators on aggressive behavior to differential expression of genes encoding the subunits that form the pentameric $GABA_A$ receptor complexes. Emerging data from gene deletion and pharmacological antagonism studies suggest a structural dissociation between the anxiety-attenuating, sedative, and aggression-heightening effects of $GABA_A$ receptor positive modulation, primarily due to the differential role of alpha subunits. In addition to the $GABA_A$ receptor, the $GABA_B$ receptors are widely distributed throughout the neuroaxis. The population of $GABA_B$ receptors in the dorsal raphé nucleus modulates serotonin cells, and this may be the mechanism via which $GABA_B$ receptor agonists can increase aggressive behavior in mice.

Norepinephrine

Catecholaminergic and serotonergic pathways contain reciprocal anatomical links which provide the basis for extensive functional interactions. Particularly, intense arousal that is associated with salient life events, among them certain types of aggressive behavior on just observing a fight, is based on elevated activity in noradrenergic cell bodies in locus coeruleus and cortical noradrenergic terminals. Pharmacological blockade of beta receptors may achieve its calming effects in patients with intensely aggressive, hostile outbursts by reducing noradrenergic hyperactivity, although alternatively, beta blockers also act as antagonists at $5\text{-}HT_{1A}$ receptors. Molecular manipulations of the genes encoding for the noradrenergic transporters, or metabolic enzymes such as COMT have so far resulted in inconsistent results with regard to aggressive behavior and traits.



Aggression. Fig. 1. $GABA_A$ positive allosteric modulators and aggression. Biphasic effects of $GABA_A$ receptor positive modulators on aggression in rats (*top*) and mice (*bottom*). Low doses of alcohol (filled hexagon), the benzodiazepines diazepam (filled diamonds, rats only) and midazolam (filled circles), and the neurosteroid allopregnanolone (filled triangles, mice only) increase the mean (±SEM, vertical lines) number of attack bites, expressed as a percentage of vehicle control, while higher doses decrease this measure of aggression. Triazolam (filled upward triangles) increases attack bites in rats but not mice. No increase in aggression was seen after treatment with zolpidem, the alpha1-preferring agonist (filled downward triangles, mice only). The dotted horizontal line represents the baseline at 100%. (From Miczek et al. 2007.)

Dopamine

Specific dopamine (DA) pathways and DA receptor subtypes critically contribute to the neurobiological mechanisms of species-typical and escalated, pathological types of aggressive behavior. Anatomical and pharmacological data provide evidence for serotonergic receptors on soma of DA neurons in the VTA and substantia nigra suggesting modulation of ascending DA pathways by 5-HT.

The most widespread option for pharmacotherapeutic management of aggressive individuals relies on antipsychotic medication that acts via blockade of dopamine (DA) D_2 receptors, although the antiaggressive effects of ► first-generation antipsychotics such as ► haloperidol or ► chlorpromazine are embedded in sedative and motor-incapacitating side effects. At present, the so-called ► atypical antipsychotic drugs with more complex mechanisms appear to be preferred as antiaggressive medication on account of a more favorable side-effect profile. Clearly, there continues to be a need for more satisfactory medication development.

Case studies point to ► amphetamine intoxication as a potentially triggering event for lethal violence. At intermediate doses, amphetamine disrupts many types of social behavior and at lower doses, it may increase aggressive behavior, probably due to its antifatigue and arousing effects. Increased corticolimbic DA can be detected via in vivo measurement and imaging techniques in individuals who react defensively to an aggressive confrontation and who prepare for such an event. Anatomical and temporal analysis with higher resolution may enable a more precise delineation of DA activity in different phases and types of aggressive behavior.

Genetic disruption of the genes that are critically involved in the inactivation of ► catecholamines, COMT, and MAO-A can promote aggressive behavior in male mice. It is tempting to relate these preclinical data to the specific polymorphism in the gene for COMT which is associated with increased aggressive behavior in schizophrenic men.

MAO

Considerable evidence links monoamine oxidase (MAO)-A to traits of violent behavior. It remains to be determined which of the monoamines is primarily responsible for the effects of mutations or deletions of the gene for this enzyme or for the effects of its pharmacological inhibition. An early influential study illustrated how acts of violence by the male members of a Dutch family who were also mentally retarded, appears to be linked to a missense mutation in the gene for this enzyme on the X chromosome. In preclinical research, mice lacking this gene were found to initiate injurious aggressive behavior faster. Probably, the most significant findings link the allelic variant with low activity of MAO-A to the antisocial and violent behavior only in those adult males who were severely maltreated in childhood, whereas the allelic variant with high MAO-A activity or the absence of maltreatment had no such influence in adults. A variable-number tandem repeat polymorphisms of MAO-A may also be associated with the increased probability of a life history of aggressive behavior, particularly aggression involving dysregulated affect. However, there is also evidence that links lower MAO-A activity to aggressive tendencies independent from polymorphisms in MAO-A. While MAO-A is one of the leading candidates, a number of inconsistent findings obscure the causal relationship between the expression of the MAO-A gene, its interaction with early life experiences, and traits of hostile, antisocial, aggressive outbursts.

The differential expression of specific genes for MAO-A in aggressive and nonaggressive individuals is often associated with alterations in the brain serotonin system, based on additional pharmacological studies. A wide array of methodological approaches has implicated the serotonin system in aggressive traits, impulsivity, and also in the initiation and termination of certain types of aggressive behavior. A venerable hypothesis postulated a serotonin deficiency as the characteristic of the trait of ► impulsive aggression, receiving early support from the 5-HT assay data obtained from the hindbrain of isolated aggressive mice and CSF 5-HIAA samples of patients. The significance of CSF 5-HIAA measures is compromised by the uncertainty as to their precise anatomical origin. Direct challenges of brain 5-HT functions with either an agonist or a tryptophan-depleted diet demonstrated a blunted prolactin response in violent patients with various diagnoses, possibly due to actions on 5-HT_{1A} and 5-HT_{2A} receptors. Instead of relying on a single sample of CSF, a peripheral marker, or an endocrine response to a single pharmacochallenge, in vivo microdialysis reveals no changes in cortical 5-HT during the phase of initiating an attack, but then 5-HT begins to decline once the fight is progressing and terminating. The termination of an anticipated aggressive confrontation is accompanied by a decrease in accumbal 5-HT suggesting a potentially significant role for 5-HT in the inhibition of aggressive behavior. Thus, the tonic levels of 5-HT activity have been linked to aggressive traits, and phasic changes in 5-HT may be relevant to the termination of an aggressive burst.

SERT

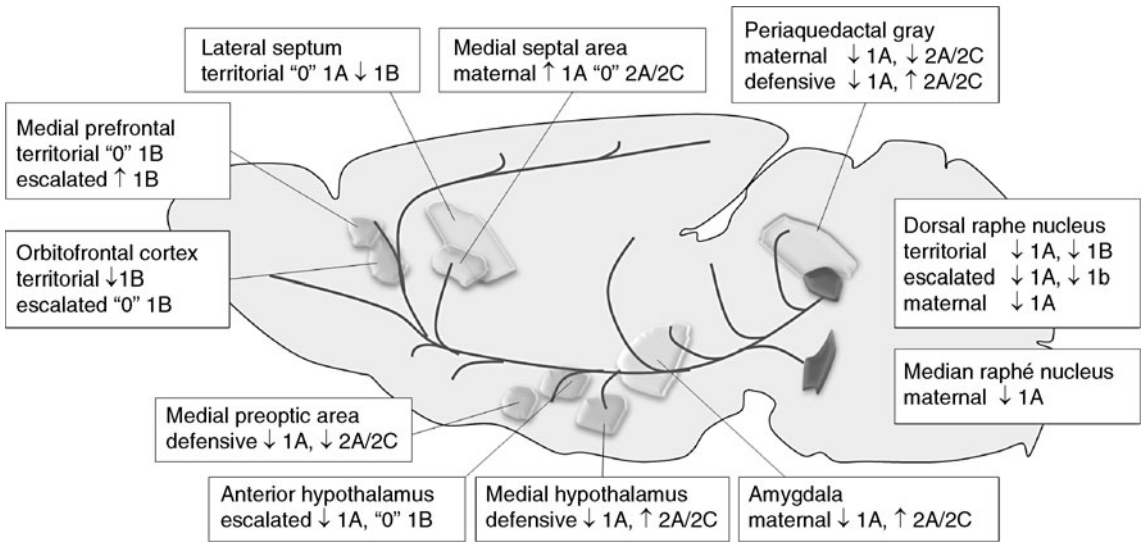
Several receptor families and the 5-HT transporter (SERT) have been characterized in terms of their genetic

basis and molecular features. Pharmacological and molecular genetics studies have begun to implicate the 5-HT_1 and 5-HT_2 receptor families and SERT in different types of aggressive behavior. Agonists of the 5-HT_{1A} and 5-HT_{1B} receptors reduce aggressive behavior; and the antiaggressive effects of the 1B receptor subtype are behaviorally specific and especially, effective in situations that engender escalated levels of aggressive behavior, although these effects remain to be translated to the clinic. Microinjection studies provide evidence that 5-HT_{1A} and 5-HT_{1B} receptor agonists can achieve their antiaggressive effects via action at either somatodendritic autoreceptors in the dorsal raphé nuclei or the presynaptic terminal autoreceptors or the postsynaptic heteroreceptors (Fig. 2). If, in fact, the decrease in extracellular levels of corticolimbic 5-HT after 5-HT_{1A} and 5-HT_{1B} receptor stimulation constitutes a critical mechanism of action for the antiaggressive effects, a significant revision of the serotonin deficiency hypothesis is required. Genetic deletion studies of 5-HT_{1A} and 5-HT_{1B} receptors generate a more complex pattern of results that appears to be influenced by the genetic background of the mouse or by developmental compensations in mutant mice. Similarly, associations between ▶ polymorphisms of 5-HT_{1A} and 5-HT_{1B} receptors and aggressive traits in humans remain inconsistent.

5-HT Receptors

Antagonism of 5-HT_{2A} receptors represents the mechanism via which some atypical antipsychotic compounds achieve their calming effects in patients with diagnoses that range from schizophrenia, dementia, depression, and posttraumatic stress disorders (PTSD). Yet, the side-effect profile of these agents highlights the problematic nature of this new class of antipsychotic agents. Preclinical studies of the 5-HT_{2A} and 5-HT_{2C} receptors have to await the development of more selectively acting molecular tools, since at present it is not possible to differentiate between the antiaggressive effects of agonists and antagonists at these receptor subtypes. Similarly, linkage studies between polymorphisms in the 5-HT_{2A} receptor and impulsive-aggressive or antisocial traits require replication.

Blockade of the reuptake mechanism for 5-HT via the SERT reduces aggressive episodes in most patients, especially when given over extended periods. Large meta-analyses have identified the exceptional nature of the occasional reports of increased aggressivity and suicidal tendencies among those treated with selective serotonin reuptake inhibitors (SSRI). Preclinical studies have shown that acute and chronic treatment with SSRIs reduces aggressive behavior in species ranging from invertebrates to primates. Chronic SSRI administration can also restore competent agonistic



Aggression. Fig. 2. Modulation of aggressive behaviors in rodents by microinjections of 5-HT_{1A}, 5-HT_{1B}, and 5-$HT_{2A/2C}$ receptor agonists. Text boxes show that local injections of 5-HT_{1A} receptor (1A), 5-HT_{1B} receptor (1B), or 5-$HT_{2A/2C}$ receptor (2A/2C) agonist increases (↑), decreases (↓), or has no effect ("0") on territorial, escalated, maternal, and defensive aggressive behaviors. Serotonergic neurons originate from the raphé nuclei and project to several brain areas.

interactions in placid laboratory strains of rats that do not show intact species-typical aggressive behavior.

The short-length allele in the serotonin-transporter gene-linked polymorphic region (5-HTTLPR) leads to lower SERT expression and lower serotonergic activity relative to those with the long-length allele. Some evidence supports the association of the short allele with increased hostility, impulsivity, and aggressiveness, primarily in males. The contribution of the 5-HTTLPR to the variation in aggressive personality traits is relatively small and appears to depend on epistatic influences and on environmental triggers. Early stressful life experiences in monkeys and humans may increase the probability of escalated aggression toward others and themselves, particularly in those individuals who carry the short-length allele. A more adequate understanding of SERT expression in corticolimbic regions promises to be relevant for the display of aggressive personality traits.

Brain serotonin modulates and is modulated by other amines, amino acids, and also neuropeptides and neurosteroids. For example, serotonergic projections in specific hypothalamic nuclei may regulate the release and action of vasopressin (VP), a neuropeptide that is associated with high rates of aggressive behavior in several animal species via action at 5-HT_{1A} and 5-HT_{1B} receptors. Similarly, the modulation of serotonergic neurons by corticotrophic releasing factor (CRF) and opioid peptides provides the anatomical basis for functional interactions that appear relevant to aggressive behavior. The promising information on CRF, GABA, and glutamate in amygdaloid connections with hypothalamic and brainstem structures during displays of intense emotion should prompt a detailed examination of these mechanisms in escalated types of aggressive behavior.

Cross-References

- ▶ Aggression, Clinical
- ▶ Antidepressants
- ▶ Antipsychotics
- ▶ Social Stress
- ▶ SSRI

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Aggressive Behavior

- ▶ Aggression
- ▶ Aggressive Behavior: Clinical Aspects

Aggressive Behavior: Clinical Aspects

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Synonyms

Aggressiveness; Aggressive behavior; Agonistic behavior; Impulsive aggression; Violence

Definition

Behavior by an individual directed at another person or object in which either verbal force or physical force is used to injure, coerce, or express anger.

Role of Pharmacotherapy

Types of Clinical Aggression

Human aggression constitutes a multidetermined act that results in physical or verbal injury to self, others, or objects. It appears in several forms and may be defensive, premeditated (e.g., predatory), or impulsive (e.g., nonpremeditated)

in nature. Defensive aggression is generally seen as dictated by particular external realities and within the normal range of human behavior. Premeditated and impulsive aggressive behaviors are commonly viewed as pathological. Specific acts of aggression may be situational, but the tendency to behave aggressively represents a behavioral trait. While the frequency of aggressive acts tends to decrease with advancing age, numerous studies document that the trait of aggressiveness begins early in life and continues through adulthood. Both impulsive and premeditated aggression represents the potential for significant physical and psychological harm to the individual, to those subjected to the effects and to society in general. However, a converging pattern of empirical data from a variety of studies consistently links *impulsive*, but not premeditated, aggression to biological, environmental, and pharmacological or psychological treatment response factors.

One guiding principle to the consideration of human aggression is that biological and psychological factors contribute significantly to this behavior. Biological factors contribute to aggressive behavior through reduced inhibitory, and/or increased facilitatory, neuronal inputs to behavior. Research in this area has found utmost support for the role of inhibitory behavioral inputs modulated by brain serotonin (5-HT) function. The role of various neurotransmitter systems in increasing facilitatory input for aggressive behavior has received less attention and, in contrast to 5-HT, the results have been somewhat inconsistent. On the other hand, psychotherapy outcome research has successfully focused attention in this general area, vis-a-vis the relationship between the impulsive aggressive individual and his/her external/internal environment as facilitatory in generating impulsive aggressive behavior. Here, the focus is on the hypothesis that vulnerable individuals manifest impulsive aggressive behavior in response to external/internal stimuli perceived as "provocative" or "aversive" in nature which lead to variable states of anger that drive susceptible individuals (e.g., individuals with reduced central 5-HT function) to exceed their "threshold" for effective behavioral inhibition so that an impulsive aggressive outburst is initiated. If so, treatment aimed at increasing central (5-HT mediated) behavioral inhibitory tone and reducing states of high anger (i.e., negative emotionality) should be an effective strategy in treating impulsive aggressive behavior in human subjects. To date, research has shown the potential efficacy of (1) pharmacological approaches to reducing impulsive aggressive outbursts and, (2) psychological approaches to reducing states of acute (and chronic) anger. To date, however, neither approach has been combined or compared in the same study.

Impulsive Aggression Expressed as a Dimension

Behavioral Genetics of Impulsive Aggression

Data from twin, adoption, and family studies suggest genetic influence on aggression. Heritability estimates for measures of aggression are moderately substantial in adults ranging from 44% to 72% and a recent meta-analysis confirmed the presence of a substantial genetic influence for aggression. Heritability estimates were most pronounced for aggression measures reflecting anger and hostility, or anger, impulsiveness, and irritability. It is noteworthy that these same phenomena are associated with the clinical profile of intermittent explosive disorder (IED).

Psychosocial/Environmental Correlates of Impulsive Aggression

The most important psychosocial factors involved in the development of aggression appear to be low socioeconomic status, ineffective parenting style, as well as physical punishment in childhood and exposure to aggression within and outside of the family. Notably, harsh discipline and child abuse (regardless of SES status) have been found to predict the development of *impulsive*, but not nonimpulsive, aggressive behavior in children. In one study, 41% of children abused in the first 5 years of their life became *impulsively* aggressive later in life, compared with 15% of nonabused children; in contrast, none of the nonimpulsively aggressive subjects had a history of child abuse.

Neurochemical Correlates of Impulsive Aggression

Among all of the biological factors potentially involved in aggression, the most studied factors relate to brain neurochemistry, specifically monoamines such as serotonin (5-HT) and other centrally acting neurotransmitters (Brown et al. 1979; Coccaro and Siever 2005; Coccaro et al. 1989). Evidence of a role of brain 5-HT in human aggression is especially strong and points to an inverse relationship between brain 5-HT activity and aggression in animal models, nonhuman primates, and humans. In human studies, various measures reflecting central (as well as peripheral) 5-HT function have been shown to correlate inversely with life history, questionnaire, and laboratory measures of aggression. Most importantly, the type of aggression associated with reduced central 5-HT function appears to be *impulsive*, rather than nonimpulsive aggression (Linnoila et al. 1983). In human studies, there are selective cases where the relationship between 5-HT and aggression is positive in direction or does not exist at all. This may be due to the presence of other factors (e.g., diagnostic group; drug dependence; developmental stage) which may involve differential

contributions from other neurotransmitter systems that also influence the tendency to react aggressively in social contexts. Limited evidence also supports a role for Non-5-HT brain systems and modulators in impulsive aggression. These findings suggest a permissive role for ► dopamine, ► norepinephrine, vasopressin, testosterone, and an inhibitory interaction between neuronal nitric oxide synthase and testosterone in rodents.

Functional Neuroanatomy of Aggression-Related Disorders in Humans

While IED is the only DSM-IV disorder (see later) for which aggression is the cardinal symptom, both borderline personality disorder (BPD) and antisocial personality disorder (AsPD) share a number of attributes associated with aggression as a dimension. At their most basic level, all three disorders are associated with increased anger and irritability as well as self- and other-directed aggression. All three diagnostic groups demonstrate a number of the deficits associated with the orbital ► medial prefrontal cortex (OMPFC)-amygdala tract including deficiencies of executive functions and socioemotional information processing. For IED, a series of PET studies on "impulsive aggressive" patients with both IED and BPD fail to parallel the increase in OMPFC metabolism by normal controls in response to acute administration of serotonin agonists, suggesting an important reduction in OMPFC function in impulsive aggressive individuals (New et al. 2002). Notably, however, chronic administration of a serotonin agonist over 12 weeks can both increase OMPFC metabolism and reduce impulsive aggressive behaviors. A study of temporal lobe epilepsy patients with and without IED, found that a subgroup of 20% of the IED patients (BPD status not assessed) had "severe" amygdala atrophy. In contrast to these studies, the only available imaging data from subjects with IED, demonstrate that IED subjects (even those without BPD or AsPD) have augmented Amygdala (AMYG), and reduced OMPFC, fMRI blood oxygenated level dependent (BOLD) signal activation to angery faces (Coccaro et al. 2007). In contrast to IED, there is a larger imaging literature among patients with BPD and AsPD. Structural MRI studies show only weak support for the existence of reduced frontal volumes for either disorder with equally equivocal support for morphological changes in the amygdala. In contrast, PET and fMRI studies have produced a fairly consistent pattern of altered corticolimbic activation for both disorders. Three PET studies have reported reduced metabolism in the frontal (e.g., OMPFC) cortex in BPD subjects. Both BPD and AsPD populations show decreased OMPFC activation during emotional information processing (e.g., trauma scripts, a conditioned aversive stimulus) compared to control populations. Psychopaths also evidence less activation to abstract words in the right lateral frontal cortex. Both groups show increased amygdala activation to emotional stimuli; BPD subjects display enhanced amygdala activation to unpleasant pictures, as well as fearful and neutral words (viewed as negative by BPD subjects). While psychopaths showed increased amygdala activation when passively viewing negatively valenced pictures, amygdala activation for psychopaths may be attenuated/eliminated during emotional learning/conditioning tasks.

Recurrent, Problematic, Impulsive Aggressive Behavior as a Target for Study and Intervention: Intermittent Explosive Disorder

Although the term IED has only been in the DSM since the third edition (1980), the "construct" of a "disorder of impulsive aggression" has been in the DSM since its inception in 1956. Currently, it describes individuals with recurrent, problematic episodes of aggression not accounted for by other medical or psychiatric factors (Coccaro et al. 2005). While DSM-IV does not specifically refer to the aggression in IED as impulsive in nature, premeditated aggression is typically a characteristic seen in antisocial personality disorder.

Clinical Description

Aggressive outbursts in IED have a rapid onset, often without a recognizable prodromal period. Episodes are typically short-lived (less than 30 min) and involve verbal assault, destructive and nondestructive property assault, or physical assault. Aggressive outbursts most commonly occur in response to a minor provocation by a close intimate or associate, and IED subjects may have less severe episodes of verbal and nondestructive property assault in between more severe assaultive/destructive episodes. The episodes are associated with substantial distress, impairment in social functioning, occupational difficulty, and legal or financial problems.

Epidemiology

In the largest epidemiological study to date, the lifetime prevalence of IED by "Narrow" DSM-IV criteria is estimated at 5.4% with 1-year prevalence estimated at 2.7% (Kessler et al. 2006).

Age of Onset and Demographics

IED appears as early as childhood and peaks in mid-adolescence, with a mean age of onset in three separate studies ranging from 13.5 to 18.3 years. The average

duration of symptomatic IED ranges from 12 to 20 years to the whole lifetime. While initially thought to be more common in males, recent data suggest the gender difference in prevalence of IED may be closer to 1:1. Sociodemographic variables (e.g., sex, age, race, education, marital and occupational status, family income) do not appear to differ meaningfully as a function of IED status.

Laboratory Studies

To date, published data have reported IED subjects as having altered ▶ serotonin function compared with non-IED subjects or healthy controls. Other studies demonstrate a reduction in prolactin responses to ▶ fenfluramine challenge, in the numbers of platelet 5-HT transporters in IED subjects compared with non-IED subjects. Two FDG PET studies report low FDG utilization after D,L-fenfluramine challenge in frontal areas of the brain and low FDG utilization after m-CPP challenge in the anterior cingulate in IED subjects compared with healthy controls. A ligand binding study of the 5-HT transporter also reports reduced low 5-HT transporter availability in the anterior cingulate in IED subjects versus healthy controls. Finally, fMRI study demonstrates increased activation of AMYG, and reduced activation of OMPFC, to angry faces, in IED subjects compared with healthy controls.

Family Study

Family history study of IED subjects demonstrates a significantly elevated morbid risk for IED in relatives of IED, compared with healthy controls, probands (0.26 vs. 0.08, $p < 0.01$). Elevation in morbid risk for IED was not due to the presence of comorbid conditions among IED probands (e.g., history of suicide attempt, major depression, alcoholism, drug use disorder, etc.) and not due to elevations in morbid risk of other non-IED disorders in relatives (e.g., major depression, alcoholism, drug use disorders, anxiety disorder, and any other disorder).

Treatment of Impulsive Aggression and IED

Impulsive Aggression

Several psychopharmacologic agents appear to have effects on impulsive aggression. Classes of agents shown to have "antiaggressive" effects in ▶ double-blind, ▶ placebo-controlled trials of individuals with "primary" aggression (i.e., not secondary to psychosis, severe mood disorder, or organic brain syndromes) include mood stabilizers (e.g., ▶ lithium), 5-HT uptake inhibitors (e.g., fluoxetine) and, anticonvulsants (e.g., diphenylhydantoin, ▶ carbamazepine). While norepinephrine beta-blockers (e.g., ▶ propranolol, nadolol) have also been shown to reduce aggression, these agents have exclusively been tested in patient populations with "secondary" aggression (e.g., mental retardation, organic brain syndromes, etc.). Classes of agents which may have also "pro-aggressive" effects under some conditions include ▶ tricyclic antidepressants (e.g., ▶ amitriptyline), ▶ benzodiazepines, and stimulant and hallucinatory drugs of abuse (e.g., amphetamines, ▶ cocaine, ▶ phencyclidine). Emerging evidence of differential psychopharmacology is of critical importance, and findings from the literature of double-blind, placebo-controlled, clinical trials suggest that antiaggressive efficacy is specific to *impulsive*, rather than nonimpulsive, aggression.

Intermittent Explosive Disorder: Effect of Psychopharmacologic Intervention

▶ Fluoxetine demonstrates clear antiaggressive efficacy for reducing impulsive aggressive behavior in IED subjects compared with placebo (Coccaro et al. 2009). Fluoxetine's antiaggressive effect is most clearly seen on verbal aggression and aggression against objects. Despite this effect, somewhat less than 50% of IED subjects treated with fluoxetine achieve remission. Gains made with fluoxetine typically dissipate within 1 month after discontinuation but can be achieved again when the drug is reinstituted. Notably, fluoxetine has not been shown to increase aggression in IED subjects in placebo-controlled trials. Another placebo-controlled study of IED involving divalporex reported a favorable effect of this agent on overt aggression but only in IED subjects with comorbid cluster B personality disorder.

Intermittent Explosive Disorder: Effect of Psychosocial Intervention

While there are very few studies on the psychosocial treatment of impulsive aggression in adults, the efficacy of treatments that address the related constructs of anger dyscontrol and/or interpersonal aggression have been evaluated and suggest that relaxation training, interpersonal skill training, cognitive therapy, and multicomponent treatments all have moderate to large effects in the treatment of anger, and that the anger-reducing effects of anger treatment remain at follow-up. Of the different approaches for treating individuals with anger and aggression problems, cognitive restructuring, interpersonal skills training, multicomponent treatments, and relaxation skills had the strongest influence on aggression with effect sizes (Cohen's d) for the four types of treatment ranging from 1.06 to 1.87. Recently, a well-controlled study of cognitive behavior therapy in IED focusing on cognitive restructuring, relaxation and coping skills

training has been published, demonstrating significant reduction in impulsive aggressive behavior and in hostile automatic thoughts (McCloskey et al. 2008). The antiaggressive response in this study was similar to that seen with fluoxetine, suggesting the possibility that the two interventions, together, may be very effective in treating the impulsive aggression seen in individuals with IED.

Cross-References

- ► Aggression
- ► Neurotransmitters
- ► Serotonin
- ► SSRIs and Related Compounds

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Aggressiveness

- ► Aggression
- ► Aggressive Behavior: Clinical Aspects

Agomelatine

Definition

A melatonin MT1 and MT2 receptor agonist and 5-HT_{2C} antagonist, known to be effective in acute treatment and relapse prevention in major depressive disorder, it also has proven efficacy in Generalized Anxiety Disorder. It seems better tolerated than some SSRIs and ► venlafaxine, with fewer treatment-emergent side effects and a reduced burden of discontinuation symptoms.

Agonist

Synonyms

Receptor activator

Definition

A substance that binds to a receptor and alters the receptor state, resulting in a biological response. The response mimics the effect of the endogenous activator of the receptor. A compound can be a full agonist, which leads to the maximum possible response of the system under study, or a partial agonist, an agonist that under specified conditions does not elicit as large an effect as a full agonist. This is in contrast to antagonists that have affinity but no efficacy at a receptor, and hence have no observable effects except to modify the actions of an agonist at that receptor. Inverse agonists are compounds that produce a pharmacological response that is opposite in direction to that of an agonist.

Cross-References

- ► Allosteric Modulator
- ► Antagonist
- ► Inverse Agonists
- ► Partial Agonist

Agonistic Behavior

Definition

Refers to aggressive acts, postures, and displays to which the opponent reacts defensively and eventually displays submissive postures or flees.

Cross-References

- ► Aggression
- ► Aggressive Behavior: Clinical Aspects

Agoraphobia

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Synonyms

Avoidance of feared places and situations: Anticipatory anxiety; Fear of being alone; Fear of crowded areas; Fear of public places; Fear reaction to somatic anxiety symptoms; Phobic anxiety

Definition

Agoraphobia is an anxiety syndrome in which patients experience severe anxiety or distress in certain places or situations. This can lead to the avoidance of these situations. The places often represent those from which escape might be difficult or embarrassing e.g., public transport, supermarkets, crowds, or lifts. However, symptoms can also occur when the patient is alone in any place where they anticipate that they will be unable to obtain help should "the worst" happen. It often starts after unexplained spontaneous symptoms of anxiety or ► panic attacks, and the fear of anxiety symptoms rather than the actual attacks becomes predominant leading to a heightened state of anticipation.

Role of Pharmacotherapy

Diagnostic Categories

Currently, ► Panic attacks and agoraphobic avoidance are seen as independent yet closely related anxiety factors. Therefore, two main types of disorder involving agoraphobia are defined according to the major classification systems (APA 2000):

(a) Agoraphobia
(b) Panic Disorder with Agoraphobia

► Panic Disorder in combination with agoraphobia is more common as many patients with Panic Disorder go on to develop agoraphobia eventually. Agoraphobia develops when avoidance behavior intensifies and it results in impairment of personal work and social functioning. Some patients cannot leave the house alone and can become fearful when left alone at home. Agoraphobia without a history of panic disorder is rare in clinical studies (Kessler et al. 2006), but this may be because of the nature of the disorder e.g., strong fear of travel and widespread avoidance, would make clinic visits extremely difficult. In confirmation of this, it is more commonly found when researchers visit the home of the patient, as in community studies (Perugi et al. 2007). Agoraphobia also occurs as a ► comorbid condition with other Anxiety Disorders e.g., ► Social Anxiety Disorder, Generalized Anxiety Disorder, or with ► Depressive Disorders and it is also associated with Axis II personality disorders such as Avoidant or Dependent Personality Disorder. The risk of ► substance abuse, usually of alcohol or benzodiazepines, is increased in these patients when they need to travel or face situations they fear. The onset of agoraphobia is usually gradual and can easily become chronic if not recognized. Severe agoraphobic avoidance can be hidden for years and the disorder is therefore often inadequately treated.

A range of drugs is available to treat agoraphobia with and without panic disorder. However, after establishing the diagnosis, it is important to explain the nature and symptoms of anxiety to the patient clearly so that they do not present to numerous medical facilities searching for a physical rather than a psychological explanation for their somatic symptoms. Patients fear that panic symptoms signal imminent danger in terms of a heart attack, collapse, going mad, or death. Their understanding of bodily functions can be overestimated and simple explanations about ► hyperventilation and palpitations are extremely valuable. The value of regular exercise in understanding bodily symptoms and reducing tension and the frequency of panic attacks should also be explained. In addition, it is helpful to outline the negative impact of using both stimulant and sedative substances on symptoms. For example, large amounts of coffee (► caffeine) are likely to increase shakiness and heart rate and although ► Alcohol may lead to some temporary reduction in anxiety, its consumption is likely to lead to ► dependence, if used for this purpose.

Drugs used to Treat Agoraphobia With and Without Panic Disorder

Drug treatment and ► cognitive-behavioral therapy (CBT) have been shown to be equally effective in the acute treatment of agoraphobia with and without panic disorder (Mitte, 2005). However, it is essential to consider severity of agoraphobic avoidance, local service availability, and patient preference when selecting or combining treatments as some studies indicate that CBT is more acceptable to patients (Otto et al. 2001). The drug treatments which have been shown to be effective in the acute treatment of agoraphobia are shown in Table 1. Slightly higher doses than those recommended for depression may be necessary to control symptoms enough to promote behavior change.

Agoraphobia. Table 1. Therapies shown to be effective in the treatment of agoraphobia.

Drug	
SSRIs	Usual therapeutic dose (mg/day)
Paroxetine	20–40
Sertraline	100–200
Citalopram	20–30
Escitalopram	10–20
Fluvoxamine	100–200
Fluoxetine	20
TCA	
Clomimpramine	100–200
Imipramine	100–200
Benzodiazepines	
Alprazolam	4–6
Clonazepam	1–2
Diazepam	15–30
Lorazepam	1–4
Other antidepressants	
Venlafaxine	75–150
Reboxetine	8–10
Psychological	No of sessions
Cognitive behavior therapy	16–20
Behavior therapy – exposure	16–20

Although Tricyclic ► antidepressants (TCAs) and ► Selective Serotonin Reuptake Inhibitors (SSRIs) have been found to be equally effective in reducing both the severity and the number of panic attacks (Bakker et al. 2002), SSRIs are currently recommended as the first line of drug treatment. Initial side effects, to which anxious patients are especially sensitive, can be minimised by slowly increasing the dose. When first prescribing drug treatment, it is important to explain certain principles to the patient (Table 2).

If the patient has responded to the drug therapy by 12 weeks, treatment should be continued for a further 6 months. When stopping treatment, the dose should be reduced gradually over several weeks to avoid discontinuation and rebound symptoms. If longer term treatment is required, both ► paroxetine and ► sertraline have shown efficacy for long-term maintenance or for prophylactic use to prevent relapse (Perugi et al. 2007). However, CBT with exposure should be considered as there is evidence that this approach reduces relapse rates (Nathan and Gorman, 2002). If the patient has not responded to

Agoraphobia. Table 2. Principles of Drug Treatment for Agoraphobia.

1	The medication should be taken regularly.
2	The medication will not work immediately and may take several weeks.
3	The medication should not be stopped without discussion with the prescriber.
4	Any unwanted effects should be reported to the prescriber.
5	The dose of medication may need to be increased for it to be effective.
6	Additional behavioral treatment may be necessary to tackle avoidance, especially if it is longstanding.

treatment after 12 weeks, the prescriber should consider switching to a different treatment or combining drug and psychological approaches.

1. *Efficacy.* All the drug treatments shown in Table 1 have been shown to be more effective than placebo. SSRIs have been shown to be effective treatments for agoraphobia. They reduce panic severity, eliminate attacks, diminish agoraphobic avoidance, and improve overall quality of life. They are recommended as the first line of drug treatment. TCAs are also effective in reducing panic attack severity and the number of attacks and benzodiazepines have shown similar efficacy to antidepressants.
2. *Side effects and toxicity.* SSRIs can cause nausea and gastric side effects and decrease ► libido whereas ► benzodiazepines can cause sedation and impair some motor and memory functions. However, both SSRIs and benzodiazepines have relatively benign side effect profiles. TCAs can cause unpleasant ► anticholinergic side effects and weight gain and are dangerous in overdose.
3. Advantages and disadvantages of different agents. SSRIs are considered the first choice of treatment for agoraphobia because they combine therapeutic efficacy with safety and tolerability. However, they can increase activation levels leading to agitation and anxiety at the start of treatment and patients should therefore be started at low doses which are gradually increased. Tricyclic antidepressants (TCAs) are the second choice of treatment but their side effects can also lead to drop-outs or reduced ► adherence at the beginning of treatment. ► Benzodiazepines have been shown to be effective in the treatment of agoraphobia. They are also quicker acting and better tolerated than antidepressants. However, benzodiazepines

can cause tolerance, dependence, and withdrawal effects (► Sedative, Hypnotic, and Anxiolytic Dependence) and because of their palatability, they are also prone to misuse and ► diversion. These factors limit their usefulness and they should only be prescribed either when other drugs have not been effective or for short periods at the beginning of treatment, i.e., to counteract increased anxiety which can be caused by the antidepressant or until it takes effect. Some studies have examined the combination and found that patients who received combined treatment showed faster improvement than those receiving either drug alone but that the benefit was only apparent up to 6 weeks of treatment (Perugi et al. 2007). Benzodiazepines used as combined therapy in this way should therefore be tapered off after 6 weeks.

Other Medications

When no response occurs to the evidence-based drug treatments in Table 1, then, ► monoamine oxidase inhibitors (MAOIs) provide an alternative treatment. ► Phenelzine has been shown to help some patients but the dose has to be titrated on an individual patient basis as it can vary between 15 and 90 mg/day. ► Tranylcypromine has been used at doses of 10–60 mg/day. However, these drugs need careful supervision as they can cause toxicity if patients do not adhere to strict dietary and concomitant drug restrictions. The evidence for the efficacy of the reversible inhibitor of MAO, ► moclobemide, is mixed but it has proved effective at a dose of 450 mg/day in at least two studies.

Psychological Treatment

Behavior therapy comprises graded exposure in vivo to a personally constructed hierarchy of feared situations to target agoraphobic avoidance. ► Cognitive behavior therapy aims not only to change behavior but to challenge and modify beliefs focussed on the catastrophic misinterpretation of bodily symptoms. Both approaches have been shown to be effective but because CBT combines behavioral and cognitive approaches, it is more robust.

Combined Treatment

Several narrative or unsystematic reviews of combined psychological and drug treatment have been done but provided mixed results. However, a recent systematic review completed a ► meta-analysis of 23 studies which examined the effects of combining psychotherapy and antidepressant drug treatment for panic disorder with agoraphobia (Furukawa et al. 2006). The authors found that combined treatment was superior to antidepressant treatment alone. The combination decreased the global severity of the disorder and social dysfunction. The superiority was still evident at follow-up. In addition, combined treatment was more effective than psychotherapy alone at the end of acute phase treatment but this diminished at follow-up. A separate meta-analysis of 13 studies using patients with agoraphobia alone showed similar results. A systematic review of the combination of psychotherapy and benzodiazepines has been carried out (Watanabe et al. 2009). However only three trials were found and this was insufficient to show any advantage for combined therapy over either therapy alone.

Conclusion

Agoraphobia is often overlooked and undertreated. Early intervention is important as it can develop into a chronic, relapsing condition. Effective drug treatment is now widely available and access to psychological therapy has improved. The combination of antidepressant drug treatment and psychotherapy is especially effective in acute treatment and produces more improvement than drug treatment alone at follow up.

Cross-References

► Alcohol
► Antidepressants
► Benzodiazepines
► Caffeine
► Cognitive Behavior Therapy
► Depressive Disorders
► Meta-Analysis
► Monoamine Oxidase Inhibitors
► Panic
► Panic Disorder
► Sedative, Hypnotic, and Anxiolytic Dependence
► Social Anxiety Disorder
► SSRIs

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Agouti-Related Peptide

Definition
Orexigenic peptide produced by cells in the hypothalamic arcuate nucleus. This peptide is the natural antagonist to α-melanocyte-stimulating hormone, and as such, it has a potent orexigenic effect.

Cross-References
► α-Melanocyte-Stimulating Hormone

AIF

► Apoptosis-Inducing Factor

Akathisia

Definition
A syndrome of increased motor activity and/or subjective sense of desire for motor activity believed to be due to functional irregularities in the extrapyramidal motor system in the brain. Most blatantly, akathisia may involve fidgeting, inability to remain seated, shuffling gait, shortened stride, cogwheel rigidity, reduced accessory movements such as arm-swing while walking or gesturing, and pacing. It may include more subtle phenomena such as wandering (with attendant boundary issues) and excessive talking (which the patient may be aware of, but unable properly to control). Akinesia can also affect small muscle groups, such as those of the face and/or larynx, leading to a reduced amount and range of facial expression and/or monotonous voice tone. Subjectively, akathisia is frequently experienced as an unpleasant, dysphoric state.

Cross-References
► Depressive Disorder of Schizophrenia
► Medication-Induced Movement Disorders

Akinesia

Synonyms
Pseudo-parkinsonism

Definition
Reduced spontaneous movements.

Alarm Calls

► Distress Vocalization

Alcohol

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Synonyms
Ethanol; Ethyl-alcohol; EtOH

Definition
Alcohol (chemical formula C_2H_5OH or $CH_3–CH_2–OH$) is a volatile, flammable, and colorless liquid. Due to its psychoactive properties, it is the most widely used recreational drug, and the term "alcohol" generally refers to alcohol-containing beverages that vary in alcohol concentration, usually between 3 and 60%.

Pharmacological Properties

History
Alcohol is thought to be the earliest drug in common use, probably dating back to the paleolithic age (around 8,000 BC). Initially, alcoholic drinks were obtained through yeast-induced conversion of sugars (fermentation) from a variety of carbohydrate-based liquids, such as honey and grains steeped in water or fruit/vegetable juices. Fermentation-obtained beverages have a maximum alcohol content of about 12%, since alcohol concentration above that level causes the yeast to die, thus preventing further fermentation. Around 800 AD, Arabs discovered a process of distillation of fermented liquids, which produces beverages of much higher alcohol content, sometimes as high as 80%. The use of both types of alcoholic beverages – fermented

drinks such as beer, wine, or mead and distilled drinks ("spirits"), such as whiskey, vodka, or gin – is widely spread throughout the history as well as in modern times, and it plays a significant role in social and religious customs of many cultures.

Acute Effects

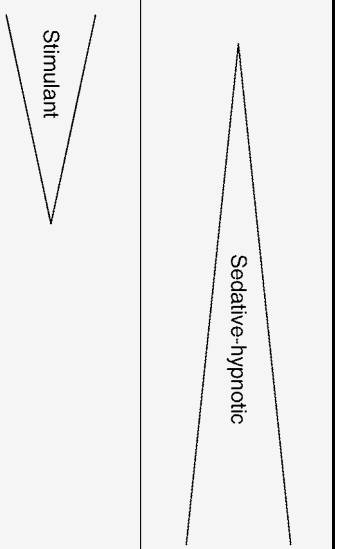
Alcohol exerts a number of effects, ranging from stimulant and pleasurable to sedative, anxiolytic, attention reduction, amnestic, anticonvulsant, muscle relaxant, hypnotic anesthetic, and can lead to death. The effects of alcohol are biphasic: at low blood alcohol concentrations (BAC) it is disinhibitory, thereby facilitating spontaneous behavior and having stimulant properties, while its effects at high BAC are sedative–hypnotic (Table 1). Acute alcohol poisoning (BAC $\geq$ 40%) may result in death due to the formation of edema (swelling) in the base of the brain (medulla), where centers of respiratory and cardiovascular regulation are located. Behavioral reaction to alcohol intake depends upon several factors, including the rate of alcohol absorption, alcohol metabolism, and ► tolerance.

Pharmacokinetics

Alcohol is a molecule soluble in water, which has low lipid solubility and which, like water, is easily absorbed into the bloodstream from the stomach and the duodenum (the top part of the small intestine). Since the majority of absorption occurs in the duodenum, the absorption rate tends to be slower for the stronger spirits than for the beverages of medium alcohol content, such as wine, because the high alcohol content of spirits inhibits the opening of the pyloric valve that allows for the stomach contents to pass into the duodenum.

The mode of alcohol transport in and out of the cells is passive diffusion, which is determined by the concentration gradient across the cell membranes. Thus, the absorption of alcohol into the body tissues depends on the level of vascularization (blood supply) of those tissues as well as the alcohol concentration of the beverage. In healthy adults, 80–90% of absorption occurs in the first 30–60 min following ingestion, although this is delayed and reduced if food is present in the stomach. Table 2 presents the number of standard drinks required to obtain a given BAC. The gender difference in the achieved BAC and, consequently, in the behavioral effects of the same dose of alcohol is thought to be due to the difference in the distribution of the body mass between men and women (Graham et al. 1998). Men have higher ratio of muscles to fat than women and thus proportionally more blood in the body (fat tissue lacks blood supply). Consequently, the same amount of alcohol is more diluted in the blood of men than women and less will be absorbed into the tissues due to the lower concentration gradient. Additionally, women have been suggested to metabolize alcohol more slowly, due to reduced levels of the metabolizing enzyme, ► alcohol dehydrogenase (► ADH),

Alcohol. Table 1. Progression of behavioral changes corresponding to increased BAC (modified from Koob and Le Moal 2006).

BAC	Behavioral changes	Biphasic alcohol effect
0.01–0.08%	Personality changes	
	Relief from anxiety	
	Social lubricant (more talkative, assertive, eloquent)	
	Disinhibition	
0.08–0.15%	Significant disinhibition ("life of the party")	
	Impaired judgments	
	Impaired cognition	
	Impaired motor function	
0.15–0.30%	Marked ataxia (staggering; slurred speech)	
	Major motor impairment	
	Impaired reaction time	
	Blackouts	
0.30–0.40%	Increased sedation/hypnosis (stuporous but conscious)	
	Approaching general anesthesia	
	Approaching coma	
$\geq$0.40%	Lethal dose for 50% of nondependent drinkers	

Alcohol. Table 2. Average BAC in men and women in relation to body weight and the number of drinks consumed.

Approximate BAC for men								
Number of drinks[a]	Body weight							
	45 kg (100 lb)	55 kg (120 lb)	64 kg (140 lb)	73 kg (160 lb)	82 kg (180 lb)	91 kg (200 lb)	100 kg (220 lb)	109 kg (240 lb)
1	0.04	0.03	0.03	0.02	0.02	0.02	0.02	0.02
2	0.08	0.06	0.05	0.05	0.04	0.04	0.03	0.03
3	0.11	0.09	0.08	0.07	0.06	0.06	0.05	0.05
4	0.15	0.12	0.11	0.09	0.08	0.08	0.07	0.06
5	0.19	0.16	0.13	0.12	0.11	0.09	0.09	0.08
6	0.23	0.19	0.16	0.14	0.13	0.11	0.10	0.09
7	0.26	0.22	0.19	0.16	0.15	0.13	0.12	0.11
8	0.30	0.25	0.21	0.19	0.17	0.15	0.14	0.13
9	0.34	0.28	0.24	0.21	0.19	0.17	0.15	0.14
10	0.38	0.31	0.27	0.23	0.21	0.19	0.17	0.16
Approximate BAC for women								
1	0.05	0.04	0.03	0.03	0.03	0.02	0.02	0.02
2	0.09	0.08	0.07	0.06	0.05	0.05	0.04	0.04
3	0.14	0.11	0.10	0.09	0.08	0.07	0.06	0.06
4	0.18	0.15	0.13	0.11	0.10	0.09	0.08	0.08
5	0.23	0.19	0.16	0.14	0.13	0.11	0.10	0.09
6	0.27	0.23	0.19	0.17	0.15	0.14	0.12	0.11
7	0.32	0.27	0.23	0.20	0.18	0.16	0.14	0.13
8	0.36	0.30	0.26	0.23	0.20	0.18	0.17	0.15
9	0.41	0.34	0.29	0.26	0.23	0.20	0.19	0.17
10	0.45	0.38	0.32	0.28	0.25	0.23	0.21	0.19

Subtract 0.01% for each 40 min of drinking. http://www.alcohol.vt.edu/Students/alcoholEffects/estimatingBAC/index.htm#educator

[a]1 drink=1 shot (40 ml/1.25 oz) of 40% spirit, 1 can (350 ml/12 oz) of 4.1% beer or 1 glass (150 ml/5 oz) of 12% wine

although this has not been demonstrated unequivocally (Graham et al. 1998).

The effects of alcohol consumption are determined not only by the rate of absorption but also by the rate of its metabolism and elimination. Less than 10% of alcohol is eliminated unchanged via lungs, urine, and perspiration. Most of the ingested alcohol (approximately 90%) is metabolized in the liver via several metabolic pathways. The main pathway of alcohol metabolism in the liver is the oxidative process involving the enzyme ADH. ADH is located in the cytoplasm of liver cells and utilizes the coenzyme ► nicotinamide adenine dinucleotide (NAD) to convert alcohol into ► acetaldehyde. Another metabolic mechanism in the liver which contributes to the conversion of alcohol into acetaldehyde is the ► microsomal ethanol-oxidizing system (MEOS) involving the enzyme CYP2E1. This process, however, only accounts for 10–15% of the total hepatic metabolism of alcohol, and its activity plays a more pronounced role only during heavy and sustained drinking (see below).

The first by-product of alcohol, acetaldehyde, is a highly toxic substance but its levels are usually very low as it is rapidly converted into acetic acid by the second oxidative process mediated by another cytoplasmic liver enzyme, aldehyde dehydrogenase (ALDH). Acetic acid is then released into the hepatic venous blood where it binds to coenzyme A forming acetyl CoA which is subsequently oxidized into carbon dioxide and water.

Some of the ingested alcohol is also metabolized in the stomach and the duodenum, prior to absorption into the bloodstream. However, since the gastric and intestinal levels of ADH are comparatively low, this "first-pass" metabolism is less efficient than the hepatic metabolism and may only exert a more significant effect on the BAC

when alcohol is ingested together with food, which tends to slow down the absorption of alcohol due to food-induced closure of the pyloric valve.

The average rate of alcohol metabolism is approximately 7–10 ml (6–8 g) of alcohol per hour and the rate-limiting factor is the ADH and the NAD availability. However, significant genetic differences exist in the efficiency of alcohol metabolism. Individuals with the allelic variations of the ADH genes-1B and -1C (ADH1B and ADH1C) show a reduced rate of conversion of alcohol into acetaldehyde, which results in an increased level of intoxication. Similarly, individuals with the allelic variation of the ALDH2 gene, which results in inactivity of the ALDH, experience accumulation of the toxic acetaldehyde in the blood and thus experience the "flush reaction" to alcohol. Flush reaction includes more intense feelings of intoxication, facial flushing, nausea, tachycardia, hypotension, and increased body sway. One of the drugs for the treatment of ► alcohol abuse and dependence, ► disulfiram ("Antabuse") is based on the same principle. Disulfiram pharmacologically blocks ALDH resulting in aversive reaction to alcohol which promotes abstinence.

Due to increased propensity of adverse reactions to alcohol, individuals with the ADH1B, ADH1C, and ALDH2 genotypes usually completely abstain from alcohol consumption. These genotypes are more common among the Asian population, where up to 80% of individuals in some subgroups posses at least one copy of one of these genes (Eng et al. 2007).

Tolerance

Tolerance to alcohol can be acute or chronic. ► Acute tolerance is observed during a single drinking session when some effects of alcohol are more pronounced during the ascending, compared to the descending, phase of the BAC curve. This so-called Mellanby effect has been suggested to occur due to the acute behavioral or cellular adaptations to the effects of alcohol (see below). It is also evident during the descending phase of the BAC curve, when subjective feelings of intoxication decline faster than the rate of decline of the BAC. Indeed, the subjective intoxication may entirely disappear during the descending phase of the BAC curve, even with BAC as high as 0.03–0.05% (Martin and Moss 1993). Chronic tolerance occurs as a result of repeated exposure to alcohol and is manifested by the reduced effectiveness of the same doses of alcohol, which were effective previously. This type of tolerance occurs as a result of metabolic (pharmacokinetic) or pharmacodynamic (cellular, molecular, functional) adaptations.

Metabolic tolerance is characterized by a diminished peak BAC obtained by a given dose of alcohol, resulting from increased absorption or clearance of alcohol from the bloodstream, which in turn result in a diminished alcohol effect. While repeated alcohol exposure may result in an increase in the ADH activity, this is unlikely to be the main mechanism underlying metabolic tolerance. This is because the degree of ADH activity is limited by the rate of the regeneration of the coenzyme NAD, which is insufficient to keep pace with the increased ADH production. Instead, it seems that the main mechanism underlying metabolic tolerance is the upregulation of the second major hepatic metabolic pathway involving the enzyme CYP2E1. This metabolic pathway is upregulated following chronic alcohol use, leading to as much as double the rate of alcohol breakdown in alcoholics when compared with moderate drinkers (Koob and Le Moal 2006). As a result of metabolic tolerance, peak BAC for the tolerant individual is much lower than for the nontolerant individual at the same dose of alcohol. Metabolic tolerance effect, however, is transient and is usually lost after as little as 3 weeks of abstinence.

► Pharmacodynamic tolerance occurs independently of the metabolic tolerance and is expressed as the shift to the right of the BAC dose-response curve. That is, a higher BAC is needed to produce the same degree of intoxication as previously obtained with a lower BAC, suggesting that the target central nervous system (CNS) tissues have become less responsive to alcohol. This is thought to be due to counteradaptive neuronal and molecular changes involving neurotransmitter release, receptors and secondary messenger systems including cAMP and G-proteins (Feldman et al. 1997; Pandey 1998). One proposed mechanism of pharmacodynamic tolerance involves latent hyperexcitability, resulting from alcohol-induced depression of neuronal activity. This depression of neuronal activity may result from desensitization or reduction of the number of existing receptors, making the postsynaptic targets less responsive to alcohol-induced neurotransmitter release. Another proposed mechanism involves reduction in neurotransmitter release, which may result from neurotransmitter depletion (e.g., not enough neurotransmitter synthesized to keep pace with the release) or end-product inhibition (stimulation of presynaptic autoreceptors inhibiting further release). Both these opponent mechanisms of pharmacodynamic tolerance are thought to contribute to the rebound phenomenon of acute alcohol ► withdrawal when effects opposite to those of alcohol are observed (e.g., sedation/anxiolysis during intoxication, ► hyperactivity/anxiety during withdrawal).

Pharmacodynamic tolerance and, to a lesser extent, metabolic (pharmacokinetic) tolerance are also revealed through the phenomenon of ► cross-tolerance, whereby heavy drinkers and alcoholics who display tolerance to alcohol are also tolerant to other drugs, particularly to pharmacologically related compounds. This has important clinical implications because the level of alcohol use needs to be taken into account when determining a therapeutic dose of a prescription drug.

Tolerance to alcohol as well as the rebound withdrawal symptoms are mediated not only by the adaptive processes occurring in response to the presence of the drug in the body but may also be ► conditioned drug effects, whereby environmental cues associated with alcohol use trigger the adaptive opponent process in anticipation of alcohol consumption. For an extensive review of different types of tolerance, see Fadda and Rossetti (1998).

Individual differences in sensitivity to the effects of alcohol are thought to be partly heritable and underlie differential susceptibility to ► alcohol abuse and dependence, with social drinkers who initially have low level of response to alcohol being more vulnerable (Schuckit et al. 2004).

Withdrawal

Withdrawal symptoms occur after abrupt cessation of prolonged heavy alcohol use, and in milder form withdrawal-like symptoms may also occur in social drinkers following alcohol binges ("hangover" effect). ► Alcohol withdrawal syndrome consists of two or more of the following symptoms and signs: autonomic hyperactivity (increased sweating and pulse rate), increased hand tremor, insomnia, nausea and vomiting, psychomotor agitation, anxiety, and irritability (Stage I). Following a longer history of alcohol dependence, Stage I symptoms become more severe and the following additional symptoms can be observed: transient visual, tactile or auditory hallucinations, grand mal seizures or even full-blown epileptic seizures (Stage II). A few days after the initial stage I and II withdrawal symptoms have diminished, between 1 and 15% of patients experience ► delirium tremens (Stage III). This is characterized by confusion, disorientation, and agitation, as well as terrifyingly vivid persecutory hallucinations, which are usually perceived as real by patients, even after the recovery. Between 1 and 15% of the patients who experience delirium tremens die due to cardiovascular collapse (Feldman et al. 1997).

Withdrawal symptoms result from acute and chronic neuroadaptive changes which also underlie tolerance to alcohol (Fadda and Rossetti 1998). Acute alcohol withdrawal produces long-lasting neurodegenerative changes, and there is evidence that previous repeated withdrawal episodes exacerbate these neurodegenerative processes, not only producing a worsening in withdrawal-associated hyperexcitability (the so-called "kindling of withdrawal") but also leading to neurotoxicity associated with cognitive impairment and emotional incompetence (Duka et al. 2004). Withdrawal-induced neurodegeneration may be one of the main factors contributing to brain damage observed in individuals suffering from alcoholism.

Chronic Effects

Chronic alcohol abuse and dependence lead to a number of morphological, neurophysiological, and biochemical changes in the CNS and the associated cognitive deficits (Fadda and Rossetti 1998). While some of these changes are due to direct effects of alcohol and alcohol withdrawal, others are more indirect, resulting from nutritional deficiencies common in this population. Postmortem studies of the brains of heavy drinkers and alcoholics as well as in vivo brain imaging studies reveal a number of morphological changes, including brain shrinkage, increased ventricle size, reduction in the volume of white matter in the cerebral hemispheres, and thinning of the corpus callosum (Fadda and Rossetti 1998; Feldman et al. 1997).

Approximately 10% of alcoholics develop alcohol amnestic disorder (► Korsakoff's syndrome) or alcoholic dementia. While the former is characterized by anterograde memory impairment with relative preservation of intelligence and other cognitive functions, the latter is characterized by global severe dementia and intellectual impairment. Some of the cognitive impairments and morphological changes observed after chronic alcohol use may be reversible by abstinence, while others, such as cerebellar atrophy seen after prolonged excessive alcohol use, appear to be irreversible (Feldman et al. 1997).

Mechanisms of Action

Alcohol has multiple mechanisms of action on the CNS.

Alcohol acutely facilitates γ-aminobutyric acid (GABA) transmission by potentiating GABA-stimulated Cl^- flux at the $GABA_A$-benzodiazepine (BDZ) receptor complex, inhibits glutamatergic transmission via its interaction with the *N*-methyl-D-aspartic acid (NMDA) receptors, increases serotonin (5-hydroxytryptamine; 5-HT) transmission by slowing its reuptake, and enhances 5-HT action at $5\text{-}HT_3$ receptors. Alcohol acutely increases the release of opioid β-endorphin and indirectly activates

mesolimbic dopamine (DA) system, via its actions on opioid system as well as the 5-HT_3 serotonin receptors. In addition to this, alcohol exerts a number of other effects, including enhancement of cholinergic function and increase on the levels of the corticosteroid hormones released from the adrenal glands. More recently, attention has been drawn to the effects of alcohol on ► neurosteroids which seem to contribute to neurophysiological and behavioral effects of alcohol. The most important of these actions are briefly discussed as follows:

$GABA_A$

The acute alcohol effects on ► GABAergic transmission contribute not only to the anxiolytic and sedative–hypnotic properties but also to its intoxication including motor incoordination. Alcohol induces allosteric changes in several ► $GABA_A$ Receptor subtypes, which is associated with increased function of these receptor subtypes. However, it is not clear yet which $GABA_A$ receptor subtypes are involved in the effects of alcohol. Alcohol is also found to increase the release of GABA in several brain areas, although the mechanism associated with the GABA presynaptic release is not yet clear.

Chronic effects of alcohol on $GABA_A$ receptor function and GABA release leads to functional adaptations of GABAergic system in several brain areas. Such neuronal adaptations contribute to the hyperexcitability like anxiety or even seizures seen during alcohol withdrawal (Pandey 1998). BZDs, which bind to $GABA_A$ receptors and facilitate GABAergic function are the treatment of choice for alcohol withdrawal symptoms.

Glutamate

Alcohol interacts with ► glutamate, the major excitatory neurotransmitter in the mammalian brain. Alcohol acutely inhibits glutamatergic synaptic transmission mediated by NMDA receptor that contributes to alcohol's anxiolytic effects. Neuronal plasticity mediated by ► NMDA receptors is also inhibited by alcohol; this alcohol effect on neural plasticity may contribute to its strong amnestic effects. NMDA receptor antagonists such as the drug ► ketamine have been reported to produce subjective effects resembling ethanol intoxication in healthy subjects as well as in detoxified alcoholics (Krystal et al. 2003).

Chronic alcohol exposure induces changes in NMDA receptor number and function as a result of compensatory mechanisms to counteract the inhibitory effects of acute alcohol. At withdrawal glutamatergic systems are disinhibited, leading to neuronal hyperexcitability and to neuronal damage induced by alcohol. ► Acamprosate, a drug that is thought to act by inhibiting neuronal activation probably due to an interaction with the glutamatergic neurotransmission is currently used as a treatment for alcohol addiction. Furthermore, a number of drugs that target glutamatergic transmission are currently being developed or tested for their efficacy in the prevention of relapse in alcoholism.

Dopamine

DA release in the mesolimbic system, from ventral tegmental area (VTA) into nucleus accumbens (NAcc), underlies motor stimulant and positive reinforcing effects of alcohol and other drugs of abuse. However, dopaminergic action of alcohol does not appear to be critical for maintaining alcohol reinforcement, since depletion of the mesolimbic DA did not significantly alter alcohol self-administration in animal studies.

Serotonin

Enhancement of 5-HT activity at the 5-HT_3 receptors contributes to alcohol's positive reinforcing and stimulant effects, since the densely distributed 5-HT_3 receptors in the mesolimbic DA-containing neuronal terminals enhance DA release. Consequently, 5-HT_3 receptor blockade was found to reduce alcohol-induced enhancement of DA release as well as alcohol consumption in humans. However, although the effects of alcohol on 5-HT and DA have been studied in the hope of developing new drugs for the treatment of alcoholism, the effectiveness of these drugs has been equivocal.

β-endorphin

The opioid system, particularly the β-endorphin, is thought to mediate positive hedonic effects of alcohol and to contribute to its reinforcing properties via indirect stimulation of DA release into NAcc (part of the reward pathway). Opioid receptor antagonists reduce alcohol-induced DA release, as well as alcohol consumption in animals and in humans. ► Naltrexone, an opioid antagonist, is commonly used as a treatment for alcoholism. Reduced consumption during naltrexone treatment may result either from reduction of the positive hedonic effects of alcohol ("liking") or by reduction of the positively reinforcing properties of alcohol ("wanting").

Due to its variety of actions in the CNS, alcohol produces a ► discriminative stimulus complex, or compound cue, composed of distinct components that are mediated by different receptor systems and which are not uniformly amplified as the ethanol dose is increased. This would account for the biphasic effects of alcohol described above. For instance, DA release into NAcc

underlies the stimulant effects of alcohol at lower doses, while at higher alcohol doses, despite further increase in DA release, the stimulant effects disappear due to increased sedative effects of ethanol, mediated by the GABAergic system; finally intoxication with even higher doses of alcohol may occur due to its interaction with the NMDA receptors.

Cross-References

- ► Acamprosate
- ► Alcoholism
- ► Alcohol Abuse and Dependence
- ► Conditioned Drug Effects
- ► Disulfiram
- ► Naltrexone
- ► Pharmacokinetics

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Alcohol Abuse and Dependence

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Synonyms

Alcohol addiction; Alcoholism; Alcohol use disorder; AUD

Definition

Pharmacological treatment of alcohol dependent subjects includes both treatment of the acute physical withdrawal syndrome and relapse prevention treatment (Anti-► craving).

Whereas today withdrawal treatment is highly standardized, on the basis of randomized controlled trials and clinical experience from several decades, relapse prevention treatment represents a fairly new intervention. The available compounds are not widely prescribed and proved evidence for differential pharmacotherapeutic strategies is lacking.

Role of Pharmacotherapy

Physical Withdrawal Treatment: General Pharmacological Withdrawal Strategies

In the majority of cases, treatment of patients suffering from alcoholism starts with the termination of alcohol use and treatment of withdrawal symptoms. The general consensus is that the complicated ► alcohol withdrawal syndrome (severe physical withdrawal or withdrawal with seizures, ► alcohol hallucinosis or ► delirium tremens) requires pharmacological treatment. It is also agreed that adequate hydration, electrolyte compensation, thiamine substitution and monitoring of the cardiovascular parameters are required during all phases of the withdrawal syndrome. In addition to curative therapy, avoidance of seizures and reduction of the risk for delirium tremens should be considered.

For the treatment of a moderate to severe withdrawal syndrome, administration of ► benzodiazepines such as ► chlordiazepoxide or ► clomethiazol, a sedative hypnotic, is preferred. Comparative studies did not show a difference in efficacy between benzodiazepines and clomethiazol. In cases of delirious and hallucinatory syndromes, additional medication with neuroleptics is often applied; ► butyrophenones are preferred due to a somewhat lower risk of seizure during withdrawal. In outpatient treatment, substances such as tiaprid, ► carbamazepine, and clonidine, which have no dependence potential, achieved good results.

Specific Pharmacologic Withdrawal Strategies

Benzodiazepines

Benzodiazepines are the first choice in the treatment of alcohol withdrawal syndrome, delirium tremens, and

seizures during withdrawal. This is based on a broad cross tolerance with alcohol, the large therapeutic window and the fast onset of effect. Benzodiazepines are sedative, hypnotic, anti-convulsive, anxiolytic, and muscle relaxing and thus appropriate for the reduction of withdrawal symptoms as well as the prevention of delirium, hallucinations and withdrawal seizures. Allergic reactions and pulmonary complications are rare. Different benzodiazepines in equivalent doses have a similar effect in the treatment of uncomplicated alcohol withdrawal syndrome. Substances such as ▶ diazepam and clordiazepoxide, which have a long half-life, are most frequently used in the treatment. Shorter acting benzodiazepines (▶ oxazepam, ▶ lorazepam), however, include benefits due to a lower accumulation (especially in terms of liver cell damage), a reduction of aversive effects, and better controllability.

Treatment with diazepam is presented as an example. Diazepam is nearly totally reabsorbed; the oral bioavailability amounts to 95%. The half-life period adds up to 20–40 h and is extended in cases of liver cirrhosis and at higher age. It is mainly eliminated through the liver by forming active metabolites (half-life period up to 100 h). Diazepam is not known to have hepatotoxicity.

A dose based on the clinical symptoms should be favored rather than a schematized administration, as the effect on the alcohol withdrawal syndrome cannot be predicted.

Sellers et al. (1983) recommend an oral diazepam "loading" with 20 mg initially and consecutive administrations after gaps of 1–2 h, until the withdrawal syndrome is significantly reduced or the patient is slightly sedated. The maximum dose per day is 150 mg. During the next couple of days, the dose should be reduced to 25–50% to avoid accumulation of active metabolites (e.g., N-desmethyldiazepam). The benefits of this therapy are fast saturation, rapid onset of effect and the "shielding" of patients during the course of the withdrawal syndrome due to the long half-life period of diazepam (20–40 h) and its metabolite (30–40 h).

Side Effects and Contra-Indications

During treatment with benzodiazepines, reduction of blood pressure, which increased during alcohol withdrawal syndrome, and sedation occur. Undesired side effects can be respiratory paralysis, tachycardia, intestinal atony and muscle relaxation. Myasthenia gravis and a known oversensitivity are absolute contra-indications. Special care should be taken in cases of sleep apnoea syndrome. Benzodiazepines initially improve sleep quality but after cessation, a rebound can occur, which can trigger a relapse.

In cases of overdosing of benzodiazepines, a benzodiazepine antagonist (anexate) can be administered. Dosage: initially 0.2 mg slowly i.v., later, medication of 0.1 mg up to a maximum of 1 mg at an interval of at least 1 min. An outpatient withdrawal treatment with benzodiazepines can be considered under continuous monitoring over a maximum period of 1 week, considering the dependence potential of the substance.

Clomethiazol

This medication is not used in Anglo-Saxon countries. However, it is widely prescribed in other parts of the world, such as central Europe. ▶ Clomethiazol is a synthetic derivate of the thiazole portion of vitamine B1 (thiamine). The exact mechanism of action is still unknown, but includes the potentiation of GABAergic inhibition, possibly via a direct effect on the chloride channel. Clinically, clomethiazole acts sedatively, hypnotically, anticonvulsively and anxiolytically. The risk of developing a delirium tremens is reduced.

Clomethiazol is metabolized via the liver by forming inactive metabolites with a half-life period of approximately 4–6 h and is excreted renally. In cases of impaired liver function, the half-life period is extended and increases the risk for accumulation, while the half-life period is abbreviated in alcohol-dependent individuals without liver damage. Clomethiazole is not hepatotoxic.

The dose titration should be adjusted according to clinical symptomatology rather than a merely schematized administration. A too careful up-dosing can often lead to the development of a delirium, whereas a too slow dose reduction does not consider the dependence potential of the substance.

In case of severe physical withdrawal syndromes and during pre-delirium, 2–4 capsules should be administered. If sedation is insufficient, 6–8 capsules can be administered additionally after approximately 30 minutes during the first 2 h. Later on, a maximum of 2 capsules/2 h, depending on the symptoms and the state of the cardiovascular system, should be administered.

The average dose in the clinical routine is about 10–15 capsules/day. A careful dose reduction of approximately 2–4 capsules/day can be considered the second day. In case of pronounced symptoms, a plateau phase of 3–5 days is recommended. Because of its addictive effect, clomethiazole should be tapered within 8–10 days.

Side Effects and Contra-Indications

Oral administration can cause a decrease in blood pressure, which increased during alcohol withdrawal and a reduction of tachycardia. However, cardiovascular

insufficiency requiring treatment is rare. The risk of a hypoventilation and unconsciousness is also very low when administration is done orally. Further undesirable side effects are rashes, irritations of the throat and sneezing, tears and stomach problems. Bronchial secretion is increased. If taken for a long period, medication carries the risk of developing a dependence.

Sleep apnoea syndrome and central respiratory problems are absolute contra-indications. Clomethiazole should not be administered in case of bronchial asthma or acute lung or bronchial diseases. A concomitant administration of other hypnotics, tranquilizers, neuroleptics or alcohol can have life-threatening effects due to effect intensification, which is difficult to assess.

Outpatient treatment with clomethiazole should not be considered because of a dependency potential, as well as possible serious side effects, especially in cases of overdosing and alcohol consumption.

Tiapride, Carbamazepine, Oxcarbazepine and Clonidine

A combination treatment with tiapride and carbamazepine, especially oxcarbazepine, offers a good alternative, especially for outpatient treatment and leads to good results in treating vegetative symptoms within the withdrawal syndrome and offers concomitant seizure prevention.

Tiapride is a selective D2-receptor antagonist and belongs to the group of benzamide derivates. The special field of application of the substance is the treatment of extrapyramidal motor diseases. However, long-term experiences in pharmacotherapy for alcohol withdrawal syndrome exist as well. Tiapride has psychomotor effects and is sedative and anxiolytic, but does not have an effect on the seizure threshold during alcohol withdrawal. The low rate of undesired effects, the lower sedative effect, and especially the non-dependence potential seem to be advantages, compared to clomethiazole or benzodiazepines. Undesired side effects are tiredness, vertigo, orthostatic dysregulation and, sometimes, extrapyramidal motor symptoms. As tiapride lacks anti-convulsive efficacy, a combination therapy with carbamazepine has been suggested. A major advantage of carbamazepine, besides its anti-convulsive effect and lack of interaction with alcohol, is the reduction of the kindling effect. The half-life period is 15 h, but is reduced by enzyme induction after prolonged intake. It is eliminated via hepatic oxidation and renal elimination. The active metabolite carbamazepine epoxy has a half-life of approximately 8 h. Because of this fact and the delayed onset, no retarded release preparation of carbamazepine should be administered during withdrawal treatment.

Patients with liver dysfunction can be treated with oxcarbazepine, a derivative of carbamazepine that does not have liver toxicity. It showed good effects, as its elimination requires no hepatic metabolisation.

Patients receiving outpatient treatment should be monitored daily; after 1 week, detoxification is usually concluded. A dose increase of tiapride up to 1,800 mg per day in cases of severe withdrawal symptoms has been suggested; for inpatients, the recommendation is upto 2,400 mg per day.

If arterial blood pressure increases, the administration of the imidazole derivate clonidine can be helpful. Clonidine acts sympathicolytically via stimulation of presynaptic inhibitory alpha-two receptors located in the locus coeruleus. It reduces cardiovascular stress during alcohol withdrawal and decreases agitation, anxiety, tremor, and tensions in the muscular system. The substance does not have anti-delirious or anti-convulsive effects. The oral bioavailability amounts to 75% and the half-life period is 20 h. When administered parenterally, the effect appears after 10 min. Elimination happens 60% renally and 40% via hepatic metabolisation.

In cases of slight to moderate alcohol withdrawal syndrome, clonidine should initially be administered at a dose of 75 µg orally; the max. daily dose is 600 µg. Typical side effects are drop in blood pressure (initially also rise in blood pressure!), bradycardia, tiredness, xerostomia, and muscle relaxation. Contra-indications are AV-block II and III grades, sick sinus syndrome, phaechromocytoma, pronounced hypotonia, and depression.

Therapy for Delirium Tremens

Only about 5% of alcohol-dependent individuals with a vegetative withdrawal syndrome develop delirium tremens. While hallucinations (mainly optical, rarely acoustic) can also be observed during severe vegetative withdrawal syndromes, the presence of disorientation is the critical differential-diagnostic criterion, recommending the diagnoses of delirium tremens. Additionally, visual, tactile and acoustic hallucinations can occur, and, rarely, grand mal seizures, as well as disorders of consciousness and cognitive abilities. Psychomotor hyperactivity is also a typical symptom.

The presence of delirium tremens is a life-threatening situation that always requires immediate referral to an intensive care unit. Pharmacotherapeutic treatment prefers ► benzodiazepines, usually in combination with neuroleptics (e.g., ► haloperidol 5 mg/4 h) which are injected i.v. for electrolyte and liquid compensation. Under this medication, a delirium tremens usually subsides in 2–4 days. In this case, a tapering dose of the medication is

important. The administration of thiamine (50 mg slowly i.v., 50 mg i.m.) is usually necessary for the prophylaxis of Wernicke's encephalopathy.

Pharmacological Relapse Prevention

About 40–60% of patients relapse within 1 or 2 years after treatment. This proves the necessity for additional medication to prevent a relapse. Recent studies show that "anti-craving" compounds, especially during the first months after discharge from an inpatient withdrawal treatment, reduce the relapse risk (O'Brien 2005). So far, substances with an effect on the cholinergic, glutamatergic, serotonergic, dopaminergic, gabaergic and opioidergic systems have been examined (Spanagel and Kiefer 2008).

Acamprosate

Acamprosate, a calcium-bis-acetyle-homotaurinate, has been approved for preventing relapse of alcohol dependence. In cases of chronic alcohol consumption, a higher activity of the glutamatergic system can be seen, caused by a counter regulation of the acute inhibiting effect of alcohol on the excitatory glutamatergic neurotransmission. ▶ Acamprosate binds on the NMDA receptor and thus inhibits the increased excitability. After confirmation of experimental results in animal models, the effect of acamprosate on alcohol dependence was also examined in numerous controlled clinical studies. Evidence-based reviews have confirmed the efficacy of acamprosate on abstinence rate and number of drinking days and recommend clinical application (Mann et al. 2009).

Acamprosate has an effect on alcohol dependence especially when given concomitantly with psycho-therapeutic or psychosocial measures. The COMBINE Study included 1,383 recently alcohol-abstinent patients (Anton et al. 2006) and showed no effect of acamprosate on abstinence proportion, in contrast to the majority of European studies on this topic. Patient characteristics suggest that subjects who had no physical withdrawal syndrome requiring withdrawal treatment were mainly included in the Combine study. As acamprosate's efficacy is associated with its ability to modulate withdrawal-induced hyperglutamatergic states inducing craving, the specific pharmacological target for acamprosate might have been missing in the patients included in this study.

Acamprosate does not cause any interaction to other medications, does not increase alcohol toxicity, and does not have any dependence potential or other psychotropic effects. Frequent but usually transient side effects are diarrhea, other gastrointestinal conditions, headaches, and pruritus. Contra-indications are pregnancy and lactation periods, serum creatinine $>120\,\mu$molg/L in patients with renal insufficiency and the presence of severe liver insufficiency. The medication should be administered after detoxification in patients motivated for abstinence. A treatment period of 12 months is recommended. Treatment should be maintained even after short term relapses. The combination with alcohol bears no safety risks.

The daily dose of acamprosate is 3×2 tablets (à 333 mg). According to the manufacturer, the medication should be started after achieving abstinence and continued for approximately 1 year. It has been suggested that acamprosate has also an anti-withdrawal and a neuroprotective effect. With respect to the kindling phenomenon, administration of acamprosate should be considered one week prior to withdrawal. This would include a period of 7 days until the brain is in a steady state.

Naltrexone

▶ Naltrexone acts antagonistically mainly at mu-opiate receptors, counteracting alcohol craving. It is assumed that the endorphin-mediated, subjectively pleasant and positive reinforcing effects of alcohol are inhibited (O'Brien 2005). In animal models, the alcohol-antagonistic effect of naltrexone was demonstrated. Various placebo-controlled studies verified this effect in humans as well. Naltrexone has proved especially effective in combination with psychotherapeutic treatments. Yet several large trials did not show a superiority of naltrexone over the placebo. A Cochrane meta-analysis, however, confirmed a reduction in alcohol consumption, even if the time to first alcohol consumption was not always extended (Johansson et al. 2007).

Nausea, gastrointestinal disorders, and headaches are the main side effects of the otherwise well- tolerated substance. Contra-indications are acute hepatitis or severe liver dysfunction. Prior to treatment it should be ensured that at least some days of abstinence were observed, to avoid a concurrence of possible gastrointestinal side effects and withdrawal syndrome. The opiate-antagonistic effect should be considered for the indication of the further course of treatment. An actual or recent opiate consumption, taken as addictive drug or as pain relief, is an exclusion criterion for the administration of naltrexone. An opiate analgesia, necessary under administration of naltrexone, requires special precautions, especially if discontinuation of the medication cannot be done in time. Treatment with naltrexone should be continued for more than 3 months and not interrupted or discontinued after a timely, limited relapse. Naltrexone does not increase the toxicity of alcohol and does not possess any

dependence potential. The recommended daily dose of nemexine® is 50 mg.

Disulfiram

► Disulfiram has caused more controversies than any other medical treatment for alcoholism . While in Scandinavia and Great Britain up to 50% of alcohol-dependent individuals have been treated with this substance during the last decades, no considerable prescriptions were given in Germany after an initial success during the last two decades of the twentieth century. Only the increasing discussion on the prescription of anti-craving substances for relapse prevention led to a reconsideration of the administration of disulfiram. A special treatment concept for severely alcohol-dependent individuals was also performed (Ehrenreich et al. 1997). It showed the efficacy of the substance under daily supervised intake. A prescription, however, implies detailed knowledge of the mode of action and especially of the possible life-threatening side effects. It should only be prescribed under strict supervision.

Disulfiram affects the metabolisation of alcohol. The acetaldehyde dehydrogenase is blocked, so that a further decomposition to acetic acid is interrupted, resulting in an accumulation of ► acetaldehyde. This leads to unpleasant symptoms such as flushes, headaches, nausea, vomiting, diarrhea, drop in blood pressure and potentially to syncopes. These symptoms can be ascribed to the toxicity of acetaldehyde. A genetically conditioned lack of an isoenzyme of the aldehyde-dehydrogenase can be found in 50% of the Asian population, though in only around 5% of Caucasians. Alcohol consumption leads to the clinical symptoms described above, especially in homozygous carriers of this variation.

According to specialty information the following dose is recommended: First day: 1.5 g disulfiram, equivalent to 3 antabus, 0.5 dispergettes. Second day: 2 dispergettes. Third day: 1 antabus, 0.5 dispergette, which should also be the maintenance dose.

Contra-indications are: Coronary heart disease, severe cardiac arrhythmia, clinically manifest cardiomyopathy, impaired cerebral blood flow, advanced arteriosclerosis, oesophageal varices, hypothyroidism. Disulfiram should not be administered in cases of non alcohol-related depressions and schizophrenic psychosis. The same holds true in cases of severe hypotonia, decompensated liver cirrhosis and asthma bronchiale.

A treatment with disulfiram and concomitant alcohol consumption leads to aversive symptoms as mentioned above. Some rare cases of death were reported when administration was not supervised. This means that today treatment with disulfiram should be regarded as the "therapy of last choice." On the other hand direct and indirect comparisons with other anti-craving substances suggest a possible superiority.

Two open randomized studies compared disulfiram with naltrexone and with acamprosate (de Sousa and de Sousa 2005). In both cases disulfiram showed a significant superiority. A further study with a concomitant comparison with naltrexone, acamprosate and disulfiram has been published. The superiority of disulfiram over naltrexone and acamprosate was also confirmed in some international meta-analyses (e.g., Berglund et al. 2003). These results confirm earlier indications, concluding that disulfiram requires a re-evaluation. Recent reviews agree with this view.

Differential and Combined Treatment

Pharmacological relapse prevention in alcoholics is currently based on three extensively tested medications: acamprosate, naltrexone, and disulfiram.

It is being discussed whether individuals respond differently to different drugs. Individualized treatment with the "right drug" could thus increase the effects of pharmacotherapy significantly. At least the effects of acamprosate and naltrexone appear to relate to different aspects of drinking behavior, with the former primarily stabilizing abstinence and the latter primarily decreasing alcohol consumption. However, due to large differences in baseline characteristics, it is unreliable to compare studies retrospectively.

A prospective study performed in Germany that compared and combined both drugs under RCT conditions showed that both prolonged the time to first drink and the time to first relapse into heavy drinking compared to the placebo. The combination of both drugs was more effective than both placebo and monotherapy with acamprosate (Kiefer et al. 2003). Feeney's open cohort study replicated these results (Feeney and Connor 2005). A larger comparative study addressing this issue and involving 1,383 recently alcohol-abstinent patients (Anton et al. 2006) showed no treatment effects of acamprosate on abstinence proportion and no additive effect of combining naltrexone with acamprosate. Only naltrexone showed a significant but modest treatment effect on one out of two predetermined endpoints (return to heavy drinking vs. percent days abstinent). Patient characteristics suggest that patients without a physical withdrawal syndrome requiring withdrawal treatment were mainly included in the Combine study.

Since acamprosate and naltrexone have an effect on different neurotransmitters, neurobiologically-based a

priori examinations could provide indications on specific predictors concerning the response to each of these medications. A prospective study targeting biologically based endophenotyes including fMRI, PET, and psychophysiology is currently under way (Mann et al. 2009).

Biological matching of patients with their specific treatment holds the potential of moving the field of pharmacotherapy of alcoholism forward.

Cross-References

- ► Acamprosate
- ► Alcohol
- ► Disulfiram
- ► Naltrexone

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Alcohol Addiction

► Alcohol Abuse and Dependence

Alcohol Dehydrogenase

Synonyms

ADH; ALDH

Definition

Alcohol dehydrogenase is an enzyme that is responsible for catalyzing the formation of alcohols into aldehydes or ketones. There are five classes of alcohol dehydrogenases in humans, and the hepatic form, which is used primarily, is alcohol dehydrogenase class 1. Class 1 dehydrogenase catalyzes the oxidation of ethanol to produce acetaldehyde.

Cross-References

- ► Acetaldehyde

Alcohol Dependence

Synonyms

Alcoholism

Definition

Alcohol dependence is characterized as a maladaptive pattern of drinking, leading to clinically significant impairment, as manifested by a compulsion to drink, a lack of control over the amount of alcohol consumed and continued drinking, despite a knowledge of the problems associated with it. DSM-IV defines alcohol dependence as current if any three or more of the following seven criteria are present in the past 12 months:

1. Tolerance – as defined by either of the following – a need for markedly increased amounts of alcohol to achieve intoxication or desired effect, or markedly diminished effect with continued use of the same amount of alcohol.
2. Withdrawal.
3. Alcohol is often taken in larger amounts or over a longer period than was intended.
4. A persistent desire or unsuccessful efforts to cut down or control alcohol use.
5. A great deal of time is spent in activities necessary to obtain alcohol, use alcohol, or recover from its effects.
6. Important social, occupational, or recreational activities are given up or reduced because of alcohol use.

7. Alcohol use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the alcohol (e.g., continued drinking despite recognition that an ulcer was made worse by alcohol consumption).

Alcohol (Ethanol) Choice Tests

► Alcohol Preference Tests

Alcohol (Ethanol) Drinking Preference Tests

► Alcohol Preference Tests

Alcohol (Ethanol) Reinforcement Tests

► Alcohol Preference Tests

Alcohol (Ethanol) Reward Tests

► Alcohol Preference Tests

Alcohol Hallucinosis

Definition

Alcoholic hallucinosis represents a rare complication of the alcohol withdrawal syndrome. It includes mainly auditory hallucinations, often accusatory or threatening voices. Alcoholic hallucinosis develops and resolves rapidly, involves no disorientation nor physical symptoms.

Alcohol Preference Tests

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Synonyms

Alcohol (ethanol) choice tests; Alcohol (ethanol) drinking preference tests; Alcohol (ethanol) reinforcement tests; Alcohol (ethanol) reward tests

Definition

Alcohol preference tests generally include a set of experimental procedures that allow assessment of the intake of alcohol-containing solutions by laboratory animals when there is also an availability of one or more solutions at the same time that do not contain any alcohol. Alcohol preference is measured as the amounts of the alcohol solution(s) consumed, relative to those of the nonalcoholic solution(s). Although this is the most commonly used procedure for studying alcohol preference, several related behavioral procedures have also been used to draw inferences about preference for alcohol. These other procedures are briefly described in the next section.

Impact of Psychoactive Drugs

Description of Procedures

Many behavioral procedures have been used to assess the effect of psychoactive drugs on ethanol preference in nonhumans (Egli 2005). The most common approach is to assess ethanol intake relative to the intake of an alternative fluid (e.g., water) in a procedure that allows the animal to orally self-administer both fluids at the same time. For example, many studies have offered rats and mice a choice between drinking tubes containing 10% ethanol versus water in the home cage. Other studies have used operant self-administration procedures that require the animal to make a specific response to obtain each fluid, e.g., press lever A to obtain ethanol or press lever B to obtain water (Gonzales et al. 2004; Samson and Czachowski 2003). Regardless of the procedure used, the most informative data on treatment drug effects come from studies in which the pattern of self-administration is monitored continuously over time, or from studies in which the treatment drug is assessed during short sessions (e.g., 30–60 min) that normally yield high ethanol intakes (or high blood alcohol concentrations) in vehicle-treated control animals.

As the most commonly studied species (rats, mice) do not voluntarily consume sufficient alcohol to become dependent, most studies of psychoactive drugs have been conducted in nondependent animals. However, several recent studies have examined treatment drug effects on ethanol self-administration in animals that have been made dependent by chronic ethanol exposure (e.g., intragastric infusion or gavage, liquid diet or vapor inhalation

chamber). Importantly, these studies have shown that sensitivity to the effects of some psychoactive drugs is altered by a history of chronic ethanol exposure and dependence. Several examples of such findings are noted in later sections.

The development of stable ethanol self-administration in animals generally requires a prolonged period of training that may last several days, weeks, or months. In operant procedures, this training phase might also require a special "initiation" procedure (e.g., gradual reduction in the concentration of an added sweetener as ethanol concentration is increased). Thus, most studies of psychoactive drugs have examined treatment effects on a well-established baseline of ethanol self-administration. Over the last 10–15 years, however, there has been increasing interest in procedures that mimic relapse to ethanol self-administration after a period of abstinence (e.g., Alcohol Deprivation Effect, ADE), as well as procedures that produce reinstatement of responding after extinction of operant self-administration of ethanol (e.g., exposure to priming doses of ethanol, ethanol-associated cues or stressors). The primary purpose of such studies has often been to study the effects of treatment drugs on ethanol-seeking responses (i.e., responses that were previously paired with ethanol reinforcement), rather than direct effects on ethanol self-administration. Of interest, these studies have sometimes shown divergence in the effects of treatment drugs on ethanol seeking and ethanol self-administration.

The conditioned place preference (CPP) procedure offers another approach to evaluate treatment drug effects. In this procedure, the effect of a treatment drug on ethanol reward can be measured indirectly by drug-free testing of the animal's preference for contextual stimuli that have been previously associated with ethanol given alone (vehicle control group) or in combination with the treatment drug (experimental group). CPP can also be used to test the effect of a treatment drug on ethanol's conditioned rewarding effect by giving the drug just before a post-conditioning preference test in the absence of ethanol. Performance during a CPP test can be viewed as a form of ethanol seeking that is conceptually analogous to responding during the extinction or reinstatement of operant self-administration. One limitation on the use of CPP for studying treatment drug effects on ethanol reward is that although the phenomenon is robustly observed in mice, it has been much more difficult to demonstrate reliably across laboratories in rats.

Psychoactive Drug Testing

Ethanol is known to interact directly or indirectly with a wide range of neurochemical systems in brain (Koob and LeMoal 2006; Vengeliene et al. 2008). Effects of manipulating most of those systems have been studied using one or more types of alcohol preference test. Primary emphasis has been on systems implicated in ethanol's rewarding or conditioned rewarding effects and on systems thought to underlie the negative motivational effects of withdrawal (Koob and LeMoal 2008). Because space limitations preclude a detailed review of this literature, this essay focuses on psychoactive drugs currently approved by the U.S. Food and Drug Administration (FDA) for the treatment of alcohol dependence, as well as several drugs that have been evaluated for their therapeutic potential or that are considered to be promising candidates (Heilig and Egli 2006; Tambour and Quertemont 2007; Vengeliene et al. 2008).

FDA-approved drugs: Currently, only four treatment drugs are approved for the treatment of alcoholism: oral or extended-release ► naltrexone, ► acamprosate, and ► disulfiram (Swift 2007). Disulfiram (Antabuse), which produces an aversive reaction when alcohol is ingested due to interference with ethanol metabolism, has rarely been studied in alcohol preference models and there is a mixed evidence for its efficacy in clinical trials (Heilig and Egli 2006; Swift 2007). In contrast, the more recently approved drugs (naltrexone, acamprosate), which yield more consistently positive results in clinical trials (Swift 2007), have also been effective in reducing ethanol intake and reinstatement in animals (Egli 2005; Vengeliene et al. 2008). In fact, the original naltrexone clinical trials were encouraged by animal studies that had shown a reduction in alcohol intake after injection of non-selective opioid antagonists. The mechanisms underlying the efficacy of naltrexone and acamprosate are not fully understood. Naltrexone is thought to modulate mesolimbic dopamine neurotransmission that may be involved in the direct and conditioned rewarding effects of ethanol, whereas acamprosate is hypothesized to act through its effects on ► glutamate neurotransmission (Tambour and Quertemont 2007).

Dopaminergic drugs: The mesolimbic dopamine system has long been implicated in the reinforcing and rewarding effects of most abused drugs, including ethanol. Animal studies have shown that both dopamine agonists and dopamine antagonists inhibit oral ethanol self-administration, a pattern of findings that has been difficult to reconcile (Gonzales et al. 2004). Some studies have suggested that dopamine antagonists have a greater impact on ethanol-seeking responses than on ethanol intake (Samson and Czachowski 2003). However, clinical studies with dopaminergic drugs have yielded mixed results, discouraging their use for alcoholism treatment in humans (Tambour and Quertemont 2007).

GABAergic drugs: Many of ethanol's physiological and behavioral effects have been linked to its interaction with the gamma-aminobutyric acid (► GABA) receptor system. Alcohol preference studies in animals have focused on drugs that target the ► $GABA_A$ receptor. These studies have generally shown an inhibitory effect of $GABA_A$ antagonists and benzodiazepine receptor ► inverse agonists and antagonists on ethanol self-administration. In contrast, results with $GABA_A$ agonists have been mixed, with reports of both increases and decreases in self-administration (Chester and Cunningham 2002). A few recent studies have indicated that the $GABA_B$ receptor agonist baclofen reduces ethanol self-administration, relapse after deprivation (ADE) and responding during extinction of self-administration (Heilig and Egli 2006), effects that may be mediated by suppression of mesolimbic dopamine signaling (Tambour and Quertemont 2007). Preliminary clinical studies have suggested that baclofen might also be effective in the treatment of alcoholism (Heilig and Egli 2006; Tambour and Quertemont 2007).

Recent clinical trials have also suggested that the antiepileptic ► topiramate has efficacy in the treatment of alcohol dependence (Heilig and Egli 2006; Tambour and Quertemont 2007). While topiramate is thought to alter GABA signaling, effects on glutamategic transmission and voltage dependent sodium channels have also been proposed. Topiramate's clinical efficacy has been attributed to putative indirect effects that alter mesolimbic dopamine transmission (Tambour and Quertemont 2007). The preclinical literature using alcohol preference tests is quite limited and it does not provide strong support for an inhibitory effect of topiramate on ethanol drinking (Heilig and Egli 2006).

Serotonergic drugs: Preclinical studies have shown that ► selective serotonin reuptake inhibitors (SSRIs) as well as agonists and antagonists at various ► serotonin receptors ($5\text{-}HT_1$, $5\text{-}HT_2$, $5\text{-}HT_3$) can reduce alcohol consumption (Vengeliene et al. 2008), although some of these findings may reflect non-specific effects on consummatory behaviors (Heilig and Egli 2006; Tambour and Quertemont 2007). Despite their efficacy in ethanol self-administration studies in animals, SSRIs and the partial $5\text{-}HT_{1A}$ agonist ► buspirone have not been effective in clinical trials (Egli 2005; Tambour and Quertemont 2007). However, the $5\text{-}HT_3$-receptor antagonist ondansetron appears to have relatively selective effects on ethanol self-administration in animals, an effect that some investigators attribute to a reduction in ethanol-induced dopamine release (Tambour and Quertemont 2007). Moreover, human trials have shown promising results for ondansetron in the treatment of early onset alcoholism (Heilig and Egli 2006; Tambour and Quertemont 2007).

Glutamatergic drugs: The observation that ethanol dose-dependently inhibits NMDA receptor activation has encouraged examination of glutamatergic drug effects on ethanol self-administration. However, animal studies have found few consistent effects of ► NMDA receptor antagonists on ethanol self-administration (Vengeliene et al. 2008). Thus far, the most promising preclinical studies have suggested that selective antagonists targeting the metabotropic mGluR5 glutamate receptor (e.g., 2-methyl-6-(phenylethynyl)-pyridine, MPEP) can reduce high levels of ethanol self-administration in selectively-bred alcohol preferring rats (Heilig and Egli 2006). MPEP also reduces cue-induced reinstatement of operant self-administration after extinction as well as relapse to self-administration after a period of abstinence (ADE) (Vengeliene et al. 2008). Although there have been no clinical trials with mGluR5 receptor antagonists, the preclinical and clinical efficacy of acamprosate might be related, at least in part, to antagonism of this receptor subtype (Tambour and Quertemont 2007).

Cannabinoid drugs: A potential role for the endocannabinoid system has been supported by studies showing that pharmacological blockade of the CB_1 receptor subtype reduces ethanol intake and cue-induced reinstatement of an extinguished operant self-administration response in animals (Tambour and Quertemont 2007; Vengeliene et al. 2008). The CB_1 receptor antagonist ► rimonabant is currently under investigation in a human study that is designed to test its effects on ethanol consumption in heavy drinkers (Heilig and Egli 2006).

Neuropeptides: Animal studies have suggested that ► neuropeptides implicated in stress and anxiety influence ethanol self-administration, especially those targeting the corticotropin-releasing factor (CRF) and neuropeptide-Y (NPY) systems. For example, non-selective CRF antagonists and selective CRF1 antagonists have been found to reduce ethanol self-administration, but only in alcohol-dependent animals (Heilig and Egli 2006; Vengeliene et al. 2008). CRF1 receptor antagonists have also been shown to interfere with cue- and stress-induced ► reinstatement of operant responding after extinction of ethanol self-administration (Vengeliene et al. 2008). NPY decreases ethanol self-administration in high-drinking animals, an effect that was enhanced by a period of alcohol deprivation. Blockade of NPY Y1, Y2 and Y5 receptors has also been reported to suppress ethanol drinking or operant responding for ethanol in non-dependent animals, though the effect of Y2 blockade is greater in ethanol dependent animals (Heilig and Egli 2006). Clinical

trials targeting the role of the CRF or NPY systems in alcohol dependence have not yet been reported.

Other Uses of Alcohol Preference Tests

Although this essay has focused on the use of alcohol preference tests to study effects of psychoactive drugs, it is important to note that these tests are widely used by basic scientists for many other purposes. For example, these procedures are used to study the basic behavioral processes involved in the learning, extinction, and recovery (e.g., reinstatement) of ethanol-related memories. These procedures are also commonly used to characterize the neurochemical systems, brain circuitry, and genes that underlie ethanol self-administration and excessive drinking. Finally, these procedures have been used to study the impact of addiction-related neuroadaptations on ethanol-reinforced behavior (e.g., tolerance, dependence, and withdrawal).

Cross-References

- ► Abuse Liability Evaluation
- ► Acamprosate
- ► Addictive Disorder: Animal Models
- ► Alcohol
- ► Alcohol Abuse and Dependence
- ► Conditioned Place Preference and Aversion
- ► Disulfiram
- ► Naltrexone
- ► Reinstatement of Drug Self-Administration
- ► Self-Administration of Drugs

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Alcohol Use Disorder

► Alcohol Abuse and Dependence

Alcohol Withdrawal

Definition

Alcohol withdrawal can occur after stopping alcohol use or following a reduction in use in individuals with a history of chronic use. Symptoms of alcohol withdrawal can include: autonomic hyperactivity, hand tremor, insomnia, nausea or vomiting, hallucinations, psychomotor agitation, anxiety, and seizures.

Alcohol Withdrawal Delirium

Definition

Alcohol withdrawal delirium, also known as delirium tremens, is the type of delirium that occurs during withdrawal from alcohol. It is commonly associated with tactile or visual hallucinations in addition to autonomic hyperactivity, disorientation, and agitation. It occurs in approximately 5–15% of patients in alcohol withdrawal typically within the first 72–96 h of withdrawal. Severe alcohol withdrawal delirium is a medical emergency and requires prompt treatment.

Alcohol Withdrawal-Related Anxiety

Synonyms

Alcohol withdrawal symptoms

Definition

Anxiety is an early withdrawal symptom that develops after cessation of ethanol drinking in alcoholics. Alcohol produces antianxiety effects and may be one of the factors responsible for the comorbidity of alcoholism and anxiety.

Cross-References

- ► Alcohol
- ► Alcohol Abuse and Dependence
- ► Generalized Anxiety Disorder

Alcohol Withdrawal Symptoms

► Alcohol Withdrawal-Related Anxiety

Alcohol Withdrawal Syndrome

Definition

A constellation of signs and symptoms that appears when a physically alcohol-dependent person stops drinking alcohol. The physiological basis is the alcohol tolerance: chronic alcohol intake causes reversible adaptations within the body that tend to compensate for the original alcohol effects over time. When alcohol intake is suddenly stopped or decreased, the adaptations do not immediately disappear. Unopposed by alcohol, the adaptations appear as withdrawal signs and symptoms that include tension, anxiety, sleep disturbance, increased blood-pressure and heart rate, tremor, sometimes seizures.

Alcoholism

► Alcohol Abuse and Dependence
► Alcohol Dependence

Alcohol-Related Neurodevelopmental Disorder

Synonyms

ARND

Definition

A developmental neuropsychiatric disorder with no characteristic facial dysmorphology resulting from prenatal exposure to alcohol.

Cross-References

► Foetal Alcohol Spectrum Disorders

ALDH

► Alcohol Dehydrogenase

Alexithymia

Definition

Difficulty in understanding other people's emotions and expressing one's own emotions.

Allocentric

Synonyms

Exocentric; Geocentric

Definition

Etymologically, allocentric means centred on another. In terms of spatial memory, allocentric is used to describe a frame of reference based on the spatial relations between objects in space.

Allodynia

Definition

Allodynia is a condition in which pain is produced by a stimulus that is not normally painful.

Cross-References

► Analgesics

Allosteric Modulators

Definition

In contrast to orthosteric molecules, which bind to the same receptor domain as the endogenous agonist, allosteric modulators bind to a site that is topographically different from the orthosteric binding site. Allosteric modulators produce an effect through a change in protein confirmation and can increase (positive allosteric modulator or PAM) or decrease (negative allosteric modulator or NAM) the affinity and/or efficacy of an orthosteric agonist.

Cross-References

► Agonist
► Antagonist
► Inverse Agonists
► Receptor Binding

Allosteric Potentiating Ligand

Definition

Allosteric antagonists or agonists produce unique effects by binding to a site on the receptor to produce a bias in

the receptor conformation. Allosteric modulators of nicotinergic receptors are compounds that interact with the receptor via binding sites that are distinct from those for acetylcholine and ► nicotinic agonists and antagonists. Consequently, modulators are not directly involved in the neurotransmission process they affect and hence usually do not induce compensatory processes, as direct agonists and antagonists may do (e.g., receptor ► desensitization, ► downregulation of expression).

Allosteric Site

Definition

A regulatory site of a receptor that is different from the orthosteric site in which the endogenous ligand binds to. Binding to the allosteric site can enhance or inhibit activity of the endogenous ligand to the orthosteric stie.

Allotropy

► Genetic Polymorphism

Allowable

► Legal Aspects of Psychopharmacology

(*RS*)-1-[2-(Allyloxy)Phenoxy]-3-(Isopropylamino)Propan-2-ol

► Oxprenolol

Alogia

Definition

Poverty of speech, as in schizophrenia.

S-Alpha-Hydrazino-3,4-Dihydroxy-α-Methyl-Bensemonopropanoic Acid Monohydrate

► Carbidopa

Alpha Waves

► Function of Slow and Fast Alpha

Alprazolam

Definition

Alprazolam is a high-potency, short-acting anxiolytic benzodiazepine medication used in the treatment of anxiety, panic, and phobic disorders. It has some antispasmodic and anticonvulsant effects. It is not antidepressant. It is sometimes used in conjunction with antipsychotic medication in acute psychotic episodes. Unwanted effects include sedation, headaches, paradoxical excitement, confusion, cognitive and psychomotor impairment, and confusion in the elderly. Long-term use may induce dependence with withdrawal reactions. Recreational use and abuse can occur: alprazolam is a scheduled substance.

Cross-References

► Benzodiazepines
► Minor Tranquilizers

Alternative Splicing

Synonyms

mRNA splice variants

Definition

Antisense technology has also been used to manipulate alternative splicing patterns altering the ratio of different splice variants of a gene and its function. Several diseases are linked to mutated alternative splicing of specific genes such as thalassemia, Duchenne muscular dystrophy, cystic fibrosis, and parkinsonism linked to chromosome 17. The therapeutic potential of this antisense approach, for example, to silence gene mutations responsible for defect pre-mRNA splicing is enormous.

► Antisense oligonucleotides that alter splicing should be different from those designed to downregulate gene expression and should be chemically modified such as to prevent activation of RNase H as this would destroy pre-mRNA before splicing, to have a higher nuclease resistance and affinity for the target sequence. According to ex vivo intracellular localization studies, the antisense oligonucleotides need to enter the nucleus for successful modulation of splicing. Aberrant splicing of pre-mRNA is

prevented or correct splicing is restored. In vivo confirmation of these mechanisms of action is missing.

Cross-References
► Antisense Oligonucleotides

Altricial

Definition
Offspring of certain mammalian species that are born at relatively immature stages, for example, with their eyes and ears closed, and without fur or the ability to thermoregulate.

Alzheimer's Disease

Definition
A type of dementia, neurodegenerative disease, that leads to progressive destruction of brain cells. The disease leads to severe memory loss, confusion, and often apathy. There is a progressive brain atrophy with multiple neurotransmitter changes. The degeneration of cholinergic neurons in the brain is one neurochemical loss that is commonly observed postmortem. In addition, the brains of Alzheimer's disease patients are marked by plaques (β-amyloid) and neurofibrillary tangles.

Cross-References
► Dementia

Amantadine

Synonyms
Tricyclo[3.3.1.1^{2,7}]decan-1-amine or 1-adamantanamine

Definition
Amantadine probably acts both as an anticholinergic and glutamate antagonist, releasing dopamine in the striatum/substantia nigra and possibly other central sites. Registered initially as an anti-influenza drug, amantadine is used alone or in combination with L-DOPA in idiopathic Parkinson's disease, other forms of Parkinsonism, related motor fluctuations, drug-induced extrapyramidal syndromes, and dyskinesias.

Cross-References
► Anti-Parkinson Drugs

Amenorrhea

Definition
Absence of at least three consecutive menstrual cycles in a woman of reproductive age.

Amentia

► Autism Spectrum Disorders and Mental Retardation

Amidation

Definition
The posttranslational modification at the C-terminal carboxylate group that substitutes a hydroxyl group with an amide. Since the C-terminal is responsible for a negative charge at neutral and basic pH, amidation neutralizes any negative charge by replacing the hydroxyl group.

Cross-References
► Gene Expression and Transcription

Amine Depletors

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Synonyms
Catecholamine depletion; Monoamine depletion; Tryptophan depletion

Definition
Amine depletion refers to a pharmacological or dietary manipulation that lowers levels of monoamine neurotransmitters in the brain for therapeutic or investigational purposes. An amine depletor is therefore an agent that diminishes levels of one or more monoamines in the brain.

Pharmacological Properties

Available Methodologies
The monoamines targeted by amine depletion are typically the catecholamine neurotransmitters, dopamine and

noradrenaline, and the indoleamine neurotransmitter, serotonin. Amine depletion in humans can be carried out in three principal ways:

1. Through pharmacological inhibition of vesicular storage of amines in the nerve terminal
2. Through pharmacological inhibition of neurotransmitter synthesis
3. Through dietary-induced brain depletion of amino acids required for neurotransmitter synthesis

Monoamine depletion may also occur as an adverse consequence of drug use, both licit and illicit; for example the substituted amphetamine, methylenedioxymethamphetamine (► MDMA), lowers brain serotonin levels. However, amine depletion occurring as an adverse effect will not be considered further in this article.

Inhibition of Vesicular Storage

A number of drugs including ► reserpine, ► tetrabenazine, and oxypertine bind to the vesicular monoamine transporter and thereby inhibit transport of synthesized monoamine from the cytoplasm to the vesicular storage granule. The monoamines in the cytoplasm are therefore exposed to metabolism by monoamine oxidase and monoamine levels at nerve terminals decline, lowering neurotransmission.

Reserpine has a long history in psychopharmacology and reserpine-induced depression formed the cornerstone of the monoamine theory of depression. Tetrabenazine and oxypertine have been used to treat ► tardive dyskinesia, presumably through their ability to deplete presynaptic ► dopamine levels. Tetrabenazine is still used for the treatment of abnormal movements, particularly those associated with Huntington's Chorea.

Pharmacological Inhibition of Neurotransmitter Synthesis

Under this heading, we can consider two pharmacological agents, para-chlorophenylanine (PCPA) and alpha-methyl-para-tyrosine (AMPT). PCPA irreversibly inhibits the enzyme tryptophan hydroxylase, which converts the amino acid ► tryptophan to 5-hydroxytryptophan and is the rate-limiting step in the synthesis of ► serotonin. PCPA administration therefore leads to depletion of brain serotonin. PCPA was previously used to treat carcinoid syndrome and has been employed in a limited way as an investigational tool in human psychopharmacology. For example, PCPA treatment of depressed patients who had responded to the monoamine oxidase inhibitor tranylcypromine resulted in clinical relapse showing the importance of intact serotonin function for the therapeutic action of this antidepressant. PCPA is still used extensively in animal experimental investigations as a pharmacological means of lesioning brain serotonin pathways.

AMPT is a competitive antagonist of the enzyme tyrosine hydroxylase, which converts the amino acid tyrosine to L-dopa. Administration of AMPT therefore decreases brain levels of ► noradrenaline and ► dopamine. In healthy volunteers, AMPT treatment results in sedation and can sometimes cause movement disorders such as Parkinsonism. Plasma prolactin is elevated and nocturnal melatonin secretion reduced, consistent with the known roles of dopamine and noradrenaline in the regulation of these two hormones. AMPT has been used clinically as an antihypertensive agent and in the treatment of pheochromocytoma.

AMPT has also been employed as an investigational tool in studies of the role of catecholamine pathways in depression and the mode of action of ► antidepressants. In healthy volunteers, AMPT does not reliably cause depression but in recovered depressed patients who have been withdrawn from antidepressant medication, AMPT causes a temporary clinical relapse. This suggests that in people vulnerable to depression, lowering catecholamine function is sufficient to produce clinical symptomatology. AMPT also reverses the therapeutic effect of antidepressant drugs such as desipramine which act primarily through noradrenergic mechanisms. This has been taken as evidence that intact noradrenaline neurotransmission is essential for the continued action of catecholamine-potentiating antidepressants in patients who have responded to this form of treatment (Booij et al. 2003; Ruhé et al. 2007).

Dietary-induced Brain Depletion of Amino Acids

As has been mentioned earlier, the synthesis of monoamine neurotransmitters depends on the availability of precursor amino acids to the brain. Dietary manipulations can take advantage of this fact to limit the availability of specific amino acids and thereby lower the synthesis in the brain of the corresponding neurotransmitter. The most studied manipulation is "tryptophan depletion" (TRD). In this procedure, participants are asked to ingest a balanced mixture of amino acids (traditionally about 80–100 g) from which tryptophan has been removed. This amino acid load drives protein synthesis in the liver and because tryptophan is an essential amino acid, the body has to use its own tryptophan supplies to manufacture protein. This leads to a sharp decline in plasma

tryptophan levels, which decreases the amount available for brain serotonin synthesis. In addition, amino acids compete with each other for active transport across the blood–brain barrier. The excess of other amino acids in plasma means that the small amount of tryptophan which remains available in plasma after TRD is inhibited by competition from transport into the brain. Thus, lowering levels of plasma tryptophan and decreasing its brain entry produces a substantial depletion of brain tryptophan and of serotonin synthesis. Because of the effects of the amino acid mixture on protein synthesis as well as subjective adverse effects (principally nausea), in investigational studies it is important to use a control mixture of amino acids containing a balanced amount of tryptophan.

Because of the interest in the role of serotonin pathways in psychiatric disorder and the effects of psychotropic drugs, TRD has been widely used as an investigational tool. The greatest volume of research has taken place in the field of mood disorders (Bell et al. 2005a,b). It seems fairly well established that TRD in healthy individuals with no risk factors for depression does not cause reliable effects on mood. Therefore, lowering serotonin function is not sufficient to cause depression in nonvulnerable individuals. However, TRD can cause acute depressive clinical symptomatology in some circumstances. For example, depressed patients who have responded successfully to serotonin-potentiating drugs such as ▶ selective serotonin reuptake inhibitors (SSRIs) may show a transient but striking relapse a few hours after TRD even though SSRI treatment is continued. This has been taken as evidence that the maintenance of the therapeutic response to SSRI treatment requires a sustained increase in the availability of serotonin. Interestingly, depressed patients successfully maintained on catecholamine-potentiating drugs such as desipramine do not relapse when administered TRD. This suggests that antidepressant drugs can produce therapeutic effects in depressed patients through distinct pharmacological mechanisms (Booij et al. 2003; Ruhé et al. 2007).

It is also noteworthy that patients with a history of depression, not currently on medication, can show transient clinical relapse following TRD (Smith et al. 1997). A mega-analysis revealed that female patients with a history of recurrent depression and suicide attempts were most likely to show this reaction (Booij et al. 2002). This finding suggests that in some vulnerable individuals, lowering serotonin function can be sufficient to cause clinical symptomatology. Theoretically, such individuals may have pre-existing deficits in serotonin pathways or perhaps abnormalities in the brain regions involved in mood regulation which are "revealed" in the low serotonin environment.

TRD is not particularly well tolerated since the amino acids load can cause nausea and retching. Attempts have therefore been made to use better-tolerated low-dose procedures with decreased total dose of amino acids (20–30 g). These mixtures reliably lower plasma tryptophan but their effect on mood is somewhat variable even in vulnerable individuals. However, changes in emotional processing that are congruent with depressed mood have been revealed (Hayward et al. 2005).

The success of TRD also led to dietary attempts to lower catecholamine neurotransmission by depleting plasma and brain tyrosine levels. In the body, tyrosine can be synthesized from phenylalanine, so dietary manipulations provide a mixture of amino acids lacking both phenylalanine and tyrosine. Ingestion of such a mixture produces a substantial lowering of plasma tyrosine. It also increases plasma prolactin indicative of a diminution in dopamine neurotransmission; however, nocturnal ▶ melatonin secretion is unaffected suggesting that noradrenaline function is not attenuated. This pattern of effect is consistent with experimental animal studies indicating that tyrosine depletion preferentially limits dopamine function, while apparently sparing noradrenaline neurotransmission. The reason for this is not clear but presumably relates to a greater dependency of dopamine neurons on tyrosine availability, perhaps because they have generally faster firing rate than noradrenaline neurons.

Tyrosine depletion has been less studied in experimental paradigms than TRD. Tyrosine depletion does not lower mood in healthy subjects and, in contrast to AMPT, fails to cause relapse in unmedicated recovered depressed patients. This suggests that the relapse seen in such subjects following AMPT is probably due to interruption of noradrenaline function or perhaps to a simultaneous decrease in noradrenaline and dopamine activity. Consistent with its ability to lower dopamine function, tyrosine depletion has been shown to attenuate the psychostimulant effects of ▶ methamphetamine in healthy volunteers and to diminish clinical ratings of mania in patients with ▶ bipolar disorder (McTavish et al. 2001). Tyrosine depletion does not attenuate the antidepressant effects of SSRIs arguing against theories that posit a key role for dopamine facilitation in antidepressant action.

Cross-References

▶ Acute Phenylalanine/Tyrosine Depletion
▶ Acute Tryptophan Depletion

► Aminergic Hypotheses for Depression
► Tryptophan

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Aminergic Hypotheses for Depression

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Synonyms

Catecholamine hypothesis; Indoleamine hypothesis; Monoamine hypotheses

Definition

The aminergic hypotheses of ► depression refer to theories of the role of abnormalities of aminergic neurotransmitters, or of physiologic perturbations in the functioning of neurons that contain aminergic neurotransmitters, in the cause and/or symptoms of a major depressive disorder.

Role of Pharmacotherapy

The aminergic hypotheses of ► depression were logical extensions of four landmark discoveries: that neurons communicate via the release of chemical substances called neurotransmitters; that aminergic neurotransmitters are found in high concentration in specific brain regions; that antidepressant drugs increase brain levels of aminergic neurotransmitters; and that drugs or procedures that reduce monoamine neurotransmitters induce depressive symptoms in some people. These discoveries provided the necessary scientific knowledge on which the aminergic hypotheses were based.

The theory that communication between neurons is mediated by chemical substances (neurotransmitters) rather than electrical impulses did not gain widespread acceptance until the mid-1900s. Prior to 1900, it was generally thought that neurons communicated with one another by electrical signals. The chemical theory of neurotransmission was initially based on the observation by J. N. Langley in 1901 that extracts from the adrenal gland had similar effects on end-organ targets as did stimulation of sympathetic nerves. He proposed that there could be "receptive substances" between a nerve cell ending and the target end organ that is activated when the nerve impulse reaches the nerve terminal. Elliot subsequently hypothesized in 1904 that an adrenalin-like substance might be secreted by sympathetic nerve terminals to chemically stimulate the target end organ. Many still doubted that this was relevant to communication between nerve cells, but the theory of chemical neurotransmission gained significant ground in 1921 when Otto Loewi conducted his now classic experiment showing that the liquid surrounding a heart that had had its nerves electrically stimulated to slow its rate could be transferred to a second un-stimulated heart to cause an identical slowing of the second heart's rate. Loewi proposed that the electrical stimulation of the nerves innervating the heart caused the release of a chemical substance that mediated the nerve's ability to reduce heart rate. In 1936, Loewi shared the Nobel Prize in medicine with Sir Henry Dale for their work on the discovery of chemical neurotransmission (see Tansey 1991 for a review). Subsequent research showed that other monoamine chemicals, such as ► dopamine (DA) and ► serotonin (5-HT), also served as neurotransmitters in the peripheral nervous system.

By the late 1950s, research had shown that the brain contained large amounts of several ► monoamines, including the ► catecholamine neurotransmitters ► norepinephrine (NE) and DA and the ► indoleamine 5-HT. These monoamines were localized to, and synthesized by, neurons within discrete brain nuclei. Two landmark observations,(1) that patients with Parkinson's disease showed a marked reduction in basal ganglia DA and (2) that oral administration of the metabolic precursor of DA, L-dihydroxy-phenylalanine (► L-DOPA), led to rapid improvements in the motor symptoms of

► Parkinson's disease Birkmayer and Hornykiewicz (1964), added considerable momentum to the investigation of the role of brain monoamines in behavior, and established a compelling theoretical model that greatly influenced the first aminergic hypotheses of depression (see Carlsson, 2001 for a review of the work of this time period).

The late 1950s and early 1960s saw the rapid clinical development of several drugs with potent effects on increasing or decreasing brain monoamines. This included drugs that were subsequently found to block reuptake, synthesis, metabolism, or receptors of one or more monoamines, as well as drugs and/or nutrients that served as synthetic precursors to monoamines. The drug ► reserpine (rauwolfia) had been shown in the 1950s to cause a long-lasting depletion of brain monoamines in laboratory animals, and this was associated with a profound depression-like state in laboratory animals and clinical depression in up to 18% of people receiving the drug for the treatment of hypertension. The catecholamine synthesis inhibitor alpha-methyl-para-tyrosine (AMPT) was also tested as a potential antihypertensive and a similar subset of patients developed clinical depression during the initial trials. Because reserpine caused profound sedation in humans, it was also used extensively as a sedative in agitated psychiatric patients, often in combination with other sedatives or the newly discovered antipsychotic drugs. Many other new drugs with central nervous system effects were introduced into clinical trials during the mid-late 1950s. ► Imipramine, a tricyclic compound, was being studied as a potential sedative, while isoniazid, a ► monoamine oxidase inhibitor (MAOI), was being used to potentiate antituberculosis treatments. Both drugs were noted by chance observation to cause resolution of depressive symptoms, stimulating an explosion of controlled clinical trials of these agents as potential treatments for depression. As evidence of the therapeutic effects in the depression of imipramine and its metabolites (such as desipramine) and MAOIs (such as iproniazid and tranylcypromine) accumulated, it became clear that understanding the pharmacology of these drugs might be relevant to the neurobiological underpinnings of major depression. Given that MAOIs were well known to increase brain levels of monoamines, this pharmacological property was suggested to underlie the therapeutic effects of such drugs in depression by the late 1950s (Carlsson 2001; Pare 1959).

The first fully developed aminergic hypotheses of depression finally emerged in the mid-1960s as investigators began to realize that these new antidepressant drugs potently increased brain levels of monoamines, while drugs that reduced monoamines could cause depression-like symptoms in some people. The catecholamine deficiency hypothesis of depression was based on the observation that many antidepressant drugs increased synaptic concentrations of NE, while the catecholamine-depleting drug reserpine seemed to cause depression-like symptoms (Schildkraut 1965). This hypothesis postulated that depression was due to a deficiency and mania, an excess of brain NE. The indoleamine hypothesis postulated that a deficit of brain 5-HT was responsible for depression, while drugs which increased synaptic 5-HT, such as MAOIs or 5-HT precursors such as 5-hydroxytryptophan (5-HTP) and ► L-tryptophan (TRP), relieved depression (Coppen 1967). These competing aminergic hypotheses led to an extensive body of research in the next few decades aiming to determine which of these two monoamine systems was most responsible for depression and the therapeutic effects of antidepressant drugs.

During the 1970s and 1980s, converging data made it seem as though mood disorders would turn out to be simple "chemical imbalances" of aminergic neurotransmitters. First, as the anatomy and physiology of monoamine systems began to emerge, it became clear that these systems play an important role in regulating the brain areas that are involved in core symptoms of depression, including mood, attention, sleep, sexual function, appetite, and pain perception. Monoamine systems are almost exclusively organized as large *systems* of single source divergent neurons, thereby able to simultaneously coordinate neural activity across many parts of the brain. Second, based on the theory that the antidepressants work by increasing NE and/or 5-HT, several new antidepressants that selectively inhibited the reuptake of one or two monoamines were developed. The ► selective serotonin reuptake inhibitors (SSRIs; e.g., ► fluoxetine), norepinephrine reuptake inhibitors (NARIs; e.g., ► reboxetine), and serotonin and norepinephrine reuptake inhibitors (SNRIs; e.g., ► venlafaxine) proved to be landmark drugs with comparable efficacy but greater tolerability and safety than the earlier line of drugs such as imipramine. Finally, human studies employing monoamine depletion showed that the depletion of catecholamines or 5-HT could induce a rapid return of depressive symptoms in some patients taking antidepressants. Depletion studies suggest that the 5-HT and NE effects of antidepressants may be independent of each other. For example, depleting 5-HT causes a rapid return of depression in depressed patients who have responded to fluoxetine, ► fluvoxamine, MAOIs, and imipramine, but not in those who have responded to desipramine, ► nortriptyline, or ► bupropion. Depleting NE and DA causes a rapid return of depression in those depressed patients who have

improved on desipramine, but not on fluoxetine. These results confirm that monoamines are necessary for maintaining antidepressant therapeutic response in most patients. This convergence of data on the anatomy and physiology of monoamine systems in the brain, pharmacological effects of antidepressants, and the depression-inducing effects of lowering monoamines generated considerable optimism in the field that the pathophysiology of these disorders was now close to being understood (Delgado et al. 1999; Delgado 2004).

However, there are inconsistencies and gaps in the aminergic theories. First, while antidepressants increase brain monoamine levels severalfold within minutes of their administration, the antidepressant response takes weeks to emerge. Attempts to speed up antidepressant responses by more rapidly increasing monoamine levels or using postsynaptic monoamine receptor agonists have largely failed. Further, deficiencies of NE or 5-HT or their metabolites in cerebrospinal fluid (CSF), blood, or urine have not been consistently demonstrated in depressed patients, despite extensive efforts to do so (Charney et al. 1981). When abnormalities have been found, they have tended to be nonspecific. Also, while a small subset of people with a history of prior psychiatric illness report depressive symptoms when exposed to monoamine depleting drugs or monoamine synthesis inhibitors, the majority of people exposed to these drugs or procedures do not experience clinical depression. For example, in an open treatment trial of AMPT in patients with essential hypertension, six of 20 hypertensive patients had a history of a previous depressive episode. Three of these six became agitated on AMPT, requiring drug discontinuation. In a trial of the 5-HT synthesis inhibitor para-chloro-phenylalanine (PCPA) in patients with carcinoid tumors, a subset of the patients experienced a variety of acute symptoms ranging from lethargy, irritability, anxiety, and depression to psychosis, although most subjects demonstrated little behavioral change. Neither 5-HT nor NE depletion has resulted in depressive symptoms in studies of volunteers without a personal or family history of depression (Delgado 2004).

Recent attempts to understand the slow onset of antidepressant action have focused on the "downstream" adaptive changes that temporally follow increases in synaptic levels of monoamines. This includes research on receptor adaptations, changes in second-messenger molecules, changes in ► gene expression, release of ► neurotrophic factors, and ► neurogenesis. This work has led some investigators to focus on the integrity and functioning of limbic brain areas modulated by monoamine systems as an alternative explanation for the pathophysiology of depression. Brain imaging and autopsy studies have noted marked differences in the structure and/or function of several limbic areas such as the ► prefrontal cortex, anterior cingulate gyrus, ► hippocampus, and ► amygdala that are believed to be involved in core brain functions that become abnormal in depression (Duman et al. 2004).

Current research suggests that depression is what geneticists define as a "complex" disorder, where illness results from the summation of numerous genetic and environmental factors, each of which have small effects and result in illness only when their combined effects surpass a certain threshold. If true, then the biochemical and genetic causes of major depression may differ markedly from one patient to another. This may explain the sometimes inconsistent results in research studies investigating specific biochemical abnormalities associated with depression. The results of monoamine depletion studies suggest that a simple deficiency of 5-HT or NE is not likely to be the sole cause of depression. Research pursuing causal pathways that directly cause injury to brain areas such as the frontal cortex, hippocampus/amygdala, and basal ganglia known to be modulated by monoamine systems is warranted.

Therefore, the available data suggests that the initial aminergic hypotheses were partially correct. While research supporting a causal role of monoamine dysfunction as the primary cause of depression is not sufficiently supported, the data supporting a primary role for an increase in monoamines in the initial step of antidepressant drug action is quite strong. Most or all drugs currently approved by the US Food and Drug Administration (FDA) for the treatment of depression directly or indirectly increase the synaptic availability of 5-HT and/or NE. Increasing brain NE and/or 5-HT appears to be the initial pharmacological step responsible for antidepressant efficacy in depression. This most likely includes a temporal sequence with increased monoamine levels causing alterations in presynaptic autoreceptor density and sensitivity that allow further increases in synaptic levels of the monoamines, culminating in postsynaptic receptor adaptations, and changes in neuronal plasticity and neurogenesis. The postsynaptic areas affected by the increased monoamine levels notably include most of the brain areas involved in emotion regulation, cognition, and sensory and pain perception. Increased monoamines observed as a result of treatment with 5-HT and NE reuptake inhibitors may serve to partially restore neuronal function in dysfunctional limbic circuits. The acute reappearance of depressive symptoms upon monoamine depletion in depressed patients in remission but not in

healthy people may underscore the possibility that depressed patients have greater fragility than healthy controls of the limbic networks modulated by monoamines.

Cross-References

- ▶ Acute Tryptophan Depletion
- ▶ Amine Depletors
- ▶ Antidepressants
- ▶ Antidepressants: Recent Developments
- ▶ Brain-Derived Neurotrophic Factor
- ▶ Depression: Animal Models
- ▶ Emotion and Mood
- ▶ Monoamine Oxidase Inhibitors
- ▶ NARI Antidepressants
- ▶ Serotonin
- ▶ SNRI Antidepressants
- ▶ SSRIs and Related Compounds

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Aminergic Hypothesis for Schizophrenia

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Definition

An explanation for the pathophysiology of schizophrenia and mechanism of action of antipsychotic drugs with a special focus on aminergic (dopamine, serotonin, and noradrenaline) neural systems.

Role of Pharmacotherapy

Schizophrenia is characterized by a variety of symptoms, including hallucination, delusion, and psychomotor excitement. A dopamine receptor antagonist, ▶ chlorpromazine, was introduced in the treatment of this illness in 1952 and has shown its effectiveness, which has made the dopaminergic system a primary target of research on the pathogenesis of schizophrenia as well as potential mechanisms of antipsychotic action of this type of drugs. This has led to the prototype of the dopaminergic hypothesis for schizophrenia where the increase and decrease in the dopaminergic neural transmission is attributed to its symptoms and treatment effects of ▶ antipsychotic drugs, respectively. Although this hypothesis has been revisited and further developed, the dopaminergic system cannot fully account for the mechanisms underlying this illness. Recently, other neural systems such as glutamatergic and cholinergic systems have also come to the front line of this line of research.

▶ Dopamine was the first target of research on schizophrenia, and is still considered to play a primary role in the pathogenesis of this illness and mechanisms of actions of antipsychotic drugs. The hypothesis that explains the involvement of the dopaminergic system in this illness (the dopamine hypothesis) has been supported by a vast amount of both animal and human studies and further occasionally updated with the accumulation of relevant new clinical and basic data. The first version of the dopamine hypothesis focused on the dopaminergic receptors where psychosis was considered to be due to excessive transmission at dopaminergic receptors and diminished by blocking these receptors. The most widely accepted support for this hypothesis is the fact that dopamine antagonist antipsychotic drugs can relieve psychotic symptoms. The first antipsychotic drug, chlorpromazine, was introduced in the treatment of schizophrenia in 1952. As this type of medication had been found to have a dopamine receptor blocking property, the dopaminergic system came to the forefront of scientific inquiry. While blockade of dopamine receptors had already been thought to be associated with therapeutic effects of antipsychotic medications in the 1960s and 1970s, Seeman et al. first systematically demonstrated that the degree of dopamine receptor antagonism by antipsychotics was closely associated with their antipsychotic efficacy in 1976 (Seeman

et al. 1976). This relationship is still valid after ► second-generation antipsychotics have become available, although ► clozapine seems exceptional, as we discuss next. Another frequently referred support for this hypothesis is the presence of psychotic symptoms associated with the administration of amphetamine. Both animal and human studies have demonstrated the increase of endogenous dopamine levels, following ► amphetamine administration, and shown that amphetamine-induced psychotic symptoms resemble schizophrenic symptoms. Furthermore, these amphetamine-induced psychotic symptoms are reversible with the use of dopamine antagonist antipsychotic drugs. In addition, psychotic symptoms caused by amphetamine administration in drug-free schizophrenia patients were found to be associated with exaggerated stimulation of dopaminergic transmission, compared to those who did not present those symptoms following its administration (Laruelle et al. 1996) – lending further support to this model.

In 1980, Crow proposed a hypothesis where schizophrenia could be grouped into two separate conditions: the type I syndrome characterized by positive symptoms, including delusion, hallucinations, and thought disorder, and type II syndrome characterized by negative symptoms, including affective flattering and poverty of speech (Crow 1980). In this theory, the type I syndrome was considered to be associated with high dopaminergic activity and reversible with antipsychotic treatment while negative schizophrenic symptoms were thought to be caused by deficiency in the dopaminergic function and involve a component of irreversibility. This hypothesis tried to comprehensively link potential pathogenesis and symptomatology of schizophrenia to the dopaminergic system. Although this proposal has often been criticized later due to its simple dichotomization and a lack of sufficient convincing biological support, its impacts on further investigations have still been tremendous. In 1991, Davis et al. published a landmark review and proposed the co-occurrence of high and low dopamine activities in schizophrenia to the concurrent presence of positive and negative symptoms (referred to as the dopamine hypothesis, Version II) (Davis et al. 1991). Evidence, particularly from intracellular recording studies in animals and plasma homovanillic acid (HVA) measurements, suggests that antipsychotics exert their effects by reducing dopamine activity in mesolimbic dopamine neurons. Postmortem studies have shown high dopamine and HVA concentrations in various subcortical brain regions and greater dopamine receptor densities in patients with schizophrenia, compared to healthy people. On the other hand, they attributed the negative/deficit symptom complex of schizophrenia to low dopamine activity in the prefrontal cortex, which is now known as "hypofrontality." Davis et al. hypothesized that abnormally low prefrontal dopamine activity caused deficit symptoms in schizophrenia, while excessive dopamine activity in mesolimbic dopamine neurons resulted in positive symptoms.

With further accumulation of basic and clinical data on the function of the dopaminergic system, psychopathology of schizophrenia, and potential mechanisms underlying treatment effects of antipsychotics, Kapur reviewed those findings (Kapur 2003) and linked the neurobiology (brain), the phenomenological experience (mind), and pharmacological aspects of psychosis in schizophrenia into a unitary framework. A central role of dopamine is to mediate the "salience" of environmental events and internal representations. It is proposed that a dysregulated, hyperdopaminergic state at a "brain" level of description and analysis leads to an aberrant assignment of salience to the elements of one's experience at a "mind" level. This would result in delusions as a clinical manifestation as patients make a cognitive effort to make sense of these aberrantly salient experiences. On the other hand, ► hallucinations reflect a direct experience of the aberrant salience of internal representations. Antipsychotic drugs are expected to dampen the salience of these abnormal experiences and by doing so permit the resolution of symptoms, where the antipsychotics are thought not to erase the symptoms but to provide the platform for a process of psychological resolution. Therefore, if antipsychotic treatment is stopped, the dysregulated neurochemistry returns, the dormant ideas and experiences become reinvested with aberrant salience, resulting in a relapse. Although this hypothesis does not explain the mechanisms of negative symptoms of schizophrenia, current ideas regarding the neurobiology and phenomenology of psychosis and schizophrenia, the role of dopamine, and the mechanism of action of antipsychotic medication are integrated.

In its latest iteration, Howes et al. proposed the updated version of the dopamine hypothesis (Version III), where multiple factors, including stress and trauma, drug use, pregnancy and obstetric complications, and genes, interact to result in the increased presynaptic striatal dopaminergic function in schizophrenia (Howes and Kapur 2009). This striatal dopaminergic dysregulation is considered the final common pathway of the pathogenesis of this illness, in this theory. This hypothesis suggests that current treatments act downstream of the critical neurotransmitter abnormality and emphasized the need of future drug development with a focus on the upstream factors that converge on the dopaminergic funnel point.

However, pathogenesis of schizophrenia and the resolution of its symptoms with antipsychotics are not expected to be solely related to the effects in the dopaminergic system. Superior clinical effects of clozapine despite its low dopamine D_2 receptor blocking propensity are one example of the limitations of the dopamine hypothesis. There are several others: many patients do not respond despite adequate dopamine blockade, some respond with rather low D_2 blockade, and many relapse despite adequate D_2 blockade. So, clearly the genesis of psychosis and its response depends on more than just dopamine. But, precisely what is beyond dopamine – has been harder to confirm. The involvement of other neural systems such as the glutamatergic, cholinergic, and serotonergic systems has been proposed.

Several lines of evidence suggest that the glutamatergic neural system is also involved in the pathogenesis of schizophrenia (Bubenikova-Valesova et al. 2008). ▶ Glutamate acts through several types of receptors, of which the ionotropic glutamate N-methyl-D-aspartate (▶ NMDA) receptor has been considered to be closely associated with schizophrenia (i.e. the glutamate hypothesis of schizophrenia). The most prominent support for this hypothesis is the acute psychomimetic effects of noncompetitive antagonists of glutamate NMDA receptors, such as ▶ phencyclidine and ▶ ketamine. These drugs have been shown to change both human and animal behavior and induce schizophrenia-like manifestations. For example, ketamine has been demonstrated to cause a variety of schizophrenia-like symptoms in healthy people, including positive symptoms (e.g., illusions, thought disorder, and ▶ delusions), negative symptoms (e.g., blunted emotional responses, emotional detachment, and psychomotor retardation), and cognitive symptoms, in particular impairments on tests of frontal cortical function (e.g., increased distractibility and reduced verbal fluency). In patients with schizophrenia, ketamine causes auditory or visual hallucinations while antipsychotics significantly reduce the ketamine-induced increase in positive symptoms. This hypothesis is also in line with the neurodevelopmental model of schizophrenia. Susceptibility to the psychotomimetic effects of ketamine is minimal or absent in children and becomes maximal in early adulthood, which is consistent with the fact that many schizophrenia patients experience their first episode until their 20s. Increased cellular destruction by ▶ apoptosis or changes in the function of NMDA receptors in the early development of the central nervous system are expected to be decisive for the subsequent development of ▶ psychosis, which in turn would be expected to finally manifest in their early adulthood. However, although pharmacological intervention to the NMDA receptors, using their antagonists, may lead to the development of novel therapeutic agents for schizophrenia in theory, no agent has been available until now.

The available evidence also suggests an important role for the muscarinic cholinergic system in the pathophysiology of schizophrenia (Raedler et al. 2007; Scarr and Dean 2008). ▶ Acetylcholine is synthesized in neurons from acetyl-CoA and choline in a reaction catalyzed by the enzyme ▶ choline acetyltransferase. There are two families of acetylcholine receptors: muscarinic receptors and nicotinic receptors. Muscarinic cholinergic neurotransmission has been shown to play a significant role in various cognitive functions, including learning and memory, which has lead to a hypothesis that these receptors are involved in cognitive impairment in schizophrenia (the cholinergic hypothesis of schizophrenia). Postmortem and in vivo brain imaging studies have consistently shown a significant decrease of muscarinic M1 receptor density, and this decrease is seen in patients with schizophrenia but not those with bipolar disorder or major depression. Thus, these changes are expected to be disease-specific and considered to be associated with deficits in the cognitive function in schizophrenia. Pharmacological studies of the muscarinic system in schizophrenia have indicated that targeting muscarinic M1 receptor might be an effective strategy to ameliorate the cognitive impairment in schizophrenia. Although stimulating cholinergic neurotransmission, using ▶ cholinesterase inhibitors, has not yielded promising therapeutic effects on cognitive function in schizophrenia, muscarinic M1 agonists have been shown to improve cognitive function. For example, N-desmethylclozapine, an active metabolite of ▶ clozapine, is a potent M1 agonist and has gathered attention as a new pharmacological agent for the treatment of schizophrenia although the data are still preliminary. Thus, the currently available evidence suggests that deficits in muscarinic M1 neurotransmission in brain are associated with cognitive impairments in schizophrenia. Although there is no clinically available muscarinic M1 agonist as a cognitive enhancer for the treatment of schizophrenia, the preliminary data indicate the potential benefits of targeting these receptors to improve cognitive function in patients with this illness.

The potential involvement of the serotonergic system in the pathogenesis of schizophrenia was first proposed earlier than the dopamine hypothesis. Based on a phenomenological similarity between psychosis-like effects of lysergic acid diethylamide (LSD) and symptoms of schizophrenia, it was proposed in the mid 1950s that the abnormal neural transmission in the serotonergic system

may be responsible for psychotic symptoms in schizophrenia (referred to as the serotonergic hypothesis of schizophrenia). A subsequent series of human and animal studies have confirmed that 5-HT_{2A}-receptor agonists such as LSD and psilocybin have effects that mimic schizophrenia-like symptoms (Geyer and Vollenweider 2008). These findings seem to support that psychopharmacological intervention in the serotonergic neural system may be promising for drug development, which is not the case in reality. Antipsychotic drugs such as clozapine and chlorpromazine had significantly higher affinity for 5-HT_2 than for D_2 receptors. However, as described earlier, the degree of dopamine receptor antagonism (rather than their 5-HT_2 antagonism) by these antipsychotics has been shown to be more closely associated with their antipsychotic efficacy, suggesting that 5-HT_2 blockade is not the principal mechanism of their antipsychotic action. Consistent with this contention, clinical trials have failed to provide robust antipsychotic effects of selective antagonists at 5-HT_{2A} receptors until now. Some atypical antipsychotics, including ► risperidone, have been suggested to have a safer side effect profile in motor function, which may be due to their 5-HT_{2A} antagonistic property. Although antagonism at 5-HT_{2A} when added to D_2 antagonism may contribute to the safe profile of those newer drugs, targeting solely serotonergic neural transmission is unlikely to provide antipsychotic effects for the treatment of schizophrenia.

In summary, while the current data suggest the involvement of several aminergic neural systems in the pathophysiology of schizophrenia and mechanisms of actions of antipsychotics drugs, the dopaminergic system is still considered to play a principal role. In fact, there is no effective antipsychotic that does not have an effect on the dopamine system. On the other hand, nonpsychotic symptoms, especially negative symptoms and cognitive impairment, may be reversed with the use of drugs working on nondopaminergic neural systems such as the glutamatergic and cholinergic system. Given that manipulating the dopaminergic system is effective, but not always perfect for the treatment of schizophrenia, further psychopharmacological research on other neural systems would also be needed.

Cross-References

► Amphetamine
► Animal Models for Psychiatric States
► Antipsychotic Drugs
► Atypical Antipsychotic Drugs
► Dopamine
► First-Generation Antipsychotics
► Glutamate
► Glutamate Receptors
► Hallucinations
► Monoamines
► Muscarinic Receptor Agonists and Antagonists
► Muscarinic Receptors
► Neurotransmitter
► NMDA Receptors
► Schizophrenia
► Schizophrenia: Animal Models
► Second and Third Generation Antipsychotics

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2-Amino-3-Hydroxy-N′-[(2,3,4-Trihydroxyphenyl) Methyl] Propanehydrazide

► Benserazide

(2R,3R,4R,5R)-2-(6-Aminopurin-9-yl)-5-(Hydroxymethyl)Oxolane-3,4-diol

► Adenosine

Amisulpride

Definition

Amisulpride is a benzamide derivative and is a second-generation antipsychotic with high affinity for D2 and D3 receptors. Its pharmacology is unusual in that at low doses, amisulpride preferentially blocks presynaptic D2 receptors, while at high dose it acts as an antagonist at postsynaptic D2 receptors. Amisulpride is used for the treatment of positive and negative symptoms of ► schizophrenia, as well as the management of dysthymia. Its therapeutic and safety profile is similar to that of the atypical antipsychotic ► risperidone, but amisulpride is associated with less weight gain and endocrine disturbance.

Cross-References

► Antipsychotic
► Second- and Third-Generation Antipsychotics

Amitriptyline

Definition

Amitriptyline is a ► tricyclic antidepressant with a tertiary amine chemical structure. One of the earlier tricyclics to be developed, it acts by inhibiting the reuptake of ► serotonin and ► norepinephrine, with roughly equal effects on each of these neurotransmitters. While its primary use is in the treatment of depression, it is also used in lower doses to treat migraine headache. It is metabolized to ► nortriptyline, which is itself marketed as an antidepressant. Usage of amitriptyline has declined in recent years due to its unfavorable side effect profile, including marked sedation, cardiovascular effects, and anticholinergic effects (e.g., constipation, dry mouth, blurred vision, urinary retention), and its high potential for lethality in overdose.

Cross-References

► Antidepressants
► Nortriptyline
► Tricyclics

Amnestic Compounds

► Inhibition of Memory

Amobarbital

Synonyms

Amylobarbitone

Definition

Amobarbital is a medium- to long-acting sedative ► barbiturate medication used in the treatment of severe and refractory anxiety and insomnia. It is sometimes used in conjunction with ► antipsychotic medication in acute psychotic episodes. Unwanted effects include sedation, headaches, paradoxical excitement, confusion, cognitive and psychomotor impairment, and confusion in the elderly. Interaction with ► alcohol can be hazardous. It depresses respiration and is highly toxic in overdose. It can induce liver microsomal enzymes. Long-term use induces dependence with severe withdrawal reactions. Recreational use and abuse can occur: amobarbital is a scheduled substance.

Cross-References

► Barbiturates

AMPA Receptor

Synonyms

AMPAR

Definition

The alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (or AMPA receptor) is a glutamate-activated ionotropic receptor (a ligand-gated cation channel) that mediates fast excitatory synaptic transmission and that has been linked to processes of synaptic plasticity that underlie learning and memory.

Ampakines

Definition

Ampakines are a new class of compounds that modulate ► glutamate in the brain. They work by allosterically binding to the AMPA subtype of ► glutamate receptors, which play a key role in memory formation and learning. Ampakines rapidly cross the ► blood–brain barrier and enhance the functioning of AMPA receptors to produce fast excitatory synaptic responses in the ► hippocampus. Thus, ampakines may produce cognitive benefits when

used as drugs. There is research interest in memory enhancement, stroke therapy, dementia treatment, sleep deprivation aid, and other therapeutic uses of ampakines.

Cross-References
► AMPA Receptors
► Blood–Brain Barrier
► Glutamate

AMPAR

► AMPA Receptor

Amperometry

► Electrochemical Techniques and Advances in Psychopharmacology

Amphetamine

Synonyms
Benzedrine

Definition
Amphetamine is a stimulant drug structurally related to the more potent and toxic stimulant ► methamphetamine. Amphetamine has two forms or isomers: (+)-amphetamine and (−)-amphetamine (otherwise called dextroamphetamine and levoamphetamine, respectively). The (−)-isomer has greater sympathomimetic properties; accordingly, the pure (+)-isomer is preferred for therapeutic use, although a mixture of 75% (+)-amphetamine salts and 25% (−)-amphetamine has become widely used for treating ADHD. Amphetamines were used to treat obesity due to their anorexic properties, but the tendency for tolerance reduced their effectiveness and increased the risk of dose escalation and abuse. Amphetamines are used for ► narcolepsy and chronic fatigue. Although they are also used as recreational drugs, with important neurotoxic consequences when abused, addiction is not a high risk when therapeutic doses are used as directed.

Cross-References
► Aminergic Hypotheses for Depression
► Aminergic Hypotheses for Schizophrenia
► Psychostimulants

Amphipathic

► Amphiphilic

Amphiphilic

Synonyms
Amphipathic

Definition
A molecule that is characterized by hydrophobic (nonpolar) and hydrophilic (polar) properties. When referring to peptides such as CRF, certain amino acid groups are hydrophobic or hydrophilic giving the peptide an amphiphilic surface.

Amygdala

Definition
Almond-shaped collection of nuclei in the anterior temporal lobe.

Amylobarbitone

► Amobarbital

Amyloid-Beta

Synonyms
Aβ; Abeta; Beta amyloid; β-Amyloid

Definition
A peptide derived from the amyloid precursor protein that accumulates extracellularly, regularly ordered in β-pleated sheets (which posses characteristic staining properties). The amyloid accumulation is usually surrounded by dystrophic axons as well as processes of astrocytes and microglias forming the amyloid or senile plaque, one of the hystopathological findings associated with Alzheimer's disease.

This low molecular protein is generated from amyloid precursor protein (APP) by β- and γ-secretase. β-amyloid

has neurotoxic properties and is suggested to be of causal relevance for the underlying pathology of Alzheimer's disease.

Anabolic Steroids

► Sex Hormones

Analgesia

Definition

Analgesia is a condition in which painful stimuli are perceived but not interpreted as painful. Analgesia involves a decrease in both the sensory component of pain as well as affective components such as discomfort or unpleasantness.

Cross-References

► Analgesics
► Opioids

Analgesia Tests

► Antinociception Test Methods

Analgesics

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Synonyms

Pain-relievers

Definition

Analgesics are drugs that are used to reduce pain.

Pharmacological Properties

Opioid Drugs

Opioid drugs have been the mainstay for the relief of mild to severe pain for centuries. It is worth noting that the first recorded use of ► morphine was in the third century BCE, and that it remains the first line analgesic in medical practice today. This reflects on both morphine's effectiveness in relieving pain and the inability of medical science to develop better drugs for the treatment of pain.

Opioid analgesics are defined as drugs that reduce pain by an action on opioid receptors. Before it was possible to define the protein structure of receptors, opioids were drugs whose effects could be prevented or reduced by administration of an ► opioid antagonist such as ► naloxone. Three opioid receptors, mu (named for the prototype drug that acts at this receptor, morphine), kappa, and delta receptors were defined by this method. Once the amino acid structure of receptor proteins could be determined, the definition of opioid receptor became a membrane protein with a structure that had considerable amino acid homology with the mu opioid receptor. Kappa and delta receptors continued to qualify, and a new receptor termed the Nociceptin/Orphanin FQ Peptide (NOP) receptor was discovered that met this definition as well.

Because of the effectiveness of ► mu opioid agonists in reducing pain, the capacity of agonists at each of the other opioid receptors to reduce pain has been thoroughly studied. Drugs that act on the kappa and delta receptors have analgesic effects, but have no clinical use for this indication because of adverse side effects (dysphoria in the case of kappa agonists and convulsions in the case of delta agonists) and because their pain-relieving potential seems not to be superior to that of morphine-like drugs. Drugs that act on these sites remain interesting and useful in experimental studies in animals and in vitro, and drugs with primarily kappa and delta activity have considerable promise in the treatment of itch and depression, respectively. The possibility that drugs that act on the NOP receptor may present a favorable profile of analgesic action is still under consideration in animal studies; this is described in more detail in the section Novel Approaches.

A great many analgesic drugs with mu opioid receptor ► affinity and ► efficacy have been developed over the past 50 years. Prior to that time, morphine and ► codeine, both naturally occurring opioids derived from the opium poppy, were almost the only strong analgesics that were available. Heroin, easily synthesized from morphine, was also in use as was ► methadone, the first totally synthetic opioid, which was identified in Germany in 1937. Between this time and 1977, when the most recent opioid analgesic (► tramadol) was introduced in Germany, the pharmaceutical industry expended gradually decreasing efforts to synthesize new opioid drugs in the hope that a drug could be identified that had morphine's ability to reduce pain but with fewer unwanted side effects.

The side effects of morphine that are most problematic include constipation, respiratory depression, sedation, and with some routes of administration, pruritus. In addition, when used daily for the treatment of chronic pain, morphine can produce physiological dependence and a resulting uncomfortable ► withdrawal syndrome if and when the drug is discontinued. The ► abuse liability of morphine is also of considerable concern, and has biased markedly some physicians against using opioid analgesics in cases of chronic, non-cancer pain. Over the years, drugs such as ► hydrocodone and hydromorphine, etorphine, ► fentanyl, and its derivatives (sufentanil, alfentanil, remifentanil), ► buprenorphine, ► pentazocine, nalbuphine, and tramadol were synthesized and marketed for analgesic use. Although these drugs differed widely in their pharmacokinetics, efficacies, and potencies, they all produced the majority of their analgesic actions through the mu opioid receptor. Pentazocine, with a confusing profile of action that may include some kappa receptor efficacy, and tramadol, which may act on serotonin as well as mu opioid receptors to reduce pain, are two opioid analgesics with additional sites of action. Unfortunately, the side effects that morphine produced were all found to be mediated through the mu receptor, and each of the newer opioid analgesics retained this same side-effect profile to a degree commensurate with their efficacies at the mu opioid receptor. These drugs are all currently available as analgesics in many countries, and are used because of their various pharmacokinetic advantages, but none has replaced morphine as the drug of choice in most situations that require relief of moderate to severe pain (Corbett et al. 2006). Most likely because of this determination, few pharmaceutical companies are currently attempting to develop improved opioid analgesics.

Two opioid analgesics, methadone and buprenorphine, because of their long-acting ► pharmacokinetic profile of action and because they can be taken by mouth, are currently used more frequently for the treatment of heroin abuse than they are used for the treatment of pain. The mechanism of methadone's ability to reduce heroin use is unknown, but variously attributed to methadone-induced cross-tolerance to heroin and to methadone-induced reduction in opioid cravings. The same mechanisms have been applied to buprenorphine, with the additional advantage that this partial mu opioid receptor agonist has some opioid antagonist effects as well. The pure opioid antagonist, ► naltrexone, is also effective in reducing heroin abuse by blocking the reinforcing effects of heroin. Compliance with opioid antagonist therapy for heroin abuse is a serious drawback, but may be soon overcome by the development of depot forms of antagonist administration (Comer et al. 2007).

When given frequently for the treatment of chronic pain, ► tolerance can develop to the analgesic effects of morphine. This means that the dose needs to be increased in order for the pain relief to be maintained. This has been demonstrated most readily in animal models of pain relief; there remains considerable debate about whether the requirement of increasing doses of morphine to treat chronic cancer pain, for example, is due to a reduced response to morphine or to an increase in the disease-related pain over time (Ballantyne and Shin 2008).

The mechanism of tolerance to morphine's analgesic effect is also a source of debate. There is no increased metabolic degradation of morphine with chronic administration, and no change in the number of mu opioid receptors or affinity of morphine for these receptors as a consequence of frequent administration. One of the more intriguing theories to account for opioid tolerance invokes a ► dual-process mechanism whereby the original actions of the drug (analgesia) are followed in time by the opposite action (► hyperalgesia). According to this theory, with chronic administration the hyperalgesic actions occur more rapidly and to a larger extent following each drug administration and attenuate the analgesic actions, resulting in a tolerance-like effect.

Morphine and most mu opioid analgesics are effective by oral or parenteral routes of administration, although variable gastric absorption of morphine makes intravenous or intramuscular administration more common in dealing with acute pain. Codeine is more consistently absorbed when given by mouth. Allowing patients to control their analgesic administration has become increasingly popular (► patient controlled analgesia or PCA). It has been found that providing patients in pain with a button to press that causes a brief intravenous injection of morphine produces better pain relief with less drug than the previous procedure of nurse-administered analgesia on a regular, every 4-h basis (Polomano et al. 2008). Certain limits are placed on the amount of morphine than can be infused over time, but there is rarely any tendency of patients to attempt to exceed these limits, and the amount of morphine infused typically decreases as the pain subsides.

Morphine and more lipophilic opioids such as remifentanil or sufentanil are also used frequently by the ► intrathecal or epidural route of administration for childbirth pain and postsurgical pain, and for patients who are resistant to or have unacceptable side effects from morphine given by other routes. For those in the latter group, it is possible to implant an intrathecal catheter and maintain

morphine analgesia by this route for dealing with chronic pain. Pain relief can be accomplished by much smaller doses of opioids when they are delivered around the spinal cord, which decreases the risk of adverse side effects. Nevertheless, respiratory depression remains the side effect of most concern with this route of administration, nausea and vomiting continue to occur, and pruritus may be more profound following intrathecal as compared with other routes of morphine administration (Schug et al. 2006).

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs are effective analgesics for mild to moderate acute pain such as minor trauma, dysmenorrhea, or headache, and for more chronic pain that is related to inflammatory responses, such as osteo- and rheumatoid arthritis. There are currently more than 25 members of this class, including the salicylic acid derivative, aspirin, the arylpropionic acids such as ibuprofen and naproxen, the COX-2 inhibitors such as celecoxib, rofecoxib, and parecoxib, and the heteroaryl acetic acids such as diclofenac and ketorolac. All but ketorolac and parecoxib are available only for oral administration. The mechanism of action of each of these drugs is inhibition of an enzyme (cyclo-oxygenase; COX) that normally produces prostaglandins and thromboxanes, some of which sensitize spinal neurons to pain, but others of which inhibit gastric acid secretion and protect gastric mucosa (Rang et al. 2007).

There are two primary cyclo-oxygenase isoforms, known as COX-1 and COX-2. COX-1 is a constitutive enzyme, active in most tissues, including red blood cells. The prostaglandins it catalyzes have a role in the protection of gastric tissues, and platelet aggregation. COX-2, on the other hand, is active when stimulated by inflammatory reactions, and the ► prostanoids that it catalyzes often mediate inflammation. Drugs such as aspirin, ibuprofen, and naproxen block both cyclo-oxygenase isoforms. It is generally thought that the ability of these drugs to reduce inflammatory pain is related to their block of COX-2, whereas the side effects of gastric irritation, and decreased clotting time were due to block of COX-1 enzyme. A concerted effort to develop drugs that blocked only the COX-2 enzyme and thereby yield NSAIDs that reduced pain but had fewer side effects resulted in the synthesis of the coxib drugs such as celecoxib and rofecoxib. In fact, these drugs do have a reduced ability to produce gastric irritation and bleeding while retaining considerable pain relieving effectiveness. Unfortunately, it appears as though some selective COX-2 inhibitors also increase the risk of adverse cardiovascular events, apparently because of the loss of a protective effect of COX-1 inhibition. A recent meta analysis of a series of NSAIDS and the risk they pose for adverse cardiovascular effects indicates that although the COX-2 selective inhibitors are more likely to produce dose-related myocardial infarction than NSAIDS that are less COX-2 selective, there is no close correspondence between the degree of COX-2 selectivity and risk of cardiovascular damage (Farkouh and Greenberg 2009).

The side effects of use of the nonselective COX-inhibitors are primarily gastric irritation and bleeding, which can be serious and life threatening, and decreases in platelet aggregation, which is a positive effect in individuals with coronary artery disease.

Other Drugs for Pain Relief

Acetaminophen is used to reduce mild to moderate pain, in much the same manner as aspirin. Acetoaminphen has less anti-inflammatory effects than NSAIDS, but it is very effective in reducing fever, which is done by blocking prostaglandin biosynthesis under conditions of fever. This analgesic is much less irritating to the GI tract than are NSAIDS, and does not alter blood coagulation as significantly as NSAIDS do. The primary risk factor of acetoaminophen is liver damage, which can occur if large doses are taken, or if an individual has a genetic polymorphism of liver enzymes that results in increased levels of a toxic acetoaminophen metabolite.

Calcium channel blockers. Although opioid drugs are recommended for moderate to severe pain, they are thought to be relatively ineffective in the treatment of neuropathic pain, or pain due to nerve damage or neuropathies. These conditions are usually chronic, making use of the large doses of opioids that are required to reduce this pain problematic. In 1994, a novel drug, gabapentin, was approved as an adjunct to the treatment of some types of seizures. It was fairly quickly discovered that ► gabapentin is also effective in reducing neuropathic pain, and it is currently widely prescribed for this purpose, although this is an off-label use. ► Pregabalin is a drug with a similar mechanism of action and spectrum of analgesic effects as gabapentin, and it is marketed for this use.

Both these drugs are structurally based on the inhibitory neurotransmitter ► GABA, but their effects are not related to the activity of this neurotransmitter. Rather, they may produce their analgesic effects through a blockade of a subunit of voltage-sensitive calcium channels in the brain and spinal cord. This blockade results in reduction in stimulated release of many neurotransmitters, including glutamate, GABA, ► substance P, and glycine, and this effect is currently thought to participate in the analgesic actions of these drugs (Taylor 2009). There are few side effects noted for these analgesic drugs.

Ketamine. This drug acts on the subtype of the ► glutamate receptor that is sensitive to *N*-methyl-D-aspartate (NMDA) application and produces both analgesia and anesthesia. ► Ketamine, the most widely used NMDA antagonist, is classified as a dissociative anesthetic because of the profound psychotomimetic effects of this drug that are apparent upon emergence. These effects are dysphoric in most individuals, limiting the use of ketamine as an anesthetic–analgesic primarily to patients with burn injuries, particularly children, who are less disturbed by the ► hallucinations produced by ketamine. Nevertheless, ketamine has a number of distinct advantages. It is rapidly effective by all routes of administration (intravenous, intramuscular, epidural, oral, rectal, and transnasal) and has analgesic, anesthetic, and amnestic effects. It does not depress respiration, and it stimulates the cardiovascular system in most patients (Aroni et al. 2009). The use of ketamine and other NMDA antagonists for the treatment of pain usually involves the use of relatively small doses in conjunction with opioid administration, frequently by means of PCA (Rang et al. 2007).

Antidepressants. The tricyclic ► antidepressants (► amitriptyline is the gold standard for analgesia) are recognized for their ability to reduce neuropathic pain. Other antidepressants, particularly the newer norepinephrine–serotonin reuptake inhibitors such as ► venlafaxine and ► duloxetine and the nonspecific reuptake inhibitors such as ► trazodone and nefazodone are inconsistently effective in this regard. The mechanism of action is likely complicated, but appears to be different from that mechanism involved in the antidepressant actions; not all antidepressants are effective analgesics. The side effects that accompany the treatment for depression remain when these drugs are used to treat pain, although the smaller doses used for analgesia tend to reduce these side effects. As with the calcium channel blockers, antidepressants have some efficacy in the treatment of neuropathic pain, and may be most useful when combined with opioid analgesics.

Novel Approaches

Although there is limited interest in opioid analgesic development currently by the pharmaceutical industry, basic science continues to search for drugs that reduce acute and chronic pain, with greater efficacy and/or fewer side effects than those currently available. Three such classes of compounds are sufficiently interesting to warrant mention. These drugs are not currently available for human use. Nevertheless, the promising profiles of these three agents, particularly given their divergent mechanisms, suggest that continued research on this topic may eventually yield more helpful pharmacotherapies for pain.

NOP receptor agonists. The Nociceptin/Orphanin FQ Peptide (NOP) receptor is the fourth type of opioid receptor (defined as a non-opioid branch of the opioid family), identified in a search for protein structures that were homologous with the mu opioid receptor. Drugs that bound to the NOP receptor were evaluated for their ability to produce analgesia. The vast majority of these tests were carried out in rats and mice, and it was found that agonists at the NOP receptor produced rather than reduced various types of experimental pain in rodents, especially when they were given centrally/supra-spinally (Lambert 2008). More recently, however, the analgesic properties of NOP agonists were evaluated in rhesus monkeys where they were found to be as effective as morphine by several routes of administration (e.g., Ko et al. 2009). More important, NOP agonists did not appear to have abuse liability in rhesus monkeys, and they did not produce pruritus, an important side effect of spinally administered morphine. Further testing in human and nonhuman primates may demonstrate the potential usefulness of these compounds as powerful analgesics devoid of the side effects associated with morphine.

Serotonin receptor agonists. Two aspects of mu opioid agonist-induced analgesia noted above, viz, the development of tolerance through a putative dual-action effect, and the relative ineffectiveness of these drugs in neuropathic pain, have prompted research into identifying a drug that produces pain initially as a "first-order" effect, but follows this with a longer lasting analgesia as a "second-order" effect. Because the dual process is likely to be neuronally mediated, this drug would be considered as potentially useful in treating chronic pain resulting from nerve damage.

Agonist actions at the serotonin 5-HT_{1A} receptor have recently been suggested as having this ability (Colpaert 2006). In contrast to morphine, which produces analgesia followed by hyperalgesia in rat models of mechanically induced pain, the 5-HT_{1A} agonist F-13640 produces hyperalgesia initially, but with further multiple injections, analgesia is obtained. Notably, following chronic administration of morphine, tolerance to its analgesic effects were observed, whereas, following chronic administration of F-13640, tolerance to its hyperalgesic effects and a resulting augmented analgesia was observed. Of particular interest was the finding that in rat models of tonic neuropathic pain, F-13640 was analgesic on initial administration, prompting the notion that the "first-order" effect of hyperalgesia may have been induced by the pain induced

by the intraplantar formalin injection, leaving the 5-HT_{1A} agonist to induce only the "second order" effect of reducing the pain sensation.

Transient receptor potential, vanilloid subfamily member 1 (TRPV1) is one of a family of cation channel receptors, and is activated by changes in temperature, acid pH, capsaicin, and some animal venoms. The receptor is located in the dorsal root gangion neurons and the trigeminal ganglion neurons as well as on a subset of primary sensory neurons (Aδ fibers) in the presence of inflammation.

Activity at TRPV1 receptors appears to sensitize the channel to other stimuli. Antagonists of TRPV1 have been targeted as analgesic agents because they seem to block the ability of the neurons to release a number of pro-inflammatory neuropeptides. Interestingly, TRPV1 agonists such as capsaicin, although they produce pain initially, also have considerable subsequent analgesic actions, probably by desensitizing sensory fibers. There is considerable ongoing experimental work targeting TRPV1 and other members of this family, searching for a profile of specificity and agonists/antagonist actions that result in the treatment of inflammatory, thermal, and other pain (Cortright and Szallasi 2009).

Cross-References

- ► Antidepressants
- ► Antinociception Test Methods
- ► Classification of Psychoactive Drugs
- ► Ethical Issues in Animal Psychopharmacology
- ► Opioid Dependence and Its treatment
- ► Opioids
- ► Pharmacodynamic Tolerance
- ► Receptors: Functional Assays

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Analytical Column

Definition

The analytical column is where the chromatographic separation takes place. It is a narrow tube, typically less than 5 mm in diameter, and 10–50 cm in length, filled with the stationary phase. The exact dimensions of the column and the characteristics of the stationary phase will depend on the application.

Anandamide

- ► N-arachidonylethanolamine
- ► Cannabinoids and Endocannabinoids

Androgens

Synonyms

Sex hormones

Definition

Androgens are a class of hormones with testosterone being the primary product of the testes. Dihydrotestosterone is an androgen metabolite of testosterone produced in target tissues due to the actions of the 5α-reductase enzyme. Dihydrotestosterone is more potent at androgen receptors than is testosterone.

Anesthesia

► General Anesthesia

Animal Model

Definition

The use of experimental intervention (e.g., drugs and lesions) in the laboratory animal in order selectively to induce defined behavioral or physiological changes. These changes show the validity of an animal model to the extent that they reproduce some aspect of a recognized human disease state.

Cross-References

► Construct Validity
► Face Validity
► Predictive Validity
► Screening Models
► Simulation Models

Animal Model with Construct Validity

► Simulation Models

Animal Models for Psychiatric States

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Synonyms

Animal models of psychopathology; Behavioral models of psychopathology; Simulations of psychopathology

Definition

Animal models of psychiatric states are procedures applied to laboratory animals that engender behavioral changes which are intended to be homologous to aspects of psychiatric disorders, and can therefore be used as experimental tools to further the understanding of human psychopathology.

Principles and Role in Psychopharmacology

Basic Concepts

The concept of modeling psychopathology in animals is as old as the use of animals in psychological investigations: its roots may be found in the work of Pavlov, Watson, and even earlier. However, for many years, practical attempts to devise animal models were sporadic, ad hoc, and unconvincing. As a result, animal models of psychiatric states were until recently viewed with justified suspicion. Over the last 20–30 years, this situation has changed, with the recognition that animal models can provide a means of investigating the neurobiological mechanisms underlying psychopathology. Indeed, given the limitations of the investigational techniques currently available for use in human subjects, animal models represent the only means of asking many important questions. Animal models can also be of great value in the process of psychotropic drug development, and again, frequently represent the only viable method of predicting novel therapeutic actions. The recent development and acceptance of animal models may thus be seen as an adjunct to the concurrent growth and maturation of psychopharmacology and biological psychiatry, where they serve as indispensable tools for ► translational research.

The definition of animal models of psychiatric states presented above includes a number of features:

1. The *procedures* used to generate models are many and varied. Broadly, they involve environmental manipulations (e.g., exposure to social or physical stressors, or training regimes), and/or alteration of the internal environment (e.g., by brain lesions or administration of psychotropic drugs), and/or identification of vulnerable individuals (by selective breeding or genomic methods). Some examples of each of these procedures are shown in Table 1.
2. While in principle any animal species could be used, in practice the scope of modeling is restricted to *laboratory animals*. The most extensively used species has traditionally been the rat, but mouse models are being increasingly developed in order to capitalize on the availability of genetically modified strains. (► Genetically modified animals) Other species used occasionally include guinea pigs, marmosets, and chicks.
3. Some earlier definitions of animal models described them as analogous to psychiatric disorders. The present definition emphasizes that models aim to be *homologous*: that is, to simulate essentially the same process across species. This issue is discussed further below.

Animal Models for Psychiatric States. Table 1. Some examples of the procedures used to construct animal models of psychiatric states.

General procedure	Specific example	Primary behavioral end point	Condition modeled
Manipulation of the external environment			
► Social stress	Social conflict	Loser in competition for food source	Anxiety[a]
	Isolation rearing	Impairment of ► prepulse inhibition	Schizophrenia[b]
Physical stress	Uncontrollable footshock	Impairment of avoidance learning ("► learned helplessness")	Depression[c]
	► Chronic mild stress	Decreased response to rewards	Depression[c]
Training[i]	Operant responding for intravenous drug administration[k]	Drug self-administration[k]	Drug addiction[d]
	Punished operant responding	Suppression of responding by a signal paired with punishment[j]	Anxiety[a]
Manipulation of the internal environment			
Drug administration	► Phencyclidine	Stereotyped behavior and decreased social contact[m]	Schizophrenia[b]
	► Scopolamine	Impairment of ability to remember information across short time delays[l]	Dementia[e]
Brain lesion	Olfactory bulbectomy	Locomotor hyperactivity	Depression[c]
	Neonatal hippocampal lesion	Locomotor hyperactivity and hyper-responsiveness to stress	Schizophrenia[b]
Identification of vulnerable individuals			
Selective breeding	Flinders sensitive line (FSL) rat	Increased immobility in the forced swim test[f]	Depression[c]
	High saccharin–consuming (HiS) rat	Self-administration of cocaine and heroin[k]	Drug addiction[d]
Genomic manipulations[h]	Transgenic rat over-expressing amyloid precursor protein	Impairment of spatial learning[n]	Dementia[e]
	5HT 1A receptor knockout mouse	Avoidance of open spaces[g]	Anxiety[a]

The models listed in this table are chosen in order to illustrate the breadth of animal models in current use. There is no implication that these are the "best" or most valid models available

[a] ► Anxiety: Animal Models
[b] ► Schizophrenia: Animal Models
[c] ► Depression: Animal Models
[d] ► Addictive Disorder: Animal Models
[e] ► Rodent Models of Cognition
[f] ► Behavioral Despair
[g] ► Elevated Plus-Maze; ► Open Field Test
[h] ► Genetically Modified Animals
[i] ► Operant Behavior in Animals
[j] ► Pavlovian Fear Conditioning; ► Punishment Procedures
[k] ► Self-Administration of Drugs
[l] ► Short-Term and Working Memory in Animals
[m] ► Social Recognition and Social Learning
[n] ► Spatial Learning in Animals

4. An animal model of a psychiatric disorder includes a behavioral end point, which represents a model of a process that is thought to be important in the disorder. The scope of models is typically limited: they aim to simulate specific *aspects* rather than the entirety of the disorder, though it may be found subsequently that further aspects of the disorder are also present. Table 1 lists the primary behavioral end points that

were the focus of the original publications on each model, but in almost every case, a variety of other behavioral changes have also been described.

5. The definition also emphasizes the purpose of animal models of psychopathology: to provide a means of studying aspects of mental disorders. Animal models are *experimental tools*, and they are developed for specific investigational purposes. Initially, the primary aim was to elucidate psychological processes, but models are now used largely to address neurobiological issues. The specific issues most commonly addressed include: mechanisms of action of psychotherapeutic drugs, the neurotransmitter, neuroreceptor, and intracellular changes underlying psychiatric states, the neuroanatomical basis of psychiatric states, and increasingly, questions about the role of specific genes.

This article discusses some general issues concerning animal models of psychiatric states; models of specific psychiatric states are discussed elsewhere. ► Animal models; ► Anxiety: Animal Models; ► Autism: Animal Models; ► Dementias: Animal Models; ► Depression: Animal Models; ► Eating Disorder: Animal Models; ► Primate Models of Cognition; ► Rodent Models of Cognition; ► Schizophrenia: Animal Models. The references at the end of this article provide further reviews of this general area, from a variety of different perspectives.

Fitness for Purpose

Because models are built to be used, they have to be viewed in relation to the broader objectives of a research program. Behavioral models are used in psychopharmacology for two distinct purposes: as simulations within which to study aspects of psychiatric states, and as screening tests for the development of new treatments. Screening tests are subject to logistical considerations: for example, the test should be completed in the shortest possible time, and ideally will respond to acute drug treatment. However, in a model of a psychiatric state, these same features may be counter-indicated. For example, antidepressant drugs are clinically ineffective if administered acutely and largely inert if administered to nondepressed people: therefore, a model of clinical antidepressant action should involve chronic drug treatment, administered within a context of abnormal behavior rather than to "normal" animals. (► Antidepressants) Thus, a particular time course of antidepressant action and a particular level of behavioral sophistication may be desirable or undesirable features, depending upon the purpose for which a procedure is being used.

Conclusions arising from the use of a model are essentially hypotheses, which must eventually be tested against the clinical condition being modeled. The more valid a model, the more likely it is that insights derived from it will hold true for the clinical condition. Therefore, an assessment of the validity of a model provides an indication of the degree of confidence that we can place in the hypotheses arising from its use. Assessment of validity is not a yes/no judgment, but rather an evaluation of strengths and weaknesses and areas of uncertainty.

The systematic validation of an animal model is no different in principle from that of any other psychological device, such as a psychometric test or a psychiatric diagnosis, and the same general approaches to validation are applicable. Several systems of evaluation have been proposed, which have the common feature that models are assessed on two or more independent dimensions. One widely used method, described below in more detail, employs the three dimensions of predictive, face, and construct validity: ► predictive validity means that performance in the test predicts performance in the condition being modeled (and vice versa); ► face validity means that there are phenomenological similarities between the two; and ► construct validity means that the model has a sound theoretical rationale.

Some reviewers have advocated the primacy of one of these three dimensions, and each has its advocates. In principle, construct validity should be considered as the most fundamental dimension. In practice, however, the construct validity of animal models of psychopathology is difficult to determine, and therefore a balanced approach is needed, in which a view of the validity of a model is formed only after considering all three sources of evidence. In all three areas, discriminant validity is a further consideration: that is, the extent to which the evidence points to a particular disorder, as distinct from a different or a nonspecific psychiatric disorder. The three sets of validation criteria provide a convenient framework for organizing large volumes of data and ensuring that when different models are compared, like is compared with like. The major issues described below are summarized in Table 2.

Assessment of Predictive Validity

The concept of predictive validity implies that manipulations known to influence the pathological state should have similar effects in the model: thus, manipulations known to precipitate or exacerbate the disorder should precipitate or exacerbate the abnormalities displayed in the model, while manipulations known to relieve the disorder should normalize behavior in the model. In

Animal Models for Psychiatric States. Table 2. Issues to consider in assessing the validity of animal models.

Predictive validity	Specificity: No false positives
	Sensitivity: No false negatives
	Relative potencies and appropriate dose ranges
	How firmly established are the clinical data on effective and ineffective treatments?
Face validity	Extent of correspondence vis-à-vis symptoms and neurobiological features
	Specificity of symptoms/features modeled
	Centrality of symptoms/features modeled
	Coherence of symptoms/features modeled: Do they co-occur clinically?
	How robust is the psychiatric diagnosis?
Construct validity	How well do we understand the model: Does it measure what it claims to measure?
	How well do we understand the disorder: Would clinicians agree with how it is being characterized?
	If there is a parallel human experimental model, how well has that model been validated?
	Do similar theoretical structures apply: Can homology be demonstrated in relation to psychological processes, anatomical localization, neurochemical mechanisms, or gene expression?

practice, the predictive validity of the animal models used in psychopharmacology is determined largely by their response to therapeutic drugs.

In this context, the primary requirements for predictive validity are that a valid test should be sensitive and specific: sensitivity means that the test should respond to effective therapeutic agents and specificity means that it should fail to respond to ineffective agents. Positive responses should occur at sensible doses, and should be demonstrable with a range of structurally diverse compounds, and where applicable, to nonpharmacological treatment modalities. Negative responses should be demonstrable with agents that cause behavioral changes similar to the therapeutic effect but achieve these effects by nonspecific actions (e.g., by changing locomotor activity). However, while sensitivity and specificity are crucial to an assessment of predictive validity, results may sometimes be distorted by species differences in drug kinetics or metabolism, which can lead to apparent discrepancies of drug action in animal models versus human patients.

In some circumstances, it may be possible to demonstrate that the relative potencies of different agents in a model correlate positively with their potencies in clinical use. This is potentially a powerful test, provided that there is sufficient variation among the chosen drugs in their clinical potencies. However, it can generate trivial data if the analysis fails to sample a range of chemically distinct compounds. For example, the positive correlation between the clinical potency of ▶ benzodiazepines and their performance in several animal models of anxiety (▶ Anxiety, animal models) serves only to confirm that these drugs act at the same receptor.

There will always be a group of drugs for which, through a shortage of research, there is uncertainty over their status as clinically effective or ineffective. Moreover, the clinical classification of drugs as active or inactive may sometimes be incorrect. Drugs thought to be active on the basis of early open trials are frequently found to be inactive in later well-controlled tests; conversely, a drug may appear to be inactive because the emergence of side effects prevents its administration at adequate dosages, a problem that is less likely to arise in an animal model. It follows that the failure of an animal model to predict accurately will tend to weigh against the model, but may sometimes call instead for a reevaluation of the clinical wisdom. This illustrates an important principle: that the validity of a model is absolutely limited by the quality of the clinical information available to describe the condition modeled.

Assessment of Face Validity

Face validity refers to a phenomenological similarity between the model and the disorder modeled. On the one hand, the model should resemble the disorder; on the other, there should be no major dissimilarities. The checklist approach to psychiatric diagnosis adopted by the Diagnostic and Statistical Manuals of the American Psychiatric Association (▶ DSM) provides a useful starting point for enumerating areas of potential comparison. In DSM, psychiatric diagnoses are established by reference to a checklist of core symptoms and a further checklist of subsidiary symptoms, with a requirement to demonstrate the appropriate number of symptoms from each list. If several points of similarity are demonstrable between a model and the disorder, then it is necessary to ask whether the cluster of symptoms identified forms a coherent grouping that might realistically be seen in a single patient, or whether they are drawn from a variety of diagnostic subgroups. Frequently, animal models focus on a single behavioral endpoint. In that case, it is important to

assess whether this models a core symptom or a subsidiary symptom. For example, if the behavior in the model consists simply of a change in locomotor activity, this is likely to be of peripheral relevance to most psychiatric disorders. Similarly, the face validity of the model is less strongly supported if the symptom modeled is common to a several different psychiatric disorders (discriminant validity).

While a comparison with DSM provides an extremely useful starting point for assessment of face validity, other relevant comparisons should also be considered. For example, if the clinical condition only responds to chronic drug treatment (e.g., depression), then the model should also respond only to chronic drug treatment. Any neurobiological parallels between the model and the disorder also contribute to face validity.

Similarity between behavior in the model and the clinical symptom modeled should be demonstrated, rather than assumed. The demonstration of similarity requires a thorough experimental analysis, which, sadly, is often lacking. This can result in specious claims for face validity being advanced on the basis of unsupportable interpretations of behaviorally unsophisticated models. For example, many animal models of depression are based on a decrease in locomotor activity. (► Depression: animal models) It is certainly possible that a decrease in locomotor activity might simulate symptoms of depression such as psychomotor retardation or loss of motivation, but without further behavioral analysis, these remain unsupported analogies. As a general rule, the less sophisticated the behavior (in the sense that its interpretation is less open to experimental investigation and analysis), the lower is the possibility of making a judgment of face validity.

A fundamental consideration in assessing face validity is that the comparison of symptoms between a model and the clinical condition can only proceed in respect of symptoms that are expressed behaviorally. Many symptoms of psychiatric disorders are only known from patients' verbal reports, and these symptoms, in principle, cannot be modeled. An example is suicidal ideation in depression. However hard we worked, we could never know if a rat was feeling suicidal (or to take an actual research example, if it was feeling a state of "despair"), (► Behavioral despair) and therefore, this question falls outside the realm of scientific discourse: we simply cannot ask it. Nevertheless, it may sometimes be possible to express subjective symptomatology in behavioral terms. ► Hallucinations are subjective phenomena that should be out of bounds for modeling in animals, but from careful observation of patients who are hallucinating, a set of operational criteria was developed to define associated behavioral phenomena (such as staring intently at an invisible object), thus enabling the inclusion of hallucinations as symptoms that in principle could be simulated in animal models of schizophrenia. (► Schizophrenia: animal models) The rule, then, is that if a symptom can be expressed behaviorally and defined operationally, we can attempt to model it, but if it can only be expressed verbally, we cannot.

It is also important to remember that most DSM diagnoses are poorly established hypothetical constructs that can change radically between successive revisions of the manual. Again, the assessment of the validity of animal models is limited by the quality of the clinical data.

Assessment of Construct Validity

In order to evaluate the theoretical rationale of an animal model (construct validity), we require a theoretical account of the disordered behavior in the model, a theoretical account of the disorder itself, and a means of bringing the two theories into alignment. This can only be done if the clinical theory occupies an appropriate framework, which uses terms and concepts applicable also to subhuman species. Clearly, the subjective dimension of psychopathology cannot be central to such a theory, since subjective phenomena in animals are for most practical purposes outside the realm of scientific discourse. However, at the level of the cognitive processes underlying psychopathology, and the neurobiological mechanisms that underlie those cognitive processes, the possibility exists of constructing parallel theories. It follows from this analysis that the assessment of construct validity involves a number of relatively independent steps.

First, the theoretical account of behavior in the animal model requires evaluation. Just how well do we understand the model? Does it measure what it claims to measure? For example, if an animal model of depression is conceptualized as a decreased ability to respond to rewards, then at the very least, it must be convincingly demonstrated that the decrease in rewarded behavior cannot be explained by, for example, sedative effects or a nonspecific decrease in consummatory behavior (► Depression: animal models). Similarly, an animal model of dementia must demonstrate that performance failures result from a disorder of learning or memory, rather than from nonspecific causes, and further work should seek to characterize the specific memory processes involved. (► Rodent models of cognition; ► Primate models of cognition)

In some areas, human experimental procedures have been developed that are based on procedures used in animal studies. However, demonstrating that a similar

psychological process occurs in humans and animals is of limited value, since its role in the disorder also needs to be demonstrated. For example, some groups of schizophrenic patients show sensorimotor gating deficits that are very similar to those seen in animal models of schizophrenia: however, the contribution of sensorimotor gating deficits to schizophrenia remains uncertain (► Prepulse inhibition, ► Latent inhibition). It will be clear that a detailed consideration of the human disorder forms an essential step in the evaluation of animal models, and that the relatively poor state of theoretical understanding of most psychopathologies places an upper limit on construct validity.

Recent developments in neuroimaging and psychiatric genetics may help to decrease the difficulty of establishing homology between animal models and psychiatric states. A major focus of work with animal models has been to establish the brain areas responsible for the behavioral changes, and neuroimaging methods can now provide similar information for psychiatric states, making it possible to evaluate in a much more precise manner whether common mechanisms are involved. (► Magnetic resonance imaging: functional) Similarly, the identification of susceptibility genes and ► endophenotypes can now be translated directly into genetically modified animal models. (► Genetically modified animals) This is a rapidly developing area of research, and it is likely that it will be used increasingly to develop animal models of psychopathology that by definition will have a degree of construct validity.

Cross-References

► Addictive Disorder: Animal Models
► ADHD: Animal Models
► Antidepressants
► Anxiety: Animal Models
► Autism: Animal Models
► Behavioral Despair
► Benzodiazepines
► Chronic Mild Stress
► Construct Validity
► Dementias: Animal Models
► Depression: Animal Models
► Eating Disorder: Animal Models
► Elevated Plus-Maze
► Endophenotypes
► Face Validity
► Genetically Modified Animals
► Hallucinations
► Latent Inhibition
► Learned Helplessness
► Magnetic Resonance Imaging: Functional
► Open Field Test
► Operant Behavior in Animals
► Pavlovian Fear Conditioning
► Phencyclidine
► Predictive Validity
► Prepulse Inhibition
► Primate Models of Cognition
► Punishment Procedures
► Rodent Models of Cognition
► Schizophrenia: Animal Models
► Self-Administration of Drugs
► Short-Term and Working Memory in Animals
► Social Recognition and Social Learning
► Social Stress
► Spatial Learning in Animals
► Translational Research

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Animal Models of Acute Stroke

Definition

A model of acute stroke produced in a laboratory animal, generally a rodent but sometimes a higher species such as

a primate. A cerebral blood vessel (commonly the middle cerebral artery, since this is the vessel most often affected in human stroke) is occluded by clipping, electrocoagulation, or a thread. If the occlusion is not removed, this is referred to as permanent focal ischemia; if the occlusion is removed, it is called transient focal ischemia. Injection of small clots into the cerebral arteries is called a thromboembolic stroke model.

Animal Models of Psychopathology

► Animal Models for Psychiatric States

Animal Tests of Anxiety

► Anxiety: Animal Models

Animal Welfare Act

Definition

The Animal Welfare Act of 1966 (latest amendment 2006) authorizes the U.S. Secretary of Agriculture to regulate transport, sale, and handling of dogs, cats, nonhuman primates, guinea pigs, hamsters, and rabbits intended to be used in research or "for other purposes."

Anisomycin

Definition

An antibiotic isolated from *Streptomyces griseolus* that binds to 60S ribosomal subunits preventing elongation and hence inhibiting protein synthesis.

Anorectics

► Appetite Suppressants

Anorexia

► Eating Disorder: Anorexia Nervosa

Anorexia Nervosa

Synonyms

Eating disorders: animal models

Definition

Eating disorder that primarily affects women and that is characterized by an obsession with losing weight, and distorted body image. Patients suffering from anorexia nervosa will restrict their diet to levels that lead to severe malnutrition, and if left untreated, could lead to death.

Anorexigenic

Definition

Systems or endogenous factors that prevent or foreshorten eating events.

Antagonist

Synonyms

Receptor inhibitor

Definition

An antagonist binds to a receptor but causes no change in receptor activity itself. Rather, an antagonist maintains the receptor in the same state as exists when it is not bound by a stimulatory (agonist) or inhibitory (inverse agonist) substance. Thus, an antagonist has no impact on receptor activity in the absence of an agonist or inverse agonist, but prevents or reverses the effects of such substances when they are present by blocking their binding to the receptors. An antagonist may be competitive (or surmountable), that is, it binds to a region of the receptor common with the endogenous agonist. The effects of a competitive antagonist may be overcome by increasing the concentration of agonist. Alternatively, antagonists may be insurmountable, where no amount of agonist is capable of completely overcoming the inhibition. Insurmountable antagonists may bind covalently to the agonist binding site, or act allosterically at a different site on the receptor.

Cross-References

► Agonist
► Allosteric Modulator
► Inverse Agonist

Anti-anxiety agents

► Punishment Procedures

Antianxiety Drugs

► Anxiolytics

Antianxiety Medication

► Anxiolytics
► Minor Tranquilizer

Anticholinergic Side Effects

Definition

The inhibition of acetylcholine receptors can cause various side effects, including dryness of mucous membranes, diaphoresis, constipation, urinary retention, dizziness, and confusion. Tolerance occurs over time to some of these effects, while others will persist for the duration of drug use.

Anti-Cholinesterases

► Acetylcholinesterase and Cognitive Enhancement

Anticipatory Food Seeking

► Goal Tracking

Anticipatory Goal Seeking

► Goal Tracking

Anticonvulsants

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Synonyms

Antiepileptics; Mood stabilizers

Definition

Anticonvulsants are drugs defined by their efficacy in the treatment of epilepsy. They are also widely used to treat nonepileptic conditions such as neuropathic pain, migraine, and ► bipolar disorder.

Pharmacological Properties

History

Anticonvulsants were first studied and approved for the treatment of epilepsy, while their therapeutic activity in other disorders was identified later. Anticonvulsants are traditionally divided into two groups, according to the year of marketing (before and after 1990) (Beghi 2004): ► first-generation anticonvulsants (or "older"), including ► phenobarbital, ► phenytoin, primidone, ► carbamazepine, ► valproic acid, and ethosuximide, and ► second-generation anticonvulsants (or "newer"), such as ► lamotrigine, ► gabapentin, ► topiramate, ► oxcarbazepine, levetiracetam, ► pregabalin, ► tiagabine, and ► zonisamide.

In addition to their use for the management of epilepsy, anticonvulsants are also commonly used to treat a variety of nonepileptic neurological conditions, such as neuropathic pain, migraine, and essential tremor, and psychiatric disorders, such as bipolar disorder and anxiety. This presumably reflects their complex mechanisms of action involving a wide range of pharmacological effects on different neurotransmitter systems and ion channels.

Concerning their use as ► mood stabilizers, anticonvulsants began to be studied in the late 1970s, when a logical parallel was drawn between affective and seizure disorders, based on the theory that mania may "kindle" further episodes of mania (Post et al. 2007). Since the first compounds tested, namely carbamazepine and valproate, proved effective in treating the manic phase of bipolar disorder, this has led to the idea that many anticonvulsants could be mood stabilizers, especially for mania. In recent years, a number of anticonvulsants have been more rigorously investigated for their potential mood-stabilizing properties. Anticonvulsants are heterogeneous in their mechanisms of action, ► pharmacokinetics, and ► efficacy in the various mood states in bipolar illness, as well as in their safety/tolerability profiles.

Mechanisms of Action

The exact mechanism of action of anticonvulsants remains largely unknown. However, anticonvulsants have various

targets of action in the synapse and may affect pathophysiological processes regulating neuronal excitability. The main pharmacological mechanisms responsible for the clinical efficacy of anticonvulsants in epilepsy and in the various nonepileptic neurological and psychiatric disorders are likely to include increased GABAergic inhibitory neurotransmission, decreased glutamatergic excitatory neurotransmission, blockade, or inhibition of voltage-dependent sodium or calcium channels, and interference with intracellular signaling pathways (Johannessen Landmark 2008). In addition, indirect mechanisms may be involved, such as the modulation of other neurotransmitters, including the ► monoamines. Current knowledge indicates that most anticonvulsants have more than one mechanism of action, each of which may contribute to its therapeutic efficacy to a variable extent.

Anticonvulsants differ in their effects on neurotransmission and on ion channels, both of which may be related to the pathophysiology of epilepsy and nonepileptic disorders. Valproate inhibits voltage-gated sodium channels and potentiates the inhibitory action of gamma-aminobutyric acid (► GABA), by either increasing its release, decreasing its reuptake, or slowing its metabolic inactivation. Valproate may also interact with other ion channels, such as voltage-gated calcium channels, and also indirectly block ► glutamate action. Carbamazepine and structurally related oxcarbazepine may act by blocking the alpha subunit of voltage-gated sodium channels, and may also interfere with calcium and potassium channels. As with carbamazepine, the mood-stabilizing effect of lamotrigine is probably related to the inhibition of sodium and calcium channels in presynaptic neurons and the subsequent stabilization of neuronal membranes. In addition, lamotrigine may reduce the release of the excitatory neurotransmitter glutamate. Topiramate has been demonstrated to possess many molecular effects, including enhanced GABAergic activity, reduced glutamatergic neurotransmission, and inhibition of voltage-gated calcium channels. Gabapentin and pregabalin possess a selective inhibitory effect on the $\alpha_2\delta$ subunit of the voltage-gated calcium channels and may also facilitate GABAergic function. Levetiracetam binds to the synaptic vesicle protein 2A (SV2A), thereby reducing glutamate release. Tiagabine inhibits GABA reuptake, thereby increasing its postsynaptic availability.

Interference with intracellular mediators and signaling pathways is an important postulated mechanism in the pathophysiology of bipolar disorder (Rogawski and Loscher 2004). In addition, recent evidence from brain imaging and postmortem histopathology indicates that atrophy and glial death in specific brain regions, especially prefrontal cortex and hippocampus, are involved in mood disorders (Zarate et al. 2006). It has been hypothesized that mood-stabilizing agents may exert long-term beneficial effects by activating intracellular signaling pathways that promote neuroplasticity, ► neurogenesis or cell survival. Common actions on cell signaling of anticonvulsants and ► lithium, the gold standard in the treatment and prophylaxis of bipolar disorder, have been identified in recent years. As with lithium, the mood-stabilizing action of valproate and, possibly, carbamazepine has been linked to inositol depletion. Lithium and valproate block inositol monophosphatase (IMPase), preventing the conversion of inositol-1-phosphate (IP_1) to *myo*-inositol. This effect is considered to result in the stabilization of the structural integrity of neurons and the enhancement of synaptic plasticity. Valproate shares with lithium other effects on downstream signal transduction cascades, such as the inhibition of protein kinase C (PKC) and myristolated alanine rich C kinase substrate (MARKCS). The mood-stabilizing properties of lithium have also been attributed to the inhibition of glycogen synthase kinase 3β (GSK3β), an enzyme that contributes to many cellular functions, including apoptosis. Valproate and lamotrigine have similar effects on GSK3β, whereas carbamazepine does not. Other common effects of lithium and valproate are to increase the activity of the extracellular signal-regulated kinase (ERK) pathway, resulting in the enhanced transcription of neurogenesis and cell survival factors, such as antiapoptotic protein Bcl-2 and ► brain-derived neurotrophic factor (BDNF). Valproate may also regulate ► gene expression and transcription by acting as a ► histone deacetylase inhibitor.

In summary, anticonvulsants may be effective in many non-epileptic disorders. With regard to their use as mood stabilizers, anticonvulsants such as valproate, carbamazepine, and lamotrigine appear to have a clear role based on their effect on intracellular pathways. Anticonvulsants with effects on voltage-gated sodium or calcium channels, such as gabapentin, pregabalin, carbamazepine, lamotrigine, and valproate, may be particularly useful in neuropathic pain. Some agents, namely valproate and topiramate, have demonstrated efficacy in the prevention of migraine, possibly by increasing GABAergic and decreasing glutamatergic neurotransmission, thereby reducing neuronal hyperexcitability. The enhancement of GABAergic function may explain the beneficial effect of gabapentin, pregabalin, valproate, and tiagabine in anxiety disorders and essential tremor.

Animal Models

There is a limited number of fully validated and appropriate animal models of bipolar disorder for in-depth

behavioral, biochemical, histological, and pharmacological analysis (Gould and Einat 2007). The paucity of suitable animal models and difficulty in assessing the prophylactic effects of mood stabilizers is a rate-limiting step in the process of understanding the neurobiology of the disorder, as well as in the development of novel medications. Modeling bipolar disorder in animals is problematic for a number of reasons, including limited knowledge about underlying pathophysiology, susceptibility genes, and mode of action of the available mood stabilizers. In addition, in humans, the disease is cyclical and clinically heterogeneous, and there are no established biomarkers for the disease state or the effects of treatment.

The existing animal behavioral tests and models may be classified into a number of general areas, such as whether they focus on particular symptoms, bipolar endophenotypes, and pathophysiology, or response to existing medications (Gould and Einat 2007). Symptom-based models of bipolar disorder are attempts to represent aspects of either the manic or the depressive phase of the illness. Symptoms of mania that can be modeled in mania include increased activity, irritability, aggressive behavior, sexual drive, and reduced need for sleep. Models of the depressive phase are based on models previously validated in the context of depression research, and are available for symptoms such as anhedonia, fatigue, changes in sleep patterns, and changes in appetite or weight. Models based upon ► endophenotypes and pathophysiology can be neurophysiological, biochemical, endocrine, neuroanatomical, genetic, cognitive, or neuropsychological. In particular, the identification of susceptibility genes for bipolar disorder might help to define specific neurobiological processes and associated behaviors. Consequently, animal models studying the relevance of changes in the levels of proteins, circuits and synapses, and brain function, without regard to modeling of symptoms, may be particularly useful. A number of models have been developed based upon response to existing medications. They have considerable value both in understanding the mechanism of action of available drugs and in developing new treatments for bipolar disorder. In this respect, given the evidence for some overlapping signal transduction properties of lithium and valproate, it is reasonable for newly developed drugs that have effects on neuronal intracellular signaling and ion channel-mediated actions to be considered in preclinical and clinical testing for their potential effects on bipolar disorder, irrespective of whether such drugs are called anticonvulsants.

A model based on the phenomenon of "kindling," which is an animal model of epileptogenesis, was proposed as relevant to bipolar disorder pathophysiology and the mechanism of action of anticonvulsants used for treatment (Post 2007). The kindling model predicts temporal variation in the function of neural circuits and associated episodes, evolution of the illness and episode cyclicity, and might explain how events trigger affective episodes. Many anticonvulsants have demonstrated antikindling effects in vitro and this may account for their efficacy in both epilepsy and bipolar disorder.

► Pharmacokinetics

Anticonvulsants are generally well absorbed. They are lipophilic compounds that easily cross the ► blood–brain barrier and accumulate in fatty tissues. All commonly used anticonvulsants, except gabapentin, pregabalin, and levetiracetam are metabolized in the liver by cytochrome P450 isoenzymes (CYPs) or uridine diphosphate glucuronosyltransferases (UGTs). The elimination half-lives of anticonvulsants differ among the various agents, ranging between a few hours (valproate) and days (phenobarbital). Time to reach steady-state levels differs accordingly, but once- or twice-daily dosing is possible for all compounds. In this respect, extended-release formulations of valproate and carbamazepine have recently become available. As most anticonvulsants are extensively metabolized via hepatic enzymes, they may be involved in ► drug interactions. Their biotransformation can be affected by the concomitant administration of other drugs, including other anticonvulsants with inhibiting or inducing properties toward these enzymes. In addition, some anticonvulsants have prominent inhibitory or inducing effects on the activity of the hepatic enzymes that metabolize the majority of existing medications. In this respect, valproic acid is considered a broad-spectrum inhibitor of various drug-metabolizing enzymes. The first-generation anticonvulsants carbamazepine, phenytoin, and phenobarbital are broad-spectrum inducers of a variety of CYP enzymes, including CYP1A2, CYP2C9, CYP2C19, and CYP3A4, as well as UGTs and microsomal epoxide hydrolase. Compared with older agents, new anticonvulsants appear to have clear advantages in terms of a lower potential for such interactions. As the mode of action of anticonvulsants involves different effects on various neurotransmitter systems and ion channels, these compounds may be involved in potentially adverse pharmacodynamic interactions with other drugs, in particular other central nervous system (CNS) agents.

Efficacy

Although traditionally used to treat epilepsy, anticonvulsants have proven to be effective in a variety of disease

states (Spina and Perugi 2004). With regard to their ► efficacy in psychiatric conditions, three anticonvulsants, namely valproate, carbamazepine, and lamotrigine, are currently approved for the treatment of various aspects of bipolar disorder in most countries (Weisler et al. 2006). Large-scale, randomized, double-blind, well-controlled studies have documented that valproate and carbamazepine are highly effective in the treatment of acute mania. On the other hand, neither valproate nor carbamazepine has robust evidence supporting their efficacy in the treatment of acute bipolar depression. Valproate and, to a lesser extent, carbamazepine appear to be effective in the prophylactic treatment of many bipolar patients, including those refractory to or intolerant of lithium, but they are not approved for long-term maintenance therapy. While some studies have suggested that lamotrigine may be effective for the acute treatment of bipolar depression, there is strong evidence of its efficacy in preventing the recurrence of depressive episodes without the associated risks of cycle acceleration or manic/hypomanic switches (Weisler et al. 2008). Lamotrigine is currently approved only for the prophylaxis of bipolar I disorder. Concerning other newer anticonvulsants, oxcarbazepine has limited data suggesting efficacy in acute mania, while gabapentin and topiramate are ineffective as primary antimanic treatments, although they may be useful adjuncts for the treatment of comorbid conditions such as anxiety, pain, migraine, or weight problems. No controlled trial data are available for levetiracetam, tiagabine, or zonisamide.

Some anticonvulsant medications are widely used in the treatment of a number of chronic pain syndromes. Carbamazepine is commonly prescribed as first-line therapy for patients with trigeminal neuralgia. Gabapentin and pregabalin have been approved for the treatment of neuropathic pain associated with diabetic polyneuropathy and postherpetic neuralgia. Topiramate and valproate, in the form of divalproex sodium, are indicated for the prophylactic treatment of migraine.

Safety/Tolerability

Treatment with valproate is commonly associated with CNS side effects (tremor, somnolence, dizziness, ataxia, and asthenia) and gastrointestinal distress (nausea, vomiting, abdominal pain, and dyspepsia). Other important adverse events include weight gain, hair loss, and hyperammonemic encephalopathy in patients with urea cycle disorders. Hepatotoxicity and pancreatitis are rare but serious adverse effects associated with valproate therapy. The most common side effects reported during carbamazepine treatment include dizziness, somnolence, ataxia, nausea, and diplopia. Other important events less frequently observed include benign skin rashes, mild leucopenia, and thrombocytopenia, and hyponatremia, which is more common in the elderly population. Rare, but serious adverse events associated with carbamazepine therapy include severe dermatologic reactions, namely, Lyell syndrome (toxic epidermal necrolysis) and Stevens–Johnson syndrome (erythema multiforme major). The use of both valproic acid and carbamazepine during the first trimester of pregnancy is associated with an increased risk of congenital malformations, in particular spina bifida.

Lamotrigine is generally well tolerated, except for its propensity to cause rashes, including rarely the life-threatening Stevens–Johnson syndrome. Rashes by lamotrigine are in most cases reversible and can be minimized by very slow titration of the drug during the initiation of therapy and by avoiding or managing drug interactions, such as those with valproate, that raise lamotrigine levels. Further and rare side effects are vertigo, somnolence, diplopia, and gastrointestinal symptoms.

Other newer anticonvulsants occasionally used to treat bipolar disorders, such as oxcarbazepine, topiramate, gabapentin, or levetiracetam, have a relatively favorable tolerability profile. Oxcarbazepine is less sedating and has less bone marrow toxicity than its congener carbamazepine. Moreover, differently from carbamazepine, oxcarbazepine seems to possess only a modest inducing effect on hepatic drug-metabolizing enzymes and, therefore, has a lower potential for pharmacokinetic drug interactions. Topiramate is associated with weight loss and is sometimes given as an adjunct to mood stabilizers that cause weight gain.

Conclusion

In summary, anticonvulsants represent a heterogeneous group of drugs that, in addition to having proven efficacy for the management of epilepsy, are increasingly used to treat a variety of other neurological and psychiatric conditions. In particular, some anticonvulsants, namely valproate, carbamazepine, and lamotrigine, have become an integral part of the pharmacological treatment of bipolar disorder. Other newer anticonvulsants appear to have more favorable tolerability and drug interaction profiles as compared to older compounds, thus improving compliance with treatment. However, evidence for their efficacy in treating the various phases of bipolar disorder is still inadequate. Therefore, there is an ongoing need for controlled studies with a large number of patients and greater homogeneity of diagnosis in order to establish the efficacy of individual anticonvulsants in the management of psychiatric disorders.

Cross-References

- ▶ Bipolar Disorder
- ▶ Blood–Brain Barrier
- ▶ Brain-Derived Neurotrophic Factor
- ▶ Drug Interactions
- ▶ First-Generation Antiepileptics
- ▶ Gene Expression
- ▶ Gene Transcription
- ▶ Histone Deacetylase Inhibitors
- ▶ Lithium
- ▶ Mood Stabilizers
- ▶ Neurogenesis
- ▶ Second-Generation Antiepileptics

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Anti-Dementia Drugs

Definition

Drugs that give symptomatic relief to cognitive and memory dysfunction in the early stages of ▶ dementia (Alzheimer's disease). The drugs currently available enhance cholinergic and/or glutamatergic function.

Antidepressants

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Synonyms

Classification of psychoactive drugs; Thymoleptics

Definition

Antidepressants are compounds used to treat depression. Specifically, they reduce symptoms of depression. They do not elevate mood. The agents approved for the treatment of depression, however, are also useful in an array of other disorders, including anxiety disorders, pain syndromes, attention deficit hyperactivity disorder (ADHD), smoking cessation, and premenstrual dysphonic disorder. In most cases, the term "antidepressant" is still retained to refer to the class of drugs.

Pharmacological Properties

History

The first agents approved for use in depression by the US Food and Drug Administration (FDA) were discovered in the late 1950s. Roland Kuhn, a Swiss psychiatrist, was exploring compounds that might have value in depression. He observed that G 22355, a J. R. Geigy company compound, appeared to be of value in patients with endogenous depression. This compound, also known as ▶ imipramine (*Tofranil*), possessed a three-ring structure somewhat similar to ▶ chlorpromazine, an antipsychotic. This finding had enormous consequences not only for the treatment of depression, but also in providing a conceptual basis for a psychopharmacologic theory of depression (Schildkraut 1965). In subsequent years, several other tricyclic (TCA) and related heterocyclic compounds were introduced for treating depression (Nelson 2009). These agents would be the first-line agents for the treatment of depression for the next 3 decades.

Also during the late 1950s, a drug used in treating tuberculosis, iproniazid (a ▶ monoamine oxidase inhibitor [MAOI]) was observed to improve symptoms of depression. Further testing confirmed antidepressant effects and it was widely used for a short period of time. Because of concerns that iproniazid caused jaundice, its successors, isoniazid (*Marplan*), ▶ tranylcypromine (*Parnate*), and ▶ phenelzine (*Nardil*) became the MAOI agents used for the treatment of depression. Because of safety issues involving interactions with tyramine in the diet, and

interactions with sympathomimetic and other medications, the MAOI drugs were not widely used.

During the 1980s, several new antidepressants were developed. Unlike the tricyclics, which had similar chemical structures, the newer agents differed in structure but were grouped according to their function. The first of these to be marketed was ▶ trazodone (*Desyrel*). Trazodone is an antagonist at the postsynaptic serotonin 2 (5-HT_2) receptor and has antihistaminic properties. It was widely used in the 1980s but its use in depression declined with the introduction of the selective serotonin reuptake inhibitors (SSRIs). ▶ Bupropion was also introduced in the 1980s. As it was coming to market, a few patients in a bulimia study experienced seizures and its marketing was delayed while this safety issue was explored. It was reintroduced with the recommendation not to exceed 450 mg/day.

In the late 1980s, ▶ fluoxetine (*Prozac*) was approved for use in depression. It was followed later by ▶ paroxetine (*Paxil*), ▶ sertraline (*Zoloft*), and ▶ citalopram (*Celexa*). The greater tolerability of these agents led to rapid acceptance; by 1994, this class of antidepressants surpassed the tricyclics as the most widely used antidepressants. The active marketing of the SSRIs in depression coupled with new indications for ▶ panic disorder, ▶ obsessive–compulsive disorder, ▶ social anxiety disorder, ▶ posttraumatic stress disorder, ▶ premenstrual dysphoric disorder, bulimia, and ▶ generalized anxiety disorder, led to a substantial growth, in the 1990s, of the market for antidepressants in general and the SSRIs in particular. ▶ Fluvoxamine (*Luvox*), another SSRI, was approved by the FDA for use in OCD, but not in depression. ▶ Escitalopram (*Lexapro*), the s-isomer of citalopram, was the last SSRI developed for use in depression.

For a period of time in the 1980s and into the 1990s, drug development focused on these "selective" agents. While their improved tolerability and safety offered advantages, their efficacy was no better than the tricyclics, and some questioned if they were less effective. In an attempt to improve efficacy, new agents were introduced that had actions on both ▶ serotonin (5-HT) and ▶ norepinephrine (NE). These dual action agents were known as the SNRIs and included ▶ venlafaxine (*Effexor*) and ▶ duloxetine (*Cymbalta*). Recently, the desmethyl metabolite of venlafaxine (▶ desvenlafaxine [*Pristiq*]) was introduced. Each of these compounds is relatively more potent in blocking 5-HT uptake than NE uptake, but as the dose increases, NE uptake blockade increases. These compounds are relatively free of the antihistaminic, anticholinergic, and sodium channel effects of the TCAs that contributed to side effects. Venlafaxine and duloxetine were also approved for use in generalized anxiety disorder, and additionally appeared to have the beneficial effects in chronic pain syndromes shown by amitriptyline and other tricyclics. Duloxetine is now approved for use in diabetic neuropathic pain and fibromyalgia.

Two other second-generation antidepressants were marketed in the USA – nefazodone (*Serzone*) and ▶ mirtazapine (*Remeron*). Nefazodone is somewhat similar to trazodone but less antihistaminic. Its principle effect is postsynaptic at the 5-HT_2 receptor and in theory, this should have reduced side effects. While it had little effect on weight or sexual function, cases of fatal hepatic failure led to decreased use of the drug. Mirtazapine has a different mechanism of action. As the result of antagonism of $alpha_2$ adrenergic receptors, levels of serotonin and norepinephrine increase. The agent also antagonizes 5-HT_2 receptors and 5-HT_3 receptors, and is antihistaminic.

Mechanism of Action

The principal mechanism of action of most antidepressants involves the blockade of serotonin and norepinephrine at the presynaptic neuron in the brain (Charney et al. 1991). This increases the availability of these neurotransmitters at the synapse, the junction at which one neuron communicates with another. In response to the increase in these neurotransmitters, autoreceptors on the presynaptic neuron turn down the firing rate of those cells and less neurotransmitter is released. During a few weeks of treatment, these autoreceptors are desensitized and the firing rate returns to its tonic rate. At this point, neurotransmission is increased. While the feedback mechanisms in the norepinephrine system are less well understood, the net effects are similar. These delayed effects that occur over time are thought to be more consistent with the timing of symptomatic change during the treatment of depression. The confirmation of a central role for serotonin and norepinephrine in the mechanism of action of several agents came from studies depleting serotonin or norepinephrine (Delgado et al. 1993). In depressed patients who had responded to a serotonin antidepressant, the blockade of serotonin synthesis with ▶ tryptophan depletion resulted in relapse. Similar effects were noted in patients taking a norepinephrine antidepressant if NE was blocked with AMPT (alpha-methyl-para-tyrosine). ▶ Clomipramine, amitriptyline, imipramine, doxepin, venlafaxine, desmethylvenlafaxine, and duloxetine all block the uptake of serotonin and norepinephrine with varying potency. In some cases (clomipramine, amitriptyline, imipramine), the parent compound has a greater effect on serotonin uptake and the metabolite on norepinephrine. Mirtazapine also increases 5-HT and NE

concentrations, but through a different mechanism – the blockade of alpha$_2$ adrenergic receptors. Trazodone, nefazodone, mirtazapine, and some tricyclic antidepressants (amitriptyline and nortriptyline) are also 5-HT$_2$ receptor antagonists. This receptor acts in opposition to the primary serotonin receptor (5-HT$_1$), so that antagonism at the 5-HT$_2$ receptor enhances the effects of serotonin. Clinically this appears to benefit sleep and may help reduce anxiety. Bupropion appears to have a different mechanism, blocking the uptake of dopamine and norepinephrine. Both the parent drug and its metabolite, hydroxybupropion, participate in these effects.

The antidepressants also have other effects that have been thought to contribute to side effects. The tricyclics have ► anticholinergic side effects, which can contribute to dry mouth, blurred vision, constipation, and urinary hesitancy. These effects can also impair cognition and in older patients can cause delirium. Amitriptyline is the most anticholinergic of the antidepressants. The tricyclics, trazodone, and mirtazapine are antihistaminic. These effects can contribute to sedation and weight gain. Mirtazapine is the most antihistaminic antidepressant followed, by doxepin. Alpha$_1$ adrenergic effects contribute to orthostatic hypotension, the most common side effect of the tricyclic antidepressants that limits treatment. The tricyclic antidepressants also have effects on sodium channels, which prolong cardiac conduction. In most patients, this is not a problem. However, in patients who already have delayed conduction, this effect can result in heart block. This effect increases at the high plasma concentrations that are frequently achieved with overdose and is the primary reason for death with overdose.

Recently, interest in the neuroprotective effects of antidepressants has emerged (Schmidt and Duman 2007). A number of converging lines of evidence suggest this mechanism may be involved in the treatment of depression. It has been demonstrated in animals that repeated or chronic exposure to cortisol damages the hippocampus. Cortisol levels are elevated in some depressed patients. Brain imaging studies in depressed human subjects show evidence of smaller hippocampal volumes, and one study found the duration of untreated depression was correlated with smaller hippocampal volumes. A particularly intriguing finding is that antidepressants increase neuroprotective factors, such as ► brain derived neurotrophic factor (BDNF), and that antidepressant treatment regenerates nerve cell growth in the dentate gryus of the ► hippocampus. These findings suggest a role for ► neuroprotection in the action of antidepressants. It is unclear currently if these effects are involved in acute treatment response or if these effects become more important during chronic treatment. All antidepressants share this effect, so it would not explain differences among them. Some agents that are not antidepressants have these effects. This theoretical model does not appear as useful for predicting some of the synergistic effects of medication combinations as have the older synaptic transmission models.

Animal Models

There are no adequate animal models for depression. None of the animal models adequately account for all of the symptoms seen in human subjects, especially the psychological symptoms. As a result, it is not possible to use animal models to develop a comprehensive understanding of the neurobiology of depression. There are animal assay models that test certain properties of antidepressant drugs. There are also "homologous" models in which animals display behaviors that are somewhat similar to those observed in depressed subjects. These models include the reduction in motor activity induced by ► reserpine, the swim test immobility model, the syndrome in monkeys induced by isolation and separation, and the uncontrolled foot shock model (also known as the ► learned helplessness model). The chronic stress models may come closest to mimicking the physiology of depression. Recently gene "knock-out" models, usually in mice, have been used to explore the effects of specific genes on behaviors seen in depression and then test the effects of drugs on these behaviors. Selective breeding has been used to develop strains of animals with specific behaviors. While these models have aided drug development, insofar as they provide a model of what existing antidepressants do, ironically they may lead to development of drugs with profiles similar to older agents rather than to truly novel agents.

► Pharmacokinetics

All of the antidepressants described here are cleared from the body by hepatic metabolism. Various enzymes in the cytochrome P450 system in the liver participate in this process. Polymorphisms (genetic variants) of certain genes that control these enzymes can result in widely variable plasma concentrations of drugs given at the same dose. Individuals deficient in certain enzymes can develop dangerously high plasma concentrations of the drug. Alternatively, a few individuals may be "ultra fast" metabolizers and have very low, ineffective plasma levels at usual doses. Because side effects were common and limited dosing of the tricyclics, blood level monitoring was sometimes employed to achieve adequate levels without exceeding safe concentrations. With the second-generation agents, improved tolerability allowed these agents to be given at

doses high enough to be effective in most individuals and blood level monitoring is seldom employed.

► Cytochrome P450 enzymes are important for understanding drug interactions (Nemeroff et al. 1996). Drug that block the enzymes are known as inhibitors. Drugs that speed up the enzymes are inducers. Enzyme induction results from the production of more enzymes and takes 2–3 weeks. The 1A2 pathway is induced by nicotine. The 3A4 pathway is induced by ► carbamazepine, ► barbiturates, ► phenytoin, and St. John's Wort. Enzyme inhibition occurs within days and is more common. Some antidepressants are potent enzyme inhibitors. Fluvoxamine inhibits the 1A2 pathway as well as 2C9 and 2C19, fluoxetine inhibits 2D6 and the 2C family, and paroxetine inhibits 2D6, as does bupropion and duloxetine. Nefazodone inhibits the 3A4 pathway.

During metabolism, active metabolites may be produced. Their effects may differ from the parent compound. The tertiary tricyclic agents are metabolized to secondary amines (e.g., desipramine, nortriptyline, and desmethylclomipramine). The secondary amines tend to be more potent NE uptake blockers, while their parent compounds have greater effects on 5-HT. The hydroxy-metabolite of bupropion is selective for NE uptake blockade, while bupropion itself has greater effects on dopamine. The net effect of the drug, then, depends on the relative concentrations of the parent and metabolites. Among the SSRIs, fluoxetine is noteworthy for its active metabolite norfluoxetine. This metabolite has activity similar to the parent but a much longer half-life of 5–7 days. The metabolite of venlafaxine has a longer half-life than the parent and extends the action of the compound. Nefazodone has perhaps the most complicated array of three active metabolites with different effects and different half-lives.

The antidepressants are widely distributed in the body. In order to cross the ► blood–brain barrier, they are lipophilic (fat soluble). This property makes them less soluble in plasma and they are carried in the blood stream attached to plasma proteins. In most cases, they are highly bound to these proteins. Venlafaxine is an exception and protein binding is lower. As the result of hepatic metabolism, most of these compounds are conjugated to inactive substances and excreted by the kidney.

The hepatic clearance of the antidepressants is variable. Ideally, drugs with a half-life of about 24 h can easily be given once a day. Some agents such as bupropion, which has a half-life of 16 h, were initially given several times a day. Extended-release preparations allowed for less frequent dosing. As mentioned earlier, the half-lives of fluoxetine and its metabolite were considerably longer than those of the other SSRIs. This helped to reduce the effect of occasional missed doses, and at one point, the manufacturer marketed a once weekly formulation of the drug. The long half-life also resulted in a gradual decline in the plasma level, which helped to minimize discontinuation symptoms. On the other hand, the long half-life required a longer washout period – about 5 weeks – before most of the drug was out of the body.

The MAOI agents have a different pharmacology. The older compounds had irreversible effects, inactivating monoamine oxidase enzymes. As a result, the duration of their effects was unrelated to the duration of their plasma concentrations; instead, effects persisted until new MAO enzyme was produced. Usually it would take 2 weeks after stopping an MAOI for enzyme levels to return to normal. ► Moclobemide, an MAOI not marketed in the USA, is a reversible MAOI. The advantage of this compound is that foods containing tyramine do not need to be restricted in the diet. The recent ► selegiline transdermal system allows for cutaneous absorption. As a result, the drug has less effect on MAO enzymes in the gut, so at lower doses dietary restrictions are not required.

Efficacy

Antidepressants are effective in the treatment of depression, several pain syndromes, anxiety disorders, ADHD, and smoking cessation. One of the largest recent reviews of antidepressants in major depressive disorder found 182 controlled trials conducted in over 36,000 individuals (Papakostas and Fava 2009). The mean pooled response rate was 54% with drug treatment and 37% with placebo, and the difference was highly significant. This translates into an estimated number need to treat of about six, which is considered clinically meaningful. Recently it has been suggested that the published literature may overestimate efficacy because negative studies are less likely to be published; however, there is little question that these drugs are effective, and analyses of all trials reported to the FDA, published or not, have been preformed. The difference between drug and placebo is greater in more severely depressed individuals and greater if the likelihood of receiving placebo is higher. There also appears to be recent a trend toward higher placebo response rates and smaller drug-placebo differences.

Antidepressants are also effective in chronic major depressive disorder and dysthymia. Their efficacy as monotherapy in psychotic depression appears to be reduced, but they are often given with ► antipsychotics. In bipolar I disorder, antidepressants can induce mania and may aggravate rapid cycling; most guidelines recommend avoiding their use or giving them only with mood stabilizers.

In addition to being effective for the acute treatment of depression, antidepressants reduce relapse and recurrence in depression. This is particularly important because depression is usually a recurrent illness. A meta-analysis of 31 randomized controlled trials in major depressive disorder found that drug treatment reduced relapse and recurrence rates by 70% (Geddes et al. 2003). In fact, this appears to be the most potent and well replicated effect of antidepressant agents, although it is noted that this effect is demonstrated in individuals who have had an acute response to the same agent.

An area of considerable interest is whether one antidepressant or a class of antidepressants is more effective than another. A specific question raised by the widespread use of SSRI agents is whether they were as effective as the tricyclics. A review of over 100 comparison trials found comparable efficacy except for a small number of studies in inpatients (Anderson 2000). Two studies by the Danish University Group found the tricyclic clomipramine more effective than the SSRIs citalopram and paroxetine. Clomipramine has effects on both NE and 5-HT. Recently, it has been suggested that other dual action ► SNRIs (serotonin-norepinephrine reuptake inhibitors) might also be more effective. Reviews of venlafaxine and duloxetine studies found some evidence to support this; however, the largest meta-analysis of 93 trials of dual action drugs found that while the difference was statistically significant, it was sufficiently small to be of doubtful clinical importance. Another question of great interest is whether there are predictors of response to one agent or another. In the pre-SSRI era, the MAOIs were found to be superior to tricyclics in ► atypical depression, a syndrome in which mood is reactive to current events and sleep and appetite are increased. However, the second-generation antidepressants do not appear to differ in efficacy in this syndrome. Few prospective trials of symptom predictors have been performed and there is no well-established pattern of symptoms that predicts response to a particular drug class. Investigators have also examined if there are biological differences that might predict response in depression to a particular drug class. Recently, this exploration has shifted to looking for genetic predictors. To date, no reliable biologic predictor has been identified.

Uses in Other Disorders

Antidepressants, tricyclics in particular, have been extensively studied in chronic pain syndromes. Evidence suggests the magnitude of the effect (effect size) may be larger in pain than depression. It appears that dual action NE – 5-HT drugs are most effective, followed by NE uptake inhibitors, with SSRIs least effective for chronic pain. Duloxetine is the first antidepressant approved by the FDA for use in diabetic neuropathic pain and fibromyalgia.

Although imipramine was the first antidepressant shown to be effective for panic disorder and generalized anxiety disorder, it was never approved for use in these conditions. Clomipramine was shown to be effective in OCD and has that indication in the USA. The SSRIs are the first class with FDA approval in a variety of anxiety disorders including panic disorder, OCD, PTSD, social anxiety disorder, and generalized anxiety disorder. Not all SSRIs are approved for use in each disorder but it appears likely this is a class effect. Sertraline and paroxetine are approved for panic disorder, PTSD, and SAD. Paroxetine and escitalopram are approved for generalized anxiety disorder. Four of the SSRIs are approved for use in OCD and this is the only indication for use in the USA for fluvoxamine. Fluoxetine is approved for use in bulimia. Fluoxetine and sertraline are approved for use in premenstrual dysphoric disorder. Venlafaxine and duloxetine are both approved for use in generalized anxiety disorder. It appears that agents that block 5-HT uptake, whether they are SSRIs or SNRIs, have efficacy across a spectrum of anxiety disorders. Among these serotonergic agents, differences in the indications that are approved appear to reflect marketing decisions more than real differences in efficacy; however, without controlled trials this supposition is unconfirmed.

Bupropion is approved for use in smoking cessation under the brand name Zyban. The tricyclic norepinephrine reuptake inhibitor desipramine was previously commonly used in treating childhood ADHD but cases of sudden death in children under 12 years led to a rapid decline in use. ► Atomoxetine, a more selective NE uptake inhibitor, is approved for use in ADHD. Bupropion in controlled studies appeared to be effective in adult ADHD but does not have FDA approval for that indication.

Safety and Tolerability

The tricyclic antidepressants have a variety of tolerability issues related to their anticholinergic, antihistaminic, and alpha-1 blocking properties (Richelson and Nelson 1984). Patients often experienced dry mouth, increased heart rate, and light-headedness on standing, and sometimes sedation, urinary hesitancy, and constipation. It was uncommon for a patient on a tricyclic not to notice at least one side effect. The tricyclics delayed ventricular conduction (Glassman et al. 1993). In vulnerable individuals, at high plasma levels or after overdose, this could cause heart block. Seizures also occurred with the tricyclics, and risk was higher in vulnerable individuals, at high plasma levels, or after overdose. The tricyclics could be fatal in

overdose with as little as a 10-day supply of the drug. For many years, amitriptyline was the second leading cause of death by overdose with a single agent in the USA, after acetaminophen.

The MAOIs could also cause hypotension at therapeutic doses. The main concern with this class was the possibility of a hypertensive crisis or ▶ serotonin syndrome. A hypertensive crisis could occur when a patient on an MAOI ingested foods rich in tyramine or other drugs with sympathomimetic properties. The hypertensive crisis could result in a stroke. As a result, patients taking a MAOI needed to follow a diet low in tyramine and avoid certain drugs. These risks appeared reduced with the reversible MAOI meclobemide. The selegiline transdermal system (patch), because it is absorbed through the skin, has less effect on MAO enzyme in the gut, and at a dose of 6 mg/24 h does not require a tyramine restricted diet. Serotonin syndrome can occur in patients on an MAOI who ingest an SSRI or meperidine. Serotonin syndrome is characterized by confusion, fever, restlessness, myoclonus, hyperreflexia, diaphoresis, hypomania, shivering, and tremor, and can be fatal. It is thought to be caused by the excessive activation of 5-HT_{1A} receptors. The severity of these risks and the need to restrict diet and other drugs limited the use of the MAOIs.

The second-generation agents are substantially safer than the TCAs and MAOIs. They are less likely to be fatal in overdose. They do not prolong the electrocardiographic QTc interval. With the exception of bupropion, the risk of seizures is low. Perhaps the biggest difference, however, is tolerability. While few studies have assessed overall side effect burden, relatively more patients on a second-generation agent can take the drug without experiencing disruptive side effects during chronic dosing. When starting an SSRI, patients can experience nausea and some patients experience restlessness. Both are dose-related and usually transient. With long-term treatment, some patients experience sexual dysfunction or weight gain. The acute and long-term side effects of the SSRIs were shared by venlafaxine and duloxetine. Venlafaxine is associated with hypertension at high doses, e.g., 300 mg/day. This had also been observed in younger patients on desipramine and may be related to norepinephrine effects. Other uncommon events can occur. SSRIs block the uptake of serotonin into the platelet and affect platelet function. This can increase the risk of bleeding, with a risk similar to that of taking one aspirin a day. SSRIs have also recently been reported to increase bone demineralization and increase the risk of nontraumatic fractures. Although not well studied, the SNRIs, having similar effects on 5-HT uptake, would be expected to have similar risks.

Bupropion has a different side-effect profile. The most common side effects are agitation, insomnia, sweating, dry mouth, constipation, and tremor. Of the antidepressants, it is least likely to cause sedation or sexual dysfunction and is either weight-neutral or associated with weight loss. The most serious safety issue is seizures. The risk is dose related and similar to the tricyclics. This risk led to the recommendation not to exceed 450 mg/day. Seizure risk is reduced with delayed-release formulations that are associated with lower peak levels.

Mirtazapine, because of its antihistaminic properties, is the antidepressant most likely to cause sedation during initial treatment. Tolerance usually develops. Because the antihistaminic effect occurs at low doses and the alpha-2 adrenergic antagonism (which may be alerting or activating) occurs at higher doses, it was suggested that paradoxically the drug might become less sedating at higher doses. The antihistaminic effect also contributes to increased appetite and weight gain in some patients. This tends to limit the use of the agent in younger patients, but can be an advantage in older depressed patients.

Cross-References

- ▶ Aminergic Hypotheses for Depression
- ▶ Analgesics
- ▶ Animal Models for Psychiatric States
- ▶ Antidepressants: Recent Developments
- ▶ Brain-Derived Neurotrophic Factor
- ▶ Depression: Animal Models
- ▶ Drug Interactions
- ▶ Emotion and Mood
- ▶ Major & Minor & Mixed Anxiety-Depressive Disorders
- ▶ Monoamine Oxidase Inhibitors
- ▶ NARI Antidepressants
- ▶ Neuroprotection
- ▶ SNRI Antidepressants
- ▶ SSRIs and Related Compounds
- ▶ Tryptophan Depletion

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Antidepressants: Recent Developments

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Synonyms

Depression medications

Definition

Antidepressants are drugs used to treat depression, although many have been studied in and are used to treat a wide variety of conditions, including anxiety disorders, pain disorders, and others.

Pharmacological Properties

History

Since the serendipitous discovery of the ▶ antidepressant effects of tricyclics in the 1950s, depression has generally been treated by agents that boost the synaptic actions of one or more of the three ▶ monoamines (serotonin (5HT), ▶ norepinephrine (NE), and ▶ dopamine (DA)). Acutely enhanced synaptic levels of monoamines could lead to adaptive downregulation and desensitization of postsynaptic receptors over time, a pharmacological action consistent with current ▶ aminergic hypotheses of depression, which posit that the disorder may be due to the pathological upregulation of neurotransmitter receptors (Stahl 2008a). Thus, antidepressants theoretically reverse this pathological upregulation of receptors over time. Adaptive changes in receptor number or sensitivity are likely the result of alterations in ▶ gene expression and transcription. This may include not only turning off the synthesis of neurotransmitter receptors but also increasing the synthesis of various ▶ neurotrophic factors such as ▶ brain-derived neurotrophic factor (BDNF). In fact, preclinical studies demonstrate that antidepressants increase BDNF expression (Duman et al. 2001). Such prototrophic actions may apply broadly to all effective antidepressants and may provide a final common pathway for the action of antidepressants.

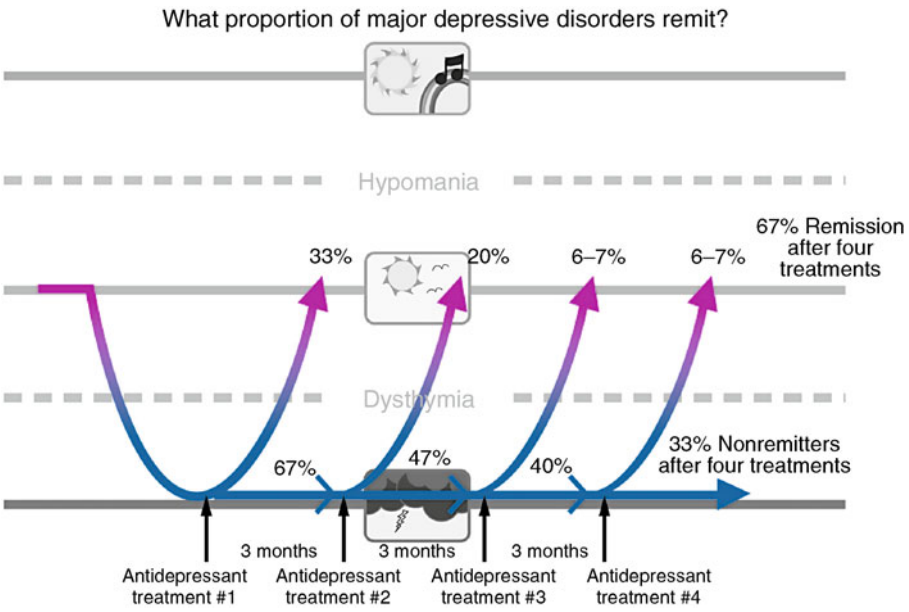
Although treatment with currently available antidepressants is effective for many patients, a large proportion experience residual symptoms, treatment resistance, and relapse. In the recent STAR*D (Sequenced Treatment Alternatives to Relieve Depression) study (Warden et al. 2007), only one-third of the patients on monotherapy with ▶ citalopram remitted initially. For those who failed to remit, the likelihood of ▶ remission with another antidepressant monotherapy decreased with each successive trial. Thus, after a year of treatment with four sequential antidepressants taken for 12 weeks each, only two-thirds of patients achieved remission (Fig. 1). Of additional concern is the fact that the likelihood of relapse increased with the number of treatments it took to get the patient to remit.

These results highlight the need for the continued exploration of more effective methods to treat major depression. A plethora of treatments are either under investigation or newly available for major depressive disorder, including new formulations of current antidepressants, new and existing agents that exploit the monoaminergic link to depression, and experimental agents with novel mechanisms of action.

New Twists on Old Drugs

One developmental focus for antidepressants is to improve the tolerability of existing agents. A recently approved hydrobromide salt formulation of ▶ bupropion allows the administration of single-pill doses up to 450 mg equivalency to bupropion hydrochloride salt, unlike bupropion hydrochloride controlled release formulations for which the biggest dose in a single pill is 300 mg. This could facilitate dosing for difficult-to-treat patients.

In addition, approval is pending for a once-daily controlled release formulation of ▶ trazodone that allows



Antidepressants: Recent Developments. Fig. 1. Remission rates in major depressive disorder with sequential monotherapies.

much more tolerable administration of high antidepressant doses (e.g., 300–450 mg). This may increase the utility of trazodone in depression, as the immediate release formulation is often not tolerated at high antidepressant doses due to its propensity to cause severe next-day sedation, and is used instead at low doses as a hypnotic.

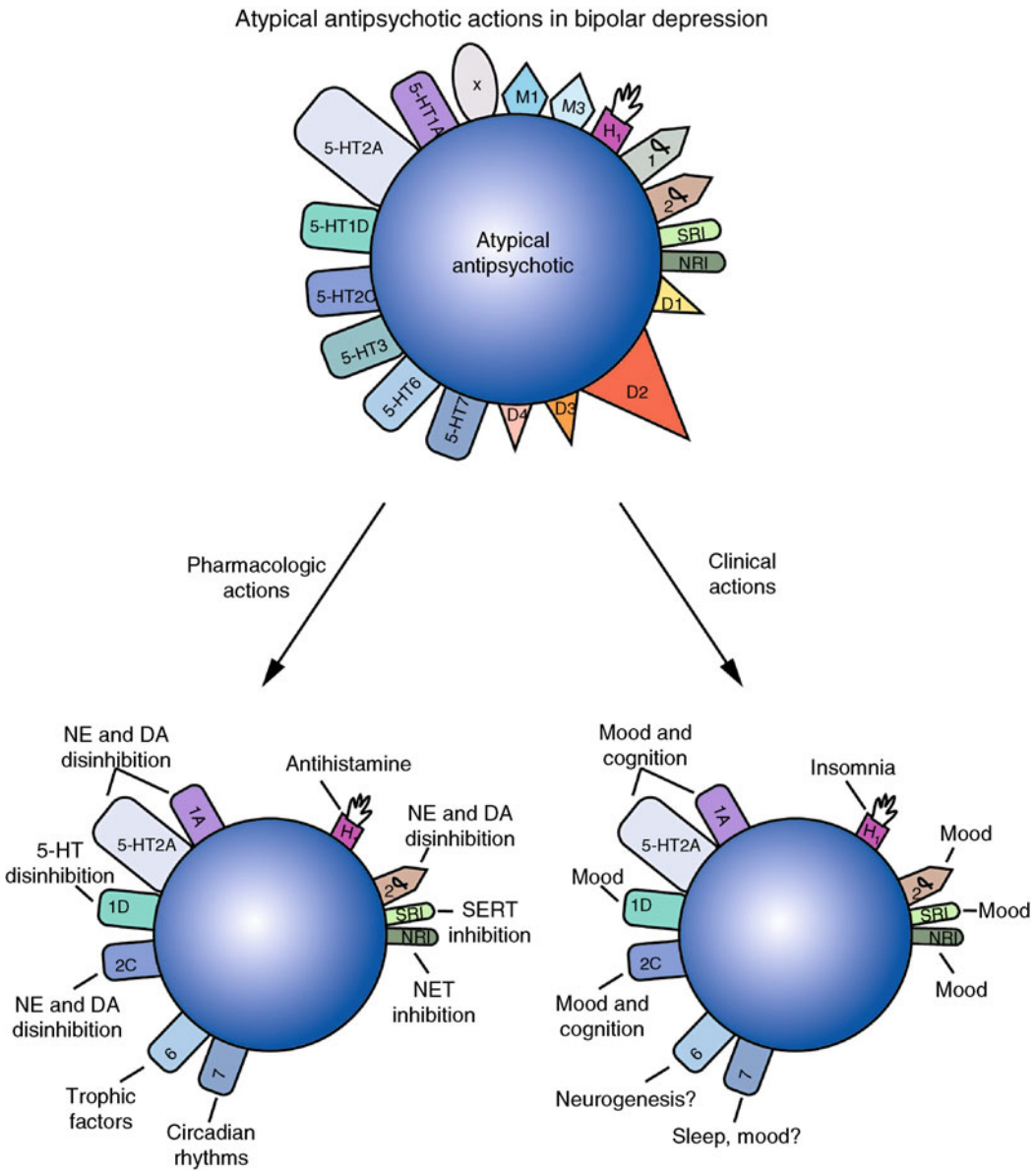
Another twist on an old drug is the availability of ► desvenlafaxine, the active metabolite of ► venlafaxine, as a unique antidepressant agent. Desvenlafaxine is formed as the result of CYP450 2D6 and thus itself bypasses this metabolic step, potentially giving it more consistent plasma levels than venlafaxine (Stahl 2009). In addition, although desvenlafaxine, like venlafaxine, is more potent at the 5HT ► transporter (SERT) than the NE transporter (NET), it has relatively greater actions on NET versus SERT than venlafaxine does at comparable doses. This greater potency for NET may make it a preferable agent for symptoms theoretically associated with NE actions, such as pain symptoms and vasomotor symptoms. In fact, desvenlafaxine was shown to be efficacious for hot flushes in perimenopausal women (Stahl 2008a; Wise et al. 2008), although it was not approved for this use due to cardiovascular safety concerns.

New Means of Monoaminergic Modulation

Atypical Antipsychotic Drugs

Currently, atypical ► antipsychotic drugs are used to treat ► bipolar disorder, with similar efficacy to each other in the manic phase but varying efficacy in treating the depressed phase. Several mechanisms are feasible explanations for how certain atypical antipsychotic drugs may work to improve symptoms in the depressed phase of bipolar disorder (Stahl 2008a). Actions at numerous receptors by different atypical antipsychotic drugs can increase the availability of 5HT, DA, and NE, which, as discussed earlier, are critical in the action of current antidepressants in unipolar depression (Fig. 2). Specifically, actions at $5HT_{2A}$, $5HT_{2C}$, and $5HT_{1A}$ receptors indirectly lead to NE and DA disinhibition, which may improve mood and cognition. Mood may also be improved by increasing NE and 5HT via actions at alpha 2 adrenergic receptors, by increasing NE via the blockade of the NE transporter, and by increasing 5HT via actions at $5HT_{1D}$ receptors and the blockade of the 5HT transporter. Antihistamine actions could improve insomnia associated with depression. Actions at other 5HT receptors may also play a role in treating depression.

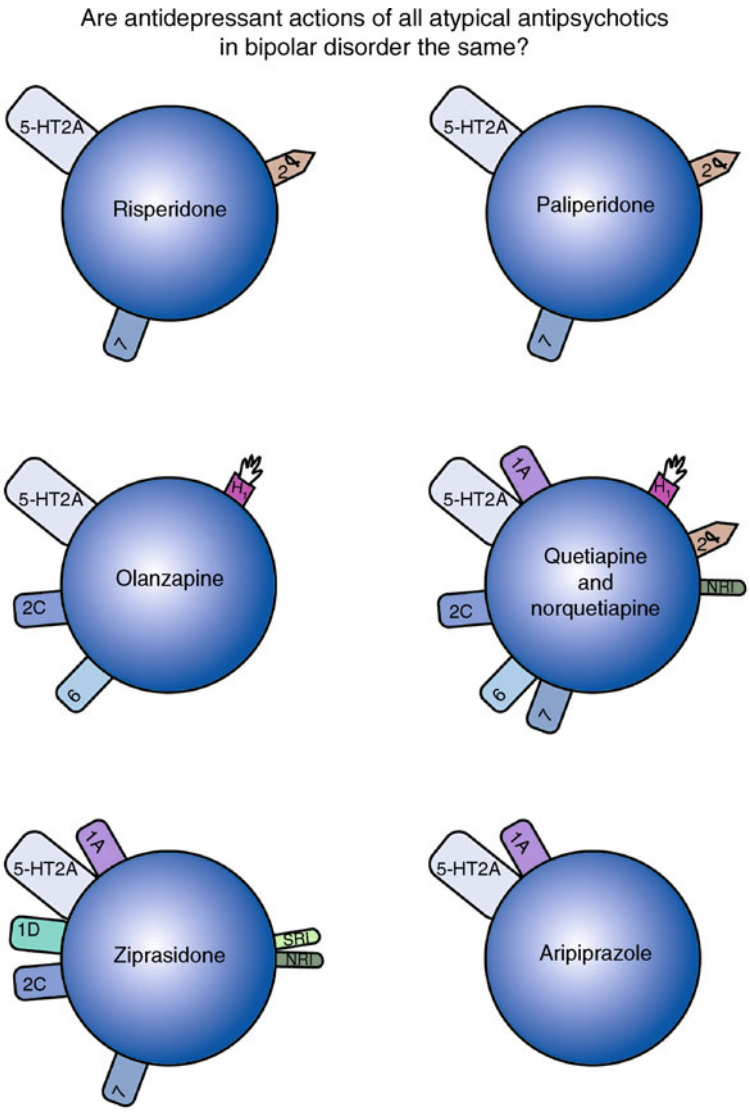
Each atypical antipsychotic has a unique portfolio of pharmacological actions that may contribute to its antidepressant actions (Fig. 3). This may explain why these agents differ in their ability to treat the depressed phase of ► bipolar disorder and also why some patients respond to one of these drugs and not to another. The agent with the most evidence of efficacy as a monotherapy for bipolar depression is ► quetiapine, which was recently approved for this indication. The effective dose of quetiapine in bipolar depression is 300–600 mg/day, lower than



Antidepressants: Recent Developments. Fig. 2. Pharmacologic properties of atypical ► antipsychotic drugs and their links to symptoms of depression.

that needed for the saturation of the D2 receptor but sufficient to cause $5HT_{2C}$ antagonism, $5HT_{1A}$ agonism, and norepinephrine reuptake inhibition, especially through the newly discovered pharmacologic actions of its active metabolite norquetiapine (Stahl, 2008a, 2009). This lends further weight to the speculative mechanisms described earlier for antidepressant action of atypical antipsychotic drugs.

Whether atypical antipsychotic drugs will be proven effective with a sufficiently favorable side effect and cost profile for unipolar depression is still under intense investigation (Papakostas et al. 2007). ► Aripiprazole was recently approved as an adjunct treatment for resistant depression (defined as failing one SSRI/SNRI trial). At its effective dose in depression – 2–10 mg/day, lower than that used for ► schizophrenia – aripiprazole is



Antidepressants: Recent Developments. Fig. 3. Atypical antipsychotic drugs: differing portfolios of pharmacologic action for bipolar depression.

primarily a D2 and D3 ► partial agonist with only weak $5HT_{2A}$ ► antagonist and $5HT_{1A}$ partial agonist properties (Stahl 2008b).

Triple Reuptake Inhibitors (TRIs)

These drugs are testing the idea that if one mechanism is good (i.e., selective serotonin reuptake inhibitors or SSRIs [► SSRIs and related compounds]) and two mechanisms are better (i.e., serotonin and norepinephrine reuptake inhibitors or ► SNRI antidepressants), then maybe targeting all three mechanisms of the trimonoamine neurotransmitter system would be the best in terms of efficacy. Several different triple reuptake inhibitors (or serotonin–norepinephrine–dopamine reuptake inhibitors) are listed in Table 1 (Stahl 2008a). Some of these agents have additional pharmacological properties as well. In particular, LuAA 24530, currently in clinical trials, is not only a TRI but also binds 5HT2C, 5HT2A, 5HT3, and alpha 1A adrenergic receptors. The question regarding TRIs is how much blockade of each monoamine transporter is desired, especially for the dopamine transporter or DAT. Too much dopamine activity can lead to a drug

Antidepressants: Recent Developments. Table 1. Antidepressants in development: triple reuptake inhibitors.

Triple reuptake inhibitor	Additional receptor targets	Development stage
DOV 216303		Phase II depression (terminated)
DOV 21947		Phase II depression
GW 372475 (NS2359)		No ongoing clinical trials in depression; Phase II for attention deficit hyperactivity disorder
Boehringer/NS2330		No ongoing clinical trials in depression; Phase II for Alzheimer dementia and for Parkinson's disease discontinued
NS2360		Preclinical
Sepracor SEP 225289		Phase II depression
Lu AA24530	5HT2C, 5HT3, 5HT2A, alpha 1A	Phase II depression
Lu AA37096	5HT6	Phase I
Lu AA34893	5HT2A, alpha 1A, and 5HT6	Phase II depression (terminated)

Antidepressants: Recent Developments. Table 2. Antidepressants in development: novel serotonin-linked mechanisms.

Novel serotonergic targets	Agent	Additional receptor targets	Development stage
$5HT_{2C}$ antagonism	Agomelatine	Melatonin 1,2	Approved EMEA with liver monitoring, Phase III depression in the USA
SSRI/$5HT_3$ antagonism	Lu AA21004	$5HT_{1A}$	Phase III depression
SSRI/$5HT_{1A}$ partial agonism	Vilazodone (SB 659746A)		Phase III depression
$5HT_{1A}$ partial agonism	Gepirone ER		Late-stage development for depression
$5HT_{1A}$ partial agonism	PRX 00023		Phase II depression, phase III for generalized anxiety disorder
$5HT_{1A}$ partial agonism	MN 305		No clinical trials in depression; Phase II/III for generalized anxiety disorder
Sigma 1/$5HT_{1A}$ partial agonism	VPI 013 (OPC 14523)	Serotonin transporter	Phase II depression
$5HT_{1A}$ agonism/$5HT_{2A}$ antagonism	TGW-00-AD/AA		Phase II depression
SRI/$5HT_2$/$5HT_{1A}$/$5HT_{1D}$	TGBA-01-AD		Phase II depression
$5HT_{1B/D}$ antagonism	Elzasonan		Phase II depression

of abuse, while not enough means that the agent is essentially an SNRI. Perhaps the desirable profile is the robust inhibition of SERT and the substantial inhibition of NET, like the known SNRIs, plus the addition of 10–25% inhibition of DAT. Some testing suggests that dopamine reuptake inhibition also increases acetylcholine release, so TRIs may modulate a fourth neurotransmitter system and act as multitransmitter modulators (Stahl 2008a). Further testing will determine whether TRIs will represent an advance over SSRIs or SNRIs in the treatment of depression.

Novel Serotonin Targets (Serotonin Agonists and Antagonists)

A large number of novel serotonin targets are in testing and are listed in Table 2 (Stahl 2008a). One particularly interesting novel serotonin target is the $5HT_{2C}$ receptor. Blockade of $5HT_{2C}$ receptors causes the release of both norepinephrine and dopamine, which is why these agents can be called norepinephrine dopamine disinhibitors (NDDIs). The novel antidepressant ► agomelatine combines this property of $5HT_{2C}$ antagonism with additional agonist actions at ► melatonin receptors (MT1 and

Antidepressants: Recent Developments. Table 3. Antidepressants in development: novel sites of action.

Novel mechanism	Agent	Development stage
Beta 3 agonism	Amibegron	Phase III discontinued
Neurokinin (NK) 2 antagonism	Saredutant (SR48968)	Phase III discontinued
NK2 antagonism	SAR 1022279	Preclinical
NK2 antagonism	SSR 241586 (NK2 and NK3)	Preclinical
NK2 antagonism	SR 144190	Phase I
NK2 antagonism	GR 159897	Preclinical
NK3 antagonism	Osanetant (SR142801)	No current clinical trials in depression; preliminary trials in schizophrenia
NK3 antagonism	Talnetant (SB223412)	No current clinical trials in depression; Phase II for schizophrenia and for irritable bowel syndrome
NK3 antagonism	SR 146977	Preclinical
Substance P antagonism	Aprepitant [MK869; L-754030 (Emend)]	Phase III for nausea/vomiting
Substance P antagonism	L-758,298; L-829,165; L-733,060	No clinical trials in depression; Phase III for nausea/vomiting
Substance P antagonism	CP122721; CP99994; CP96345	Phase II depression
Substance P antagonism	Casopitant (GW679769)	No clinical trials in depression; Phase III for nausea/vomiting
Substance P antagonism	Vestipitant (GW 597599) +/− paroxetine	No clinical trials in depression; Phase II for social anxiety disorder
Substance P antagonism	LY 686017	No clinical trials in depression; Phase II for social anxiety disorder and for alcohol dependence/craving
Substance P antagonism	GW823296	Phase II
Substance P antagonism	(Nolpitantium) SR140333	No clinical trials in depression; Phase II for ulcerative colitis
Substance P antagonism	SSR240600; R-673	No clinical trials in depression; Phase II for overactive bladder
Substance P antagonism	NKP-608; AV608	No clinical trials in depression; Phase II for social anxiety disorder
Substance P antagonism	CGP49823	Preclinical
Substance P antagonism	SDZ NKT 34311	Preclinical
Substance P antagonism	SB679769	Preclinical
Substance P antagonism	GW597599	Phase II depression
Substance P antagonism	Vafopitant (GR205171)	No clinical trials in depression; Phase II for insomnia and for posttraumatic stress disorder
MIF-1 pentapeptide analog	Nemifitide (INN 00835)	Phase II depression
MIF-1 pentapeptide analog	5-hydroxy-nemifitide (INN 01134)	Preclinical
Glucocorticoid antagonism	Mifepristone (Corlux)	Phase III depression
Glucocorticoid antagonism	Org 34517; Org 34850 (glucocorticoid receptor II antagonists)	Phase III depression
► Corticotropin releasing factor (CRF) 1 antagonism	R121919	Phase I

Antidepressants: Recent Developments. Table 3. (continued)

Novel mechanism	Agent	Development stage
CRF1 antagonism	CP316,311	Phase II (trial terminated)
CRF1 antagonism	BMS 562086	Phase II
CRF1 antagonism	GW876008	No clinical trials in depression; Phase II for social anxiety disorder and for irritable bowel syndrome
CRF1 antagonism	ONO-233M	Preclinical
CRF1 antagonism	JNJ19567470; TS041	Preclinical
CRF1 antagonism	SSR125543	Phase I
CRF1 antagonism	SSR126374	Preclinical
Vasopressin 1B antagonism	SSR149415	Phase II

MT2). Agomelatine also has $5HT_{2B}$ antagonist properties. This portfolio of pharmacological actions predicts not only antidepressant actions due to the NDDI mechanism of 5HT2C antagonism but also sleep-enhancing properties due to MT1 and MT2 agonist actions. Positive trials of agomelatine have been completed in the USA, and it is now approved in Europe with liver function monitoring required.

Another novel serotonergic agent is LuAA21004, currently in clinical trials. This agent is a serotonin reuptake inhibitor and also an antagonist at $5HT_3$ receptors, with additional actions at $5HT_{1A}$ receptors.

Novel Targets and Mechanisms

An interesting development is the potential utility of L-5-methyl-tetrahydrofolate (MTHF) as an adjunct treatment for depression. MTHF is a key derivative of ▶ folate and plays a critical role in monoamine synthesis; thus, the administration of MTHF could theoretically boost trimonoamines (Stahl 2008a). Current research specifically suggests that MTHF may be indicated for depressed patients with low folate levels and who have not responded adequately to antidepressants (Fava 2007). Available as a "medical food," MTHF appears to be safe with few side effects, but further research is necessary to determine its ultimate role in depression treatment.

Nonpharmacological developments in the treatment of depression include the approval of ▶ transcranial magnetic stimulation, in which a rapidly alternating current passes through a small coil placed over the scalp to generate a magnetic field that induces an electrical current in the underlying areas of the brain (Avery et al. 2006), and research into ▶ deep brain stimulation, in which a battery-powered pulse generator is implanted in the chest wall with one or two leads tunneled directly into the brain, especially within the subgenual area of the ventromedial prefrontal cortex, to send brief repeated pulses there (Mayberg et al. 2005).

Finally, a large number of agents that act at several other novel targets are in preclinical or early clinical development, and are listed in Table 3 (Stahl 2008a). Many of these agents are low-molecular-weight drugs that target stress hormone release from the hypothalamic–pituitary–adrenal (HPA) axis, while many others are antagonists at neurokinin receptors.

Conclusion

In summary, there are many avenues of pursuit for increasing the effectiveness of antidepressant treatment, including not only building on existing agents and/or existing mechanisms but also exploring new and unique mechanisms and techniques. It remains to be seen which of these will ultimately represent major advances in the treatment of depression.

Cross-References

▶ Aminergic Hypotheses for Depression
▶ Antidepressants
▶ Antipsychotic Drugs
▶ Bipolar Disorder
▶ Brain-Derived Neurotrophic Factor
▶ Corticotropin Releasing Factor
▶ Gene Expression
▶ Gene Transcription
▶ SNRI Antidepressants
▶ SSRIs and Related Compounds

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Antidiuretic Hormone

► Arginine-Vasopressin

Antiepileptics

► Anticonvulsants

Antihistamines

► Histaminic Agonists and Antagonists

Antimuscarinic/Anticholinergic Agent

Definition

An anticholinergic drug is one that blocks the physiological action of the neurotransmitter ► acetylcholine in the central and the peripheral nervous system. These drugs are classified according to the receptors that are affected. Most anticholinergics are muscarinic receptor antagonists, that is, agents that reduce the activity of the muscarinic acetylcholine receptor. Others are antinicotinic agents operating on the ► nicotinic receptors. The antimuscarinic drugs are used in the treatment of a variety of medical conditions including Parkinson's disease and antipsychotic-induced parkinsonism.

Antinociception

Definition

Antinociception refers to the reversal or alteration of the sensory aspects of pain intensity. Most models for examining antinociception were developed for use in animals in order to explore alterations in sensitivity to a painful stimulus following the administration of a drug with potential analgesic (pain-relieving) properties. The term is usually used to avoid the anthropomorphic connotation of the term analgesia, which strictly means reversal of the subjective sensation of pain, the presence of which can only be inferred in animals.

Cross-References

► Analgesics
► Opioids

Antinociception Test Methods

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Synonyms

Analgesia tests

Definition

Antinociceptive tests encompass a large group of experimental procedures specifically developed for examining sensitivity to painful stimuli and the alteration of pain sensitivity following drug administration. Since most antinociceptive tests have been designed for examining pain sensitivity in animals, they provide limited

information about the affective aspects of pain perception such as discomfort or unpleasantness. These characteristics are more likely to be examined in studies with human subjects.

Principles and Role in Psychopharmacology

A number of procedures have been developed for examining the pain-relieving (i.e., ► analgesic) properties of drugs in laboratory animals. Each of these procedures involves the presentation of a potentially painful (or ► nociceptive) stimulus, followed by the measurement of a clearly observable response. Typically, data are based on the time it takes the organism to respond to or withdraw from a nociceptive stimulus. Once baseline levels of responding in response to the nocicepetive stimulus are determined and considered reliable, a drug is administered, and response latencies are then redetermined in the presence of the drug. If the time it takes the organism to respond to the stimulus is longer following drug administration, and importantly, if this change is not because the animal is unable to make the response due to the sedative or motor effects of the drug, then the drug is said to produce antinociceptive effects.

Although this experimental paradigm appears relatively simple and straightforward, it becomes far more complex when one considers the multiple variables that influence the data that can be obtained with these procedures. For example, the type of nociceptive stimulus (e.g., thermal, mechanical, electrical, or chemical), its intensity, and the duration and outcome of its effect determine the drug-induced alterations in response latency, and therefore, these must be quantified very precisely. Similarly, the nature of the response itself – whether it involves an elementary reflex response or a more integrated escape or ► avoidance response – can influence the interpretation of a drug's effect. Antinociceptive tests also attempt to differentiate nonspecific response alterations from those that are specific to the nociceptive stimulus. This is particularly important in the assessment of drug-induced alterations in response to the nociceptive stimulus since a drug may produce motor effects that interfere with the ability of the organism to execute a particular response. A more extensive discussion of these issues can be found in a classic review by Beecher (1957) and a recent review by Le Bars et al. (2001). For the discussion of parallel issues related to pain assessment in humans, see Turk and Melzack (2001).

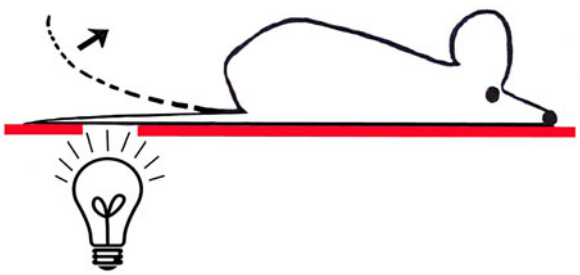
Although antinociceptive procedures vary in many ways, it is convenient to place them in one of two larger groups – those that involve acute pain and those that involve more persistent pain as might occur with tissue injury or nerve damage.

Models of Acute (or Phasic) Pain in Animals

In general, antinociceptive tests for examining acute pain involve the presentation of a brief thermal, mechanical, or electrical stimulus that is delivered to the skin, paws, or tail of an animal. One of the most common procedures in this category is the *tail-flick procedure,* originally developed by D'Amour and Smith (1941). In this procedure, a high intensity light is focused on an area close to the tip of the tail as shown for a mouse in Fig. 1, and the time (response latency) taken by the mouse to remove (i.e., flick) its tail from the light source is determined. The light intensity can be adjusted to yield baseline response latencies that are relatively short (i.e., between 3 and 5 s) or long (i.e., between 8 and 10 s).

Typically, the time taken by the mouse to remove its tail from the heat source is measured prior to the drug administration to determine baselines response latencies. After baseline latencies have been determined, drug administration takes place, and tail flick latencies are determined either once or multiple times over a set time period. However, caution has to be taken with repeated measurements, as the tail-flick response is prone to ► habituation. The tail flick response is easy to observe, and it is considered to involve simple spinal reflexes. It can be measured either with a stopwatch or through a system that uses photocells to determine when the tail has been removed from the light source. ► Opioid analgesics such as ► morphine are very active in this procedure, though their effects depend on the intensity of the thermal stimulus. For example, if the light intensity is very high and elicits short tail flick latencies, a higher dose of morphine is usually required to alter the tail flick latency than when the light is set at a lower intensity.

One very important characteristic of the tail flick procedure, and almost all other acute antinociceptive procedures, is the use of a cutoff time to prevent tissue damage. The *cutoff time* is defined as the maximal time



Antinociception Test Methods. Fig. 1. This figure provides a simple schematic of the tail-flick procedure, showing the position of the mouse's tail over a light source.

that an animal is exposed to the nociceptive stimulus. For example, if a high intensity light is used in the tail flick procedure and the animal (e.g., a mouse) does not remove its tail from the light source within 10 s (cutoff time), the mouse is removed from the apparatus by the experimenter. The cutoff time also influences certain aspects of the data analysis since it is one of the variables in the formula commonly used to quantify antinociceptive drug effects.

A drug's effect in the tail flick procedure is usually quantified by determining the difference between the response latency obtained under baseline conditions and response latency obtained after drug administration. This difference is then divided by the difference between the cutoff time and the baseline latency and a *percent maximal effect (%MPE)* is derived from these measures.

$$\%\text{MPE} = \frac{\text{latency (s) following drug administration} - \text{latency (s) under baseline conditions}}{\text{cutoff time(s)} - \text{latency (s) under baseline conditions}}$$

Since baseline latencies vary between animals, this formula accommodates individual differences in response to the nociceptive stimulus.

The *tail-withdrawal test* (Janssen et al. 1963) is a modification of the tail-flick test. In this procedure, mice or rats are gently restrained, and their tail is placed into a water bath maintained at temperatures between 48° and 56°C. Some investigators have also used cold water as the painful stimulus, although this is less common. Latency to remove the tail from the water is measured, much in the same way as in the tail flick procedure, and data are usually described with the percent maximal effect formula described for the tail flick procedure.

The *tail-withdrawal test* has also been used in primates and the procedure parallels those used in rodents. In this procedure, a monkey is placed in a restraint chair and the lower portion of their tail is immersed in water maintained at a specific temperature (40, 50, or 55°C). The latency to remove the tail from the water is then determined. Typically, monkeys do not remove their tails from 40°C water; however, response latencies might average 10 s when the water is 50°C and 5 s or less when the water is 54°C (Dykstra and Woods 1986). If the monkey does not remove its tail from the water within the predetermined cutoff time (e.g., 20 s), the tail is removed by the experimenter and the latency assigned a value of 20 s (cutoff time). Investigators have shown that reliable data can be obtained with this procedure and tail withdrawal responses can be measured every 15–30 min for periods as long as 3 h.

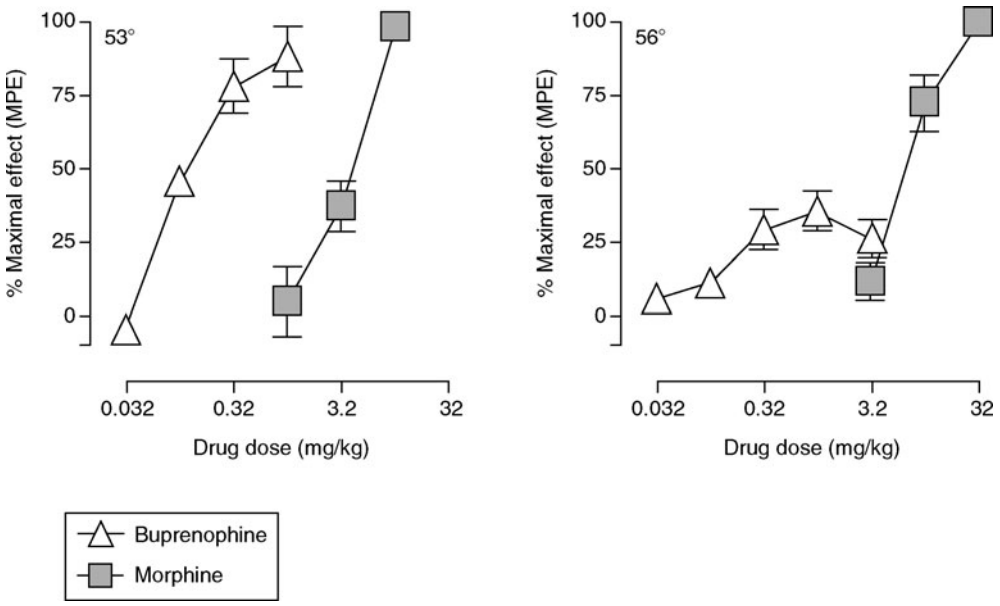
The *hot plate procedure* is another acute antinociceptive test that is commonly used to assess drug effects. In this procedure, an animal (usually a rodent) is placed on a flat surface maintained at a set temperature (e.g., 52–56°C). The baseline nociceptive response to the hot plate is evaluated by recording the latency to lick or shuffle the hind paw(s), or jump from the hotplate surface. Following the determination of baseline response latencies, drug administration is initiated. Figure 2 illustrates data obtained with this procedure. Responses are measured using a stopwatch and a predetermined cutoff time is established to prevent tissue damage. If an animal does not exhibit a nociceptive response after this cutoff period, they are manually removed from the hot plate and assigned a response value equal to the cutoff time.

Figure 2 shows data obtained at two different hot plate temperatures following the administration of two different opioid analgesics, a high efficacy opioid, morphine, and a lower efficacy opioid, ▶ buprenorphine. The left portion of Fig. 2 shows data obtained when the hot plate temperature was 53°C. Under these conditions, both morphine and buprenorphine produced dose-dependent increases in the percent maximal possible effect (%MPE), with morphine producing 100% maximal effect at 10 mg/kg. The right portion of Fig. 2 shows data obtained when the hot plate temperature was 56°C. Under these conditions, a higher dose of morphine was required to produce 100% maximal effect (32 mg/kg), and buprenorphine's effects were markedly attenuated at the higher temperature. (Adapted from Fischer et al. 2008.)

In contrast to the procedures described above, which usually involve assessment of an unlearned response following presentation of an acute stimulus, a few procedures, especially those conducted in primates, involve a period of training. In the titration procedure, monkeys are trained on an avoidance task in which a stimulus such as an electric shock is presented to the monkey's tail (or foot) in increasing intensities. If the monkey makes one or more responses on a lever, the shock is turned off (avoided) for a period of time and the intensity is reduced when the shock resumes again. The intensity at which each monkey maintains the shock is then used as a measure of sensitivity to the potentially painful stimulus. One advantage of this procedure is that the animal, rather than the experimenter determines the level at which the stimulus is maintained. Moreover, responding can be maintained for relatively long periods of time with this procedure, which provides a convenient way to examine onset and termination of a drug effect (Allen and Dykstra 2001).

Models of Persistent (Tonic) or Neuropathic Pain

Antinociceptive test methods that involve persistent or long duration pain typically administer an irritant, which



Antinociception Test Methods. Fig. 2. Antinociceptive effects of several doses of morphine or buprenorphine on a hot plate set either at 53°C (left) or 56°C (right).

produces inflammation, or they induce injury, often by ligation of a nerve such as the sciatic nerve. These procedures often examine multiple aspects of pain sensitivity, including heightened sensitivity to pain (► hyperalgesia) or ► allodynia, a condition in which stimuli that are not normally painful are perceived as painful.

The *abdominal constriction (or writhing)* test is one example of a persistent pain model. In the abdominal constriction test, an irritant is injected directly into the peritoneal cavity of a mouse, resulting in a characteristic writhing response. Although a number of compounds have been used in this assay (acetic acid, acetylcholine, bradykinin, hypertonic saline, phenylquinone, etc.), a solution of 0.6% acetic acid is one of the most commonly used. The onset of inflammation following acetic acid occurs about 5 min after the injection and lasts for approximately 30 min, but has been reported to last for longer periods, depending on the concentration of acetic acid. In order for this assay to produce consistent data, the writhing response must be clearly defined. For example, writhes are often defined as "lengthwise stretches of the torso with a concomitant concave arching of the back" often in combination with a reduction in motor activity and some loss of coordination. Scoring is done by experimenter observations, usually of videotaped experimental sessions. One of the advantages of this procedure is the fact that it is sensitive to weak analgesics such as aspirin and other ► nonsteroidal anti-inflammatory drugs (NSAIDs); however, the lack of specificity in response to drugs without analgesic activity (false positives) sometimes makes interpretation more difficult.

The Formalin test (Dubuisson and Dennis 1977) is one of the most commonly used tests for examining persistent pain. With this test, responses are measured following a subcutaneous injection of a formalin solution into the hind paw. Two spontaneous responses are typically measured with the formalin test, an acute, early phase response and a tonic, inflammatory phase response that occurs somewhat later. These responses are usually scored on a four-level scale, from normal posture to licking, nibbling, and/or shaking of the injected paw. Given the two types of responses elicited by the formalin injection, it is possible to examine both acute pain and tonic pain in the same animal, in response to a single injection of formalin.

Carrageenan, a substance derived from Irish sea moss, is another compound that has been used in persistent pain models as it produces inflammation and consequent hypersensitivity in rodents. In a typical procedure, a 2% suspension of carrageenan is injected subcutaneously into one of the hind paws of a mouse; the opposite hind paw is not injected. This two-paw protocol in which comparisons are made between an inflamed paw and healthy paw was first introduced by Randall and Selitto

(1957) and is now the standard protocol for tests of this nature. Several hours after the carrageenan injection, mice are tested for pain sensitivity and the *Hargreaves' test* is often used for this assessment. To conduct the Hargreaves' test, mice are placed in individual, transparent chambers with a glass floor. After adaptation to the chamber, a high-intensity beam such as a projector bulb is directed at the plantar surface of the mouse's hind paw. Time to withdraw the paw is then measured.

The *von Frey test* of mechanical sensitivity provides another way to examine pain sensitivity in animals that have been treated with irritants or have experienced nerve damage. In this procedure, animals are placed in a transparent box which rests on a metal mesh floor. Von Frey monofilaments (or hairs) are then applied to the foot with a single, steady application. Since each monofilament has a different bending force, experimenters can determine the monofilament that elicits foot withdrawal 50% of the time under baseline conditions, and then following drug administration.

Another procedure that has been used to examine pain sensitivity as well as hyperalgesia and/or allodynia is capsaicin, the pungent ingredient in hot chili peppers. Exposure to capsaicin produces inflammation and allodynia, which is defined as pain that is produced by a stimulus that is not normally painful. A modification of the primate tail withdrawal procedure, using warm water rather than hot water, has been used to examine allodynia following exposure to capsaicin. The monkey is restrained and the distal part of its tail is immersed in water maintained at a comfortable temperature such as 46°C. At this temperature, monkeys usually leave their tails in the water for at least 20 s, which is used as the cutoff time. After baseline latencies are determined, capsaicin is injected above the tip of the tail. Following administration of capsaicin, allodynia develops as revealed by a decrease in tail-withdrawal latencies from 20 s to approximately 2 s. Local administration of an opioid analgesic has been shown to inhibit the allodynia induced by capsaicin under these conditions (Ko et al. 1998).

Advantages and Limitations of Antinociceptive Tests

One clear advantage of most of the antinociceptive procedures described here is that they are relatively easy to perform in animals. As a group, they require very little training time and produce reliable, repeatable, and easily quantified measures of nociception across a range of stimuli. The acute antinociceptive procedures, such as the tail flick and hot plate, are predictive of the effects of morphine-like opioid analgesics, but do not reveal activity for a number of other drugs, including the nonsteroidal anti-inflammatory drugs (NSAIDS). In contract, persistent pain procedures such as the abdominal constriction test, and formalin test, are predictive of the antinociceptive effects of nonsteroidal anti-inflammatory drugs (NSAIDS) as well as morphine-like analgesics. The fact that these procedures can predict the analgesic activity of drugs in humans, certainly verifies their usefulness as animal models. Beyond being predictive of analgesia in humans, investigations using these procedures have also advanced understanding of the multiple variables that influence the processing of nociceptive stimuli as well as the alteration in nociception following administration of different classes of drugs.

Cross-References

- ▶ Active Avoidance
- ▶ Analgesics
- ▶ Ethical Issues in Animal Psychopharmacology
- ▶ Habituation
- ▶ Opioids

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Anti-Parkinson Drugs

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Definition

► Parkinson's disease (PD): a syndrome defined in life by clinical criteria involving tremor at rest, rigidity, slowness and paucity of movement, altered posture, gait and balance with the absence of "atypical" features (Lang and Lozano 1998a,b). It is defined at autopsy by strict pathological criteria including the loss of neurons in the pars compacta of the substantia nigra, locus ceruleus and dorsal motor nucleus of the vagal nerve, and the presence of Lewy bodies.

Pharmacological Properties

Although Parkinson's disease (PD) is classified as a "movement disorder," it should also be considered as a "neurobehavioral" disorder. The diagnosis of PD is based on the presence of clinical criteria having to do purely with movements and the absence of exclusionary or atypical features, laboratory tests being of little or no value. Nevertheless, the most devastating aspects of PD are more often behavioral. Other nonmotor problems, such as sympathetic dysfunction and sleep disorders have only attracted clinical and research attention in the last few years. For perspective two studies, one a large retrospective review in Australia, and the other, a county wide prospective study with formal testing in Norway, both concluded that by the time of death, 80% of PD patients are demented. In addition, at any point in time, somewhere between 30 and 50% are depressed; 40% suffer from anxiety; 40% with apathy; 30% of drug treated patients with visual hallucinations; 5–10% of drug treated patients with delusions; and over 30% of newly diagnosed patients, untreated, suffer from fatigue unrelated to depression or the severity of their motor dysfunction.

PD in simplistic terms is often understood as a dopamine deficiency disease. While it is this, there are also abnormalities in multiple neurotransmitter systems. The dopamine motor system is the best understood and deficiencies here do cause many of the major motor problems in PD, including bradykinesia, rigidity, tremor, and gait dysfunction. Improving dopamine transmission has been the focus of modern drug therapy, starting with the introduction of the first rational designed treatment for a neurological disorder, L-Dopa.

► L-Dopa, combined with an aromatic amine decarboxylase inhibitor (AADI), ► carbidopa, has been the mainstay of the treatment of PD since it was introduced in the late 1960s (Cotzias et al. 1967). The AADI reduces the amount of L-Dopa converted in the bloodstream to ► dopamine, dramatically reducing the problem of nausea which was frequent when L-Dopa was used alone. L-Dopa is the precursor to dopamine, and in the chemical path that converts tyrosine to dopamine, L-Dopa occurs after tyrosine hydroxylase, the rate-limiting enzyme. L-Dopa is taken up by the remaining nigral cells and converted to dopamine. L-Dopa improves slowness, rigidity, akinesia, and gait, but does not usually improve speech, freezing, balance, and its effect on tremor are unpredictable. In addition to the existence of symptoms not responsive, and therefore presumably not of dopamine deficiency origin, the disease progresses and drug manipulations are unable to keep up. As more dopamine secreting cells die, the drug becomes less effective.

Long-term use of L-Dopa often leads to motor complications, which are not seen when other drugs are used in PD patients who have never been exposed to L-Dopa (Fox and Lang 2008). These include ► dyskinesias induced by the drug, as well as markedly variable responses to the drug with "on" periods, when patients have a good response to the drug, and either predictable or unpredictable "off" periods when the medicine stops producing benefit.

Other ways of enhancing dopamine transmission involve reducing dopamine breakdown or altering L-Dopa ► pharmacokinetics. The monoamine oxidase-b inhibitors (MAOb-I), ► selegiline and ► rasagaline, are both used as adjunctive agents to enhance the activity of dopamine. These drugs work both peripherally, in the bloodstream to block the degradation of L-Dopa and centrally, in the brain to reduce degradation of dopamine. In the brain, dopamine is primarily resorbed by the presynaptic neuron though the dopamine transporter, but about 10% is broken down in the synaptic cleft by monoamine oxidase b and catechol-o-methyltransferase. Blocking the degradation of dopamine in the synapse allows more dopamine to activate the dopamine receptors, thereby increasing the potency of the dopamine stimulation as well as its duration of action. Both drugs are therefore approved for the purpose of increasing "on" time in patients who suffer from clinical motor fluctuations in reponse to L-Dopa. Rasagaline is also used as a monotherapeutic drug, presumably acting in the same fashion, enhancing dopamine stimulation. Its benefits are less than those typically seen with dopamine agonist monotherapy, but its side effect profile in these patients is not much different than that of placebo.

The greatest interest in the MAO-b inhibitors lies in their possible disease "modifying" effect that is, slowing of

disease progression. There is suggestive data supporting this contention for rasagaline. The first large study to slow PD progression used selegiline, and while initially deemed a positive study, was reinterpreted in light of its mild, but statistically significant symptomatic effects. The rasagaline studies used a different research paradigm to avoid this confound (Olanow et al. 2009).

Although nonspecific MAO inhibitors hold the potential for a large number of drug and food interactions, all of these are due to MAO-a inhibition. At the doses approved for PD, the MAO-b inhibitors are free of MAO-a inhibition and are quite safe, free of tyramine interactions, and of interactions with selective serotonin reuptake inhibition (SSRI) antidepressants. However, there is a concern about an unexplained, potentially fatal interaction with meperidine.

In monotherapy, rasagaline has no significant behavioral effects. When used adjunctively with L-Dopa, all L-Dopa side effects are enhanced.

The catechol-o-methyltransferase inhibitors (► COMT-i) block the enzyme, catechol-o-methyltranserfase that, along with MAO-b, breaks down dopamine. There are two such drugs used in USA, ► tolcapone and ► entacapone, neither of which crosses the blood-brain barrier to an appreciable degree. These drugs therefore exert their effect on the pharmacokinetics of L-Dopa. By themselves, these drugs do not have any known effect on PD. Tolcapone may cause severe liver damage in a very small percentage of users. Entacopone is less effective, but is free of liver toxicity.

Since dopamine does not cross the blood-brain barrier, dopamine agonists have been used to compensate. These medications, ► bromocriptine, ► pramipexole, ropinerole, lisuride, ► rotigotine, ► cabergoline, and ► apomorphine, all directly stimulate D2 receptors (along with variable potencies at other dopamine receptors), and produce motor benefits comparable to L-Dopa at the early stages of the disease, but are less effective for the long-term. Unlike L-Dopa, these medications do not cause long-term motor side effects such as "wearing off," in which the benefit of L-Dopa declines before the next dose, unpredictable fluctuations, in which the L-Dopa doses last highly variable periods of time, or dyskinesias, which are involuntary movements, usually choreic in nature (Constantinescu et al. 2007; Jankovic and Stacy 2007). Unfortunately, these drugs produce more short-term side effects including hypotension, ► hallucinations, nausea, and generally need to be supplemented with L-Dopa within a few years. The ► dopamine agonists are often used as initial therapy to postpone the long-term side effects of L-Dopa, or may be added to L-Dopa as its benefits decline.

Anticholinergic drugs were the mainstay of drug therapy of PD until the development of L-Dopa. These drugs are helpful in reducing tremor and rigidity, but are thought to provide little benefit in slowness, or gait, two of the most functionally debilitating symptoms in PD. Additionally, these drugs have profound side effects that make them difficult to use, particularly in older people. These side effects are very common, and include dry mouth (which may be useful to reduce drooling), constipation, memory dysfunction, urinary retention, blurred vision, hallucinations. These drugs are primarily used in younger patients, who tolerate them better, particularly where tremors and drooling are problems.

► Amantadine was first reported in 1972 to ameliorate the motor symptoms of PD as a serendipitous observation when used to treat influenza in people with PD. The drug had been thought to work by increasing dopamine secretion or by blocking acetylcholine, but it is currently believed to work as an NMDA glutamate antagonist. It is helpful for all aspects of PD, including tremor, but is not as effective as dopamine agonists or L-Dopa. It has been increasingly used in recent years after it was shown to reduce L-Dopa induced dyskinesias in PD patients, without a reduction in the other drugs used to treat PD motor symptoms. Amantadine may induce psychotic symptoms, delirium, and mild anticholinergic side effects, as well as livedo reticularis (which has no negative consequences other than appearance) and pedal edema (Pahwa et al. 2006).

Although ► dementia is a common problem in PD, only one drug has been approved for its treatment (Burn et al. 2006). Most authorities believe that the three cholinesterase inhibitors probably work about equally well, but this is not based on clinical data. Since Parkinson's disease dementia (PDD) patients have a greater cholinergic deficit than Alzheimer's patients, it was assumed that the cholinesterase inhibitors might therefore work better than in Alzheimer's disease (AD). This has not been borne out by clinical observation. The mechanism of action of these drugs is presumed to be the same in PDD as in AD, blocking the degradation of acetylcholine. However, the benefits of ► rivastigmine in PDD are extremely limited, and most patients do not sustain sufficient benefits to justify the cost of the drug. ► Memantine, which is the only noncholinesterase inhibiting drug approved for treating dementia in AD, shares NMDA glutamate antagonism with amantadine, but it has not been shown to produce any motor benefit in PD. Rivastigmine is more helpful for concentration, apathy, and hallucinations than it for cognitive and memory problems (Burn et al. 2006).

No antipsychotic is approved for treating hallucinations and delusions in PD in USA, but ► clozapine, at extraordinarily low doses, is approved for this use in other countries based on two multi-center double blind placebo controlled trials (Parkinson study group 1999). In USA, ► quetiapine has been recommended as the drug of first choice by an American Academy of Neurology task force, despite the fact that no double blind trials, support its efficacy (Miyasaki et al. 2006). Clozapine is the task force's second line recommended drug.

No antidepressant has been approved for treatment of depression in PD, and none has been adequately tested to confirm benefit. Some high quality data published in 2009 indicates that depression in PD may be medication responsive, and that tricyclics may be more effective than ► selective serotonin reuptake inhibibitors (SSRI) (Menza et al. 2009). Although the SSRI's may produce tremor or parkinsonism, they have been well tolerated in PD.

Conflict of interests: JHF has received remuneration from the following companies in the past 12 months either for consultation, lectures, or research: Acadia Pharmaceuticals, Astra-Zeneca, Novartis, Glaxo, Ingelheim-Boehringer, Teva, Valeant, Cephalon, EMDSerono, Schwartz.

Novartis makes clozaril (clozapine)

Astra-Zeneca makes Seroquel (quetiapine)

Acadia is testing pimavanserin as an antipsychotic for PD

Cross-References

► Antipsychotic Drugs
► COMT Inhibitor
► Disease Modification
► Hallucinations
► Hallucinogens
► Medication-Induced Movement Disorders
► Neuroprotection

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Antipsychotic

Synonyms

Major tranquilizer; Neuroleptic

Definition

Drug that is effective against psychotic symptoms (e.g., treating schizophrenia).

Antipsychotic Drugs

► Classification of Psychoactive Drugs

Antipsychotic-Induced Movement Disorders

► Movement Disorders Induced by Medications

Antipsychotic Medication

Synonyms

Major tranquillizers; Neuroleptics

Definition

Antipsychotic medication refers to the use of a group of psychoactive drugs that is mainly used to treat patients

suffering from psychoses, most often ► schizophrenia but also mania and other delusional disorders. A wide range of antipsychotics has been developed. The first generation of antipsychotics was discovered in the 1950s. Most of the drugs in the second generation (often called atypical antipsychotics) have been developed more recently, although the first atypical antipsychotic, ► clozapine, was discovered in the 1950s. Both classes of medication block dopamine receptors in the brain and in many cases, they also act at a much wider range of receptor targets. Side effects vary greatly between different antipsychotics and include weight gain, movement disorders, and agranulocytosis (a loss of the white blood cells that help a person fight infection). The development of new antipsychotic medication and the relative efficacy of different ones is an important ongoing field of research. The most appropriate drug for an individual patient requires careful consideration.

Cross-References

► First-Generation Antipsychotics
► Schizophrenia
► Second-Generation Antipsychotics

Antipsychotic Medication: Future Prospects

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Synonyms

Ongoing and future development of antipsychotics (neuroleptics)

Definition

Antipsychotic medications are a group of psychoactive drugs used to treat psychosis, which is typified by ► schizophrenia. The currently available antipsychotic medications show some benefit to patients, but have considerable limitations in terms of efficacy and side effects. The development of new antipsychotic compounds with novel mechanisms of action is being pursued based on specific strategies and guided by various pathophysiologic hypotheses. This article focuses on novel goals and targets for therapeutic intervention and potential strategies for future development of antipsychotic medication.

Pharmacological Properties

Limitations of Currently Available Antipsychotic Medications

The introduction of newer ► second-generation antipsychotics (SGAs) represents an important advance in the pharmacologic treatment of schizophrenia since the advent of ► chlorpromazine, the prototypical ► first-generation antipsychotics (FGAs). However, current evidence suggests that the clinical benefits of SGAs in terms of efficacy are modest at best (Leucht et al. 2009), and the effect sizes on ► cognitive impairment are small. In the largest and longest effectiveness trial, the ► clinical antipsychotic trials of intervention effectiveness (► CATIE) study, no substantial advantage for the SGAs was demonstrated over the FGA for the treatment of negative and cognitive symptoms (Lieberman et al. 2005). Negative and cognitive symptom domains are recognized as a core feature of schizophrenia and play a greater role in poor functional outcome. Thus, it is obvious that there is a distinct need to identify and validate novel molecules that possess pharmacological profiles that better treat these symptom domains.

To date, the prototypical SGA ► clozapine remains the "gold standard" antipsychotic drug because of a lower liability for ► extrapyramidal motor side effects (EPS) and because it has proved superior to all other ► antipsychotic drugs in efficacy (Leucht et al. 2009), particularly in treatment-resistant schizophrenia. However, even with clozapine, a significant number of patients are unresponsive to treatment and it carries a risk of serious side effects such as agranulocytosis, weight gain, and metabolic abnormalities. Because individuals with schizophrenia have many risk factors that may predispose them to poor health and excess mortality, safety and tolerability of antipsychotic medications are an essential treatment concern. Furthermore, remission and recovery rates for schizophrenia by the treatment with current antipsychotic medications are discouragingly low. Thus, it is important to pursue the development of more tolerable and more effective antipsychotics than clozapine. To expedite the clinical development of such drugs, biological or surrogate markers of the illness and treatment effects using chemical technologies (e.g., ► PET imaging) must be identified and validated to enable more efficient and reliable proof of efficacy of novel compounds.

Challenges of Future Drug Discovery

A number of mechanisms of action of antipsychotics have been explored during the past 30 years. However, it is still unclear as to what pharmacological profile of

antipsychotic medication is necessary to show the highest efficacy and effectiveness without serious adverse effects in the treatment of schizophrenia and other psychosis. Moreover, there is still an ongoing debate as to whether drugs selective for single molecular target (i.e., "magic bullets") or drugs selectively nonselective for several molecular targets (i.e., "magic shotguns") will lead to new and more effective medications for psychosis (Agid et al. 2008; Roth et al. 2004).

All currently available antipsychotic medications target dopamine D_2 receptors, but one example of new multitarget strategies is the utility of combined dopamine D_2-like receptor antagonism and ▶ serotonin 5-HT_{1A} receptor agonism (Jones and McCreary 2008). It is suggested that the balance between D_2 antagonism and 5-HT_{1A} agonism may be critical in determining the efficacy of these compounds. In addition, further serotonergic strategies may be a key area of schizophrenia research such that combined activity at the D_2 receptor with ▶ selective serotonin reuptake inhibitor, and the use of 5-HT_{2C} receptor agonists, 5-HT_6 receptor antagonists, or 5-HT_7 receptor agonists may be of great interest in expanding treatment options (Jones and McCreary 2008).

Recent antipsychotic research has examined agents that have no direct effect on the dopamine system, although most of them have indirect effects on dopaminergic pathways. For example, with the emerging evidence for glutamatergic dysregulation in schizophrenia, a number of agents with direct or indirect activity on the ▶ glutamate system are being investigated, especially for their potential impact on cognitive and negative symptom domains (Miyamoto et al. 2005). Glutamate-based agents in various stages of development include agonists at the glycine allosteric site of the ▶ N-methyl-D-aspartate (NMDA) receptor, ▶ glycine transporter 1 inhibitors, ▶ Group II metabotropic glutamate receptor agonists, α-amino-3-hydroxy-5-methy-isoxazole-4-propionic acid (AMPA)/kainate receptor antagonists, and higher-potency ▶ ampakines. The putative antipsychotic action of these drugs has been studied as monotherapy and/or add-on treatment (Gray and Roth 2007).

It has also been suggested that the central cholinergic system is involved in the cognitive deficits observed in schizophrenia, and enhanced cholinergic activity may improve these deficits (Miyamoto et al. 2005). Currently available treatments which are potentially suitable for this purpose include ▶ acetylcholinesterase inhibitors (e.g., galantamine), partial ▶ muscarinic agonists (e.g., xanomeline), ▶ nicotinic agonists, and allosteric potentiators of nicotinic receptor function (Gray and Roth 2007). These potential ▶ cognitive enhancers may be better suited to particular stages of schizophrenia, perhaps showing efficacy in early or later stages.

In recent years, significant progress has been made on elucidating various susceptibility genes in schizophrenia, including ▶ dysbindin, neuregulin 1, catechol-O-methyltransferase (COMT), disrupted in schizophrenia 1 (DISC1), and others (Gray and Roth 2007). Many of these genes appear to be associated with the control of ▶ synaptic plasticity and glutamate transmission, especially NMDA receptor function. Research on these molecules will allow for rational drug development in which drugs are developed on the basis of targets derived from theories of pathogenesis of the disease. However, the conundrum of single-target versus multitarget agents will remain at the forefront of drug development until the etiology of the illness is fully elucidated. In the near future, optimal treatment will probably include different therapeutic agents, each uniquely targeting a specific dimension of schizophrenia (Agid et al. 2008). In other words, single-target agents will augment multitarget agents, and there is a possibility that novel biological agents will also be investigated (Nikam and Awasthi 2008).

Recently, a growing body of evidence has demonstrated that some SGAs may increase or preserve neurotrophic factor levels, ▶ neurogenesis, neuronal plasticity, mitochondrial biogenesis, cell energetic, and antioxidant defense enzymes (Lieberman et al. 2008). Moreover, specific SGAs can ameliorate the loss of gray matter in schizophrenic patients in the early stages. These neuroprotective properties of some SGAs have become more relevant in the light of the increasing acceptance by the field of a progressive pathophysiological process and possibly neurodegenerative process coincident with the onset of schizophrenia that may underlie the clinical deterioration. Ongoing research on the neuroprotective effects of antipsychotics may reflect another mechanism of action that antipsychotics can act through that is clinically relevant and should stimulate the search for new agents for psychosis with novel mechanisms beyond the monoaminergic systems (Lieberman et al. 2008).

New Preparations of Antipsychotic Medications

At present, antipsychotic medications are available as tablets, liquid concentrates, orally dissolving formulations, short-acting intramuscular (I.M.) preparations, or long-acting injection (LAI) preparations. Among them, several SGA LAI preparations have been and are being developed. By increasing the available treatment choices for clinicians and patients alike, new preparations such as drug-in adhesive transdermal patches and nasal spray are

a welcome development. Researchers must study these preparations beyond the usual registration package.

Moving Toward the Future Individualized Treatment

There is a great need for the development of novel methods to identify optimum individualized treatment plans. In particular, the efficacy and tolerability of antipsychotics could be directly influenced by genetic variations in ► cytochrome P450 (CYP) enzymes. Their activity may also be influenced by genetic alterations affecting the drug target molecule, such as monoaminergic receptors, neurotransmitter transporters, and enzymes. In the future, genetic tests for the pretreatment prediction of drug metabolic status, antipsychotic response, and drug-induced side effects such as EPS and weight gain are expected to bring enormous clinical benefits by helping to chose the medication, adjust therapeutic doses, and reduce adverse reactions (Arranz and de Leon 2007). Further development of genetic tests and ► pharmacogenetic research into genetically determined drug metabolic polymorphisms as well as ► pharmacogenomic strategies to the identification of novel factors influencing response would lead to a better understanding of the rational basis for the personalization of antipsychotic treatment. In addition, antipsychotic drugs may also be targeted to specific patient subgroups based on profiling and the identification of endophenotypes of schizophrenia. Clinical implementation of this practice may have a strong impact in reducing adverse effects and improving treatment adherence and efficacy (Arranz and de Leon 2007).

Conclusion

Future drug discovery approaches will have to be truly revolutionary, but there is a hope that we could obtain novel antipsychotic drugs with greater efficacy and improved safety profiles. These drugs, however, alone may not produce a complete cure. It is essential that all of the pharmacologic tools should always be used in combination with psychosocial and psychotherapeutic intervention to optimize overall ► quality of life and return patients to the best level of functioning.

Cross-References

► Ampakines
► Chlorpromazine
► Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study
► Cognitive Impairment
► Dysbindin
► Glycine Transporter 1
► Group II Metabotropic Glutamate Receptor
► NMDA Receptor

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Antipsychotic Drugs

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Synonyms

Neuroleptics; Major tranquilizer

Definition

Antipsychotics are drugs used to treat all kinds of psychoses, although the best evidence for their clinical effects stems from studies in the treatment of schizophrenia.

Pharmacological Properties

History

Antipsychotics, as we use the term now, were introduced into clinical psychiatry in the 1950s. They were originally

called neuroleptics, a term still broadly used in medical jargon which is derived from Greek and loosely translated as "grasping the nerve." This reflects the fact that originally the sedative effects of these drugs were in the foreground of clinical interest. This was also the origin of the American term "major tranquilizers."

Over the last two decades antipsychotics has become the preferred term for this class of drugs based on their main indications and clinical effect. While it was originally felt that antipsychotic efficacy was inextricably linked to ▶ extrapyramidal motor side-effects (EPS), the introduction of ▶ clozapine in the early 1970s demonstrated that this was not the case, as this drug proved to be an excellent antipsychotic with only a minimal risk to induce EPS. This also triggered a new classification of antipsychotics, which had so far been differentiated either by their chemical structure (e.g., ▶ phenothiazines, ▶ thioxanthenes, and ▶ butyrophenones) or their affinity to the dopamine D2 receptor (high and low potency neuroleptics). The fact that clozapine was found to be an effective antipsychotic without inducing motor side-effects was considered an "anomaly," and the term "atypical" was coined to describe clozapine and to differentiate it from the older "typical" drugs with their considerable potential for such adverse events. Consequently, antipsychotics which were developed following clozapine's introduction and which shared at least some of its characteristics were also subsumed under the category "▶ atypical antipsychotics." It soon became clear that "atypical antipsychotics" represent a rather inhomogeneous group, both from preclinical and clinical pharmacological perspectives. As the receptor pharmacology of these drugs is complex and provides no solid basis for differentiation, the field agreed upon classifying these drugs based upon a less contentious base, namely a more historical dimension. Thereby, all drugs developed until the advent of clozapine were called ▶ first-generation antipsychotics (or sometimes "classical" or "traditional") while the drugs that were introduced after clozapine and shared its low risk for EPS are now called ▶ second-generation antipsychotics. We are now on the threshold of a ▶ third-generation of antipsychotics, initiated with the registration of ▶ aripiprazole, the first licensed antipsychotic which is not a D2 antagonist.

Mechanisms of Action

It took about 10 years after the clinical efficacy of these drugs had been established until it was realized that antipsychotics block ▶ dopamine receptors. This finding can be seen as the cornerstone of the dopamine hypothesis of schizophrenia. More than adecade later, Seeman et al. (1976) published their classic paper on the correlation between D2 dopamine receptor affinity and clinically effective doses of antipsychotics, demonstrating that drugs with high receptor affinity required lower doses than drugs with lower affinities. All currently licensed antipsychotics with the exception of aripiprazole, a partial D2 agonist, block postsynaptic dopamine D2 receptors. The fact that most of these drugs also influence other receptor systems has given rise to a number of alternative attempts to achieve antipsychotic effects. The most prominent targets were various subtypes of the serotonin receptor (e.g., $5HT_{2A}$, $5HT_{1A}$) and lately the glutamatergic system, including both ionotropic and ▶ metabotropic receptors (Miyamoto et al. 2003).

Countless clinical and preclinical experiments link the effects of antipsychotics to the dopaminergic system. In very general terms, the acute administration of antipsychotics leads to an increased firing rate and neurotransmitter turnover in dopaminergic neurons while these effects are reversed after chronic administration (Grace 1992). In this respect older drugs, such as ▶ haloperidol, are different from newer ones such as clozapine insofar as haloperidol demonstrates these characteristics both in neurons originating in the substantia nigra (A9 dopaminergic neurons) as well as in those which project from the ventral tegmentum (A10 neurons) while clozapine only blocks A10 neurons. This has been replicated many times using different electrophysiological, neurochemical, and imaging techniques and is considered the reason why clozapine exerts antipsychotic effects without affecting the motor system (Miyamoto et al. 2003).

Clinically, the introduction of single photon emission tomography (▶ SPECT) and positron emission tomography (▶ PET) have provided the most relevant neurobiological leads into the effects of antipsychotics in humans. All available antipsychotics bind to striatal (and possibly extrastriatal) dopamine receptors in varying degrees. A dose–response relationship between human D2 receptor affinity and clinical profile is very likely, albeit it is challenged by the findings that the highly effective antipsychotic clozapine and also ▶ quetiapine only loosely bind to this receptor (Stone et al. 2009).

In summary, all evidence taken together clearly points to a disruption of dopaminergic function in schizophrenia patients and strongly suggests that a restoration of balance in this system contributes to the therapeutic efficacy of antipsychotics.

As outlined earlier, other receptor systems have also been investigated in this context. As clozapine has high affinity to a number of other neurotransmitter receptors (including ▶ serotonin, histamine, and ▶ noradrenaline),

these systems have been explored regarding their potential contribution to the drug's benefit–risk profile. The hypothesis most vigorously explored was the one that linked its serotonin ($5HT_2$) antagonist properties to the clinical profile. In conjunction with previous preclinical research which had found that serotonin antagonists can counteract extrapyramidal motor side-effects of neuroleptics, Meltzer et al. (1989) formulated the hypothesis that $5HT_2$ antagonism which is proportionally larger than D2 antagonism is responsible for the advantages that clozapine and all other drugs sharing this profile have over the older drugs in terms of lower EPS risk. In addition, they and other authors feel that these pharmacological characteristics also contribute to enhanced clinical efficacy, especially with regard to negative symptoms and cognitive impairment. Although an intriguing and well thought through hypothesis, it is somewhat challenged by the pure dopamine antagonist ► amisulpride which has no direct effects on the serotonergic systems, yet shares a lot of the clinical effects with $5HT_2$/D2 antagonists (McKeage and Plosker 2004).

The glutamate system is intricately linked with dopaminergic neurotransmission throughout the central nervous system (CNS), a topic reviewed by Carlsson et al. (2001). It functions as a modulator of dopaminergic neurotransmission. This has led to a number of clinical experiments aiming at investigating drugs that do not directly act via the dopaminergic systems. Both the glycine sites of ► NMDA receptors and ► metabotropic glutamatergic receptors have been the targets of such investigations. Clinical studies are encouraging but have not yet led to licensed medications (Miyamoto et al. 2005).

Other neurotransmitter systems have mostly been considered in the context of drug safety. Many antipsychotics which block noradrenergic α_1 receptors have been found to affect blood pressure. Antihistamine effects have been related to sedation and weight gain, just to provide a few examples.

Animal Models

There is no reliable and valid animal model for schizophrenia. All available models are either derived from the dopamine hypothesis of schizophrenia or from the actions that effective antipsychotics induce in laboratory animals. Many of them are related to non-therapeutic effects of antipsychotics such as those which affect the motor system. At the most, we may optimistically assume that these models are in some approximation to the clinical syndrome of the disorder. Nevertheless, animal models, imperfect as they may be, are still a cornerstone of antipsychotic drug development (Lipska and Weinberger 2003). Conditioned ► active avoidance is a classic among these models. All antipsychotics block conditioned avoidance and this test is therefore one of the early screening experiments in the development of potential antipsychotics.

Another set of experiments involve the various motor effects of this class of drugs. Spontaneous locomotor activity as well as pharmacologically enhanced psychomotor activity is usually decreased after the administration of antipsychotic drugs. First- and second-generation antipsychotics are nicely differentiated by the dose needed to induce catalepsy, which is a good indicator for clinical EPS risk.

More recent models which can also be performed in humans include various variants of sensory motor gating studies. One example for these is ► prepulse inhibition (PPI), which is based on the finding that a weak prepulse reduces the startle reflex to a given, usually acoustic, stimulus. It is seen as part of the information processing capabilities of the CNS. PPI can be disrupted by both dopamine agonists and NMDA antagonists, thereby providing a model within the dopamine/glutamate hypothesis of schizophrenia. As antipsychotics restore PPI in animals in which it has been disrupted, such sensory motor gating models are also seen as indicative of potential antipsychotic effects.

► Pharmacokinetics

Antipsychotics are generally well absorbed and most of them are metabolized by hepatic ► cytochrome P450 isoenzymes. They are generally highly lipophilic and therefore cross the ► blood-brain barrier well and accumulate in fatty tissues. The benzamides ► sulpiride and ► amisulpride are an exception to these rules.

The elimination half-lives of antipsychotics are distributed over a wide range between a few hours (► quetiapine) and days (aripiprazole). Steady-state levels differ accordingly, but as a rule of thumb once-daily dosing is possible. It is important to note that elimination from the brain and the drugs' target organs has been shown to be much slower than from plasma (Gruender 2007).

Given that all drugs with the exception of the benzamides are metabolized via cytochrome isoenzymes in the liver, the potential for interactions with other drugs which compete for these enzymes needs to be considered. Pharmacodynamic interactions are to be expected when antipsychotics are coadministered with drugs that target the same receptor systems, either centrally or peripherally. These include drugs with antihistamine and antiadrenergic effects which can lead to a potentiation of sedation, weight gain, or hypotensive adverse events.

Efficacy

Next to antipsychotic effects, i.e., reducing ▶ delusions and ▶ hallucinations, most antipsychotics also have sedative properties. Furthermore, they have been shown to reduce negative symptoms, enhance cognitive functions, ameliorate affective symptoms (both manic and depressive) in patients suffering from schizophrenia and, most likely as a secondary effect, improve the quality of life and psychosocial reintegration (Miyamoto et al. 2003). Although most research with antipsychotics has been performed in schizophrenia patients, the therapeutic actions of these drugs extend beyond this diagnosis. Indications include mania, psychotic depression, ▶ schizoaffective disorder, ▶ bipolar depression, psychotic symptoms in the context of organic disorders from delirium to ▶ dementia, personality disorders, and treatment-resistant obsessive compulsive disorder, just to list the better researched disorders. As most of these are be covered in other entries, only general treatment principles in schizophrenia patients are briefly reviewed.

Recent evidence indicates that the onset of antipsychotic action in schizophrenia can be seen within days of commencing treatment (Agid et al. 2006), although it may take up to 6 months to achieve full remission of symptoms. Close to two thirds of first-episode schizophrenia patients reach symptom remission within this time if the duration of previously untreated psychosis is not too long. Response patterns become less favorable with increasing chronicity of the disorder. Next to acute symptom control and stabilization, antipsychotics also have powerful relapse-preventing properties (Kane 2007). Regularly taking medication over long periods of time protects about 80% of patients from a psychotic relapse. Having said that, compliance is one of the major challenges of the long-term management of schizophrenia (Fleischhacker et al. 2003). To aid uninterrupted dosing, depot antipsychotics that are injected at regular, long intervals have been developed. So far ▶ risperidone and ▶ olanzapine are the only second-generation antipsychotics available for this method of administration (Fleischhacker 2009).

Clozapine plays a special role in the management of schizophrenia. On the one hand, it is the drug of choice in patients with a treatment-resistant course of the disorder; on the other hand, it has a 1% risk to induce agranulocytosis which makes it a third line drug despite its excellent efficacy (Tandon et al. 2008).

Safety/Tolerability

For first-generation antipsychotics, sedation as well as acute and tardive extrapyramidal motor side effects represented the biggest safety obstacles that also translated into tolerability and compliance problems. Next to that, these drugs, depending on their receptor profiles, induced a number of other adverse events including anticholinergic side effects, orthostatic hypotension, weight gain, hormonal aberrations including sexual disturbances, dermatologic problems including acne-like manifestations and photosensitivity, disturbances of gastrointestinal motility, hematological side effects, cardiac arrhythmias, seizures, and the ▶ neuroleptic malignant syndrome, just to name the clinically most relevant. Apart from potentially life-threatening adverse events such as clozapine-induced agranulocytosis, tachyarrhythmia, and the neuroleptic malignant syndrome, many of these side effects constitute problems affecting subjective tolerability rather than objective health risks. Prevalence rates differ considerably between drugs, and the incidence of these side effects is difficult to predict on an individual level. Therefore, patients treated with antipsychotics have to be well informed and monitored regularly.

Second-generation antipsychotics as a group have a considerably lesser risk to induce EPS than the older drugs. This applies to both frequency and severity of acute and chronic motor side effects. Some of these drugs, most notably clozapine and olanzapine, have a substantial propensity to induce weight gain and metabolic disturbances such as hyperlipidemia and reduced insulin sensitivity. Apart from these concerns the newer drugs appear to be tolerated appreciably better than traditional neuroleptics. Clearly, despite this, the same recommendations regarding patient information and monitoring must be followed (Miyamoto et al. 2003).

Conclusion

In summary, antipsychotics represent a crucial component of the pharmacotherapeutic options in psychiatry. A large array of effective drugs is available. Antipsychotics are employed over a broad range of indications with a very favorable benefit–risk profile. It is hoped that their main therapeutic limitations, namely efficacy beyond psychotic symptoms, will be overcome with the exploration of pharmacologic mechanisms which extend beyond the dopamine system.

Cross-References

▶ Butyrophenones
▶ Clozapine
▶ Extrapyramidal Motor Side Effects
▶ First-Generation Antipsychotics
▶ Neuroleptic Malignant Syndrome (NMS)
▶ Phenothiazines

► Second-Generation Antipsychotics
► Third-Generation Antipsychotics
► Thioxanthenes

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Antisaccade Task

Definition

An important variant of the prosaccade task, in which participants are required to saccade to the mirror image location of a sudden onset target. Healthy participants typically make errors (prosaccades toward the target) on around 20% of trials. This figure is increased in patients with lesions to the dorsolateral prefrontal cortex and patients with schizophrenia. The task indexes cognitive processes associated with goal activation and inhibitory control.

Antisense DNA

► Antisense Oligodesoxynucleotides
► Antisense Oligonucleotides

Antisense Oligodesoxynucleotides

Synonyms

Antisense DNA; Antisense oligonucleotides

Definition

Antisense oligodesoxynucleotides are relatively short, single-stranded synthetic DNA molecules (between 13 and 25 nucleotides) that are complementary to a chosen mRNA causing translational arrest. Chemical modifications improve their cellular uptake and intracellular stability. Functionally, they are antisense oligonucleotides.

Also, ribozymes and DNA enzymes have antisense properties (Fig. 1D). Ribozymes are RNA enzymes that are catalytically active oligonucleotides that bind to and cleave their target mRNA. These RNA processing capabilities are of potential interest for their use as antisense agents. A number of ribozymes have been characterized, including the most widely studied form called the hammerhead ribozyme.

Cross-References

► Chemical Modifications
► Ribozymes

Antisense Oligonucleotides

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Synonyms

Antisense DNA; Antisense oligodesoxynucleotides; Antisense RNA; Ribozymes; RNA interference; siRNA; Short interfering RNA

Definition

► Antisense oligonucleotides are relatively short, single-stranded DNA (► antisense oligodesoxynucleotides) or single- (► antisense RNA) or double-stranded (► short interfering RNA, ► siRNA) RNA molecules (between 13 and 25 nucleotides or *mer* from Greek *meros*, "part") which are complementary to a chosen (coding or non-coding) mRNA. The potential of oligonucleotides to act as antisense agents that inhibit viral replication in vitro was discovered by Zamecnik and Stephenson (1978). Both in vitro and in vivo, their common mechanism of action is the complementary binding to a specific target mRNA via Watson–Crick base-pair hybridization; thus inhibiting translation of mRNA and blocking the transfer of the genetic information from DNA to protein; thereby reducing the availability of the gene product within a given tissue. Synthetic, antisense oligonucleotides can be potentially used as therapeutic agents for selective gene silencing, and are currently used as tools to study gene functions in preclinical research including psychopharmacology (antisense technology).

Principles and Role in Psychopharmacology

Modes of Action of Antisense Oligonucleotides

There are several main intracellular mechanisms of actions of antisense oligonucleotides to prevent the expression and translation of the target protein (Dias and Stein 2002, Fig. 1a–e). The first mechanism is based on the disruption of protein translation of target mRNA by base-pairing of single-stranded antisense oligodesoxynucleotides (► antisense DNA) to the respective complementary mRNA strand and physically/sterically obstructing the translation machinery, prevention of ribosomal complex formation, and translation of mRNA into the gene product (translational arrest) (Fig. 1b). The second main mechanism is also based on the complementary binding between the antisense oligodesoxynucleotides (antisense DNA) and the target mRNA. This DNA/RNA hybrid can then be degraded by the enzyme RNase H, a mechanism which significantly enhances the efficacy of antisense potency (Fig. 1c). The RNase endonuclease specifically cleaves RNA in DNA/RNA heteroduplexes. Short-term effects of antisense oligodesoxynucleotides inhibiting neuronal responsiveness without altering gene protein content and availability have been described in neuroendocrine cells (Fig. 1d) (Neumann and Pittman 1998).

Also, ► ribozymes have antisense-like properties (Fig. 1d); those RNA molecules bind to and cleave their target mRNA.

A revolutionary development in antisense research is the finding that 20–25 nucleotide double-stranded RNAs, called siRNA, can efficiently block gene expression (Figs. 1e and 2) via the ► RNA interference (► RNAi) pathways. Any gene of interest with known sequence can be targeted by siRNAs that match the mRNA sequence.

Cellular Uptake of Antisense Oligonucleotides

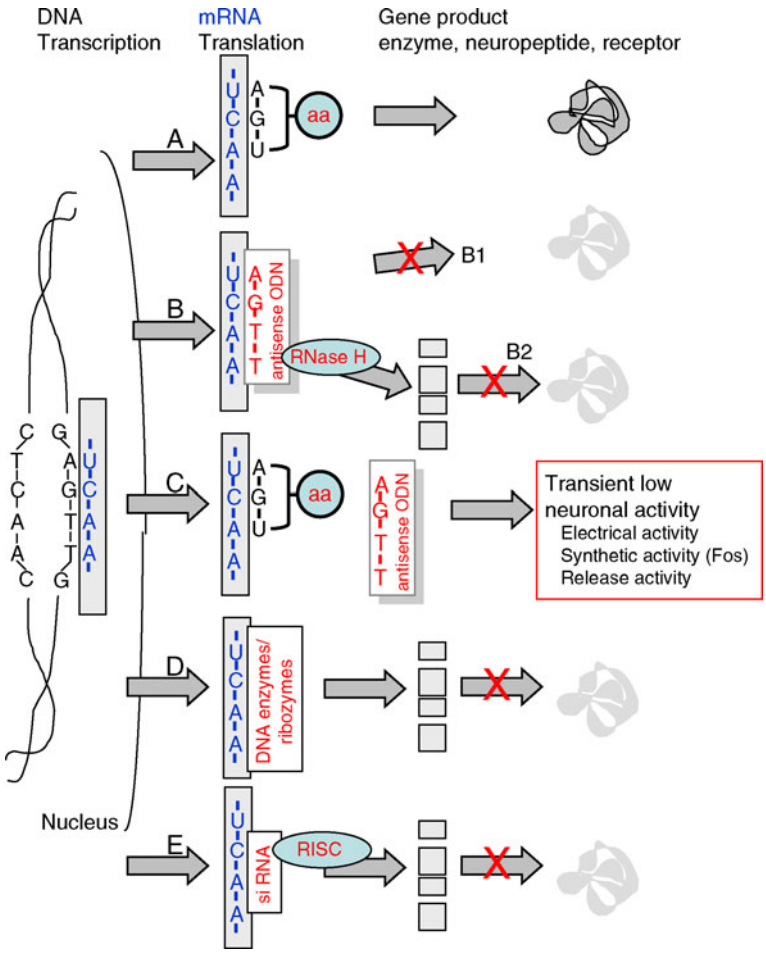
A main problem for antisense technologies is the limitation of cellular uptake of these nucleic acids due to their hydrophilic nature. This is true for negatively-charged siRNA, or chemically modified antisense oligodesoxynucleotides with uncharged backbones such as methylphosphonates, phosphorothioates, or morpholino-derivatives.

For improved efficacy of antisense uptake, agents that enhance transmembrane permeation, i.e., cell-penetrating peptides (CPP) and drugs that target specific receptors, i.e., cell-targeting ligands (CTL) are discussed (Juliano et al. 2008). Also, antisense oligonucleotides tend to localize in lysosomes and endosomes where their antisense properties are poor. The use of vectors (liposomes, i.e., vesicular colloid vesicles) increases stability and cellular internalization. There are commercially available vectors (so-called eufectins), which are used in basic research.

In vivo, the cellular uptake of antisense oligonucleotides into the target tissue is further impaired by several biological barriers (capillary endothelium, extracellular matrix), degradation by serum and tissue nucleases (liver, spleen), and rapid excretion via the kidney; but if oligonucleotides are bound to plasma proteins, ultrafiltration is retarded (Juliano et al. 2008). In order to target the brain tissue, the blood–brain barrier prevents their uptake as polyanionic molecules, and antisense targeting the central nervous system (CNS) requires direct infusion.

In vivo Delivery of Antisense Oligonucleotides

If brain tissue is targeted, antisense oligonucleotides need to be directly infused either into the ventricular system or the target region to circumvent the ► blood–brain barrier; and they are relatively easily taken up by neurons. Prolonged action and slow delivery within the target region can be achieved by use of biotechnical modifications or polymer microparticle encapsulation with high biocompatibility (Choleris et al. 2007).

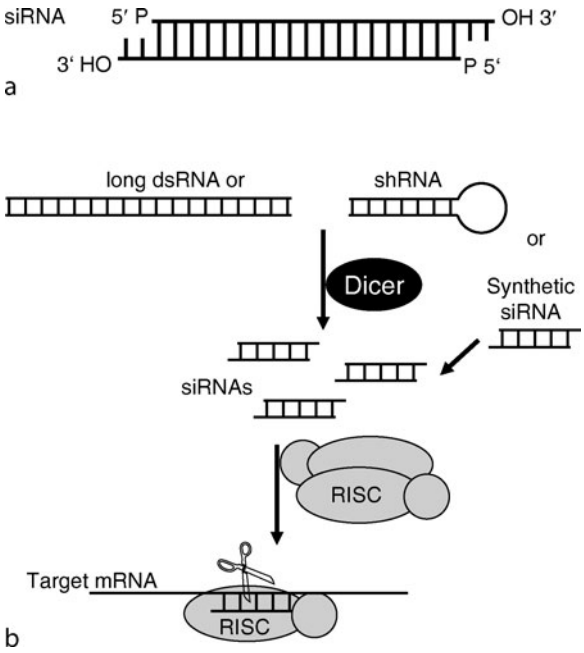


Antisense Oligonucleotides. Fig. 1. Mechanisms of action of antisense oligonucleotides. (**A**) Regular transcription of a gene and translation of mRNA into the gene product. (**B**) Antisense oligonucleotides bind to the complementary strand of gene target mRNA and (B1), sterically block the translation process or (B2), the mRNA/oligonucleotide complex activates an RNase H cleaving the mRNA and preventing translation. (**C**) Short-term effects of antisense oligonucleotides on neuronal responsiveness via unknown mechanisms. (**D**) DNA and RNA enzymes (ribozymes) result in cleavage of mRNA. (**E**) siRNA activate intracellular mechanisms resulting in mRNA cleavage and translational arrest via the RNA interference (RNAi) pathway (see Fig. 2).

The most common strategy for siRNA in vivo delivery is to construct expression vectors driven by a constitutively active RNA polymerase III (Pol III) promoter (e.g., the U6 promoter), to drive transcription of small hairpin RNA (shRNA). shRNA are sequences of RNA that make tight hairpin turns upon intramolecular Watson–Crick base-pairing (Fig. 2b), with perfect duplex RNA of 18–25 nucleotides in length. Cellular enzymes, most likely involving Dicer, process shRNA into siRNA molecules that are capable of performing gene silencing via the RNAi pathway. Although plasmid vectors are effective at delivering shRNA and consequently, siRNA to cultured cells and for the generation of transgenic plants or mice, there are limitations for their use, e.g., in somatic cells of adult brain tissue. To overcome these limitations, viral vectors for the delivery of siRNA have been developed, including lentiviral vectors derived from human immunodeficiency virus-1 (HIV-1) and adenoviral and adeno-associated viral vectors that are used to deliver siRNA into selected brain regions of rodents (Kühn et al. 2007).

Chemical Modifications of Antisense Oligonucleotides

Antisense oligonucleotides are rapidly degenerated by intracellular enzymatic activity. In order to increase efficiency, the cellular uptake and intracellular stability can be



Antisense Oligonucleotides. Fig. 2. Specific knockdown of a target mRNA by siRNA via the RNAi pathway. (**a**) Molecular hallmarks of an siRNA molecule are 18- to 23-nucleotide duplexed RNA region with 2-nt unphosphorylated 3′ overhangs and 5′ phosphorylated ends. (**b**) Mechanism of inhibition of gene expression by siRNA. Long siRNA or shRNA are cleaved by the RNase III family member Dicer to produce siRNA molecules. Alternatively, siRNA can be chemically synthesized and transfected into cells. These siRNAs are then unwound by RISC and incorporated as single-stranded antisense RNA to guide RISC to mRNA transcripts of complementary sequence. This leads to selective endonucleolytic cleavage of the matching target mRNA with subsequent elimination by further cellular RNases.

improved by ► chemical modifications of antisense oligonucleotides (Dias and Stein 2002). The most common chemical modifications employed are replacing an oxygen group of the phosphate-diester backbone with either a methyl group (methyl phosphonate oligonucleotide) or a sulfur group (phosphorothioate oligonucleotide) which have been introduced into clinical therapeutic trials. Increased specificity and efficacy of phosphorothioates are achieved with chimeric oligonucleotides in which the RNase H-competent segment (the phosphorothioate moiety) is bounded on both termini by a high-affinity region of modified RNA. Other chemical modifications include 2′-OH modifications, locked nucleic acids, peptide nucleic acids, and morpholino compounds or hexitol nucleic acids. Although high RNA affinity and high stability have been reported, they do not support RNase H activation. Nevertheless, they can exert their antisense activity via translational arrest or modulation of ► alternative splicing.

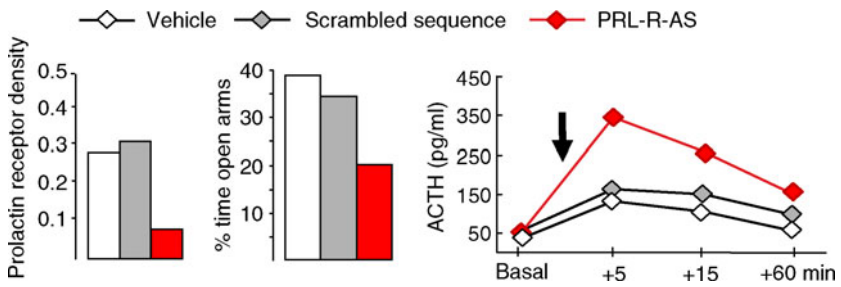
Antisense Oligonucleotides in Psychopharmacology

Antisense oligonucleotide technologies including oligodeoxynucleotides and siRNA are used in psychopharmacology to sequence-specifically, transiently, and locally downregulate the expression of target genes (neuropeptides and their receptors, neurotransmitter receptor subtypes and subunits, steroid receptors, neuronal enzymes, transcription factors), identified by microarray and proteomic approaches or by human genetic studies in vivo in addition or alternatively to established pharmacological means (selective ► agonists and ► antagonists, generation of knockout mice) (Hoyer et al. 2006; Landgraf et al. 1997; McCarthy 1998) for detailed methodological description (Fendt et al. 2008).

Functional consequences of antisense-induced downregulation of neuronal gene products in the brain can be monitored in a behavioral, neuroendocrine, or neuronal context. Antisense oligonucleotides need to be directly infused into the brain ventricles or into a selected brain target region over several days using an osmotic minipump or repeated infusions. They are relatively easily taken up by neurons, have a relatively high stability in neurons and in CSF – likely due to negligible cell proliferation within the brain and lack of exo- and endonucleases within the CSF (McCarthy 1998). Nevertheless, in order to increase central efficiency, mainly phosphodiester and phosphorothioated antisense oligonucleotides are used in psychopharmacology, but unspecific effects were repeatedly described making respective controls essential.

Both acute effects on neuronal functions after single infusion as well as long-term effects after repeated or chronic administration have been described. Often, short-term, antisense-induced blockade of neuronal activation without altering the availability of the gene product (Figs. 1 and 2) is likely to contribute to the observed behavioral, neuroendocrine, and neuronal effects of antisense oligonucleotides, especially if neuropeptides are targeted and stored in rather large amounts (Neumann and Pittman 1998).

Various neuropeptides and their receptors have been targeted using antisense oligonucleotides in the absence of highly selective receptor antagonists (Hoyer et al. 2006; Landgraf et al. 1997; McCarthy 1998), including the receptors for neuropeptide Y_1, corticotropin-releasing hormone (CRH), oxytocin and its receptor, vasopressin



Antisense Oligonucleotides. Fig. 3. Antisense oligodesoxynucleotides targeting the brain prolactin receptor (PRL-R-AS, icv, 6 days) reduced PRL-R density in the choroid plexus, increased anxiety-related behavior on the plus-maze, and elevated the acute stress-induced rise in plasma ACTH in virgin rats. (Data from Torner et al. 2001.)

and its V1a receptor, or the long form of prolactin receptors (Fig. 3).

Antisense oligonucleotides have also been used to target the expression of other neurotransmitter and steroid receptors including the receptors for 5-HT_{2A}, dopamine (D_2), progesterone, as well as NMDA receptor subunits and metabotropic glutamate receptor subtypes. Also, immediate early genes (c-fos, c-jun) and enzymes essential for neurotransmitter synthesis (GABA, 5-HT) have been successfully targeted in order to reveal local effects and behavioral and other functional consequences.

Essential Controls for Antisense Oligonucleotides

To exclude sequence-independent, unspecific effects of mostly chemically modified antisense oligonucleotides in vivo and in vitro, appropriate control groups are essential, i.e., the use of oligonucleotides with identical chemical modification and length which do not match a particular gene. Possible controls include a sense-strand sequence from the same site of mRNA, a scrambled sequence of the nucleotides used in the antisense oligonucleotides in random order, a nonsense oligonucleotide of same length but consisting of a different nucleotide composition without complementarity to any known mRNA sequence.

siRNA in Psychopharmacology

Among the earliest studies of siRNA in the brain were the attempts to perform icv infusion of synthetic siRNA using osmotic minipumps in rodents and concomitant behavioral analysis (Hoyer et al. 2006). To establish this strategy, enhanced green fluorescent protein overexpressed in a transgenic mouse line was successfully targeted in several brain regions. Also, targeting the dopamine transporter (DAT) resulted in reduced DAT mRNA and protein levels in substantia nigra, ventral tegmental areas (VTAs), and nucleus accumbens (Hoyer et al. 2006) accompanied by behavioral changes. Additional proof of concept for siRNA in rodent models of neuropsychiatric disease was provided by siRNA-induced reduction in serotonin transporter (SERT) mRNA in the raphe nucleus after 2 weeks of icv siRNA infusion with antidepressant-like behavioral consequences.

In addition, targeting the ► metabotropic glutamate receptor subtype 7 (mGluR7) by selective siRNA resulted in robust emotional and stress-related changes despite limited local mRNA knockdown (25%) (Fendt et al. 2008).

The use of viral vectors for RNAi in the mammalian brain is particularly suited for local gene knockdown even in small brain nuclei (Hoyer et al. 2006).

Advantages and Limitations of siRNA Procedures

The major advantages of siRNA over classical antisense oligonucleotides and ribozymes appear to be threefold (Zamecnik and Stephenson 1978): siRNA is generally more potent, efficient, and selective because it utilizes natural and efficient cellular machinery, i.e., the RNAi pathway providing assistance at multiple steps for the actions of siRNA, while antisense oligonucleotides and ribozymes hybridize to their targets without any assistance (Dias and Stein 2002). siRNA approaches always result in efficient endonucleolytic cleavage and subsequent elimination of the target mRNA, whereas antisense oligonucleotides not recognized by RNase H result in translational block only via steric hindrance (Neumann and Pittman 1998). Antisense oligonucleotides require relatively high concentrations to target their matching mRNA because at least one oligonucleotide per target RNA is required for

translational blockade or RNase H degradation resulting in toxic side effects. In contrast, one guide strand of siRNA incorporated in RISC (RNA-induced silencing complex) can sequentially bind to and eliminate several mRNA transcripts (multiple turnover).

Limitations of siRNA approaches include (Zamecnik and Stephenson 1978) their capacity to induce cellular virus defense mechanisms, mainly interferon gene induction and cellular arrest and (Dias and Stein 2002) possible unspecific off-target effects on closely related sequences making careful design of the siRNA sequence and use of different siRNA molecules targeting the same mRNA transcript essential.

Cross-References

► Agonist
► Antagonist

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Antisense RNA

Definition

Antisense RNA is naturally occurring single-stranded RNA with properties of antisense oligonucleotides that is complementary to an mRNA strand regulating gene expression machinery of the cell as found, for example, in bacterial plasmids. Transcription of longer noncoding antisense RNAs is a common phenomenon in the mammalian transcriptome including within the brain. No general function of these noncoding antisense RNAs has been elucidated. In contrast to antisense oligodesoxynucleotides, antisense RNA still lacks effective design, biological activity, and efficient route of administration. The effects and mechanisms of antisense RNA should be well separated from those of small interfering RNA (siRNA) and RNA interference (RNAi).

Cross-References

► Antisense Oligonucleotides
► RNA Interference (RNAi)
► Small Interfering RNA (siRNA)

Anxiety

Definition

Anxiety is an emotion shared by all mammals when challenged with dangerous threatening situations at risk for their physical or intellectual integrity. In this case, anxiety is an adaptive response and therefore shaped along the ages by the evolution. Anxiety disorders occurs as a pathological condition, involving unwanted reactions (behavioral and neurovegetative) that are either extreme or occur to inappropriate eliciting stimuli or situations.

Cross-References

► Defensive Behavior: Fear
► Emotional State

Anxiety: Animal Models

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Synonyms

Animal tests of anxiety; Experimental models of anxiety

Definition

Animal models of anxiety refer to experimental preparations developed for one species, generally rodents, with the purpose of studying different facets (e.g., etiology, symptomatology, physiopathological basis, and treatment) of human anxiety. In most of the existing models, anxiety is inferred from defensive responses to artificial (e.g., electric shocks) or ecological (e.g., loud noises and predators) threatening stimuli. Both normal subjects and selected animals (e.g., strain lines resulting from selective breeding, transgenic, knockout animals, and animals with brain lesions) have been used for this purpose.

Current Concepts and State of Knowledge

Anxiety has been defined as an emotional state aroused by the perception of threat, which is subjectively experienced as unpleasant. In its full expression, behavioral, autonomic/endocrine, affective, and cognitive/perceptual changes are manifested. Although usually adaptive, leading to harm avoidance, anxiety may turn out to be disruptive, giving rise to different pathologies. In modern psychiatric classifications, such as the Diagnostic and Statistical Manual, 4th edition, revised (DSM-IV-RT) of the American Psychiatric Association, anxiety is considered pathological when excessive, disproportional to the eliciting event, causing significant distress, disrupting interpersonal relationships, and impairing social and occupational functioning. According to the symptomatology and time course of development, anxiety disorders are classified into different nosological categories, such as ► generalized anxiety disorder (GAD) and ► panic disorder (PD).

The first question one should face while using animal models is that none of the existing models is capable of modeling all aspects of human anxiety. Accordingly, while behavioral and neurovegetative features of this emotion can be successfully assessed in animals, its cognitive/perceptual aspect is invariably left apart, given the vast differences in cognitive abilities between humans and laboratory animals.

After acknowledging this limitation, a subsequent question should be formulated: what makes possible to relate animal defensive behavior to human anxiety? The most accepted answer is phylogenetic continuity as advocated in the theory of evolution.

Charles Darwin himself laid the ground for this line of thought in his book "The Expression of Emotions in Man and Animals" by proposing that behavioral characteristics, no less than physical, would be acquired as a result of natural selection. This view justifies the use of experimental animals to study the neurobiology of psychological functions. Since several environmental constraints are similar across species, many adaptations are species-general, among which stand the basic emotions. Although emotional expression varies from one species to another, functional behavioral classes, such as escape and avoidance from danger or approach to sources of food, remain the same and constitute the basis for the classification of basic emotions (Panksepp 1998). No wonder that the neural substrate of such emotions is conserved along biological evolution. On this basis, Panksepp has proposed that basic emotions are represented by inborn neural networks that coordinate behavioral strategies allowing animals to deal with enduring environmental (including social) challenges.

In this context, anxiety and the related emotional states of fear and panic are rooted in defensive reactions displayed in situations of threat to the physical integrity or survival of the organism. Consequently, anxiety disorders may be viewed as pathologies of defense.

Defensive Reactions in Animal Models of Anxiety

Existing animal models of anxiety may differ in many aspects. For instance, sources of danger that evoke defensive reactions may be manifold, including predators, environmental stimuli or situations, such as height, illumination, painful stimuli, novel places or objects, and confrontation or competition with animals from the same species. To deal with these challenges, animals use defensive strategies such as escape, immobilization, defensive attack, and submission (Blanchard et al. 2008). In the experimental setting, the expression of one particular strategy will be driven by several factors, such as the characteristics of the environment, distance from the threatening stimulus and previous experience with the stimulus and/or environment.

To evaluate to which extent a given response in the animal model is related to the aspect of human anxiety intended to be modeled (generally symptoms of anxiety), three criteria of validation (► Animal Models for Psychiatric States) have been commonly used: analogy or ► face validity, predictability of drug response, and homology or theoretical ► construct validity. As pointed out by Joel (2006), "Face validity refers to a phenomenological similarity between the model and the disorder it simulates. Ideally, the model should resemble the condition it models in its etiology, symptomatology, treatment and physiological basis. ► Predictive validity means that performance in the test predicts performance in the modeled condition. In principle, predictive validity can rely on etiology, physiology and response to treatment, but in practice, predictive validity is usually based in the latter. Construct validity means that the model has a sound theoretical rationale, and depends on the degree of homology between the behavior that is being modeled and the behavior in the model (two behaviors are considered homologous if they share a similar physiological basis), and on the significance of the modeled behavior in the clinical picture."

Earlier attempts to validate animal models of human psychopathologies, including anxiety disorders, have tended to be concentrated largely on the assessment of face validity. It was soon realized that this criterion could be misleading, since in different species similar behaviors often serve different adaptive functions and, conversely, distinct behaviors may lead to the same goal. For instance, rat probe-burying behavior is attenuated by anxiolytics, although it does not resemble any symptom of GAD. However, this model has good correlation with the latter disorder (De Boer and Koolhaas 2003).

With the consolidation of the role of drug therapy in modern psychiatry, the pharmacological investigation of a given model turned out to be the gold standard in the validation process. However, although important, the predictive criterion alone is insufficient to grant a given test the status of an animal model of anxiety, since correlation between the drug response in the model and in the clinics may happen, despite differences in brain mechanisms of pathophysiology and drug effect. For instance, a behavioral index may detect classical anti-anxiety drugs, such as the ► benzodiazepines, and predict their therapeutic outcome only because it involves γ-aminobutyric acid type A ($GABA_A$) receptor mechanisms. However the mechanisms unpinning the behavior may be entirely different from those implicated in the pathophysiology of anxiety and, as a consequence, the model will fail to detect non-GABAergic anxiolytics.

It may be concluded that only homology fully qualifies an animal model as representative of a given psychopathology. Although this goal is being currently pursued, it is hampered by limitation of the available knowledge on the etiology and pathophysiology of anxiety disorders.

Yet, in this respect, animal models of anxiety fare rather well, when compared to other psychiatric disorders, such as schizophrenia or even depression.

Animal Models of Anxiety: Past and Present

Early animal models of anxiety were developed within the conceptual framework of experimental psychology, before classifications of psychiatric disorders split pathological anxiety into distinct nosological entities. These animal models of anxiety rely on either inhibition of ongoing behavior elicited by conditioned stimuli that predict unavoidable electric shock (conditioned suppression) or on the inhibition of rewarded responding by response-contingent electric-shock (► punishment). The latter relates to clinically-derived constructs that emphasize the role of inner conflict in pathological anxiety, and this may be the reason why these tests became known as conflict models. Early pharmacological analysis has shown that conflict tests have a higher predictive value than conditioned suppression and, as a result, punishment tests have become paradigmatic for assaying anxiolytic drugs.

However, classical conflict tests failed to consistently detect the anxiolytic action of drugs that act primarily on serotonin (5-HT)-mediated neurotransmission, such as ► buspirone and ritanserin (Serotonin Agonists and Antagonists). Such false-negative results undermined the general confidence in conflict models, although many arguments may be summoned to their defense, as for instance the time course of drug action. Unlike benzodiazepine anxiolytics, newer drugs need several weeks of continuous administration to become clinically effective, initial doses being sometimes anxiogenic. Therefore, single administration of these agents should not be expected to have anxiolytic effects in animal models. In spite of this, it became generally accepted that conflict tests were good only for anxiolytics that acted primarily on the neurotransmission mediated by ► GABA, such as ► barbiturates and ► benzodiazepines.

A theoretical shift from the experimental analysis of behavior to the systematic observation of animals in their natural environment (Ethology) has also contributed to the discredit of conflict models, which have been

criticized because of their artificiality and the confounding influence of appetitive drives, such as hunger and thirst, and of pain (Graeff and Zangrossi 2002). As a result, a search for ethologically-based animal models of anxiety has occurred. The most widely used animal model of anxiety resulting from this trend has been the ▶ elevated plus maze, which is based on the natural aversion that rats have for the open arms of the apparatus. Yet, this model has also failed to consistently detect non-benzodiazepine anxiolytics, unless behavioral items shown by the rodents while exploring the elevated plus-maze are measured.

As this development was taking place in basic research, the split of anxiety disorders into distinct diagnostic categories, a trend initiated by the DSM III classification, became accepted world-wide. As a consequence, the search for models that represent specific anxiety disorders has started.

The trend towards theoretically-based models that represent specific anxiety disorders has been strongly influenced by the work carried out by Robert and Caroline Blanchard on predatory defense in rats and mice (Blanchard et al. 2008). As a result of this investigation, the Blanchards have established that the type of defense strategy is mainly determined by the presence or absence of the predator, by the distance between the predator and the prey, and by the availability of an escape route. The first pattern of defense occurs when the predator is absent, but had already been met by the prey in the same environment; it also occurs when the context is new, thus containing both potential reward and harm. These instances generate approach-avoidance conflict, and the resulting defense strategy consists of cautious exploration aimed at risk-assessment. The second defense pattern occurs when the predator is present, but is placed at a safe distance from the prey, thus characterizing distal threat. If an exit is available, the animal rapidly escapes, but if not, the animal remains in tense immobility, a posture known as "▶ freezing" behavior that impairs detection by the predator. Finally, when the predator is close or makes actual contact with the prey (proximal threat), the animal reacts with flight or defensive fight.

Although different species show quite distinct behavioral responses to the above types of threat, (e.g., birds fly, while rats run away from danger), antipredator defense is generally organized in the same way, ranging from risk assessment to tense immobility, escape, defensive threat and defensive attack as the danger grows nearer. The same strategies are used in conspecific agonistic interactions, except for submission, an additional defense pattern with the function of establishing social rank, thus minimizing injury and, sometimes, avoiding death of the contenders. Bridging the gap between these defense strategies and animal models of anxiety disorders, the above strategies of antipredator defense have been related to normal and pathological emotions: potential threat with anxiety and GAD, distal threat with fear and phobias (▶ agoraphobia), and proximal threat with dread and PD, respectively. In addition, submission has been related to shyness and ▶ social anxiety disorder.

In terms of neural organization, animal research has indicated that potential and distal threat engage mainly forebrain brain structures, such as the ▶ prefrontal cortex, the ▶ hippocampus and the ▶ amygdala, while proximal defense is chiefly organized in the ▶ hypothalamus and the midbrain periaqueductal gray matter (PAG). Functional neuroimaging results in humans have accordingly shown that brain activation shifts from the prefrontal cortex to the PAG as a virtual threat approaches a virtual prey, and the intensity of punishment increases (Mobbs et al. 2007).

This knowledge underpins theoretical constructs that implicate forebrain structures in the pathophysiology of GAD and the PAG, in PD. Therefore, animal models with theoretical validity can be derived from the same perspective. One clear example of this trend is the elevated T-maze (ETM), which is derived from the elevated plus-maze by shutting off one of its enclosed arms. In this apparatus, the same rat performs two tasks in succession: inhibitory avoidance of the open arm, when placed for three successive times at the end of the enclosed arm, and one-way escape, when placed for three times at the end of one of the open arms. Pharmacological validation studies have shown that not surprisingly, the inhibitory avoidance has predictive value for GAD, since it is another version of a conflict test. More interesting are the findings that chronic, but not acute treatment with antidepressants impairs one-way escape, whereas the panicogenic agent CCK enhances its performance, both changes correlating with drug effects that have been observed in panic patients (Pinheiro et al. 2007). Moreover, the ETM has been successfully used to test hypotheses on the role of serotonin (5-HT) in anxiety and panic, and is being used to screen potentially antianxiety and/or antipanic agents in extracts from plants.

Based on the same rationale, other models of GAD and/or PD have been developed (e.g. the mouse defense test battery and the electrical/chemical stimulation of panic related brain areas such as the dorsal aspect of the PAG and medial hypothalamus). A detailed description of these models as well as a comparative analysis of their

validity and feasibility can be found in Graeff and Zangrossi (2002)

Finally, animal models for social anxiety disorder, ► obsessive compulsive anxiety disorder and ► traumatic stress disorder have also been developed following the present trend towards theoretically-based models addressed to specific anxiety disorders. Nevertheless, their pharmacological validation is still under way.

Cross-References

► Agoraphobia
► Animal Models for Psychiatric States
► Benzodiazepines
► Elevated Plus Maze
► Generalized Anxiety Disorder
► Obsessive Compulsive Anxiety Disorder
► Panic
► Social Anxiety Disorder
► Traumatic Stress (Anxiety) Disorder

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Anxiety Neurosis

► Generalized Anxiety Disorder

Anxiety or Mixed States

► Adjustment Disorders

Anxiety-Reducing Drugs

► Anxiolytics

Anxiogenic

Definition

An anxiogenic substance is one that causes anxiety. Anxiogenic effects can be measured by, for example, the hole-board or elevated plus maze in rats and mice. A number of agents are used to provoke anxiety (anxiogenes) or panic (panicogenes) in experimental models.

Anxiolytic Dependence

► Sedative, Hypnotic, and Anxiolytic Dependence

Anxiolytics

Synonyms

Antianxiety drugs; Anxiety-reducing drugs; Minor tranquillizers

Definition

Anxiolytics are drugs that are prescribed for the treatment of symptoms of anxiety. ► Benzodiazepines are the most widely used class of drugs for treating anxiety states. Recently, drugs that act on 5-HT_{1A} receptors in the brain have been introduced as anxiolytics because they cause little sedation. β-adrenoceptor antagonists such as ► propranolol reduce physical symptoms of anxiety (e.g., tremor, palpitation, etc.) but have no effect on the affective component.

Cross-References

► β-Adrenoceptor Antagonists
► Barbiturates
► Benzodiazepines

APOE

► Apolipoprotein E

Apolipoprotein E

Synonyms

APOE

Definition

APOE is essential for the normal catabolism of triglyceride-rich lipoprotein constituents. APOE was initially recognized for its importance in lipoprotein metabolism and cardiovascular disease. More recently, it has been studied for its role in several biological processes not directly related to lipoprotein transport, including Alzheimer's disease (AD), immunoregulation, and cognition.

The APOE gene is polymorphic with three major alleles: ApoE2, ApoE3, and ApoE4, which translate into three isoforms of the protein:

E2 is associated with the genetic disorder type III hyperlipoproteinemia and with both increased and decreased risk for atherosclerosis.

E3 is found in approximately 64% of the population. It is considered the "neutral" Apo E genotype.

E4 has been implicated in atherosclerosis and Alzheimer's disease, impaired cognitive function, and reduced neurite outgrowth.

Apomorphine

Definition

Apomorphine is a drug used to treat impairments in motor function (tremor, slow movement, and difficulty walking and speaking) in Parkinson's patients. It is sometimes used for erectile dysfunction. In larger doses, it has emetic effects and was used in aversion therapies. It is a nonspecific dopamine agonist with actions at several subtypes of dopamine receptors, both presynaptic and postsynaptic. As a pharmacological tool for probing the function of dopamine receptors, it has been largely replaced by more selective substances. It does not have morphine-like effects and does not interact with opioid receptors.

Cross-References

► Anti-Parkinsonism Drugs
► Sexual Disorders

Apoptosis

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Synonyms

Physiological cell death; programmed cell death

Definition

Apoptosis is a form of regulated physiological cell death that is important during ontogenesis but which may also contribute to tissue homeostasis as well as pathology.

Current Concepts and State of Knowledge

Characteristics of Apoptosis

Apoptosis may be triggered by signals from within the cell or proximal and distal cells, as well as exogenous agents; apoptotic cell death may also result from the withdrawal of trophic factors (► nerve growth factors). All of these triggers initiate a cascade of events that results in the elimination of cells without releasing harmful substances into the surrounding areas. Apoptosis is not associated with an inflammatory response; in situ, apoptotic cells are phagocytosed by macrophages or neighboring epithelial cells, whereas the fragments of cells that have undergone apoptosis in vitro are eventually lysed.

In its original sense, the term apoptosis was used to refer to a form of "programmed cell death" that depends on the activation and/or repression of ► gene transcription to delete biologically redundant or dysfunctional cells. Growing knowledge of how cell death is triggered and of the processes that lead up to it indicate a degree of overlapping mechanisms in different forms of cell death; this has resulted in a blurring of how apoptosis should be defined. However, the consensus is that apoptosis can only be ascertained through the morphological observation of chromatin condensation with evidence of DNA cleavage, nuclear fragmentation, cell shrinkage, blebbing of the nuclear and plasma membranes, and formation of membrane-bound apoptotic bodies in cells that otherwise have an integral plasma membrane. At the biochemical level, apoptotic cells show signs of mitochondrial dysfunction. Specifically, the mitochondrial membrane

potential is perturbed and results in a leakage of mitochondrial proteins, such as cytochrome *c*, into the cytoplasm; cytochrome *c* is a soluble protein whose ability to transfer electrons plays a key role in energy generation.

Apoptosis Versus Necrosis

In contrast to apoptosis, cell death through necrosis may be considered to occur "accidentally" following direct disruption of cellular homeostasis of cellular functions by a toxin or noxious stimulus (e.g., hypoxia, hypothermia), resulting in an influx of water and extracellular ions. Morphologically, this form of cell death, which differs from apoptosis, is characterized by swelling of the cytoplasm and mitochondria and the ultimate disintegration of the plasma membrane, leading to the leakage of lysosomal enzymes that lyse a group of contiguous cells (typically apoptosis affects only individual cells), usually followed by an inflammatory response. Other important features that distinguish apoptosis and necrosis are (1) DNA fragmentation in apoptosis occurs through the actions of specific DNA-cleaving enzymes (endonucleases) while the cell is still intact, whereas DNA breakdown in necrotic cells occurs only after cell lysis and the DNA fragments are of random size; (2) apoptosis is an energy (ATP)-dependent process, whereas necrosis is a passive process; and (3) whereas necrosis results from a massive influx of calcium in the cell, apoptosis is triggered by moderate increases in calcium influx. Various assays that are based on the above-mentioned morphological and cytological descriptions serve to discriminate between apoptotic and necrotic cells both in vivo and in vitro; in addition, researchers increasingly rely on other biochemical and molecular markers to detect early- and late-stage apoptosis.

Apoptotic Mechanisms

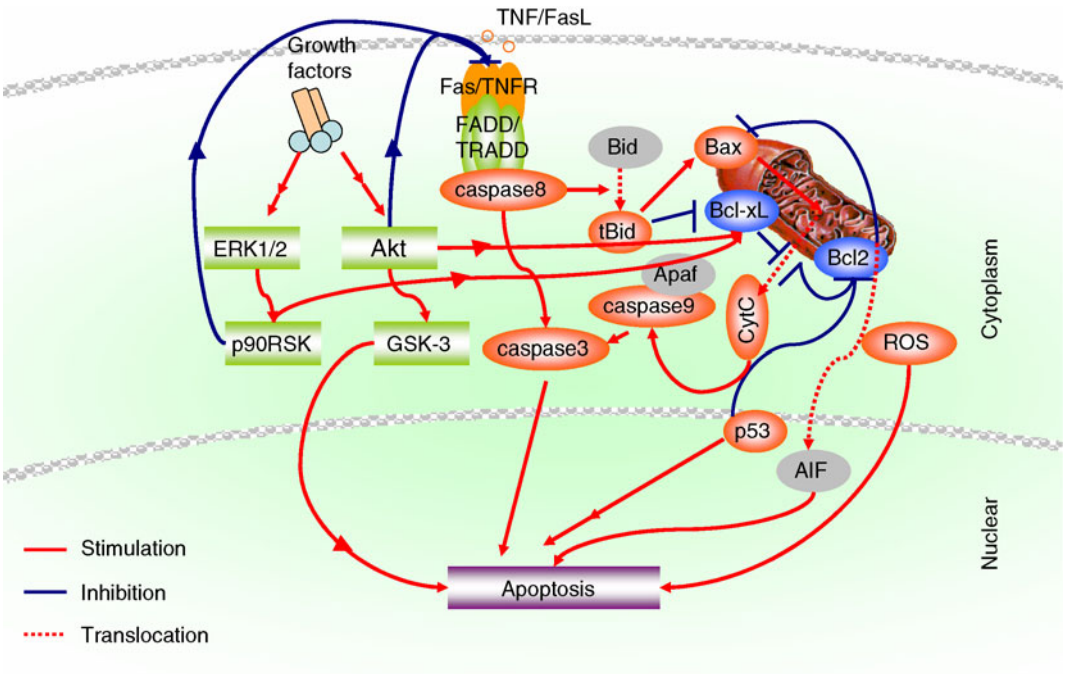
An understanding of the molecular and cellular basis of apoptosis has grown immensely in the last decade. While the molecular processes that lead to apoptosis are initiated in the cytoplasm or the membranes of organelles, the final execution of the apoptotic process takes place in the nucleus where irreversible, Ca^{2+}/Mg^{2+}-dependent internucleosomal DNA fragmentation occurs in a sequential fashion, mediated by endonucleases.

In general, apoptosis results through one of two cellular pathways, the intrinsic and extrinsic pathways; however, growing evidence points to the possibility that these pathways may converge under certain circumstances. The sequential activation of caspases is central to both pathways; the activation of caspase 3, a so-called executor caspase serves as a good biochemical marker of apoptosis. In addition, apoptosis may occur independently of caspase activation. Several stimuli, including DNA damage, and oxidative and excitotoxic stress, cause the translocation of apoptosis-inducing factor (AIF) from the mitochondrial intermembranous space to the nucleus where AIF binds to DNA and initiates apoptosis by promoting chromatin condensation (Fig. 1).

The intrinsic pathway is initiated by the perturbation of the mitochondrial transmembrane potential, which is rheostatically regulated by the availability of pro- (e.g., Bax, Bid) and anti-apoptotic (e.g., Bcl-2, Bcl-X_L) members of the Bcl-2 family of proteins. A shift in the ratio of these proteins in favor of the pro-apoptotic members leads to the release of mitochondrial cytochrome *c* (a heme-containing protein involved in electron transfer) which, in turn, binds to apoptosis protease activator factor-1 (Apaf-1), forming an apoptosome that subsequently cleaves and activates pro-caspase 3. In the extrinsic pathway, the binding of either Fas ligand, tumor necrosis factor (TNF) α, or tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) to their corresponding membrane receptors results in the formation of a complex between liganded and pro-caspase 8. When cleaved, caspase 8 can activate caspase 3 directly, or indirectly by cleaving the pro-apoptotic protein Bid in the cytoplasm; truncated Bid (tBid) translocates to the mitochondrion where it disrupts that organelle's permeability transition pore, resulting in cytochrome *c* release and the ultimate activation of caspase 3.

Neuronal apoptosis may be triggered by both, pro-apoptotic signals as well as limited availability of (neuro) trophic molecules (nerve growth factors); the latter mechanism is important in both physiological and pathological contexts and led to the discovery of pro-survival signaling pathways that act to suppress the cell death machinery. Among the best-characterized survival pathways are the Ras-MAPK (mitogen-activated protein kinase) and the PI3K (phosphatidylinositide-3′-OH kinase)-Akt pathways.

It is estimated that neurons undergo apoptotic death within 6-12 h from first being exposed to a pro-apoptotic stimulus. Under normal circumstances, apoptosis occurs widely in the developing brain; it also occurs throughout postnatal life, albeit at a much reduced rate. It is estimated that apoptosis results in the elimination of up to 70% of neurons during early brain development; accordingly, it is thought to serve a physiological role, serving to ensure appropriate structure and function of the brain and the



Apoptosis. Fig. 1. The pathways to apoptotic cell death. Two pathways, the so-called intrinsic and extrinsic pathways, regulate apoptosis. In both pathways, caspases, a family of cysteine proteases, play a central role. The arrival of apoptotic signals leads to the activation of initiator caspases (e.g., caspase-8, -9) and sequential cleavage/activation of downstream effector caspases; caspase-3 is the last caspase in this cascade and is known as the "executor caspase" since the process cannot be reversed once this caspase is activated. The extrinsic pathway is triggered after the binding of FasL or TNF to their respective cognate receptors (Fas and TNFR), followed by the activation of caspase-8 through the adaptor protein FADD/TRADD. Activated caspase-8 can stimulate apoptosis through one of two cascades: direct activation of caspase-3 or cleavage of Bid. Truncated Bid (tBid) translocates to the mitochondrion where the extrinsic pathway converges with the intrinsic pathway in which the formation of pores in the outer mitochondrial membrane and the leakage of cytochrome *c* is a central event. Cytochrome *c* binds Apaf1 to form an activation complex with caspase-9, an event critical to the activation of the intrinsic pathway. Members of the BCl-2 family of proteins, including the anti-apoptotic proteins Bcl-2 and Bcl-xL and pro-apoptotic protein Bax, rheostatically control apoptosis by determining the integrity and permeability of mitochondrial membranes and thus, cytochrome *c* release. The tumor suppressor protein p53, which is activated following DNA damage, induces the transcription of Bax, which, in turn, disrupts the mitochondrial potential. More recently, another apoptotic mechanism involving mitochondrial release of apoptosis inducing factor (AIF) was identified. AIF translocates to the nucleus and directly triggers the internucleosomal degradation of DNA. Reactive oxygen species (ROS) can also directly induce apoptosis by damaging DNA strands. On the other hand, anti-apoptotic signals, including growth factors and cytokines, act by inducing the phosphorylation of signaling molecules such as Erk1/2 and Akt. Erk1/2 activates p90RSK, which upregulates the expression of the anti-apoptotic proteins Bcl-xL and BCl2 and inhibits the Fas pathway; similarly, activated Akt regulates the expression of members of the Bcl2 family and of Fas while inhibiting GSK-3 signaling.

ability of the brain to adapt to changing demands. As neuronal apoptosis is essential to normal brain development and function, it is conceivable that it may contribute to brain pathology and pathophysiology if it arises at an inappropriate time or location, or in excess or an insufficient extent.

Neuronal Birth, Death, and Plasticity

Ensuring the correct number of functional neurons in a given brain area depends on the coordinated birth and death of neurons. Extensive neuronal birth (► neurogenesis) in the mammalian brain ceases during postnatal life; two areas, the ► hippocampus and

olfactory bulb however continue to show neurogenesis throughout life although the rate of cell birth tapers off with age.

The mechanisms that regulate neurogenesis are common to other forms of cell proliferation, and include the expression of cyclin-dependent kinases that drive the dividing cells through the various stages of the cell cycle in a temporally coordinated fashion. The end of cell proliferation (mitosis) is marked by the expression of proteins that induce cell cycle arrest; however, whereas most other cell types can go through repeated mitotic cycles, differentiated neurons are considered to be in a permanent postmitotic state. While differentiated neurons are sensitive apoptotic stimuli, undifferentiated or migrating young neurons appear to be particularly sensitive and their elimination through apoptosis (probably through the programmed withdrawal of neurotrophic support nerve growth factors) is responsible for giving the brain its final structure. Importantly, a growing body of evidence shows that some mature neurons may reenter the cell cycle, namely by reactivating several of the molecular components that typify mitosis; however, this reentry into the cell cycle is abortive and ends in apoptosis, a mechanism now thought to be of importance during brain development and neurodegenerative disease such as Alzheimer's disease (► dementias and other amnesic disorders).

Brain structure and function undergoe dynamic – plastic – changes from early development through to old age. Neurogenesis and neuroapoptosis are essential parts of this process insofar as they determine communication between individual neurons (adjacent or at a distance), and whole pathways or networks and even whole systems, as well as interactions with supporting glial and vascular tissues. Additionally, the balanced relationship between neurogenesis and apoptosis can be expected to be important to histogenetic constancy (stability) as well as flexibility (► synaptic plasticity); computational models suggest neuronal turnover to play a facilitative role in learning and information recall (memory) by, respectively, filtering relevant information from irrelevant information and reducing interference from other information (► long-term potentiation and memory).

Why IS Apoptosis of Interest to Neuropsychiatry?

In the mature brain, apoptosis occurs at a low rate but that may, nevertheless, be sufficiently significant to contribute to the reorganization of neuronal circuits. Neuropsychiatric diseases are thought to be neurodegenerative or neurodevelopmental in origin. Neuronal death, including that occurring through apoptosis, is a defining pathological feature of neurodegenerative diseases (► neurodegeneration and its prevention) such as ► Parkinson's disease, ► Alzheimer's disease, ► Huntington's disease, amyloid lateral sclerosis (or Lou Gehrig's disease), and human immunodeficiency virus (HIV)-associated dementia. Aberrant neuronal apoptosis may also underlie neurodevelopmental disorders such as ► schizophrenia, ► autism, and ► fragile X syndrome. Some of the known effects of various classes of psychoactive drugs on neuronal survival are summarized in Table 1.

Loss of neurons through apoptosis appears to underlie ► fetal alcohol syndrome, a neurodevelopmental disorder

Apoptosis. Table 1. Influence of various psychoactive drugs on neuronal survival.

Agent	Examples	Properties/Uses	Neuronal survival
Stimulants and addictive drugs ► psychomotor stimulants and abuse, ► abuse liability evaluation		Inhibit serotonin (5HT) and norepinephrine (NE) reuptake, increase glutamatergic activity, and stimulate dopamine (DA) release to produce "reward"	Associated with cerebral atrophy; increase cellular oxidative stress (due to increased DA catabolism) and activate apoptotic signaling pathways
	Amphetamine, metamphetamine, "ecstasy" (3,4-methylenedioxy-N-methylamphetamine, MDMA), ► cocaine, ► psychostimulant abuse	Enhance locomotion and repetitive behavior; tolerance and dependence develop after chronic use, addictive/used recreationally for feelings of euphoria, energy, increase sensory perception, sense of well being, alertness, mental acuity, and creative thinking	Induce apoptosis (intrinsic pathway)

Apoptosis. Table 1. (continued)

Agent	Examples	Properties/Uses	Neuronal survival
	► Methylphenidate (cognitive enhancers)	Inhibits DA reuptake; enhances cognition, may cause anxiety and general nervousness, emotional lability, aggression and paranoia; treatment of attention-deficit hyperactivity disorder, narcolepsy, and chronic fatigue syndrome; likely to be abused	Reportedly protective against excitotoxicity but also pro-apoptotic
	Ampakines (cognitive enhancers)	Alkaloid analgesic; tolerance and dependence may develop after chronic use; addictive/clinical management of pain	Neuroprotective (increase neurotrophin production)
	Morphine (prototypic opiate) (► opioids)	Alkaloid analgesic; tolerance and dependence may develop after chronic use; addictive/clinical management of pain	Pro-apoptotic
	Heroin (opioids)	3,6-diacetyl ester of morphine recreational to obtain a "rush"	Pro-apoptotic (intrinsic and extrinsic pathways)
	► Caffeine	Xanthine alkaloid, antagonizes adenosine receptors; may produce tolerance, physical dependence, and craving, irritability, nervousness, anxiety, insomnia, and headache/most common nonprescription psychostimulant ("energizer") in food and beverages	Regulates cell cycle checkpoint proteins and DNA repair and may protect against Parkinson's disease
	► Nicotine	Affects cholinergic, DA-, NE-, and 5HT-ergic, and neuropeptidergic transmission; highly addictive/in cigarettes, to produce euphoria/pleasure, relaxation, increased arousal/alertness and memory (low doses), reduced appetite and induce sedation and pain (high doses); treatment of nicotine addiction (only medical use)	No consensus; suggested reduced risk of Parkinson's and (possibly) Alzheimer's disease; may be risk factor for schizophrenia

Apoptosis. Table 1. (continued)

Agent	Examples	Properties/Uses	Neuronal survival
Sedatives and anxiolytics		Suppress neuronal activity by acting as GABA mimetics, and modulating activity of NMDA, opioid and cannabinoid receptors; highly addictive; reduce attention and slow reflexes; are not addictive but ''discontinuity symptoms'' arise upon abrupt withdrawal	
	Opiates, general anesthetics (► analgesics, ► opioids)	Some, such as phencyclidine (''angel dust'') may cause hallucinations, delirium, mania and disorientation/in anesthesia (phencyclidine now replaced in anesthesia by ketamine, another NMDAR antagonist)/analgesia and anesthesia; opiates are subject to abuse	Phencyclidine and ketamine are pro-apoptotic; opiates also induce apoptosis
	► Barbiturates, ► benzodiazepines and other ► anticonvulsants	Block Na+ channels and bind to GABA receptors; anti-convulsant, anxiolytic, hypnotic/have high-abuse potential/treatment of epilepsy and ► bipolar disorder (barbiturates now rarely used); also used as recreational drugs	Barbiturates and benzodiazepines are pro-apoptotic, especially in developing brain
	Ethanol/(alcohol abuse and dependence)	Impairs problem solving, abstract thinking, concept shifting, psychomotor performance, and performance in memory tasks (severe amnesia in extreme cases), and may cause dementia; causes attention-deficit hyperactivity disorder and learning difficulties in childhood and high incidence of major depression and psychosis in later life/in pharmaceutical preparations; widely used for recreational purposes	Pro-apoptotic; acute doses cause dendritic re-arrangements; fetal exposure results in apoptosis of developing neurons and causes diminished brain size (causes fetal alcohol syndrome by increasing reactive oxygen species production, while reducing defenses against them; and hyperactivation of GABAergic transmission and increase of glutamate excitotoxicity)
	5HT 1a receptor agonists (e.g., buspirone)	Lower anxiolytic potency than benzodiazepines, but do not cause sedation and have less-severe effects on cognition; have no abuse potential	Anti-apoptotic, currently being tested in models of stroke, brain trauma, and ethanol-induced apoptosis

Apoptosis. Table 1. (continued)

Agent	Examples	Properties/Uses	Neuronal survival
► Anti-psychotic drugs (neuroleptics)	*Typical:* haloperidol, chlorpromazine; *atypical or second-generation*: olanzapine, risperidone, quetiapine	Activate DA D2 receptors and inhibit DA release; may cause one or more of the following: tardive dyskinesia, acute dystonia, akathisia, parkinsonianism (rigidity and tremor), lethargy, seizures, psychosis, intense dreams, or nightmares/treatment of schizophrenia	Possibly induce neuronal apoptosis through excitotoxic mechanisms, disruption of the mitochondrial respiratory chain, or reduced neurotrophic support
► Anti-depressants			Generally, increase neurotrophic support and promote neuroplasticity, although cell culture studies indicate that many have the potential to trigger oxidative stress and activate apoptotic pathways
	► Monoamine oxidase inhibitors (MAO)	MAO-A inhibitors reduce breakdown of 5HT, and NE/treatment of depression, bipolar disorder, and agoraphobia (social anxiety); MAO-B inhibitors reduce catabolism of DA/treatment of Parkinson's disease	Appear not to cause apoptosis in neural cell cultures
	Tricyclic compounds	Inhibit presynaptic reuptake of 5HT and NE; some tricyclics interfere with memory performance, many reduce histamine actions (H1 receptor), producing sedation/treatment of major depression, and insomnia, migraine, anxiety, attention-deficit hyperactivity disorder, chronic pain, (sometimes) schizophrenia	Induce neurogenesis and neuroplasticity
	Selective serotonin- or NE-reuptake inhibitors (► SSRIs and related compounds, ► SNRI antidepressants)	Increase 5HT and NE levels in synaptic cleft by inhibiting their presynaptic reuptake/treatment of major depression and anxiety disorders, as well as eating disorders and chronic pain	Induce neurogenesis and neuroplasticity
	Neuropeptide receptor antagonists	Block pituitary receptors for hypothalamic peptides that stimulate adrenal activity/in trials for use as antidepressants and anxiolytics	► Corticotropin-releasing hormone (CRH), implicated in depression and anxiety, appears to be neuroprotective

Apoptosis. Table 1. (continued)

Agent	Examples	Properties/Uses	Neuronal survival
► Mood stabilizers and ► anti-convulsants	► Benzodiazepines, barbiturates, GABA analogs, and inhibitors of GABA breakdown (e.g., vigabatrin), hydantoins (e.g., phenytoin), carbamates, carboxamides	Anti-convulsant actions result from blockade of Na+ channels and enhancement of GABAergic-mediated inhibition of neuronal firing or block glutamatergic transmission/treatment of acute and recurrent seizures	Reduce neurotrophic molecules, leading to neuronal apoptosis (may account for microcephaly and impaired neurodevelopment and cognitive functions); some drugs disrupt neuronal migration in the developing brain
	► Valproic acid	Inhibits GABA transaminase, increasing GABA production; affects long-term gene expression by inhibiting ► histone deacetylase (HDAC)/treatment of epilepsy and manic phase of bipolar disorder	Interferes with neuronal migration and induces neuronal apoptosis in developing brain; is neuroprotective in postnatal neurons (via insulin-dependent activation of PI3-K/Akt
	► lithium	Respectively, decreases and increases NE and 5HT release; inhibits glycogen synthase 3β (GSK-3β)/treatment of manic phase of bipolar disorder	Promotes neuronal survival by inhibiting GSK-3β, activating the PI3-K/ Akt pathway, increasing neurotrophin production factors, heat shock proteins (hsp 70) and anti-apoptotic proteins (e.g., Bcl-2)
Hormones	Sex hormones (estrogens, androgens, progestins)	Act through nuclear receptors (transcription factors), but may also rapidly alter membrane properties and neuronal firing rates; cognition, reward processes, mood and emotion are positively influenced by estrogens and androgens; progestins induce anxiolysis, sedation and somnogenesis by allosteric modulation of $GABA_A$ receptors; all are involved in aggressive and affiliative behaviors/naturally produced by the gonads, may be prescribed for a variety of endocrine dysfunctions and during aging; androgens may be used as anabolics	Anti-apoptotic actions resulting from phospho-activation of the MAP and Akt pathways, stimulation of neurotrophin production and altered anti- and pro-apoptotic protein ratios; estrogens can scavenge oxygen free radicals

Apoptosis. Table 1. (continued)

Agent	Examples	Properties/Uses	Neuronal survival
	Glucocorticoids (natural hormones include cortisol and corticosterone; synthetic glucocorticoids include prednisolone and dexamethasone)	Bind to nuclear receptors – mineralocorticoid (MR) and/or glucocorticoid receptors (GR) – in an amplitude-dependent fashion to induce or repress gene transcription; have anxiogenic and depressogenic properties, interfere with learning and memory/naturally produced by the adrenal cortex, glucocorticoids may be prescribed as anti-inflammatory agents and for shock and certain cancers; also used in endocrine diagnostics	Activation of GR by high glucocorticoid levels leads to neuronal apoptosis, low glucocorticoid levels that selectively occupy MR are neuroprotective; glucocorticoids also inhibit neurogenesis and neurotrophin synthesis, and induce dendritic retraction

that is associated with hyperactivity, learning disabilities and depression during childhood, and psychoses in adulthood. Convincing data demonstrate that ethanol (► alcohol abuse and dependence) stimulates neuronal apoptosis in a variety of cortical regions by interfering with GABAergic and glutamatergic neurotransmission during developmental stages characterized by a high rate of synaptogenesis. Similar mechanisms are also thought to be responsible for the apoptotic actions of a number of drugs that have medical applications (anesthesia, epilepsy) but which are also subject to abuse.

An etiologic role for enhanced apoptosis has also been proposed in major depression, although post mortem examinations have led some authors to challenge its importance. Although increased levels of apoptosis are observed in some animal models of depression (► depression: animal models) based on chronic stress paradigms that elevate glucocorticoid secretion and despite strong evidence that glucocorticoids are potent pro-apoptotic (and anti-neurogenic) hormones, a causal link between neuroapoptosis and depression remains to be firmly established. Studies showing that stress and glucocorticoids induce dendritic reorganization and synaptic connections suggest a rather more important role for these mechanisms in the etiology of depression. While a number of ► antidepressants have been shown to induce apoptosis in neuronal cultures, the majority of studies in animals indicate that antidepressants might exert their therapeutic actions by stimulating neurotrophin (► nerve growth factors) production and therefore, neuroplasticity. The known inhibition of neurotrophin expression by glucocorticoids may be the link between stress and psychiatric diseases such as depression and anxiety (► emotion and mood). In addition, elevated glucocorticoids have been clearly shown to impair cognition; besides their ability to modulate neuronal firing patterns and synaptic plasticity, ► glucocorticoids have been recently shown to promote the aberrant processing and posttranslational modification of proteins implicated in mild and severe forms of dementia (► dementias and other amnesic disorders).

In addition to glucocorticoids, several endogenous peptidergic and steroid hormones have emerged as being potentially important in neuropsychiatry. ► Corticotropin-releasing hormone and ► arginine vasopressin are examples of neuropeptides that have gained considerable attention; both peptides act on the pituitary and ultimately stimulate glucocorticoid secretion and because they have marked influences on ► emotion and mood and cognition in animals, they have been implicated in ► major and minor and mixed anxiety-depressive disorders. Progestins and their derivatives (► neurosteroids) are well known for their sedative and anxiolytic effects that are mediated by $GABA_A$ receptors, and estrogens (► sex hormones) appear to have mood- and cognition-enhancing (► cognitive enhancers) effects that are attributed to their neurotrophic and anti-apoptotic actions.

Conclusion

Many psychoactive drugs have been studied for their possible apoptotic effects on neurons. Studies of such

effects during brain development raise concerns that drug-induced apoptosis can have a major impact on the development of neuropsychiatric conditions in childhood and later life. Demonstrations of psychoactive drug-induced apoptosis in the mature brain are important in that they may account for some of the undesired side effects of therapeutic agents, the ▶ antipsychotic drugs being a good case in point (see Table 1). However, caution is called for in the interpretation of results since many of them derive from experiments in artificial cell culture settings that may differ in terms of kinetics and which lack the normal drug metabolism mechanisms that operate in the whole organism; also, to be considered is the fact that the disposition and action of a drug varies according to the context in which it is administered (▶ pharmacokinetics, ▶ sex differences in drug effects). Physicians' prescribing decisions are guided by evidence of therapeutic efficacy and immediacy, and careful risk-benefit analysis on a case-by-case basis.

Cross-References

▶ Abuse Liability Evaluation
▶ Alcohol Abuse and Dependence
▶ Analgesics
▶ Antidepressants
▶ Antipsychotic Drugs
▶ Arginine Vasopressin
▶ Barbiturates
▶ Benzodiazepines
▶ Bipolar Disorder
▶ Caffeine
▶ Cocaine
▶ Cognitive Enhancers
▶ Corticotropin Releasing Hormone
▶ Dementias and Other Amnesic Disorders
▶ Depression: Animal Models
▶ Dysthymic Mood Disorder
▶ Emotion and Mood
▶ Histone Deacetylase Inhibitors
▶ Lithium
▶ Long-Term Potentiation and Memory
▶ Major and Minor and Mixed Anxiety-Depressive Disorders
▶ Nerve Growth Factors
▶ Neurodegeneration and Its Prevention
▶ Neurogenesis
▶ Neurosteroids
▶ Nicotine
▶ Opioids
▶ Pharmacokinetics
▶ Psychostimulant Abuse
▶ Schizophrenia
▶ Sex Differences in Drug Effects
▶ Sex Hormones
▶ SNRI Antidepressants
▶ SSRIs and Related Compounds
▶ Synaptic Plasticity

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Apoptosis-Inducing Factor

Synonyms

AIF

Definition

It is a protein found on the inner leaflet of mitochondrial membranes. Upon the arrival of an apoptotic stimulus, AIF contributes to the increased permeability of mitochondrial membranes, resulting in its own entry into the cytosol and nucleus.

Apoptosome

Definition

It is the term used to describe the multimeric cytoplasmic complex that forms when cytochrome *c* is released from

mitochondria into the cytosol and binds to apoptosis protein-activating factor 1 (Apaf1), dATP, and initiator caspases such as caspase 9. The apoptosome plays a key role in the activation of ► apoptosis.

Apparent Volume of Distribution

► Volume of Distribution

Appetite

Definition

The desire to eat. A willingness to consume food that can be indexed by the tendency to engage in activities that will procure food, and by the rate, duration, and quantity of food consumed. Appetite can be aroused by external food stimuli (such as the sight or smell of food) and enhanced or diminished by the oral sensory qualities of the taste, flavor, and texture of foods as they are eaten. Specific appetites (or cravings) may occur in relation to specific physiological imbalance, illness, or external food cues.

Cross-References

► Hunger
► Palatability
► Satiety

Appetite Stimulants

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Synonyms

Hunger-mimetics; Hyperphagics; Orexigens

Definition

Appetite stimulants are agents that promote the motivation to eat through actions on psychological, neurochemical, metabolic, or endocrine processes. Their actions may increase ► hunger and the desire to eat, promote the anticipation of, or craving for food, and/or enhance hedonic responses to the sensory properties of foods. These psychological effects may cause over consumption by increasing the salience of, and attention to, food stimuli and so advance the initiation of eating, or by increasing meal frequency, meal size, or meal duration. Drugs that increase ► appetite and/or food intake, and that may be used for the amelioration of loss of appetite and body weight associated with illness or radical medical treatments of disease.

Pharmacological Properties

History

Unlike the substantial commercial and academic research efforts that have been devoted to the development of appetite suppressant treatments, relatively few resources have been expended on the rational design of appetite stimulants. Several classes of drug possess the ability to increase appetite and food intake, but these effects are often poorly characterized side effects of treatments that were primarily intended for other clinical purposes. Multiple neurochemical and endocrine systems have been implicated in the stimulation of appetite through the hyperphagic actions of endogenous or synthetic receptor ligands. These include gamma-aminobutyric acid (► GABA), agouti-related peptide (AgRP), neuropeptide Y (► NPY), melanin-concentrating hormone (MCH), ghrelin, the endogenous ► opioids, and the ► endocannabinoids. With recent progress in the characterization of the systems involved in appetite control and body weight regulation, a wide range of experimental compounds that act as agonists or antagonists at specific receptors have been shown to have orexigenic effects in animal models. However, for most of these agents, their use is restricted to experimental probes for the study of neural appetite-control pathways.

Mechanisms of Action

Some drugs have hyperphagic effects that are widely acknowledged in clinical populations, but for which clear mechanisms have yet to be identified – despite considerable knowledge about their principal pharmacological actions being available. Appetite stimulation and the development of overweight or obesity are not uncommon side effects of drugs used to treat psychiatric disorders (Schwartz et al. 2004). Intriguingly, of the more classical drug groups, agents with anxiolytic-sedative properties are most likely to exert hyperphagic actions – at least under laboratory conditions. These agents include ► benzodiazepines, some antihistamines, ► barbiturates, ► opiates, and ► cannabinoids.

The majority of experimental agents that have exhibited orexigenic efficacy in animal models have not been assessed

in relation to that activity in humans: the few that have, rarely – if ever – progress beyond the preclinical stages of development. Similarly, clinical exploitation of the hyperphagic side effects of psychotropic drugs and other medicines are often poorly studied, with a dearth of controlled clinical trials. In the long term, continuing research into the central and peripheral processes that mediate appetite control and energy balance will ultimately clarify specific processes through which the orexigenic properties of drugs come to be expressed. Currently, however, precise mechanisms of action are defined for only relatively few of these drugs. Therefore, the main emphasis here will be on a largely phenomenological description of those drugs which have demonstrable hyperphagic actions in humans and for which clinical applications for the treatment of appetite and weight loss have been actively pursued.

Clinical Application of Appetite Stimulants

An often-overlooked area in a world obsessed by obesity is the treatment of clinical conditions in which the progress of a disease is associated with involuntary weight loss. For example, wasting, or cachexia, is a common feature of the later stages of diseases such as AIDS and metastatic cancer, and is a significant factor in their morbidity. Cachexia is characterized by the loss of fat and lean mass resulting from abnormalities in protein synthesis/degradation, lipid and glucose metabolism, and energy utilization. Additionally, sufferers typically fail to exhibit any compensatory increase in eating motivation to counter these changes – as would be the case with weight loss caused by fasting. Disease-related wasting may be further exaggerated by the effects of radical drug or radiation therapies, which frequently lead to loss of appetite and malnutrition, sometimes as a consequence of treatment-induced nausea, vomiting, and taste aversions. Wasting and loss of appetite are also clinically important features of aging, particularly in relation to the dementias.

Cannabinoids

Of all the drugs that might be discussed here, alkaloids (► cannabinoids) derived from Cannabis *sativa* (marijuana) have the most widely recognized and well-documented hyperphagic actions. Cannabis, or pharmacologically active preparations derived from the plant, has been ascribed appetite stimulant effects for centuries, and this medicinal application is evident in the pharmacopeia of many cultures throughout history. With the identification of the psychoactive molecules in cannabis in the 1970s, such as Δ^9-tetrahydrocannabinol, it became possible to standardize cannabinoid-dosing regimen for both clinical and research purposes - although the extent of research, and clinical use, of THC is relatively limited.

Using animal models, the underlying mechanisms responsible for cannabinoid ► hyperphagia have been established to involve the stimulation of cannabinoid CB_1 receptors within the central nervous system. Exogenous CB_1 agonists, such as THC, and the natural ligands for these receptors (the endocannabinoids; e.g., anandamide, 2-arachidonoylglycerol, noladin ether) all exert orexigenic actions in animal models. Conversely, CB_1 blockade by antagonist drugs such as ► rimonabant will not only prevent agonist-induced eating, but also suppress food intake in its own right. Additionally, brain levels of endocannabinoids have been shown to increase in response to fasting, and increased brain endocannabinoid activity has been associated with overeating of palatable foods and diet-induced obesity.

Overall, current evidence indicates that cannabinoid hyperphagia reflects alterations to the incentive and reward aspects of eating motivation (Kirkham 2005). Cannabinoid receptor agonists can energize food-seeking behavior independently of need or energetic status: advancing the onset of feeding even in satiated animals, and increasing the effort an animal will expend to obtain food. Additionally, there are data that support specific modulation by endocannabinoids of the hedonic aspects of eating, with CB_1 agonists specifically enhancing the liking for foods.

These findings are in line with anecdotal evidence from cannabis users and laboratory experiments in healthy human volunteers with cannabis cigarettes, and oral THC. Thus, it is frequently reported that cannabis can promote the anticipation and enjoyment of food, while it has been demonstrated empirically that THC will amplify the normal pre-meal rise in hunger and promote the overconsumption of palatable foods.

There are indications that cannabinoids produce their effects on appetite in part by the modulation of other neurotransmitters that have been implicated in the control of food intake. For example, cannabinoid receptor antagonists can block the hyperphagic effects of the putative peptide "hunger" signal ghrelin, and of the potent orexigenic peptides NPY and MCH. Of particular interest, is the apparent relationship between endocannabinoids and the endogenous opioid peptides (e.g., beta-► endorphin).

Overall, current evidence supports an important role for endocannabinoids in the instigation of hunger and food seeking, the anticipation of food, and eating pleasure. Within the brain, these different processes are linked to pathways that center upon the ► nucleus accumbens, a region that is intimately associated with incentive and reward processes. Mesolimbic dopaminergic neurons,

originating in the ▶ ventral tegmental area (VTA) and projecting to the nucleus accumbens are linked to incentive motivation, and the generation of emotional arousal and behavioral activation in response to stimuli that predict reward. Food stimuli cause dopamine release in the nucleus accumbens, and this effect is mimicked by both THC and anandamide. By contrast, accumbens dopamine release provoked by palatable foods is blocked by rimonabant, suggesting that endocannabinoids normally facilitate the mesolimbic dopamine signaling that gives rise to appetite. Endocannabinoids may thus be essential for the orientation to food stimuli, the attribution of incentive salience and reward anticipation, and the elicitation of hunger, food seeking, and eating initiation.

Mesolimbic dopamine neurons synapse with accumbens opioid neurons that are critical to the experience of pleasure. The opioid peptides have an established role in the hedonic evaluation of foods, with opioid receptor agonists and antagonists respectively increasing or reducing the liking of foods. The hyperphagic effects of THC and anandamide are both blocked by the opioid receptor antagonist ▶ naloxone; while a simultaneous blockade of cannabinoid and opioid receptors produces a very dramatic suppression of appetite. Such findings provide evidence of an important functional relationship between endocannabinoids and opioids in appetite, particularly in relation to food ▶ palatability and the enjoyment that is derived from eating. THC has been shown to stimulate beta-endorphin release in the accumbens – a phenomenon also associated with the consumption of palatable foods and the associated pleasure response. Importantly, both anandamide and the opiate ▶ morphine increase the liking of sweet solutions when injected into the same sites within the nucleus accumbens.

The ability of cannabinoids such as THC to promote appetite through combined effects on specific neural mechanisms that promote eating and mediate eating pleasure thus provides clear medical opportunities. Given the low toxicity of cannabis or THC, combined with their established ability to elevate mood, prevent nausea and vomiting, and to impede the acquisition of conditioned taste aversions (such as might be associated with the symptoms of disease, or the consequences of chemo- or radiotherapy), cannabinoids could provide effective therapies for appetite loss and wasting. Largely misguided political interference has prevented a comprehensive investigation of medicinal uses of cannabinoids. However, clinical studies in cancer and AIDS patients have shown positive benefits of a pharmaceutical form of THC (▶ dronabinol), leading to approval for the clinical use of the drug in the treatment of AIDS-associated anorexia and weight loss.

Steroids

Although the underlying mechanisms are largely unknown, steroids have been administered for their appetite-stimulating and weight-enhancing properties. The best example is megasterol acetate (a synthetic form of the hormone progesterone), which is reported to improve appetite and promote weight gain in patients with cystic fibrosis, AIDS, and cancer, as well as in the frail elderly (Chinuck et al. 2007). Treatment often involves very high doses (up to 800 mg per day) and is associated with a wide range of, often serious, side effects, with the consequent risks to the patient potentially overriding any desired clinical benefits. In addition, the weight gain that accompanies improved appetite with megasterol may result primarily from an increase in adipose mass rather than of lean tissues, the loss of which is a critical factor in the wasting associated with disease and aging. Growth hormone and testosterone have been shown in some trials to promote increases in lean body mass. However, the extent to which such improvements are related to changes in appetite is unknown, and side effects associated with chronic administration again restrict the use of these agents. Overall, the specific benefits of growth hormone and testosterone in relation to appetite remain to be assessed in properly controlled studies and their likely modes of action are currently little understood.

Antihistamines, Antipsychotics, and Antidepressants

One of the older pharmaceutical orexigenic treatments involves the antihistamine cyproheptadine. This drug, which also has anticholinergic properties and acts as a ▶ serotonin antagonist, has been shown to have beneficial effects in some clinical trials of disorders involving weight loss or wasting, including asthma, tuberculosis, and HIV–AIDS (but is seemingly less effective in relation to cancer cachexia). Additionally, there are some tentative findings that the drug may have positive consequences in relation to the treatment of anorexia nervosa (Powers and Santana 2004). The precise mechanism of cyproheptadine action is unknown, which is perhaps unsurprising given the broad pharmacological profile of the drug. However, animal experiments have implicated histamine in appetite control processes, and specifically the inhibition of eating. Thus, the blockade of hypothalamic histamine H_1 receptors by antagonist drugs stimulates eating, while agonists suppress food intake.

Actions on histamine systems may also partly underlie the well-known weight increasing effects of ► antipsychotic drugs (coincidentally, the first widely prescribed neuroleptic drug, ► chlorpromazine, was initially developed as an antihistamine). Both older neuroleptics and the newer atypical antipsychotics (e.g., ► olanzapine and ► clozapine) can stimulate appetite and promote significant weight gain in patients (Casey and Zorn 2001; Kluge et al. 2007; Wirshing 2004). Some studies have demonstrated significant increases in food craving, and even binge eating, in patients treated with atypical antipsychotics. Obviously, these phenomena can both impair general health (by causing or exacerbating comorbidities such as diabetes and cardiovascular disease) and reduce patient compliance with continuing treatments. Although a variety of possible mechanisms may explain these effects (including changes to the peripheral regulation of glucose utilization and fat storage), preclinical data suggest that antipsychotics that are antagonists with high affinity for H_1 are more likely to promote eating and weight gain. Additionally, antipsychotic-induced weight gain has also been linked with antagonistic actions at dopamine D_2, muscarinic ► acetylcholine M_1 and serotonin 5-HT_{2C} receptors, and agonist actions at 5-HT_{1A} receptors. Weight gain in patients taking atypical neuroleptics has also been linked to increased levels of ghrelin.

Weight gain is also a common feature of ► antidepressant treatment. The older tricyclic and monoamine oxidase inhibitors, and some of the selective serotonin reuptake inhibitors (SSRI) can produce significant weight gain, particularly with longer treatments at higher doses. Of the new atypical antidepressants, ► mirtazapine (a noradrenergic and specific serotonergic antidepressant), has pronounced appetite stimulant– and weight gain–inducing properties that have been explored clinically. Mirtazapine hyperphagia has again been attributed to actions on histamine systems, although other mechanisms cannot be precluded.

Benzodiazepines

The ► benzodiazepines have been widely exploited as anxiolytics, ► anticonvulsants, and hypnotics. But, in addition to these effects (and often in conjunction with them), benzodiazepines can exert extremely potent hyperphagic actions. These agents act via specific high affinity benzodiazepine receptors to enhance the inhibitory effects of GABA neurotransmission. In animal models, the hyperphagic actions of benzodiazepines are among the most profound of any class of orexigen, and involve the specific enhancement of the palatability or rewarding properties of food. These effects on appetite appear dissociable from the other psychological effects of benzodiazepines. Surprisingly, although appetite stimulation and substantial increases in food intake have been shown in humans under laboratory conditions, little is known about benzodiazepine effects on food intake or body weight in clinical populations. Despite their potent hyperphagic actions, and adoption by veterinarians to encourage eating in domestic animals, there is little or no recognition within the human clinical literature of these effects of benzodiazepines. However, it is evident from anecdotal reports on various user-oriented Web sites that increased appetite and overconsumption are recognized by patients themselves.

► Mood Stabilizers

A final group of drugs that may stimulate appetite comprises agents with anticonvulsant and/or mood-stabilizing properties used to treat epilepsy and ► bipolar disorder (Ben-Menachem 2007; Martin et al. 2009; Torrent et al. 2008). Within this group (which may also include the benzodiazepines and atypical neuroleptics), ► valproate and ► lithium in particular are associated with significant, unwanted weight gain. Again, the precise mechanisms have yet to be determined. However, valproate (► valproic acid) has been linked to an increase in the motivation to eat, as well as changes in appetite-related neuroendocrine factors – including an increase in levels of the orexigens ghrelin and NPY. Hyperphagic- and weight-increasing tendencies of valproate treatment are of particular concern in relation to childhood epilepsy and the risk for the development of obesity with lifetime treatment. It should be noted however that other anticonvulsants, such as topiramate, are associated with weight loss.

Specificity of Drug Action

Although there are tentative neuroendocrine mechanisms to account for overeating and increased body weight following the administration of different psychotropic drugs, what is missing in relation to most of the agents we have discussed is a clear description of more fundamental psychological/behavioral factors that might contribute to weight gain. For example, it is likely that (in addition to any specific action on appetite control processes or energy balance), sedative effects of neuroleptics, antidepressants, or other agents compound a patient's already diminished ability to maintain a good diet, or to engage in an active, non-sedentary lifestyle. Even if a drug does exert a specific action on appetite, it is unlikely that these effects have been studied in great detail in people (as

opposed to laboratory species). In the absence of detailed behavioral measurements, there is often the implicit assumption that weight gain results from specific motivational adjustments and increased food intake, but this may not be the case. Similarly, it is common to read statements that are largely unsupported by empirical data – such as that a particular drug causes craving for foods high in carbohydrate. Until these issues are properly addressed, appetite stimulant actions of many drugs are likely to remain as little more than an interesting footnote in clinical pharmacology texts, or a side effect listed in the pharmacopeia. A concerted research effort with properly controlled studies is required to identify the most useful and effective drugs that can be used for the specific purpose of increasing appetite, and to understand the mechanisms by which hyperphagia/weight gain may accompany the principal actions of psychiatric drugs.

Conclusion

Overeating and increased body weight are common side effects of many different psychiatric drugs and other medications. However, these phenomena are generally unwanted consequences of treatments: considerable effort is directed toward ameliorating such effects, rather than exploiting them in clinical situations where facilitating appetite and increasing body mass are the desired outcomes. The majority of drugs discussed here provide uncertain benefits in terms of clinically significant appetite stimulation or weight gain, produce their effects through unknown mechanisms, and their administration may entail a broad spectrum of unwanted and potentially health-threatening side effects. By contrast, cannabinoid receptor agonists have established hyperphagic actions, which can be understood in terms of specific neurochemical pathways that mediate appetite control and eating motivation. That these effects may be obtained in the absence of toxic side effects, and at doses below those that induce unwanted psychotropic actions, indicates that this class of drugs is a suitable target for the development of clinically useful appetite stimulants.

Cross-References

- ▶ Acetylcholine
- ▶ Anandamide
- ▶ Anticonvulsants
- ▶ Antidepressants
- ▶ Antihistamine
- ▶ Antipsychotics
- ▶ Benzodiazepines
- ▶ Cannabinoids
- ▶ Endocannabinoids
- ▶ Endorphin
- ▶ GABA
- ▶ Lithium
- ▶ Mirtazapine
- ▶ Naloxone
- ▶ Neuroleptics
- ▶ Neuropeptide Y
- ▶ Opioids
- ▶ Rimonabant
- ▶ Serotonin
- ▶ Steroids
- ▶ Valproate

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Appetite Suppressants

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Synonyms

Anorectics; Hypophagics; Weight control drugs; Weight loss; Weight management drugs

Definition

Any drug that alters ► energy balance by changing eating behavior to reduce caloric intake, thereby producing an energy deficit. These drugs are most often used for the treatment of obesity (excessive body mass) and the cardiometabolic risk factors associated with adiposity (excessive body fat). This contrasts with other pharmacological approaches to weight control which (1) inhibit nutrient digestion or absorption, or (2) prevent the storage or increase the utilization of energy within the body.

Pharmacological Properties

History

Appetite suppressants have traditionally been used to distract patients from feelings of severe ► hunger and for weight control. However, appetite suppressants provide only an option for weight management and historically numerous devices, diets, and other pharmacological treatments have been employed to control body weight. The commercialization of weight control products dates from the start of the mass production of these products and a plethora of "dieting" products have since been marketed. These include diuretics and preparations containing metabolic stimulants such as thyroid hormones.

The first modern appetite suppressant was ► amphetamine. Amphetamine (marketed as Benzedrine) became popular for weight control in the 1930s, and the treatment of obesity became one of its many legitimate medical uses. Amphetamine (dexamphetamine, not metamphetamine) remained available in some countries for weight control until quite recently, despite its psychological effects, effects of blood pressure, and abuse potential. However, after the Second World War amphetamine alternatives were sought. Some of these monoaminergic acting agents were the beta-phenethylamine derivatives, which had lower abuse potential. ► Phentermine became available in 1959 and is still used (under a multiplicity of names including Duromine, Fastin, Adipex, and Lonamin) to treat obesity in many countries despite its amphetamine-like nature. Other amphetamine-like drugs used for weight control, often "off label," include Diethylcathinone (Diethylpropion, Tenuate, Tenuate Dospan, Amfepramone), Mazindol (Mazanor or Sanorex), and ► Phenylpropanolamine (Acutrim and Dexatrim). Along with cardiovascular stimulation, side effects such as insomnia, anxiety, and irritability remain an issue with many of these drugs (Haddock et al. 2002).

From the late 1960s and 1970s the beneficial effects of the amphetamine-related compound ► fenfluramine on body weight were noted. Fenfluramine differed from the other amphetamine alternatives as it primarily acted on serotonergic rather than catecholaminergic systems. It was as effective as amphetamine but lacked the side effect profile and abuse potential (Blundell 1977). Fenfluramine (Pondimin) became available for medical use in the early 1970s and was eventually used in combination with phentermine as "Fen-Phen." The more serotonin (5-HT) selective isomer of fenfluramine, D-fenfluramine (Redux, Adifax), was approved in 1996 in the US for the treatment of obesity, although the drug was widely available outside the US prior to this date. However, in 1997, all forms of fenfluramine were withdrawn from the global market due to serious side effect issues (see side effect section later).

The withdrawal of fenfluramine-based treatments coincided with a growing awareness of the treatment of obesity and obesity-related disease by national health care systems, and the launch of two new antiobesity drugs, the gastrointestinal lipase inhibitor, Orlistat (Xenical, Alli) and the appetite suppressant, ► Sibutramine (Merida, Reductil). Sibutramine is a noradrenergic and serotonergic reuptake inhibitor originally developed in the late 1980s and early 1990s for the treatment of depression. However, it was soon apparent during clinical testing that the drug produced significant weight loss. Further research confirmed that this was primarily due to its selective effects on human appetite. The drug was approved for obesity treatment in the US and other markets in 1997 and despite periodic concerns over safety the drug has remained in use. Despite the growing obesity problems, prescription use of sibutramine and orlistat remained fairly constant and it was not until 2006 that another appetite suppressant successfully came to market.

The endocannabinoid CB_1 receptor antagonist ► Rimonabant (Acomplia) was approved in Europe in 2006 as pharmacotherapy for obesity and resulting comorbidities. However, the drug failed to gain similar approval in the US in 2007 because of persistent concerns over safety data (see later). Due to incidents of adverse psychiatric events, it was later recommended that the drug not be given to those with a history of suicide or related psychiatric problems. In 2009 the drug was withdrawn from all markets. Despite an inability to successfully develop new appetite-suppressing drugs for the treatment of obesity over the last decade, many drugs licensed for other indications produce changes in appetite and body weight. A few of these drugs may eventually become legitimate antiobesity drugs. For instance the glucagon-like peptide (GLP)-1 analog Exenatide (Byetta), approved in the US for the management of type 2 diabetes, has been shown to produce changes in appetite and persistent weight loss in obese diabetics.

Appetite Regulation

Signals that serve to terminate eating behavior and act as powerful inhibitors of further intake are generated from the start of consumption. There is an important distinction between the short-term satiety signals produced by the physiological consequences of meal intake (episodic), and the longer-term signals created by the body's constant metabolic need for energy (tonic). Episodic signals such as GLP-1 are a crucial factor in the meal-by-meal regulation of energy intake, and are critical to both the appetite fluctuations and patterns of eating behavior we undertake throughout the day (Halford and Blundell 2000). Tonic inhibitory signals, by contrast are generated by the storage and metabolism of energy. Whilst episodic and tonic factors comprise separate aspects of appetite regulation, generated by markedly distinct processes, both ultimately act to inhibit food intake via common hypothalamic circuitry (Halford and Blundell 2000).

It is not only the peripheral targets which provide opportunities for drug development. Within the central nervous system (CNS), a complex array of chemicals and structures regulate the expression of appetite, particularly the brain stem and the hypothalamus. The arcuate nucleus (ARC) of the hypothalamus is considered to play a key integrative role between the these afferent signals from the periphery such as glucose, ▶ leptin, insulin, and ghrelin and other CNS changes such as serotonin function. The ARC has neuronal subpopulations that produce ▶ orexigenic (▶ neuropeptide Y (NPY) and ▶ agouti-related peptide (AgRP)) as well as ▶ anorexigenic peptides (α-melanocyte-stimulating hormone (α-MSH)), galanin-like peptide (GALP), and cocaine-and-amphetamine-regulated transcript (CART)). The ARC neurons project to "second-order" neurons implicated in the control of feeding, such as the paraventricular nucleus of the hypothalamus (PVN), the dorsomedial hypothalamic nucleus (DMN), and the lateral hypothalamic area. However, appetite expression is not exclusively a process of homeostatic energy regulation. Our motives for eating are also based in pleasure and other systems, such as the endogenous opioids and endocannabinoids implicated in liking and dopamine implicated in wanting. These are critical in stimulating appetite and sustaining eating behavior (see ▶ Appetite Stimulants). These also provide pharmacological targets for potential antiobesity treatments.

Mechanisms of Action of Past and Present Drugs

With regard to past appetite-suppressing antiobesity drugs, amphetamine and amphetamine-like drugs generally stimulate central noradrenaline and dopamine release and these effects may be mediated by a number of receptors such as α1 and β2 adrenoceptors, and dopamine D_1 and D_2 receptors found in the hypothalamus and other areas of the limbic system. These receptors are probably involved in both, the satiating and rewarding (i.e., "wanting") aspects of food intake. However, any selective effects of amphetamine on the motivation to feed tend be masked by other behavior changes which disrupt feeding (e.g., hyperactivity). Of all the monoamine neurotransmitters, it is ▶ serotonin (5-HT) that has been most closely linked with the process of ▶ satiation and the state of ▶ satiety. Both fenfluramine and D-fenfluramine are 5-HT releasing agents and have been shown to induce satiety in both rodent and animal models. These effects appear to be mediated by the 5-HT_{1B} and the 5-HT_{2C} receptors on neurons projecting from the ARC into the hypothalamus. Unfortunately, activation of other serotoninergic receptors, particularly 5-HT_{2B} receptors in the periphery, led to the withdrawal of these drugs. This has driven research into far more selective 5-HT based antiobesity drugs.

Sibutramine is a selective noradrenergic and serotonergic reuptake inhibitor. Upon administration sibutramine is rapidly broken down into its first (BTS 54354) and then second (BTS 54505) metabolites. The metabolites are both far more potent reuptake inhibitors in vivo and it is to these metabolites that sibutramine predominately owes its action. Selective antagonism of sibutramine ▶ hypophagia has demonstrated that α1 adrenoceptors are critically involved in sibutramine's effect on food intake, with some role also for β2 adrenoceptors and serotoninergic $5\text{-HT}_{2A/2C}$ receptors. Sibutramine produces changes to feeding behavior in rodents and appetite in humans similar to those produced by D-fenfluramine and other 5-HT drugs, suggesting changes in feeding behavior may be mediated by central serotonin mechanisms (Halford et al. 1998; Heal et al. 1998).

With regard to rimonabant, the drug is an ▶ inverse agonist of the CB_1 receptor, which is widely distributed throughout the CNS and periphery. The role of endocannabinoid receptors in the natural operation of appetite has yet to be fully determined (see ▶ Appetite Stimulants) and surprisingly little published data on the effects of CB_1 drugs on human appetite expression are available. However, evidence suggests that the endocannabinoid system may be more involved in hedonic rather than homeostatic aspects of appetite control (Tucci et al. 2006).

Animal Models

Feeding is an essential part of an animal's behavior and, in this respect, need not be artificially modeled. Rodents,

like humans, show a tendency to gain weight when exposed to a highly palatable energy dense diet and during this period they demonstrate marked ▶ hyperphagia. Animal models of obesity provide important indices for the assessment of potential therapeutic effects such as changes in adiposity and body fat distribution, and in key endocrine and metabolic factors. Behavioral indices such as hyperphagia are necessary for assessing the potential efficacy of appetite-suppressing, antiobesity drugs. The nature of drug-induced hypophagia is critical in determining if a potential appetite-suppressing antiobesity drug can progress into clinical trials. Drugs can reduce food intake in rodents and humans in a variety of ways, through the induction of nausea or malaise, or through CNS-related effects such as hyperactivity or sedation. Such effects, even if secondary to drug action on mechanisms of satiety or food preference, prevent the compound being of any clinical value. One of the most detailed behavioral assays of drug action on appetite expression is the behavioral satiety sequence (BSS) (Halford et al. 1998 for review). The BSS examines the microstructure of rodent behavior, and the sequence consists of a stochastic progression of behavior from an initial phase of eating, through peaks of active and grooming behavior, to an eventual phase of predominately resting behavior. The BSS appears robustly related to the processes of satiation (meal termination) and the development of satiety (post-ingestive inhibition of eating).

Assessing the Effects of Drugs on Human Feeding Behavior

A variety of approaches to measuring the effects of antiobesity drugs on human food intake can be employed. Laboratory-based observation studies provide more precision and reliability at the expense of "naturalness" (Hill et al. 1995). In human studies, researchers are able to assess the effects of drugs on subjective experiences of appetite to confirm any satiety-enhancing effect. Self-report scales have been used to determine the nature of a drug's effect on food intake in some of the earliest human studies (Hill et al. 1995). The measures come in a variety of forms but the most widely accepted format is the Visual Analog Scale (VAS). It is interesting to note that ratings of appetite sensations are not only predictors of energy intake but also of body weight loss (Drapeau et al. 2007). The effects of drugs on parameters within a meal have also been studied for nearly 30 years. Rogers and Blundell (1979) clearly demonstrated that whilst amphetamine and fenfluramine both reduced food intake, the increase in eating rate produced by amphetamine represents the activating effects of the drug, whilst the reduction in eating behavior produced by fenfluramine represents enhanced satiety. Sibutramine appears to produce similar effects to fenfluramine on eating rate (Halford et al. 2008).

Efficacy

Many drugs produce changes in appetite expression and reduce food intake in humans. In fact, serotonergic drugs such fenfluramine, D-fenfluramine, the selective serotonin reuptake inhibitors fluoxetine and sibutramine have all been shown to reduce caloric intake, premeal hunger and enhance postmeal satiation in humans. In contrast, other centrally acting agents such as ▶ opioid antagonists have been shown to decrease the liking for pleasant or preferred foods demonstrating the distinct role of the endogenous opioid system in hedonic aspects of appetite control. Endocannabinoid CB_1 receptor antagonists/inverse agonists such as rimonabant and taranabant have been show to reduce caloric intake in humans also. The nature of this drug-induced reduction in food intake remains unclear with little strong evidence to suggest how they alter human appetite expression. A number of peripheral factors have been shown to reduce food intake and enhance satiety. These include CCK, GLP-1 and Peptide YY (PYY). GLP-1 and PYY remain the basis for a number of potential antiobesity drugs under development (Halford 2006).

The ultimate test/indication of efficacy of any antiobesity drug is sustained and clinically meaningful weight loss (usually accepted as 5–10% reduction from baseline) rather than short-term reductions in intake. In addition, regulatory authorities also demand reductions in risk factors for cardiovascular and metabolic diseases. These include high fasting and postprandial blood glucose, HbA_{1c} (glycosylated hemoglobin), insulin, total plasma cholesterol, low density lipoproteins (LDL), triglycerides, uric acid, and blood pressure. Very little reliable data are available regarding the efficacy effects of amphetamine or other early appetite suppressants. Similarly, the published data for fenfluramine and fen-phen are limited. Meta-analysis suggests that fenfluramine could produce placebo-subtracted weight loss of 2.4 kg in trials over an average of 10 weeks. D-fenfluramine produces average placebo-subtracted weight loss of 3.8 kg over an average of 33 weeks. Sibutramine produces averaged placebo-subtracted weight loss in the region of 4.3 kg over 1 year (seen in the first 6 months of treatment), which compares to 2.7 kg over 1 year produced by orlistat (a non-appetite suppressant antiobesity drug) and 4.8 kg produced by the recently withdrawn rimonabant. These changes are accompanied by significant improvements in

aforementioned cardio-metabolic risk factors (Haddock et al. 2002; Padwal et al. 2003).

Safety/Tolerability

Because of their diverse mechanisms of action, the safety and tolerability of appetite suppressants vary greatly between drugs. Amphetamines are now virtually withdrawn across the globe and are not recommended because of significant cardiovascular and CNS side effects and a potential for dependence. However, phentermine and diethylpropion are still used in some countries but are not recommended for routine or prolonged use. Side effects with phentermine include increased heart rate and blood pressure, nervousness, restlessness, and insomnia. Diethylpropion possesses a similar side effect profile including dizziness, headache, sleeplessness, nervousness, and the possible risk of pulmonary hypertension. The side effects associated with fenfluramine-based treatments include diarrhea, dry mouth, and drowsiness. These drugs were withdrawn due to valvular heart disease and pulmonary hypertension.

The side effects associated with sibutramine include cardiovascular effects (such as an increase in systolic and diastolic blood pressure, an increase in heart rate, tachycardia, palpitations, and vasodilatation), and gastrointestinal effects (including constipation and nausea). Other effects include dry mouth, insomnia, light-headedness, paraesthesia, and aesthesia. Most side effects occur within the first 4 weeks of treatment and decrease in severity and frequency with time. With rimonabant, the most commonly reported side effects were nausea, dizziness, diarrhea, and anxiety. FDA approval for rimonabant was withheld over concerns over suicidality, depression, and other related side effects associated with use of the drug. Reports of severe depression were frequent. This led to the recent withdrawal of the drug. With regard to the GLP-analog exenatide (Byetta), the most commonly recorded side effects are gastrointestinal and warnings have been issued by regulatory authorities over acute pancreatitis.

Cross-References

- ► Appetite Stimulants
- ► Cannabinoids
- ► Cholecystokinins
- ► Hypocretins/Orexins
- ► Leptin
- ► Liking and Wanting
- ► Palatability
- ► Somatostatin

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Appetitive Conditioning

► Conditioned Taste Preferences

Appetitive Responses

Synonyms

Approach response; Preparatory behavior

Definition

These are responses evoked when an organism is exposed to stimuli previously associated with a reinforcer, such as the application of a natural goal object or a self-administered drug. The responses are ones that bring

the organism into contact with the actual reinforcer. They serve a searching or preparatory function.

Cross-References

► Conditioned Place Preference and Aversion
► Conditoned Reinforcer
► Conditioned Taste Preferences

Approach-Avoidance

► Punishment Procedures

Approach Response

► Appetitive Responses

Approval and Marketing of Psychotropic Drugs

► Ethical Issues in Human Psychopharmacology

2-Arachidonoylglycerol

Definition

An endocannabinoid, abbreviated 2-AG.

N-Arachidonylethanolamine

Synonyms

AEA; Anandamide

Definition

An endocannabinoid; also called anandamide.

ARC

► Addiction Research Center

ARCI

► Addiction Research Center Inventory

Area Under the Curve

Synonyms

AUC

Definition

The area under curve, AUC, corresponds to the integral of the plasma concentration versus an interval of definite time. In practice, the approximation is used: AUC = $\int$ ([C] $\times$ Dt), where [C] is measured concentration and Dt is interval of time between two measurements. The precision of the AUC grows with the number of measurements of concentration taken. The AUC is expressed in mass (mg, g) $\times$ L^{-1} $\times$ h.

Cross-References

► Bioavailability
► Elimination Half-Life or Biological Half-Life
► Pharmacokinetics

Arginine-Vasopressin

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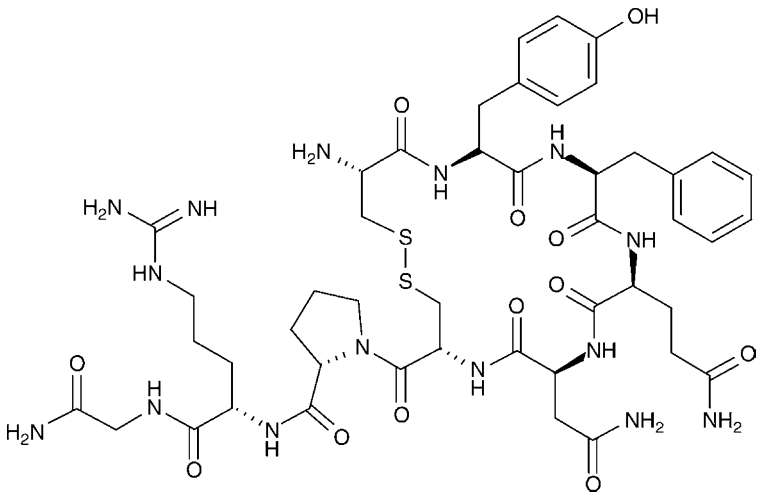
Synonyms

ADH; Antidiuretic hormone; AVP; Vasopressin

Definition

Arginine-vasopressin (AVP) is a nine-amino acid peptide, which is synthesized and released from nerve terminals in the central nervous system (CNS) (Fig. 1). In the brain, AVP acts as a modulator of neuronal function and is involved in the control of stress, anxiety, cognitive behaviors, ► circadian rhythms, and autonomic function. AVP is also released from nerve terminals into the blood stream where it regulates water absorption and urine production



Arginine-Vasopressin. Fig. 1. Arginine-vasopressin (AVP).

in the kidney, and glucose and fatty acid metabolism in the liver, and it increases arterial blood pressure and heart rate.

Pharmacological Properties

The Neuroanatomy of the Central AVP System

AVP is synthesized in neurons of the hypothalamus (Ring 2005). AVP-containing neurons are located in three hypothalamic structures: the supraoptic nucleus (SON), the paraventricular nucleus (PVN), and the suprachiasmatic nucleus (SCN). AVP produced in the SON is transported to nerve terminals of the posterior pituitary and is released in response to changes in plasma osmolality and decreased blood pressure. AVP from the PVN is released into the hypothalamic–hypophyseal portal blood, which supplies the anterior pituitary. The AVP-containing neurons of the PVN also project to the regions of the hindbrain and spinal cord, which are involved in control of the autonomic function. The AVP neurons of the SCN are involved in the control of circadian rhythms. AVP synthesis occurs also in the bed nucleus of the stria terminalis (BST) and the medial amygdaloid nucleus (MeA). The vasopressin neurons in the BST project to the lateral septum, amygdaloid areas, the locus coeruleus, and the dorsal raphe, while MeA neurons project to the ▶ hippocampus and lateral septum. These neuronal pathways are likely to underlie the effects of AVP on stress, anxiety, fear, and social cognitive behavior (▶ Social Recognition and Social Learning). The degree of AVP expression in the brain is gender specific, with males having denser AVP levels than females (Frank and Landgraff 2008) due to an effect of ▶ sex hormones on AVP expression. Sex hormones may exert some of their effects on social cognitive behaviors, such as pair-bonding and parent-offspring relationships, through influencing AVP expression in the CNS.

Arginine-Vasopressin Receptors in the CNS

The biological effects of AVP are mediated via interaction with a family of ▶ G-protein-coupled receptors (▶ GPCRs) (Ring 2005). There are four known vasopressin receptor subtypes (V_{1a}, V_{1b} (V_3), V_2, and oxytocin (OT)) defined on the basis of differences in pharmacology and tissue distribution. Activation of the V_{1a}, V_{1b}, and OT receptors stimulates a number of signal transduction pathways via Gq G-protein coupling to phospholipase C, while activation of the V_2 receptor by AVP stimulates adenylyl cyclase via Gs coupling (▶ Receptors; Functional Assays).

The V_{1a} receptor is the predominant AVP receptor found in the brain, localized in the cortex, hippocampus, ▶ amygdala, septum, ▶ hypothalamus, and thalamus. The V_{1a} receptor plays a dominant role in the behavioral effects of AVP. In the periphery, V_{1a} receptors are expressed in vascular smooth muscle cells, hepatocytes, ▶ platelets, adrenal cortex, uterus cells, kidney, spleen, and testis. The V_{1b} receptor is expressed in corticotrophs of the anterior pituitary and throughout the brain, especially in the pyramidal neurons of the hippocampal CA2 field, although at lower levels than the V_{1a} receptor. In the anterior pituitary, the V_{1b} receptor modulates adrenocorticotrophin (ACTH) secretion. The V_{1b} receptor is also expressed in kidney, pancreas, and adrenal medulla, although the functional significance of expression in these tissues is unclear. Vasopressin V_2 receptors are primarily

expressed in the kidney, where their primary function is to respond to AVP by stimulating mechanisms that concentrate the urine and maintain water homeostasis. The V_2 receptor is understood to have a limited expression in the CNS. The OT receptor is expressed in the CNS in the amygdala and hippocampus and brain regions involved in the regulation of stress (► Social Stress) responses and social behavior (► Social Recognition and Social Learning). The OT receptor is also expressed in uterus and mammary gland, where its primary function is to induce uterine contractions and milk ejection.

The Effect of AVP on CNS Function

Effects on Neuronal Excitability: AVP directly controls neuronal excitability and hence, is described as a modulator of synaptic transmission (Raggenbass 2008). In general, AVP exerts an excitatory effect on neuronal activity (e.g., in hippocampus, amygdala, spinal cord), although an inhibitory influence of AVP has also been described (e.g., in the lateral septum). AVP alters neuronal excitability, and hence synaptic transmission, through modulation of ion-channel activity, leading to activation of a cationic inward current and/or reducing potassium conductance. In the rat hippocampus, for example, AVP enhances excitatory post-synaptic currents and long-term potentiation (LTP) (► Long Term Potentiation and Memory; ► Synaptic Plasticity). Hippocampal LTP is the long-lasting improvement in synaptic communication which is postulated as one of the cellular mechanisms underlying learning and memory. Thus, the benefits of AVP on cognitive function may be exerted by virtue of its influence on LTP.

Control of cardiovascular function: Brain AVP is suggested to play a role in the regulation of blood pressure under both normal and pathophysiological conditions (Toba et al. 1998). Central AVP influences the cardiovascular system via modulation of both sympathetic and parasympathetic function (Raggenbass 2008). Administration of AVP into the CNS results in an increase in blood pressure and heart rate which is most likely to be mediated via enhancement of sympathetic nervous system outflow from the CNS to the heart and vasculature.

Temperature regulation: Administration of AVP directly into the CNS of rats causes a reduction in body temperature, although there is little evidence to suggest that AVP plays a role in normal thermoregulation. However, AVP arising from BST has been described as an antipyretic, in that it can reduce increases in temperature during fever (Pittman et al. 1998).

Water homeostasis: AVP derived from the neurons of the PVN and SON of the hypothalamus is released into the circulation following osmotic challenge, for example, dehydration and high sodium levels. Under these conditions, plasma AVP, via activation of V_2 receptors, induces increased reabsorption of water in the kidney. Inadequate secretion of AVP from the posterior pituitary and/or abnormal kidney responsiveness to AVP results in diabetes insipidus, which is characterized by excessive urination and thirst.

Circadian rhythms. The SCN of the hypothalamus is the site of the master circadian clock which generates 24-h circadian rhythms in mammals. AVP is one of the dominant neuropeptides expressed within the SCN and exhibits a diurnal pattern of synthesis and release, with increased levels of AVP secretion occurring during the day in both rats and humans (Ingram et al. 1998). Brattleboro rats, which lack vasopressin peptide due to a mutation in the AVP gene, still express circadian rhythms, although of reduced amplitude. Thus, AVP is not critical to circadian clock function but plays a role in amplifying clock rhythmicity. The AVP-containing neurons of the SCN transmit a circadian signal to the other parts of the brain by which they may regulate behavioral, neuroendocrine, and autonomic nervous system processes in a circadian fashion, for example, controlling the rhythmic release of cortisol and the circadian pattern of motor behavior and appetite.

Social recognition and social learning: Social relationships are a key feature of many species. Although the underlying neurobiology of social behavior/cognition is not well understood, there is an emerging hypothesis that AVP may play a role (Donaldson and Young 2008). Rats and mice are an excellent model species for studies of the involvement of AVP on social behavior given their natural tendency to explore unfamiliar individuals. In rats and mice, direct administration of AVP into the brain prolongs the duration of social memory. By contrast, vasopressin receptor antagonists impair social memory, probably due to disruption of the acquisition, storage, and/or recall of social olfactory cues (Frank and Landgraff 2008). Studies in which vasopressin receptor antagonists or V_{1a} receptor ► Antisense Oligonucleotides are applied directly into specific brain regions implicate a role for the V_{1a} receptor in the lateral septum in the regulation of social recognition. Furthermore, mice which lack the V_{1a} receptor exhibit deficits in social recognition behaviors which can be restored upon reexpression of the V_{1a} receptor in the lateral septum. Deficits in social recognition behaviors have also been described in V_{1b} receptor knock-out mice. A possible role for AVP in the regulation of parental behavior has also been described. Paternal behavior in the male prairie vole is enhanced following

AVP administration into the CNS, whereas vasopressin receptor antagonists disrupt this behavior. AVP is also implicated in maternal care, with increased brain AVP levels being described during the late stages of pregnancy, parturition, and lactation in the rat. Thus, enhanced parental behavior is correlated with increased AVP function.

The exact effects of AVP on social behaviors can vary from one species to the next, most likely due to differences in the pattern of brain V_{1a} receptor expression between species. For example, the differences in pair bonding observed between the monogamous prairie vole and the polygamous montane vole are regulated by the pattern of V_{1a} receptor expression in the brain (Donaldson and Young 2008). Male prairie voles exhibit mating-induced partner preferences, care for their offspring, and exhibit ► aggressive behavior to other males within the same species, unlike the polygamous montane vole. Analysis of V_{1a} receptor distribution shows that the polygamous montane vole exhibits a lower level of receptor expression in the ventral forebrain/ventral pallidum in comparison with the monogamous prairie vole. Expression of the prairie vole V_{1a} receptor gene in the ventral pallidum of the meadow vole resulted in increased pair bond formation, in a manner similar to the prairie vole. Genetic studies have identified an insertion of approximately 500 base pairs of a repetitive sequence (microsatellite) upstream of the prairie vole V_{1a} receptor gene. By contrast, the same region upstream of the montane vole V_{1a} gene is only around 50 base pairs long. This microsatellite region may influence the expression pattern of the V_{1a} receptor, leading to differences in mating behavior between these two species.

It is a challenge to extrapolate the data obtained from the rodent studies described above, where social behaviors are heavily reliant on olfactory cues, to humans, where social behaviors are more dependent upon auditory and visual cues. To date, the modulatory effect of AVP on social behavior in humans has not been extensively studied. Even so, in humans, there is an emerging hypothesis that genetic variations in the V_{1a} receptor locus may also influence behaviors such as partner bonding and parental care (Donaldson and Young 2008). Variations in the V_{1a} receptor gene have also been associated with the social behavioral deficits underlying autism (► Autism Spectrum Disorders and Mental Retardation). Deficits in social behavior are a key feature of other psychiatric diseases such as ► schizophrenia, social phobia (► Social Anxiety Disorder), and depression. As such, gaining a better understanding of the role of AVP in the regulation of social behavior may lead to the development of treatments that are able to address the social deficits of these disorders.

The involvement of AVP in nonsocial cognitive function is unclear. The majority of studies in rodents point toward a facilitatory effect of AVP on nonsocial memory, mainly via an effect on memory retrieval (► Cognitive Enhancers). Loss of vasopressin receptor function, either via genetic knock-out or through antagonist administration, can alter performance in some but not all tests of nonsocial cognitive behavior. Clinical data also indicate that AVP enhances ► attention and arousal but does not have a direct effect on memory per se. Indeed, AVP does not improve cognitive function in individuals suffering from age-related memory impairment.

Regulation of stress and emotional behaviors. The hypothalamic pituitary adrenal (HPA) axis is the main neuroendocrine system involved in regulation of the "flight, fight, fright" response to a stressful stimulus. Exposure to stress (social stress) results in the release of AVP and ► corticotrophin releasing factor (CRF) from the hypothalamus into the portal vessel system. Both AVP and CRF act on receptors on the anterior pituitary (V_{1b} and CRF1, respectively) to stimulate ACTH release. In turn, ACTH stimulates the release of glucocorticoids such as cortisol (in humans) or corticosterone (in rodents). Glucocorticoids trigger physiological changes (e.g., glucose mobilization, suppression of the immune response, increased cardiovascular tone) required to enable the organism to respond appropriately to a stressor. Studies suggest that CRF plays a critical role in both basal and acute-stress-induced ACTH release whereas AVP, which has weaker secretory activity, may have a lesser role (Aguilera and Rabadan-Diehl 2000). However, when co-released, AVP can act synergistically with CRF to amplify the ACTH release response.

There is mounting evidence suggesting that abnormalities in HPA axis responsiveness may underlie psychiatric disorders that are associated with impaired stress-coping (e.g., depression, anxiety) and a shift toward AVP drive of HPA axis function underlies these abnormalities. Exposure to repeated or chronic stress causes an upregulation of AVP levels, increased V_{1b} receptor expression, and downstream signaling. Through this mechanism, AVP may contribute to the sensitization of the ACTH/cortisol response that occurs following chronic stress. Both clinical and animal studies show a correlation between increased anxiety behavior and elevated AVP levels. In studies where the cholecystokinin B receptor agonist, pentagastrin, (► Cholecystokinins) is used to stimulate anxiety in healthy volunteers, a correlation between the severity of symptoms and AVP levels has been observed. Vasopressin-deficient Brattleboro rats exhibit less anxiety-related behaviors in comparison with normal rats. Rats and mice that have been selectively bred

for high anxiety-related behaviors in the ► elevated plus-maze anxiety model (► Anxiety: animal models) exhibit increased brain AVP expression in comparison with low-anxiety behavior counterparts (Frank and Landgraff 2008). Application of V_{1a} receptor antagonists to "high anxiety" rats reduces anxiety-related behaviors. In addition, over-expression of the V_{1a} receptor gene in the lateral septum significantly increases anxiety-related behavior, implicating the V_{1a} receptor in the anxiety response.

► Aggression: There are strong data from animal studies suggesting that AVP promotes aggressive behavior (Ferris 2005). Administration of AVP directly into the brain facilitates attack behavior in rats and hamsters. The effects of AVP on aggressive behavior probably occur through an interaction with the serotonin system (Serotonin agonists and antagonists); serotonin being associated with a reduction in aggressive behavior. Studies with knock-out mice or vasopressin receptor antagonists indicate that the effects of AVP on aggressive behavior are mediated through both the V_{1a} and V_{1b} receptors. In patients with personality disorders, increased cerebrospinal fluid (CSF) levels of AVP are correlated with a life history of aggressive behavior. Furthermore, intranasal AVP administration in men causes an enhanced emotional response to neutral stimuli, consistent with an increased perception of threat. From a clinical perspective, interpersonal violence can be a feature of antisocial behavior which can exist alongside psychiatric illnesses, such as ► bipolar disorder, ► attention-deficit hyperactivity disorder (ADHD) (► Attention Deficit and Disruptive Behavior Disorders), post-traumatic stress disorder (► Traumatic Stress (Anxiety) Disorder), and autism (► Autism Spectrum Disorders and Mental Retardation). However, the involvement of AVP in regulation of aggressive behavior associated with psychiatric disorders in humans has not yet been established.

Involvement of AVP/Vasopressin Receptors in Psychiatric Disorders

Anxiety: Anxiety disorders (► Generalized Anxiety Disorder) are associated with feelings of apprehension, tension or uneasiness. The ► amygdala is the region of the brain which is proposed to play a pivotal role in anxiety and fear. This brain structure contains high levels of vasopressin receptors and AVP causes excitation of amygdala neurons. Furthermore, animal studies have demonstrated a clear correlation between AVP levels and anxiety behavior (► Anxiety: animal models), and data are emerging to suggest that this correlation may also exist in humans. Unfortunately, the data linking alterations in the AVP system to clinical anxiety disorders are sparse, and more research in this area is warranted. Nevertheless, the preclinical data indicate that vasopressin receptors are a suitable target for the development of drugs for the treatment of anxiety-related disorders.

Depression: Major depressive disorder is characterized by depressed mood and lack of pleasure or interest and may include symptoms such as appetite disturbances, sleep abnormalities, concentration difficulties, and suicidal thoughts. Clinical studies have shown that the central AVP system is altered in depressed individuals (Ring 2005). Elevated AVP concentrations in the brain and CSF, and alterations in V_{1a} receptor density in post-mortem analysis of brain tissue from depressed individuals have also been described. Elevated AVP levels in the plasma of depressed patients have also been observed, and the neuroendocrine response to vasopressin agonists is increased in depressed subjects in comparison with healthy volunteers. These data have led to the suggestion that AVP receptor antagonists may prove useful for the treatment of the symptoms of depression (► Antidepressants: Recent Developments).

Schizophrenia: A feature of ► schizophrenia is a deficit in the ability to filter out unnecessary information. These deficits are exhibited in measures such as ► prepulse inhibition (PPI) in which a weaker prestimulus inhibits the reaction of an organism to a subsequent strong startling stimulus. Deficits in PPI have been described in V_{1b}-receptor knock-out mice, indicating that loss of vasopressin receptor function can cause sensorygating abnormalities. Abnormalities in levels of plasma, CSF, and brain AVP in schizophrenic patients have been described, but not consistently across all studies. Given that AVP has been implicated in regulation of social cognitive behaviors and dysfunction of these behaviors are a core symptom of schizophrenia, it is possible that abnormalities in the central AVP system may underlie these symptoms. However, the data supporting this hypothesis should be considered as being preliminary.

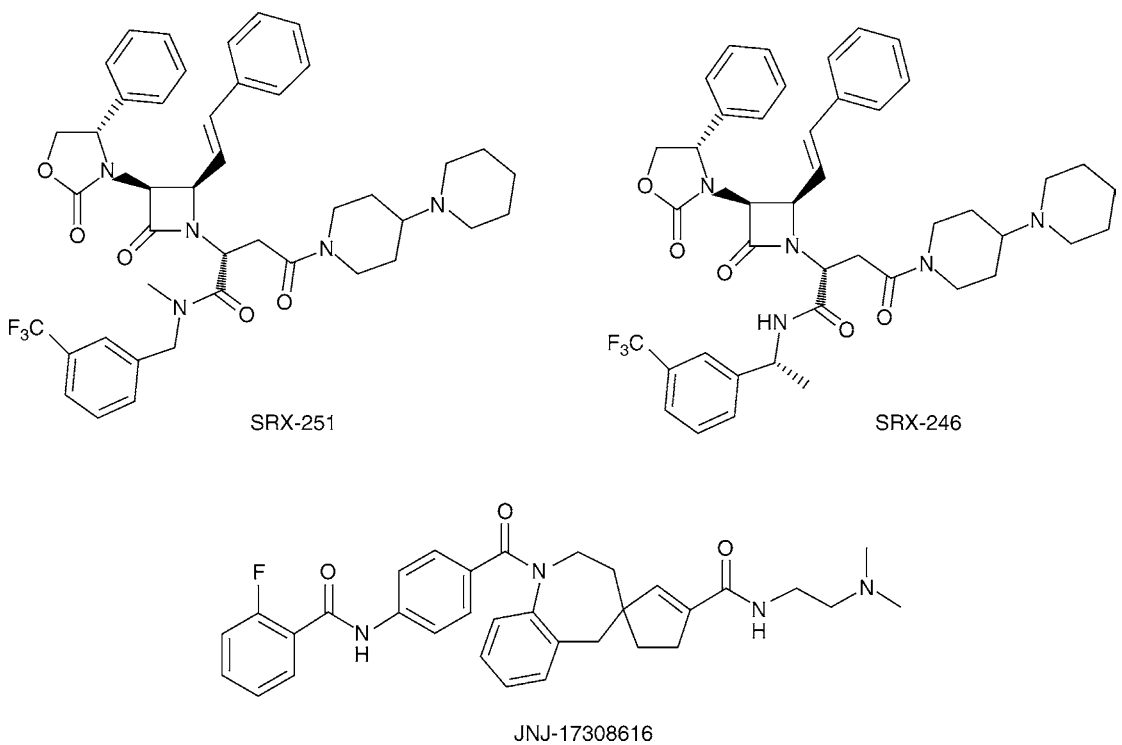
Autism: Individuals diagnosed with autistic disorder (► Autism Spectrum Disorders and Mental Retardation) generally appear to be uninterested in social contact, exhibit impaired communication, and display patterns of repetitive behavior. Autistic disorder is believed to result from a complex interaction between several genetic and environmental factors, although the exact mechanisms involved are poorly understood. Considering that a role for AVP in modulation of social behavior has been established, it is plausible to suggest that alterations in the AVP system may underlie at least some of the behavioral abnormalities that are associated with autism (Frank and Landgraff 2008). Genetic analysis of the regulatory region

upstream of the V_{1a} receptor gene has identified a polymorphic microsatellite which is associated with autism. However, little is known about the functional impact of these genetic variations on V_{1a} gene expression, and whether they contribute to the behavioral changes associated with autism is open to debate. Further studies are therefore required to establish whether alterations in the AVP system contribute to the symptoms of autism.

Vasopressin Receptor Antagonists in Psychiatric Drug Development

Vasopressin V_{1a} and V_{1b} receptor antagonists are widely recognized to represent a novel approach for the treatment of depression and anxiety. The identification and development of high-affinity, nonpeptidic ligands with the desired drug-like properties for oral bioavailability (and CNS penetration), however, is proving challenging.

V_{1a} Antagonists: A number of pharmaceutical companies have developed potent-selective V_{1a} antagonists for peripheral indications such as cardiovascular/circulatory indications and dysmenorrhoea (pelvic pain associated with menstruation). Few V_{1a} antagonists, however, have been identified with good brain penetration, a prerequisite for psychiatric drug development given the localization of the V_{1a} receptor. Azevan Pharmaceuticals describe two CNS penetrant compounds: SRX-246 (4-(bipiperidin-1′-yl)-4-oxo-2(R)-[2-oxo-3(S)-[2-oxo-4(S)-phenyloxazolidin-3-yl]-4(R)-(2-phenylvinyl)azetidin-1-yl]-*N*-[1(R)-phenylethyl]butyramide) and SRX-251 (4-(bipiperidin-1′-yl)-*N*-methyl-oxo-2(R)-[2-oxo-3(S)-[2-oxo-4(S)-phenyloxazolidin-3-yl]-4(R)-(2-phenylvinyl) azetidin-1-yl]-*N*-[3-(trifluoromethyl)benzyl]butyramide), achieving brain levels of compound ~100 times in vitro receptor affinities following oral dosing. SRX-251 is being evaluated in the clinic for the treatment of pain associated with primary dysmenorrhoea and preclinically for the management of agitation and violence. SRX-251 reduces aggression in a hamster model of offensive aggression with no effect on olfactory communication, motor activity, or sexual motivation (Ferris 2006). SRX-246 is currently in preclinical development for the treatment of anxiety/depression. Johnson and Johnson have described JNJ-17308616 (*N*-(2-(dimethylamino)ethyl)-1-(4-(2-fluorobenzamido)benzoyl)-1,2,3,5-tetrahydrospiro[benzo[b]azepine-4,1′-cyclopent[2]ene]-3′-carboxamide), a potent and selective V_{1a} antagonist both in vitro and in vivo. The anxiolytic activity of JNJ-17308616 has been demonstrated by a number of groups in a variety of

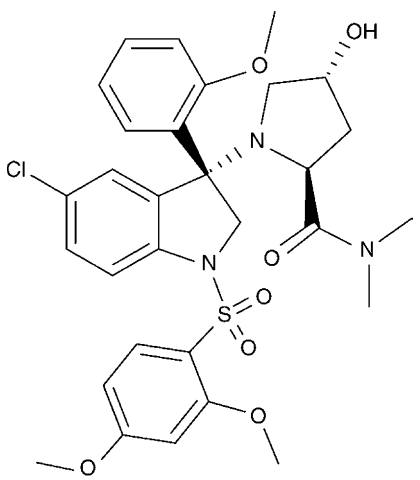


Arginine-Vasopressin. Fig. 2. V_{1a} Antagonists in psychiatric drug development.

animal models of anxiety behavior (► Anxiety: animal models), including the rat-elevated plus-maze, rat-elevated zero-maze, rat-conditioned lick suppression, rat- and guinea pig-pup separation-induced ultrasonic vocalization and mouse marble burying. JNJ-17308616 was also shown to reduce isolation-induced aggression in mice. JNJ-17308616 neither impaired social recognition, induced sedation nor reduced locomotor activity (Fig. 2).

V_{1b} Antagonists: Given the localization of the V_{1b} receptor in the anterior pituitary, and the role of this receptor in driving the neuroendocrine stress response, CNS penetration may not be a requirement for a V_{1b} antagonist aimed at treating psychiatric disorders. To date, only two pharmaceutical companies, Sanofi-Aventis and Abbott Laboratories, have progressed selective V_{1b} antagonists into clinical development. Nelivaptan (SSR-149415) was being evaluated by Sanofi-Aventis in clinical trials for the treatment of anxiety and depression, but was discontinued for both indications in 2008. Preclinical data reported by Sanofi-Aventis have shown that nelivaptan (SSR-149415) (Fig. 3) reduces CRF- and AVP-induced increases in plasma ACTH in male rats (Frank and Landgraff 2008). Nevilaptan (SSR-149415) is reported to strongly reverse stress-induced behavior as measured in the rat-elevated plus-maze, mouse defense test battery, rat- and guinea pig-pup separation-induced ultrasonic vocalization models (► Anxiety: animal models), supporting the rationale for a V_{1b} antagonist in the treatment of stress-induced anxiety. Anti-depressant-like activity was also demonstrated in the forced swim test model of depression (► Depression: Animal Models) and in the differential reinforcement of low rate 72s (DRL-72s) model (► Operant Behavior in Animals). Abbott Laboratories are investigating a series of selective V_{1b} antagonists in the clinic for the potential treatment of depression and anxiety. In preclinical studies, two compounds ABT-436 and ABT-558 (structures not reported) were shown to inhibit vasopressin- and stress-induced increases of stress hormones in mice, a preclinical model of the HPA axis dysregulation implicated in depression and anxiety. ABT-436 and ABT-558 were shown by Abbott to have comparable antidepressant and anxiolytic effect to nelivaptan (SSR-149415) in preclinical behavioral models (Fig. 2).

The identification and development of vasopressin antagonists targeting CNS receptor subtypes represents a promising new therapeutic class for the treatment of anxiety and depression. As such, selective V_{1a} and V_{1b} and mixed V_{1a}/V_{1b} antagonist programs remain a focus for many pharmaceuticals with increasing numbers of novel chemical series appearing in the patent literature.



Nevilpatan (SSR-149415)

Arginine-Vasopressin. Fig. 3. V_{1b} Antagonists in psychiatric drug development.

Cross-References

► Excitatory postsynaptic currents
► G-protein-coupled receptor
► Glucocorticoid

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ARND

► Alcohol-Related Neurodevelopmental Disorder
► Foetal Alcohol Spectrum Disorders

Aripiprazole

Definition

Antipsychotic drug of the second generation, atypical category with partial agonist properties at dopamine D2 receptors, as well as at serotonin$_{1A}$ receptors, and in addition antagonist properties at serotonin$_2$ receptors.

Aropax

► Paroxetine

Arousal Disorders

► Parasomnias

Arylalkylamines

► Trace Amines

Asperger's Disorder

Definition

Asperger's disorder exhibits a qualitative impairment in social interaction and repetitive and stereotyped patterns of interests, behavior, and activities. There is no delay in language ability, cognitive development, or adaptive behavior.

Cross-References

► Autism Spectrum Disorders and Mental Retardation

Assessing Brain Function

► Magnetic Resonance Imaging (Structural)

Assessments

► Rating Scales and Diagnostic Schemata

Associated Depression in Schizophrenia

► Postpsychotic Depressive Disorder of Schizophrenia

Associative Learning

► Classical (Pavlovian) Conditioning
► Verbal and Non-Verbal Learning in Humans

At-Risk Mental State

► Pre-psychotic States and Prodromal Symptoms

Ataxia

Definition

Unsteady gait resulting from impaired motor coordination or balance.

Ataxin-3 Transgenic Mice

Definition

A transgenic method that expresses a mutant form of ataxin-3, which accumulates inside the cells and leads to progressive neuronal degeneration.

Atomoxetine

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Synonyms

(3R)-*N*-methyl-3-(2-methylphenoxy)-3-phenyl-propan-1-amine; Tomoxetine; Atomoxetine hydrochloride;

LY139603; Methylphenoxy-benzene propanamine; Strattera™

Definition

Atomoxetine is a highly selective centrally acting norepinephrine reuptake inhibitor (SNRI), licensed for the treatment of attention-deficit hyperactivity disorder (ADHD) in USA, United Kingdom, and elsewhere. Atomoxetine is a white solid intended for oral administration.

Pharmacological Properties

► Pharmacokinetics

Following oral ingestion with or without food, atomoxetine is rapidly absorbed with peak plasma levels occurring at approximately 1–1.5 h (Sauer et al. 2005). With regular dosing, steady-state concentrations are obtained by day 10, with trough plasma concentrations of ~30–40°ng/mL. The metabolism of atomoxetine is dependent primarily on the hepatic ► cytochrome P450 (CP450) system, which is highly polymorphic such that individuals can be classified into extensive metabolizers (EMs) or poor metabolizers (PMs) (Trzepacz et al. 2008). The majority of people (>90%) are EMs, while rarer PM individuals or individuals taking enzyme inhibitor medications, show fivefold greater peak plasma concentration and slower ► half-life elimination. Following a single oral dose, EMs exhibit an atomoxetine half-life of ~5.2 h with plasma clearance of ~0.35 L/h/kg, while PMs exhibit half-life of ~21.6 h and clearance of ~0.3 L/h/kg.

Neurochemical Mechanisms

Atomoxetine selectively inhibits human ► norepinephrine transporters in vitro with high potency, and has relatively low affinity for ► serotonin and ► dopamine transporters (Bymaster et al. 2002). In vivo, atomoxetine rapidly penetrates the rat ► blood–brain barrier via mainly passive mechanisms; and increases levels of noradrenaline and dopamine (but not serotonin) approximately threefold in the rat ► prefrontal cortex, a region critically implicated in cognition (Bymaster et al. 2002). In contrast to ► psychostimulants, atomoxetine does not increase dopamine levels in the accumbens and striatum, thereby limiting its abuse potential as compared to this other class of agent (Wee and Woolverton 2004). Thus, atomoxetine may offer benefits over psychostimulants in terms of lower addictive potential due to its more selective neurobiological effects.

Cognitive Effects

Noradrenaline and dopamine have been strongly implicated as neurochemical substrates of cognition. Consequentially, and in light of the above findings, it is important to question whether atomoxetine can enhance cognition and ameliorate cognitive deficits in the context of neuropsychiatric disorders. Most translational studies to date have focused on measuring the effects of short-term atomoxetine treatment on laboratory-based measures of impulsivity, assessed in terms of inappropriate and/or premature motor responses on cognitive tasks. This focus on impulsivity stems from the utility of atomoxetine in the treatment of ADHD (discussed in the following section).

On the ► five-choice serial reaction time task (5-CSRT), atomoxetine reduced premature impulsive responses in rats across three studies (Robinson et al. 2008). In humans, atomoxetine was found to improve impulse control on the ► stop signal reaction time task (SSRT) in healthy volunteers, and in adult patients with ADHD (Chamberlain et al. 2006, 2007). By combining the SSRT with ► functional magnetic resonance imaging (fMRI), it was subsequentially found that atomoxetine augmented activation in the right inferior frontal gyrus during inhibitory control in healthy volunteers, with this region being critically implicated in impulse control and in the neuropathology of ADHD (Chamberlain et al. 2009).

The effects of longer-term treatment with atomoxetine on cognition have received scant attention. In work by Spencer and colleagues, 3-week treatment with atomoxetine was associated with improvements on a measure of inhibition from the Stroop task in adult ADHD patients, particularly in those patients with poor baseline performance (Spencer et al. 1998).

Treatment of Neuropsychiatric Disorders

Atomoxetine was first explored as a potential antidepressant, but then the focus shifted to its potential utility in the treatment of ADHD. Atomoxetine is licensed for the treatment of ADHD in children and adults in USA and UK. Meta-analysis of data from nine randomized placebo-controlled trials indicated that atomoxetine was superior to placebo in the treatment of childhood and adolescent ADHD (number needed to treat, NNT, 3.43) (Cheng et al. 2007). Adverse events occurring significantly, more commonly than under placebo, were reduced appetite, somnolence, abdominal pain, vomiting, dyspepsia, dizziness, fatigue, infection, and pruritis (listed in decreasing frequency of occurrence; number needed to harm, NNH, range 9–120). No evidence of liver injury was detected in initial clinical trials. Two reported cases of elevated hepatic enzymes and bilirubin linked with treatment have been detected in >2 million patients during the first two years after initial marketing (www.fda.gov/medwatch). As with other medications used in the

treatment of childhood psychiatric disorders, there has been some concern regarding atomoxetine and suicidality. In one analysis, six suicide related events were identified in 1,357 pediatric ADHD patients taking atomoxetine compared to zero events in 851 patients taking placebo (Virani 2005), leading to the FDA instructing that increased risk of suicidal thinking be added to the box-warning for this product. Although rare, these findings indicate the importance of monitoring for the emergence of adverse events relating to hepatic function, and suicidality in patients.

Atomoxetine appears similarly effective versus ► methylphenidate in the treatment of childhood ADHD albeit with evidence of significantly higher rates of mild to moderate adverse events. In UK, guidance from the National Institute for Health and Clinical Excellence (NICE), published in 2008, posits either methylphenidate or atomoxetine as first-line drug treatment in children with severe ADHD, as part of a comprehensive treatment program (www.nice.org). In terms of cost-effectiveness, a UK economic modeling study indicated that the cost of atomoxetine compared favorably with immediate release methylphenidate per Quality Adjusted Life Year gained in the treatment of childhood ADHD (Cottrell et al. 2008).

It is established that 40–60% of children with ADHD continue to exhibit clinically impairing symptoms into adulthood. However, in comparison to the child literature, few adult treatment studies using atomoxetine exist to date. The available data suggest similar efficacy and side-effects profiles to those identified in the treatment of children and adolescents (Faraone et al. 2005).

Summary

The SNRI atomoxetine is playing a growing role in the treatment of ADHD. Translational studies indicate that this agent modulates prefrontal noradrenaline (and dopamine), and is capable of improving response inhibition, a cognitive function dependent on the right inferior frontal gyrus and under likely noradrenergic control. Further clinical trials are required to explore the efficacy and safety of atomoxetine into the longer term in the treatment of ADHD, in children and in adults, and to evaluate the efficacy of this agent in the treatment of other disorders. For example, registered ongoing trials are exploring the utility of atomoxetine in the treatment of alcohol/substance abuse, Parkinson's disease, and Binge Eating disorder (www.clinicaltrials.gov). In addition to further clinical trials, it will also be important to explore the role of different components of the brain noradrenaline system in cognition (i.e., sub-receptors) in translational research; and to evaluate the effects of atomoxetine on the spectrum of cognitive deficits exhibited across neuropsychiatric disorders.

Cross-References

► Attention Deficit and Disruptive Behavior Disorders
► Impulse Control Disorders
► Impulsivity
► Methylphenidate and Related Compounds
► Rodent Models of Cognition

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Atomoxetine Hydrochloride

► Atomoxetine

A

Attention

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Synonyms

Vigilance

Definition

Attention describes a range of cognitive processes and capacities that support the ability to detect stimuli that occur rarely, unpredictably, and over longer periods of time (sustained attention), to discriminate such stimuli from non-target stimuli (or "noise"; selective attention), and to perform in situations requiring attention to multiple stimuli, multiple sources of stimuli, stimuli presented in multiple modalities, and/or the processing of multiple and competing stimulus–response rules (divided attention).

Impact of Psychoactive Drugs

Psychopharmacological research on attentional functions has intensified during recent years, fostered in part by an increasing understanding of the fundamental relevance of attentional capacities for learning and memory (Sarter and Lustig 2008), the identification of neuronal mechanisms and brain systems mediating attention (Raz and Buhle 2006), and the development and validation of tasks for the measurement of attentional processes and capacities in laboratory animals and humans. Psychopharmacological research in rodents has enormously progressed as a result of the introduction of translational tasks for the measurement of attentional capacities, particularly the ▶ five-choice serial reaction time task (Robbins 2002) and operant sustained and divided attention tasks (Arnold et al. 2003). Research in humans likewise has evolved, due in part to advances in cognitive theories of attention and the development of new test paradigms and their successful use in neuroimaging studies (Awh and Jonides 2001). The assessment of effects of psychoactive drugs on attentional performance-associated brain activity patterns ("pharmaco-fMRI") represents a particularly informative new approach as effects on attention can be attributed to modulation of activity in the distributed neuronal circuits known to mediate attention. The literature on psychotropic drug effects on attention is extensive and diverse; below, selected major research themes on the psychopharmacology of attention are briefly discussed.

Do the ▶ amphetamines facilitate attention and benefit the attentional symptoms of ADHD? Amphetamine and related stimulants, including ▶ methylphenidate, produce a wide range of effects in laboratory animals, including effects on response output and response speed that are a function of baseline response rates and the type of response required. Furthermore, these drugs affect complex motivational processes, often in interaction with the requirements for responding, the testing environment, and the animals' motivational state. Attentional performance can be affected indirectly as a result of such effects on response output or motivational processes. However, the available evidence does not conclusively indicate that psychostimulants generally and selectively enhance attentional processes or capacities. Evidence from healthy humans likewise does not indicate robust support for psychostimulant-induced enhancement of attention (Koelega 1993).

Psychostimulant treatment benefits the behavior and academic performance of patients with ADHD. However, similar to effects of these drugs in laboratory animals, the behavioral and cognitive mechanisms underlying the beneficial treatment effects in ADHD patients have remained unsettled. Furthermore, psychostimulants may act primarily by attenuating the high levels of cognitive and behavioral impulsivity of ADHD patients. Studies show that the benefits of psychostimulants on overall behavior and academic performance, indicated typically by ratings from parents and teachers, in fact were not associated with normalization of cognitive deficits. Thus, collectively, psychostimulants produce a wide range of effects that may, depending on the testing conditions, produce limited beneficial effects on attentional performance. However, it seems less likely that these compounds specifically enhance the attentional capacity of healthy subjects and/or that they specifically attenuate the attentional impairments associated with ADHD.

Do wake-promoting drugs such as modafinil enhance attention? ▶ Modafinil is a well-tolerated and relatively safe drug, and has therefore become a widely and increasingly recreationally used treatment to combat sleepiness and the cognitive components of sleepiness, including attentional impairments (Minzenberg and Carter 2008). However, numerous studies also suggested that administration of modafinil enhances cognitive performance per se, independent of its main wake-promoting properties. Similar to the psychostimulants, modafinil appears to act via stimulation of dopaminergic neurotransmission, requiring functional ▶ dopamine D1 and D2 receptors to induce wakefulness. Likewise, modafinil was not found to produce selective effects on attention in animals that were

not sleep-deprived. Furthermore, and also similar to the effects of psychostimulants, modafinil was demonstrated to enhance inhibitory response control in laboratory animals and to improve the symptoms of ADHD.

Modafinil was found to benefit the impaired attentional set-shifting capacities of schizophrenic patients, suggesting that this drug may have significant clinical usefulness as a co-treatment for this disorder. As the treatment of schizophrenic patients with amphetamine was also reported to benefit their cognitive abilities, it is intriguing to hypothesize that modafinil produces effects on attentional set-shifting by stimulating the down-regulated dopamine D1 receptors observed in the prefrontal cortex of these patients. Collectively, new wake-promoting compounds such as modafinil may produce relatively specific attentional enhancement in disorders associated with dopaminergic abnormalities in prefrontal regions.

Noradrenergic agents. Hypotheses concerning the contributions of forebrain noradrenergic afferents to the mediation of attention have originated from observations demonstrating increases in cortical "signal-to-noise" ratios following local administration of noradrenaline and the increased distractibility of animals with noradrenergic depletions. Neurophysiological recordings of the locus coeruleus, the main source of noradrenergic projections to the cortex, indicated multiple and complex contributions of phasic and tonic changes in noradrenergic activity to attention. However, the determination of specific attentional functions of the noradrenergic system in behavioral experiments, and their dissociation from more general effects on "arousal" or "alertness," continues to represent a challenging subject. These problems generalize to psychopharmacological studies on the effects of noradrenergic compounds on attention. The studies have focused overwhelmingly on the effects of alpha-2 adrenergic receptor agonists (clonidine, guanfacine, dexmedetomidine) and, more recently, the noradrenaline-reuptake inhibitor ► atomoxetine.

The evidence concerning the attentional effects of alpha-2 agonists in animals and humans is conflicting and remains inconclusive. In animals and humans, beneficial as well as detrimental effects on attention following the treatment of clonidine and guanfacine were reported. The presence and direction of the attentional effects of these drugs appear to depend on specific task parameters, testing conditions, and the subjects' level of "alertness" at baseline. The interpretation of these conflicting findings is further complicated by results indicating that alpha-2 *anta*gonists such as idaxozan and atipamezole likewise enhance aspects of attentional performance in healthy volunteers and patients. A definition of the experimental conditions that foster the demonstration of beneficial versus detrimental attentional effects of alpha-2 agonists is clearly needed. Treatment with drugs such as guanfacine may benefit the attentional impairments of particular disorders, based perhaps on an "optimization" of noradrenergic neurotransmission (Arnsten et al. 2007).

This latter statement may also hold true for the attentional effects of the noradrenaline uptake inhibitor atomoxetine. Beneficial attentional effects of this drug were demonstrated in animals with reduced levels of noradrenergic neurotransmission, but not consistently in intact animals. While recent clinical studies suggested efficacy in patients with ADHD, the precise cognitive mechanisms that are enhanced by atomoxetine is not known. Extensive psychopharmacological research, involving controlled studies and the test of hypotheses predicting specific attentional mechanisms that are modulated by noradrenergic drugs, are required in order to render conclusions about the general pro-attentional efficacy of noradrenergic drugs.

Attentional enhancement by agonists at ► nicotinic acetylcholine receptors (nAChRs). The cortical cholinergic input system represents a key branch of the forebrain circuits that mediate attentional functions and capacities (Sarter et al. 2005). Recent evidence indicated that prefrontal cholinergic activity mediates a switch from intrinsic or associational processing to the processing of external stimuli, and thereby the detection and selection of stimuli in attention-demanding situations. Neuroimaging studies suggested that administration of nicotine enhances the processing of attentional information by attenuating the activity of the brain during resting periods.

Therefore, it would be expected that drugs that block or stimulate the fast and reversible component of post-synaptic cholinergic neurotransmission, the nAChR, robustly impair or benefit, respectively, attentional performance. While robust impairments in attentional performance following nAChR blockade with ► mecamylamine can be readily shown in humans and animals, the demonstration of nicotine-evoked attentional enhancement in healthy (nonsmoking) humans and drug-naive animals has been less straightforward. Several experiments in humans and animals clarified that in interaction with increased demands on attentional performance, including the demands for top-down processing (e.g., by requiring performance during the presence of distractors), ► nicotine reliably enhances attentional performance. Collectively, these findings indicate the importance of integrating variations of the demands on attention as a secondary independent variable into experiments testing the effects of nicotine on attentional performance (Hahn et al. 2003).

Compared to the effects of nicotine, drugs that act at subtypes of the nAChR, particularly at alpha4/

beta2*nAChRs, were found to produce more robust effects on attentional capacities in humans and animal experiments. Ligands that selectively stimulate alpha4/beta2*-nAChRs and have been under investigation for treating cognitive disorders include ABT-089, ABT-418, ispronicline, and SIB1765F. Furthermore, promising effects of such drugs in tests of their therapeutic efficacy in patients with ADHD, schizophrenia, and dementia were reported. The attentional benefits of compounds acting at other nAChR subtypes, such as alpha7 nAChRs, remain less clear, largely because little evidence on the effects of these drugs has accumulated.

The neuropsychopharmacological reasons why agonists at alpha4/beta2*nAChRs may exhibit greater attentional enhancement than nonspecific agonists such as nicotine are largely unknown. However, evidence from experiments determining the effects of nAChR agonists on the transient increases in prefrontal cholinergic activity that mediate the detection of cues begins to form the basis for hypotheses. This evidence indicated that selective agonists at alpha4/beta2*nAChRs augment these transient increased without altering the "shape" (rise and clearance rates) of these transients. In contrast, nicotine, via stimulation of additional receptors and mechanisms, not only is less potent in augmenting the amplitude of these transients but drastically prolongs the duration of cholinergic activity. It is intriguing to speculate that such "blunting" of a critical neuronal signal interferes with, or at least limits, the enhancement of the detection process that is key to improving attentional performance.

Collectively, drugs that directly stimulate subtypes of nAChRs or modulate the stimulation of these subtypes by acetylcholine appear to produce specific and efficacious effects on attentional functions and thus are promising candidates for clinical use. Moreover, the accumulating evidence on the attentional effects of these drugs informs theories concerning the general neurobiological mediation of attention.

Conclusion

Although research on the modulation of attentional processes and capacities by psychotropic drugs, primarily by drugs acting at ascending modulator systems, has rapidly expanded during recent years, much of the evidence remains rather preliminary and inconclusive. The attentional effects of drugs acting at nAChRs, particularly those that bind selectively to subtypes of this receptor family, form a more consistent set of evidence than the effects of psychostimulants or noradrenergic drugs, or drugs not discussed herein, including drugs acting at serotonergic receptors. Furthermore, the interpretation of the psychopharmacological effects of nAChR agonists is supported by converging neurobiological evidence on the mediation of attentional functions by cholinergic systems. Ongoing research will demonstrate the clinical usefulness and also the psychopharmacological limitations of these treatments, in part by addressing the important question about the degree to which treatments that focus primarily on the improvement of attentional capacities benefit the overall cognitive abilities of patients. Finally, and similar to the presently increasing use of modafinil by nonclinical populations, drugs that enhance attentional abilities, particularly if associated with limited side effects, are likely to be used in the near future by non-patient groups as general cognition enhancers.

Cross-References

- ▶ Acetylcholinesterase Inhibitors as Cognitive Enhancers
- ▶ Atomoxetine
- ▶ Attention Deficit and Disruptive Behavior Disorders
- ▶ Attention Deficit Hyperactivity Disorders: Animal Models
- ▶ Cognitive Enhancers
- ▶ Nicotine
- ▶ Nicotinic Agonists and Antagonists

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Attention Deficit and Disruptive Behavior Disorders

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Synonyms

Hyperkinetic child syndrome; Minimal brain damage; Minimal cerebral dysfunction; Minor cerebral dysfunction.

Definition

► Attention-deficit/hyperactivity disorder (ADHD) affects about 8–12% of school age children, being more common in boys than in girls by a ratio of approximately 3:1. This condition is characterized by excessive inattention and impulsivity/hyperactivity for a given developmental level. In at least 50% of cases, this condition produces enduring impairment in adulthood. ADHD has deleterious impact on several areas of social development such as educational attainment, family life, and occupational stability. ADHD has a strong hereditary basis, with genetic factors accounting for about 80% of the phenotypic variance. Weak associations with ADHD have been reported for the 7-repeat polymorphism of the D4 dopaminergic receptor gene, the 10-repeat allele of the dopamine transporter (DAT1), alleles of the D2 and D5 dopaminergic receptors, the gene coding for catechol-O-methyl-transferase, and genes related to the noradrenergic and serotonergic systems.

The estimated rate of comorbidity (co-occurrence) between ADHD and other psychiatric and learning disorders is between 50% and 90%. The most common comorbidities are with disruptive behavior disorders, which includes oppositional defiant disorder, present in some 40% of patients; conduct disorder, present in ~14% of children with ADHD; anxiety disorder (~34%); tic disorders (~11%), and others such as depression, bipolar disorder, substance use disorders, and learning disabilities (Kunwar et al. 2007). ADHD is a risk factor for the appearance of disruptive behaviors, as the onset of these symptoms occurs earlier in ADHD subjects than in non-ADHD patients. Children with ADHD and conduct disorder are at a higher risk of antisocial behavior and substance abuse as adolescents and adults. This motivates attempts to provide early treatment with the hope of preventing malignant behavioral outcomes, although such has not been demonstrated.

Role of Pharmacotherapy

Currently, ADHD is subdivided into three diagnostic subtypes, defined by predominance in inattention, hyperactivity, and impulsivity, or as the combined type that includes both inattention and hyperactivity/impulsivity.

Pharmacological treatments for ADHD enhance catecholaminergic neurotransmission. This repeated observation, combined with neuroimaging evidence strongly implicate fronto-striatal and fronto-cerebellar circuits in deficits affecting behavioral organization and the ability to predict events and behavioral outcomes; a further deficit in the fronto-amygdalar loop that assigns emotional significance to predicted and detected events is also hypothesized (Swanson et al. 2007). However, no differences in medication response have been reported among the three subtypes.

Treatment: Stimulants

The first-line pharmacological treatment for all types of ADHD consists of the psychostimulants ► methylphenidate (MPH) or ► amphetamines (Table 1). The overall short-term efficacy and tolerability of these compounds have been conclusively demonstrated in both children and adults (Findling 2008; Stein 2008). About 70–80% of the patients showed improved attention when treated with a stimulant (Rappley 2005). Owing to its lower cost, the generic amphetamine, dextroamphetamine, is most frequently used in developing countries. However, between 30% and 50% of patients discontinue pharmacotherapy due to adverse effects or inadequate response. In most such cases, the next step should include changing to the other type of stimulant. Also widely approved for the treatment of ADHD is the nonstimulant, noradrenergic reuptake inhibitor ► atomoxetine (ATX). Guanfacine is an alpha2A adrenoceptor agonist indicated for the treatment of essential hypertension that also appears to be efficacious as monotherapy, but may also be particularly useful as an adjunctive agent.

Mechanism of Action of Stimulants

Amphetamines are considered to exert their effects partly by promoting the liberation of ► dopamine from vesicular transporters and inhibiting the degradative enzyme

Attention Deficit and Disruptive Behavior Disorders. Table 1. Recommended dosages for first-line medications for ADHD (data from Pelham et al. 1999; Subcommittee on Attention-Deficit/Hyperactivity Disorder and Committee on Quality Improvement 2001; Swanson and Volkow 2002, 2003; Swanson et al. 2004).

Drug	Approximate daily dose per weight (mg/kg)	Usual dose (mg)	Requires dose titration	Peak efficacy level (h) (equivalent to the onset of peak of serum concentration and brain level)	Daily dosage schedule	Duration (h)	Adverse effects and contraindications
Methylphenidate IR (Ritalin®, Methylin®)	0.3–1	5–20	No	0.75–1.5	1, 2 or 3	3–4	Loss of appetite, trouble sleeping, headaches, stomachaches, "zombie effect," sadness, motor tics, nail-biting/picking, irritability, deceleration in rate of growth, mild increase in blood pressure and heart rate. Abuse risk (more for amphetamine). Contraindicated in glaucoma and psychosis. Caution but not contraindicated in Tourette disorder and epilepsy
Methylphenidate ER-OROS[a] (Concerta®)	0.3–1	18, 27, 36, 54, 63, 72	No	2 (see OROS system below)	1	12	
Methylphenidate ER-Diffucaps[b] (Metadate CD®, Ritalin LA®)	0.3–1	20, 30, 40	No	1–2 (see diffucaps below)	1	8	
D,L-amphetamine (Adderall®)	0.2–0.8	5–30 (5–15 BID)	No	1.5–3	1 or 2	6–8	
D-amphetamine (Dexedrine®)	0.1–0.8	2,5–15	No	1.5–3	1 or 2	4–6	
Atomoxetine (Strattera®)	1.2–1.8	36, 40, 50 or 60	Yes, in 2–4 weeks (initial dose 0.5 mg/kg)	2–3	1	12–24	Decreased appetite, somnolence and fatigue. Dyspepsia, nausea, vomiting, weight loss, dry mouth, insomnia, constipation, urinary retention, erectile disturbance, decreased libido. Heart rate increase and EKG PR interval decrease. Caution in patients who have significant cardiovascular disorder. May produce liver failure, reversible with discontinuation of medication

[a]OROS® = Osmotic Release Oral System. Initial bolus of IR-MPH on capsule overcoat, and a reservoir consisting of polymer and MPH layers surrounded by a semipermeable membrane to deliver MPH at a smoothly increasing rate from 2 to 10 h after dosing

[b] Diffucaps® = Coated bead system. A capsule containing 30% of the total dose of MPH in uncoated beads to deliver the initial bolus, and 70% in beads coated with a polymer that degrades over time to deliver MPH at a smoothly increasing rate from 2 to 6 h after dosing

monoamine oxidase. These effects dramatically increase intracellular concentrations of dopamine in the presynaptic terminal, which results in massive efflux of neurotransmitter into the extracellular synaptic space. Additionally, amphetamine reversibly blockades the dopamine transporter (DAT) and enhances the internalization of DAT. These actions inhibit reuptake and prolong the increased concentration of catecholamines in the presynaptic terminal. Methylphenidate (MPH) is a pure reuptake blocker, with potent affinity for DAT and for the ▶ norepinephrine transporter (NET). The extrasynaptic dopamine increasing effect of MPH through DAT blockade has been documented in the human ▶ striatum and nucleus accumbens, and found to be qualitatively similar to ▶ cocaine effects (Volkow et al. 1998). However, pharmacodynamic kinetics differentiates MPH from cocaine in important ways that appear to account for the lower addictive potential of MPH.

Although most of the researches focus on the mechanism of action of the stimulants on the striatum, recent work in the ▶ prefrontal cortex suggests that MPH improves cognitive function (particularly the maintenance of items in working memory) by increasing endogenous stimulation of both alpha2A adrenoreceptors and dopamine D1 receptors. MPH also robustly blocks the NET, which is expressed in high concentrations throughout the cerebral cortex and cerebellum. The NET is reported to have an even higher affinity for dopamine than for norepinephrine. This finding is of interest in light of the demonstrated albeit less robust efficacy of atomoxetine and may also be related to the less thoroughly demonstrated efficacy of alpha-2 agonists like clonidine and guanfacine, which are also used to treat ADHD.

Adverse Effects

Immediate adverse effects of stimulants tend to be mild, dose-dependent, and usually diminish with continued use. The most common include loss of appetite and difficulty going to sleep; headache and stomachache are also reported but occur with almost equal frequency on double-blind placebo. More worrisome concerns have been raised regarding delayed or suppressed growth, appearance of motor and vocal tics, and possible sensitization leading to ▶ substance abuse (Biederman and Faraone 2005). Since stimulants nearly always reduce appetite to some extent, the concern over growth rates and possible enduring loss of height cannot be discarded. Nevertheless, existing albeit flawed evidence suggests that growth deficits from MPH are generally reversible. However, the much longer excretion half-lives of amphetamines would suggest that possible growth suppression effects may also be stronger than for MPH. With regard to the emergence of ▶ tics, early anecdotal evidence suggesting a causal link has been disconfirmed by systematic studies, which have highlighted familial factors. In the United States, MPH remains contraindicated for use in patients with a personal or family history of tics, although amphetamines are not so labeled, for historical reasons. Several controlled studies have shown that many children with pre-existing tic disorders can benefit from stimulants, although some do experience exacerbations that exceed the benefits derived. Nonstimulant medications are considered as a second line option in cases of risk of substance abuse, tics, and when weight loss is a significant concern.

Perhaps the most sensitive issue is the long-term risk of substance addiction. Long-term studies and meta-analyses have mostly not detected the increased risks following early stimulant treatment, and some studies have suggested that such early use may proffer a protective effect. Furthermore, despite similar mechanisms of action, the abuse potential of methylphenidate seems to be much lower than cocaine owing to the latter's more abrupt pharmacokinetic profile. This difference is especially marked for oral administration of MPH. Nevertheless, considering that ADHD subjects represent a population at risk of substance abuse, and the advantages of single daily dosing, many extended release stimulant formulas have been developed in the recent years. Comparing immediate release with extended release formulations of methylphenidate, similar peak DAT blockade levels are reached, but at different times (1.7 and 5 h, respectively), with mild reinforcing effects noted for the immediate release formula (Swanson et al. 2007). Thus, it has been proposed that kinetic factors, rather than absolute plasma concentrations may be the most relevant factor in producing subjective responses to MPH (and by extension to other stimulants). Along this line, a 10-year longitudinal study determined that misuse of stimulants only occurred with immediate-release forms; epidemiological reports indicate that users of immediate-release formulas are at a greater risk of substance abuse than users of extended release formulations (Findling 2008).

Recommended Medications for ADHD

There are three critical parameters in determining the appropriate pharmacological treatment in ADHD:

1. The duration of the effect, as multiple daily dosing increases the risk of discontinuation
2. An acceptable risk profile
3. The concern of abuse potential, especially in a population such as ADHD that may already have an elevated risk.

Methylphenidate

MPH is available in immediate release formulation (IR-MPH), in different extended release forms (ER-MPH), and as dexmethylphenidate (DMPH, the active D-isomer of MPH), which is also marketed in both immediate and extended release forms. The short-term efficacy of MPH for treating ADHD has been conclusively demonstrated by showing significant improvements on standardized rating scales, such as the Conners Global Index, the Conners Inattention/Hyperactivity with Aggression subscale, or the Clinical Global Impressions Improvements Scale (CGI-I). The landmark study, The MTA Cooperative Group report (1999), established that carefully adjusted stimulant medication (predominantly immediate release MPH, given three times per day, 7 days per week), either in combination with behavioral therapy or alone, produced a significantly greater improvement during the 14-month trial than behavioral management alone or standard community care in reducing core ADHD symptoms. In the intent-to-treat analyses, groups assigned to medication alone or medication combined with behavioral treatment did not differ, suggesting that MPH alone provides the best ratio of cost to benefit. Likewise, adverse effects were generally mild, the most common being appetite suppression, stomachache, and headache.

While the first generation "slow-release" MPH formulation left much room for improvement, formulations using an osmotic controlled release system (OROS MPH) and formulations combining rapid delivery and extended delivery elements in various proportions have been embraced by clinicians and patients. Efficacy is reported to be comparable with that of IR-MPH, with robustly significant improvements over placebo (Findling 2008). Mild adverse effects are comparable, e.g., headache (2–14% vs. 3–10% for placebo), abdominal pain (6–7% vs. 1% for placebo), emotional lability, anorexia (3–10% vs. 0–3%), and insomnia (3–7% vs. 0–5%). A new formulation consists of a MPH transdermal delivery system (MTS), which has been reported in a study sponsored by the manufacturer to show good efficacy and tolerability, with minimal adverse effects (headache was reported by 4% in both treatment and placebo groups), but a subsequent study found somewhat higher rates of adverse effects with MTS treatment than with OROS-MPH treatment (reduced appetite 26% MTS, 19% OROS, 5% placebo; insomnia 13%, 8%, and 5%, respectively; and nausea 12%, 8%, and 2%, respectively). Dexmethylphenidate (the active D-isomer of MPH) has been reported to be efficacious and well tolerated in children, and there is an extended release formulation.

Amphetamines

The first stimulant used for hyperactivity was Benzedrine, which contains equal proportions of dextro- and levo-amphetamine isomers. Because of weaker sympathomimetic effects with the dextro-amphetamine isomer, it was preferred for behavioral effects over the levo-isomer. However, the manufacturer of branded dextroamphetamine generally eschewed advertising and marketing despite substantial evidence of efficacy and nearly comparable tolerability to MPH. An alternative formulation that combines 4 amphetamine salts (75% dextro-isomer, 25% levo-isomer) has been extensively marketed in immediate release tablets and extended release capsules (mixed amphetamine salts, MAS). Whereas studies sponsored by the manufacturer have generally reported that MAS produced significantly greater improvement than MPH or placebo in aggression, defiance, and inattention/hyperactivity, children treated with MAS evidenced higher incidence of sadness and stomachache than those receiving MPH (Faraone et al. 2002; Rappley 2005). Where available, MAS is marketed in a wide range of doses, which facilitates tailoring of dose and improves compliance. Extended release MAS (XR-MAS) formulations are also efficacious and relatively well tolerated, although the duration of adverse effects can greatly exceed the duration of direct benefits. The substantial intersubject variation in pharmacokinetic parameters highlights the need for personalized treatment.

► Pemoline is a stimulant with an distinct pharmacokinetic profile that may have accounted for its greatly diminished abuse liability. Despite having been shown to be efficacious for ADHD, it is no longer recommended owing to confirmed reports of fatal liver damage (Rappley 2005) and the availability of nonstimulant alternatives.

Nonstimulants

Nonstimulant medications that modulate noradrenergic neurotransmission have also been found to be efficacious for ADHD. The first class of such medications are the tricyclic ► antidepressants, which have comparable efficacy with MPH. However, purely noradrenergic compounds such as desipramine may be more cardiotoxic than mixed noradrenergic/serotonergic drugs, although all tricyclics also produce prominent anticholinergic side effects (Biederman and Faraone 2005). The use of tricyclics, in general, and desipramine, in particular, has diminished sharply following reports of deaths of four children who were treated with recommended doses of desipramine.

In clinical trials, atomoxetine (ATX) separates from placebo in symptom improvement at all ages, with efficacy being

the strongest at the highest doses tested (1.2–1.8 mg/kg per day; Table 1). Trials sponsored by the manufacturer found no significant differences in efficacy between ATX and IR-MPH, but other trials, also commercially sponsored, have found XR-MAS and OROS-MPH to be somewhat more efficacious than ATX. In clinical practice, ATX is rarely considered a first-line medication, except for patients with ADHD and a history of substance abuse, comorbid anxiety, tics, or history of nonresponse to stimulants. Despite the generally benign effect on tics, some patients have been reported to develop tics after ATX use. Higher doses of ATX are associated with anorexia (12%) and somnolence (7–11%). ATX may produce delayed growth, which is reported to be reversible after discontinuation. Overdoses of ATX may result in seizures, which requires patients with seizure histories to take caution. Unlike tricyclic antidepressants, ATX does not have anticholinergic or cardiovascular side effects. However, a rare risk of liver injury (two cases in two million), which recovers after interruption of treatment has been reported. Therefore, ATX is not recommended in patients with jaundice or evidence of liver injury; treatment should be discontinued if patients develop pruritis, dark urine, or other symptoms of liver damage (Biederman and Faraone 2005).

The antidepressant ► bupropion has shown modest efficacy in ADHD treatment, but has been proposed to control cigarette smoking in ADHD patients, and for patients with comorbid depression, ► bipolar disorder, or substance abuse. In general, bupropion is well tolerated but is less efficacious than MPH and has a substantial risk of inducing seizures at higher doses (Biederman and Faraone 2005; Findling 2008). ► Modafinil has also some efficacy in ADHD and some studies suggest it is well tolerated, with insomnia, abdominal pain, anorexia, cough, fever, and rhinitis being the most common adverse events. However, more clinical studies are needed to determine the utility of this drug as an alternative treatment (Rappley 2005).

The alpha adrenergic agonist clonidine has been evaluated in ADHD treatment, with relatively poor results. Although it provides some benefit to patients and is well tolerated (main adverse effect is drowsiness), it is significantly less efficacious than MPH (Rappley 2005). Guanfacine is a more specific alpha agonist (alpha2A) whose effectiveness has been assessed recently in ADHD in an extended release formulation providing 1–4 mg/day (Strange 2008). Although initial studies have had confounding design flaws, improved trials have confirmed a decrease in hyperactivity/impulsivity scores and in tic frequency, even in subjects who had not responded to MPH. As with clonidine, the major adverse effects of guanfacine are sedation (16–35%) and fatigue (12–60%). Depression, headache, and upper abdominal pain have been also reported as possible adverse effects. Not surprisingly, given its primary indication, a tendency to lower blood pressure has been found compared with placebo, but the drug was well tolerated, and there was no relation between blood pressure changes and headaches or dizziness.

Prodrug Stimulants

A prodrug is a substance that needs to be transformed within the organism before it can produce its effects (Findling 2008). ► Lisdexamphetamine dimesylate (LDX) is converted into L-lysine and D-amphetamine, and its absorbance is independent of gastrointestinal processes. At least two studies reported a significant improvement in ADHD symptoms when compared with placebo, which was comparable with the benefit of XR-MAS. This finding is of interest given that, contrary to extended release formulas, the variability in absorption kinetics is much lower. Furthermore, LDX has similar tolerance levels than current stimulants. The hedonic impact of LDX was found to be much lower than that of D-amphetamine in subjects with a history of stimulant abuse, who were rated with the Drug Rating Questionnaire-Subject (DRQS), which suggests that this may be an alternative for patients with histories of substance abuse, although this indication has not yet been evaluated systematically.

Comorbidities

The NIMH Multimodal Treatment Study of ADHD found that children with ADHD and disruptive behavior disorders benefit from stimulant treatment, showing a significant decrease in aggressive behaviors (Kunwar et al. 2007). Nevertheless, behavioral intervention is recommended to promote social integration and academic performance. Though stimulants may be an effective treatment for aggressive or antisocial behavior in ADHD, ► mood stabilizers or atypical ► antipsychotics have become widely used with the intent of treating manic symptoms or aggression. Concerns are being raised regarding the serious potential for metabolic derangements with such treatments, especially with certain atypical antipsychotics. Stimulants exacerbate psychotic symptoms in a sizeable proportion of such patients. While stimulants may be modestly helpful for children with learning disabilities without prominent hyperactivity/impulsivity, they are never sufficient. Such children require additional educational support. Coexisting anxiety appears to attenuate impulsivity in ADHD. Contradictory results regarding stimulant response in ADHD children with comorbid

anxiety have been reported by well designed studies, with both poorer and equivalent response being found. Systematic studies have not examined the extent to which children with ADHD/depression or with ADHD/bipolar disorder can benefit from stimulants, although stimulants in conjunction with antidepressants have been recommended in cases of ADHD/major depressive disorder. Finally, anti-tic agents in combination with stimulants can be useful for children with ADHD and tic disorders.

Conclusions

Methylphenidate and amphetamines, preferably in extended release formulations, are the recommended first choice in children, adolescents, and adults with ADHD, including those with comorbid disruptive behavior. In cases of history of substance abuse, the use of nonstimulants or LDX may be preferred. Medications for ADHD are chronically administered over years, and require sometimes subtle adjustments in dosing, timing, and adjuncts. Establishing and maintaining a therapeutic alliance with adolescents remains one of the greatest challenges of providing psychopharmacological care for ADHD.

Cross-References

- ► Adolescence and Responses to Drugs
- ► Alcohol Abuse and Dependence
- ► Amphetamine
- ► Atomoxetine
- ► Attention
- ► Attention Deficit Hyperactivity Disorders: Animal Models
- ► Dopamine
- ► Dopamine Transporter
- ► Methylphenidate and Related Compounds
- ► Methylphenydate
- ► Norepinephrine
- ► Stimulant

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Attention Deficit Hyperactivity Disorder

Synonyms

ADHD

Definition

An axis-I neuropsychiatric disorder listed in the Diagnostic and Statistical Manual (DSM-IV, American Psychiatric Association). ADHD is characterized by inattentive, hyperactive, and/or impulsive symptoms that interfere with everyday functioning. Although initially presenting in childhood, ADHD symptoms often persist into adulthood where they can impede social relationships, contribute to criminality, and have a negative impact on the ability to work effectively.

Cross-References

- ► Attention Deficit and Disruptive Behavior Disorders

Attention Deficit Hyperactivity Disorders: Animal Models

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Synonyms

Experimental animal models of attention deficit/hyperactivity disorder; Laboratory animal models of minimal brain dysfunction; Model organisms of hyperkinetic syndrome

Definition

Nonhuman animals, because of their specific characteristics that resemble human attention deficit/hyperactivity disorder (ADHD), were selected for use in ADHD experimental research, testing, or teaching. They provide an invaluable tool for investigating ADHD etiology, its diagnosis, and treatment.

Animal models of ADHD can be induced by genetic manipulation, physical or chemical means, or selected from the normal population on the basis of their behavioral characteristics.

Current Concepts and State of Knowledge

ADHD research has long employed animal models in the study of the neural basis of this multifactorial and heterogeneous pathology. The core clinical symptoms of ADHD – namely, inattentiveness, ► hyperactivity and ► impulsivity – have been used as constructs in animal research for a long time. Following early attempts to model these symptoms in animals such as dogs and cats, laboratory models of ADHD have been developed mostly in rodents, partly because more is known about their biology and genetics. Several authors have put forward some essential characteristics of a good animal model of ADHD. They can be summarized as follows: (1) behavioral symptoms should be evident only in particular environments and stage of development, according to the specific characteristics of ADHD symptom manifestation; (2) biochemical and morphological abnormalities – as well as their etiology – should be similar to those shown by ADHD sufferers; (3) the model should respond to the same drugs used for the treatment of ADHD with a measurable improvement of the main symptoms and be able to predict the efficacy of new treatments. Thus, in preclinical ADHD research, a particular emphasis should be put on the techniques used to assess the behavioral symptoms and on the peculiar response of the model to drugs used in ADHD pharmacotherapy on those behavioral measures.

Animal models of ADHD can be divided into genetic, chemical intoxication/physical trauma, behavioral, and brain lesion models. These models are of great value because their use can help in defining the causal relations between the symptoms and the applied experimental manipulation. Moreover, they allow us to test the efficacy of new pharmacological and behavioral interventions for the treatment of ADHD, and to understand the mechanisms underlying currently used therapies.

Assessing Impulsivity and Attention Deficits in Rodents

The diagnosis of ADHD is based on behavioral criteria. Many behavioral tests commonly used in human neuropsychology have been modeled in animals. Though relatively simple tasks have been extensively used to measure locomotor activity (e.g., ► open field test), anxiety (e.g., ► elevated plus-maze), and learning and memory (e.g., ► radial-arm maze) in animal models of ADHD, more sophisticated tasks have been developed to specifically measure impulsivity and ► sustained attention.

Tasks assessing impulsivity can be broadly divided into those measuring impulsive decision-making and those measuring ► behavioral inhibition (Winstanley et al. 2006). Both subtypes of impulsivity are highly relevant to ADHD research, given the fact that affected individuals react differently to reinforcers when compared with normal subjects and that one of the core deficits in ADHD is response inhibition.

The most widely used tests of behavioral inhibition are the ► go/no-go task and the ► stop-signal reaction time task (SSRTT) (Eagle et al. 2008). These tasks have been successfully adapted to be used in animals and have shown good face and predictive validity. In the go/no-go paradigm, subjects have to respond to a cue – the "go" signal – and not to respond to a different infrequent stimulus – the "no-go" signal – to be rewarded. Children with ADHD showed impaired ability to succeed in this task when compared with control subjects.

The SSRTT is a sophisticated variant of the go/no-go task, in which the subject is required to cancel an already initiated motor response on receiving an unexpected stop signal. By varying the timing of the stop signal presentation, it is possible to measure the speed of the inhibitory process (the SSRT) (Logan 1994), which has been shown to be consistently longer and more variable in ADHD individuals. The SSRT in animals is speeded by drugs

commonly used for the treatment of ADHD, although for some drugs, the effect depends on baseline performance (Eagle et al. 2008).

Both stopping and no-go types of behavioral inhibition in humans are under the control of fronto-striatal circuits, which are differently modulated by psychostimulants in ADHD and control subjects. When putative homologous areas are lesioned in rodents by microinfusion of neurotoxins, they show inhibitory deficits qualitatively similar to those seen in ADHD patients. Eagle and colleagues showed that lesions of the orbitofrontal cortex (OFC) impair stopping performance in the rat. Moreover, SSRT is slower in rats with medial striatal lesions, a region homologous to the caudate nucleus in humans, which has been shown to be smaller or dysfunctional in ADHD patients.

Impulsive decision-making in animals is commonly assessed by means of the ► delay-discounting (DD) paradigm. In this task, impulsive choice is defined as the preference for a smaller immediate reward over a larger but delayed one. ADHD patients show faster switches of preference toward the smaller but more immediate reward when the delay to the bigger reward is gradually increased. In rodents, ► atomoxetine, ► amphetamine (AMPH), and ► methylphenidate (MPH) – drugs commonly used in ADHD pharmacotherapy – reduce impulsive choice in the DD paradigm, and some animal models of ADHD show intolerance to delay in this task (see Table 1). Cardinal and colleagues showed that lesion of the NAc core renders animals less tolerant to delays, leaving intact the preference for the large reward when no delays are interposed. In the same task, OFC lesions had less consistent effects.

Intermediate between tasks measuring impulsive decision-making and motor disinhibition are the behavioral tasks, in which the rat has to perform an action for a predetermined number of times – or to withhold from responding for a predetermined amount of time – before emitting the response that will be rewarded. Any premature interruption of these chains of actions is considered as an impulsive response. Examples of this kind of tasks are the differential reinforcement of low rates of responding (DRL) schedule, the lever-holding task (LHT), and the fixed consecutive number (FCN) schedules. In DRL schedules, a response is rewarded only if made after the predetermined amount of time has elapsed since the last response. Available studies on DRL yielded contrasting results in ADHD sufferers as well as in rodent models of ADHD. In the LHT, the subject is required not to release a lever or a button for a predetermined amount of time to be rewarded. FCN schedules require a certain number of responses in one location, before producing a single response in a different one, to receive the reward; premature interruption of these chains of responses is usually punished with a short time-out.

One of the most used tests of sustained ► attention in rodents is the ► 5-choice serial reaction time task (5-CSRTT), which was developed partly with the aim of investigating and better understanding the deficits underlying ADHD (Bari et al. 2008). The basic task is modeled on the continuous performance task used to study human attentional processes. The rat version of the task requires animals to detect brief flashes of light presented pseudorandomly in one of the five holes and to make a nose-poke response in the correct spatial location to receive a food reward. The rat is required to monitor a horizontal array of apertures and to withhold from responding until the onset of the stimulus. Generally, the accuracy of stimulus discrimination provides an index of attentional capacity, while premature responses – made before the presentation of the stimulus – are regarded as a form of impulsive behavior and hence a failure in impulse control.

Performance on the 5-CSRTT has been evaluated after lesions of discrete areas of the rat brain. Anterior cingulate (ACg) cortex lesions impair selective attention, whereas infralimbic (IL) and postgenual ACg lesions increase impulsivity, and damage to the OFC results in perseverative responding. Lesion to the medial striatum impairs response accuracy and increases both premature and perseverative responses, whereas NAc core lesions increase impulsivity without affecting response accuracy.

Depleting brain 5-HT by intracerebroventricular infusion of 5,7-dihydroxytryptamine (5,7-DHT) during adulthood produces long-lasting hyperactivity and impulsivity in the 5-CSRTT, but no attentional impairments. Finally, attentional deficits with no increase in impulsivity have been obtained by globally interfering with cholinergic neurotransmission and, under certain conditions, with the noradrenergic system (Robbins 2002).

Genetic Models

One of the most investigated animal models of ADHD is the spontaneously hypertensive rat (SHR), an inbred genetic model derived from the Wistar Kyoto (WKY) rat. Hyperactivity and impulsivity in the SHR develop over repeated testing and are particularly evident in settings with a low rate of reinforcement (Sagvolden 2000). These traits are present before the SHR develops hypertension and remain stable during adulthood. Compared with Sprague–Dawley (SD) rats, SHR show a neurochemical profile characterized by subcortical hyperdopaminergic tone and reduced ► noradrenaline (NE) function in the

Attention Deficit Hyperactivity Disorders: Animal Models. Table 1. Summary of selected models of ADHD, their behavioral characteristics, and tasks used to assess them.

Model	Impulsivity	Hyperactivity	Attention deficits
Genetic			
SHR	Yes (FI/Ext)[9] Yes (DRL, LHT) Yes/No (DD)[19] Yes (SVD)[1,15] Yes (FCN)	Yes (FI/Ext) Yes (EPM)[4] Yes (OF)[1,2] Yes (SVD)[1,15]	Yes (FI/Ext) No (5-CSRTT) Yes (Y maze)[2,8] Yes (SVD)[1,15]
TRβ-1 mouse	Yes (DD)	Yes (LA)[2] Yes (OF)	Yes (RT)
DAT-KO mouse	Yes (radial maze)	Yes (OF/LA)[1–4, 7,10,11]	Yes (radial maze)
NHE rat	?	Yes (Làt maze)[12,13]	Yes (SC)[12,13]
Coloboma mouse	Yes (DD)	Yes (OF/LA)[1, 5,14]	Yes (LI)[14]
Pharmacological			
6-OHDA lesion	Yes (EPM)	Yes (radial maze) Yes (OF/LA)[1–4, 6,18]	Yes (radial maze)
Lead exposed	?	Yes (LA)[1,2] No (OF)	?
Physical trauma			
Anoxia/Hypoxia	?	Yes (OF)[1,16]	?
X-ray exposed	?	Yes (T maze)	Yes (T maze)
Behavioral			
Poor 5-CSRTT performers	Yes (5-CSRTT)[2,18] Yes (DD) No (SSRTT)	Yes (OF) Yes/No (LA)[a] No (CC, RW)	Yes (5-CSRTT)[2]
Poor SSRTT performers	Yes (SSRTT)[1,2, 17,18]	?	?

Abbreviations: *CC* circular corridor; *DD* delay discounting; *EPM* elevated plus-maze; *FI/Ext* fixed interval/extinction schedule; *FCN* fixed consecutive number schedule; *LA* locomotor activity; *LHT* lever holding task; *LI* latent inhibition; *OF* open field; *RT* reaction time procedure; *RW* running wheel; *SC* scanning activity; *SSRTT* stop-signal reaction time task; *SVD* simultaneous visual discrimination task; *5-CSRTT* five-choice serial reaction time task.

[a]Depending on selection criteria. Numbers refer to drugs that acutely improved the specific deficit as measured by the task indicated between brackets: 1, AMPH; 2, MPH; 3, NET inhibitors; 4, SERT inhibitors; 5, alpha-2c adrenergic receptor antagonists; 6, DA D4 receptor antagonists; 7, 5-HT (2a) receptor antagonists; 8, nicotine; 9, MAO-B inhibitors; 10, 5-HT enhancing agents; 11, AMPAkines; 12, galactosylated form of DA; 13, D1 agonists; 14, NA depletion by DSP-4; 15, guanfacine; 16, acetyl-L-carnitine; 17, modafinil; 18, atomoxetine; 19, CB1 cannabinoid receptor agonists

► prefrontal cortex (PFC) (Heal et al. 2008). In theory, such catecholaminergic imbalance would predict the increased locomotor activity of SHR and the beneficial effect of drugs that regulate noradrenergic transmission on impaired ► executive functions. Conversely, there is also evidence from *in vitro* experiments for the opposite biochemical profile in SHR. NE concentrations and tyrosine hydroxylase ► gene expression have been found to be higher, whereas dopamine (DA) efflux was reduced in the striatum of SHR compared with WKY rats. These results led researchers to hypothesize that ADHD is characterized by hypofunctional dopaminergic system and hyperfunctional NE transmission in the PFC, with the latter being congruent with poor PFC regulation of NE levels by noradrenergic receptors found in the SHR. Moreover, the SHR brain displays anatomical abnormalities similar to ADHD patients as well as a decreased expression of the ► dopamine transporter (DAT) gene, which could explain the reduced responsiveness to psychostimulants (Russell 2007). Serotonin (5-HT) transmission also seems

to be abnormal in the SHR and administration of the 5-HT transporter (SERT) inhibitor ► citalopram decreases hyperactivity in the ► elevated Plus-Maze. Despite its high face validity, the SHR does not show cognitive deficits across all behavioral tasks of impulsivity and sustained attention. Moreover, the ability of drugs used in the treatment of ADHD to improve performance in this animal model have also been inconsistent, probably depending on the behavioral test employed and on the rat strain used as a control.

Mice lacking the dopamine transporter (DAT-KO) are hyperactive in new environments, have learning and memory deficits as well as impaired inhibition of ongoing behavior. DAT-KO mice are characterized by high levels of extracellular DA in the striatum and reduced phasic DA release. Hyperactivity in this model is reduced by psychostimulants and serotonergic manipulation, but not by NE transporter (NET) inhibitors. This would suggest that in this model, psychostimulants do not decrease hyperlocomotion by increasing catecholamine levels via DAT or NET blockade, but probably by modulating the serotonergic system (Gainetdinov et al. 1999). A 5-HT(2A) receptor gene ► polymorphism has been associated with human ADHD and antagonists of this receptor ameliorated DAT-KO mice deficits. However, drugs targeting the 5-HT system are of limited use in the treatment of human ADHD and it is not clear yet whether this pathology is characterized by increased or decreased DAT function.

Naples high-excitability (NHE) rats are selected for high levels of activity in the Làt maze. This model exhibits decreased DA D1 receptor availability and increased DAT and tyrosine hydroxylase activity within the PFC. It has been suggested that impaired attention and hyperactivity in NHE rats may be caused by a hyperfunctional mesocorticolimbic DA system.

The Coloboma mutant mouse bears a mutation of the synaptosomal-associated protein 25 (SNAP-25) gene and has been proposed as a model of ADHD. SNAP-25 is an important protein required for neurotransmitter release and protein translocation. Coloboma mice display impulsivity in the delayed reinforcement task and their hyperactivity is decreased by AMPH but not by MPH. It has been suggested that the hyperactive phenotype of this model is caused by an imbalance between noradrenergic hyperfunction and dopaminergic hypofunction.

Recently, a genetic mouse model based on the deletion of the β2-subunit of the nicotinic receptor has been described as having ADHD-like behavioral inflexibility and inhibitory deficits. Considering a reported association between polymorphisms of the nicotinic receptor subunit and ADHD, a high incidence of cigarette smoking in individuals with ADHD and the beneficial effects of ► nicotine administration on attentional functions, further investigation of this model is warranted.

Male transgenic mice expressing a mutant form of the human thyroid hormone receptor (TRβ-1) display increasing hyperactivity over time, impulsivity, and inattention. Thyroid hormone controls the development of brain areas involved in the regulation of executive functions. This genetic model shows increased striatal dopamine turnover and its hyperactivity is reduced by MPH administration.

Chemical Intoxication and Physical Trauma Models

Despite its high heritability, some forms of ADHD are thought to be caused by heavy metal exposure, drug intoxication, or physical traumas, at pre-, peri- or post-natal developmental stage. Some environmental factors may in fact have ► teratogenic effects on the fetus during pregnancy, which will cause ADHD symptoms in the offspring. Although exposure to chemicals and complications during pregnancy and/or delivery represent independent risk factors for the development of ADHD, it is useful to create animal models that mimic such conditions.

Heavy metal exposure in early ► ontogeny causes hyperactivity, which improves after acute AMPH or MPH administration. In animals exposed to lead, 5-HT and DA turnover is decreased in the PFC and striatum, respectively. Other heavy metals, such as manganese and cadmium, are believed to cause similar effects as lead exposure in producing hyperactive rats.

Other chemical-induced animal models are created by pre- or post-natal administration of polychlorinated biphenyls (PCBs), methylazoxymethanol, and transretinoic acid. However, these conditions have had only limited success as models of ADHD.

Prenatal ethanol and nicotine exposure can cause ADHD-like symptoms in humans and other animals. Accordingly, rats prenatally exposed to ethanol display dysregulation of dopaminergic neurons in the VTA, which is normalized by AMPH or MPH administration. However, this condition is probably better suited to model ► fetal alcohol syndrome rather than ADHD.

Physical trauma models of ADHD include, amongst others, neonatal anoxia and X-ray exposure. Neonatal anoxia is a risk factor for human ADHD and causes long-lasting behavioral impairment and monoaminergic dysregulation in the rat brain. Exposure to X-radiation during development damages the ► hippocampus and causes hyperactivity and learning deficits in rats. These models both possess predictive validity since they respond to acute AMPH administration, but are created by means

of physical insults, which are unlikely to be the cause of the majority of ADHD cases in humans.

Chemical Lesion and Behavioral Models

Animal models relevant for ADHD research can be created by lesioning of selective brain areas or interfering with neuromodulatory systems. These lesions are mainly created by microinfusion of neurotoxins during animal adulthood or at early postnatal days, to mimic abnormal neurodevelopmental processes.

The most widely used neurodevelopmental model of ADHD is the neonatal ▶ 6-hydroxydopamine (6-OHDA) lesioned rat. Shaywitz and colleagues, in 1976, showed that rats lesioned 5 days after birth by intracerebroventricular infusion of 6-OHDA display marked hyperactivity and other cognitive deficits that were claimed to be attenuated by acute administration of AMPH. Further research demonstrated that the behavioral phenotype of this model also improves after MPH administration, and that these animals (rats or mice) have decreased striatal DAT density, increased dopamine D4 receptor expression, and alterations in central 5-HT neurotransmission. These rats show patterns of hyperactivity similar to those of childhood ADHD in that their hyperlocomotion is less evident in novel environments, but then increases with repeated exposures to the testing apparatus. Thus, the 6-OHDA model presents good face and predictive validity, but lacks construct validity, as it is very unlikely that the almost complete destruction of the dopaminergic system caused by the neurotoxin mirrors the ADHD condition (Kostrzewa et al. 2008). Nevertheless, this model could provide important insights on the relationship between monoaminergic alterations in ADHD and the mechanisms underlying hyperactivity.

Rats achieving poor levels of attentional performance on the 5-CSRTT have been proposed as a model of the inattentive subtype of ADHD. These rats are hyperactive, show impulsivity – as measured by the number of premature responses – in addition to low levels of attentional accuracy. In cortical areas, 5-HT turnover of these animals is inversely related to choice accuracy, while DA and 5-HT turnover correlate positively with attentional performance and premature responses, respectively. On the other hand, rats specifically selected for high levels of premature responses in the 5-CSRTT (high-impulsive rats) have lower DA D2 receptor density in the ventral, but not in the dorsal striatum, compared with nonimpulsive rats (Dalley et al. 2007). Moreover, dopamine release and metabolism are unchanged in the nucleus accumbens (NAc) of high-impulsive rats. These behavioral phenotypes have been validated in part by their capacity to predict susceptibility to drug use (Belin et al. 2009) – for which ADHD is known to be a risk factor – and by their sensitivity to drugs used for the treatment of ADHD.

Rats that show slow inhibitory processes, as measured by the SSRTT, display differential responses to drugs used in ADHD pharmacotherapy when compared with fast stoppers in the same task. Thus, AMPH and modafinil speed stop processes only on slow stoppers and have limited effect on fast-stopping animals; MPH improves action inhibition in slow stoppers, but impairs it in fast stoppers and, finally, atomoxetine speeds SSRT in all animals independent of baseline performance (Eagle et al. 2008).

Summary

This chapter reviewed the main behavioral and neurochemical characteristics of some of the most investigated rodent models of ADHD. The collection of animal models of ADHD described here is far from complete, but is illustrative of the different approaches. Table 1 summarizes some of the behavioral tasks used to characterize ADHD-like symptoms – namely, impulsivity, hyperactivity, and attention deficits – in selected animal models and the drugs that were efficacious in ameliorating the performance of the models when compared with control animals. Some of these behavioral tasks – borrowed from clinical neuropsychological research – have highlighted the translational value of ADHD research in animals. They not only prove useful in the definition of the behavioral phenotype under investigation, but also have the potential to investigate the mechanisms of action of drugs used in ADHD. Their use, in conjunction with appropriate animal models of ADHD, can help in discovering new treatments with fewer side effects and enhanced therapeutic value.

Cross-References

▶ Animal Models for Psychiatric States
▶ Atomoxetine
▶ Attention Deficit and Disruptive Behavior Disorders
▶ Behavioral Flexibility: Attentional Shifting, Rule Switching, and Response Reversal
▶ Delay Discounting Paradigm
▶ Genetically Modified Animals
▶ Impulse Control Disorders
▶ Impulsivity
▶ Methylphenidate and Related Compounds
▶ Phasic Neurotransmission
▶ Phenotyping of Behavioral Characteristics
▶ Polymorphism
▶ Psychostimulants
▶ Rodent Models of Cognition
▶ SSRIs and Related Compounds

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Attentional Bias to Drug Cues

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Synonyms

Addiction Stroop test; Incentive properties of drug cues

Definition

Attentional bias refers to the observation that motivationally relevant cues can "grab" or "hold" selective attention, and this is related to individual differences in appetitive and aversive motivation. For example, individuals with eating disorders tend to get readily distracted by cues related to food, whereas individuals with anxiety disorders are hypervigilant for threat-related cues. In the context of psychopharmacology, the term is usually used to refer to attentional processes among individuals with drug problems. As predicted by numerous theoretical models, drug dependent individuals have an attentional bias for drug cues, such as drug-related pictures or words.

Current Concepts and State of Knowledge

Measurement

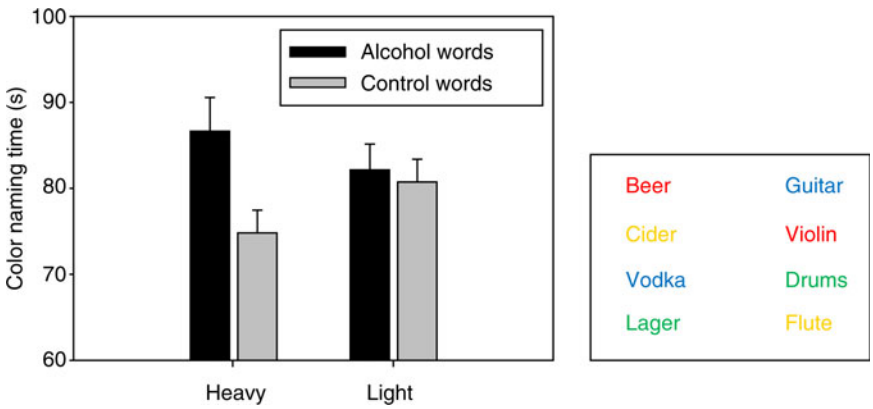
The last two decades have seen a large body of research devoted to the study of attentional biases in addiction and other disorders. A variety of experimental tasks, derived from those used in mainstream experimental psychology, have been used to assess attentional bias. For example, MacLeod et al. (1986) adapted the visual probe task, which is described below, to demonstrate that clinically anxious patients but not nonanxious controls tend to direct their attention toward threat-related words. Since this seminal study, a large volume of research has been devoted to the characterization of such attentional biases in a variety of emotional disorders (for a recent review, see Bishop 2007). More recently, researchers have used these tasks to study attentional biases for drug-related cues in addiction. With few exceptions, these tasks do not provide a direct readout of attentional processes; instead, the allocation of ▶ attention must be inferred based on a secondary measure, such as response time.

Perhaps the most commonly used task is a modified version of the classic "Stroop" task. In the classic Stroop task, participants are required to name the color in which different words are printed. A highly robust observation is that when color-related words are presented in an incongruent color (e.g., the word GREEN printed in red ink), participants are relatively slow to specify the ink color, compared to a control condition (e.g., the word TABLE printed in red ink). The interpretation of this "Stroop interference" is that people automatically process the semantic content (meaning) of words that they encounter; when the semantic content of a word (e.g., the word GREEN) conflicts with the required response (to say "red"), this leads to a slowing down of color-naming, or errors in color-naming. In the modified version of this task (the addiction Stroop), participants are required to

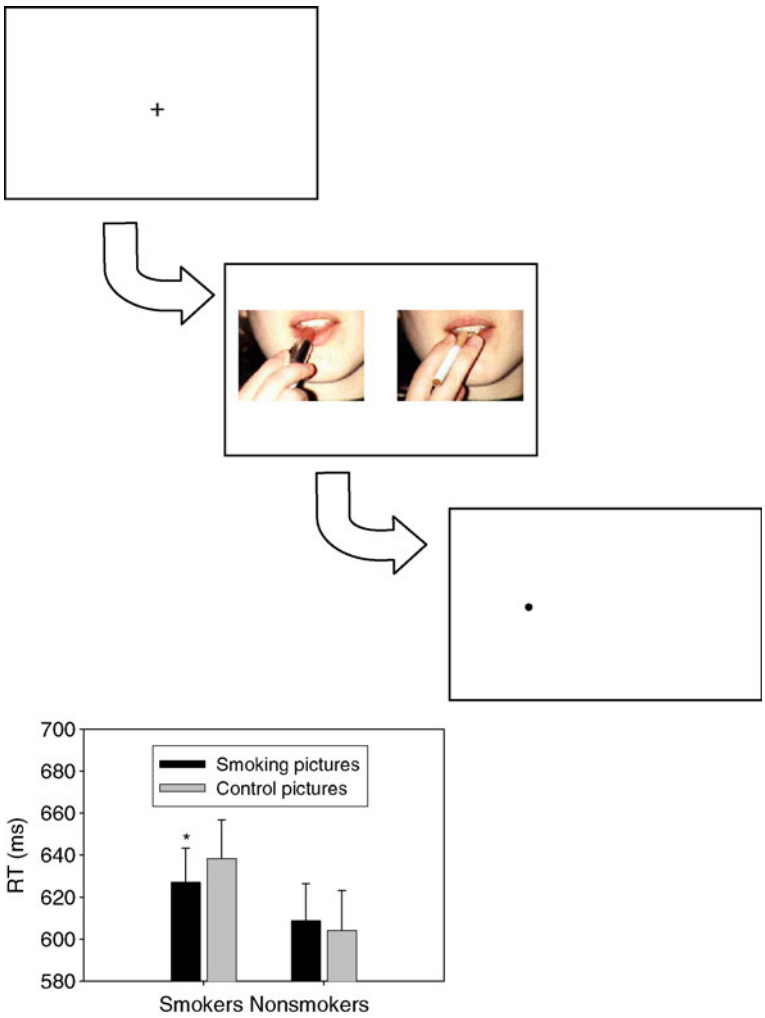
name the color in which drug-related words are printed, and their color-naming times for these drug-related words are compared to those for a control category (e.g., words related to musical instruments). See Fig. 1 for an example of the procedure and some illustrative findings. As reviewed by Cox et al. (2006), a highly robust finding in the literature is that drug users are slower to name the color in which drug-related words are presented, compared to words from a control category, but control participants do not exhibit this pattern of Stroop interference. Such Stroop interference has been demonstrated in users of a variety of different drugs, including alcohol, cannabis, cocaine, heroin, and tobacco (reviewed by Cox et al. 2006). This suggests that, compared to nonusers, drug users engage in excessive semantic processing of drug-related words, i.e., those words can "grab their attention." However, it is important to note that other explanations for this Stroop interference have been put forward, including delayed color-naming as a consequence of attempts to suppress the processing of drug-related words, or a generic slowdown in cognitive processing induced by the drug-related words, perhaps independently of any bias in selective attention (see Field and Cox 2008). Indeed, any Stroop interference that is observed may reflect the combined influence of all of these factors, and the specific influence of selective attention to drug-related words may be minimal; these issues mean that results from this task must be interpreted with some caution.

The visual probe task is an alternative measure of attentional bias that has been extensively used in psychopharmacology research, particularly over the past 5 years. In this task (see Fig. 2), a pair of pictures are presented on the left and right of a computer screen. One of the pictures is drug-related (e.g., an image of a person smoking a cigarette), and the other picture contains no drug-related content. The pictures are shown for a short period (typically between 50 and 2,000 milliseconds (ms)), and after pictures have been removed from the computer screen, a visual probe stimulus (for example, a small dot) is presented on either the left or right of the screen, in the spatial position that had been occupied by either the drug-related or the control picture. Participants are instructed to respond to the probe as quickly as possible. As reviewed by Field and Cox (2008), a robust observation is that drug users are faster to respond to probes that replace drug-related pictures, than to probes that replace control pictures. Control participants are equally fast to respond to probes that replace drug-related and control pictures. This has been demonstrated not only with tobacco smokers in several studies, but also with cannabis users, heroin users, and heavy drinkers.

Given that people are faster to detect and respond to a stimulus if it appears in a location of the visual field that they were attending to, this finding (faster reaction times to probes that replace drug-related pictures, rather than control pictures) is usually interpreted as indicating that drug users were directing their attention toward drug-related pictures. Indeed, when participants' eye movements are monitored while they complete the task (as detailed below), there is usually a large positive correlation between the index of "attentional bias" (derived from reaction times to probes) and the amount of time that



Attentional Bias to Drug Cues. Fig. 1. The addiction Stroop test. Participants are required to quickly identify the color in which words are printed. One list of words is drug-related; the other is neutral. In this study, adolescent heavy drinkers were slower to name the color of alcohol-related words, than to name the color of neutral words, but light drinkers took a similar amount of time to name the color of words in the two word lists. (Reprinted with permission from Field M, Christiansen P, Cole J, Goudie A (2007) Delay discounting and the alcohol Stroop in heavy drinking adolescents. Addiction 102:579–586.)



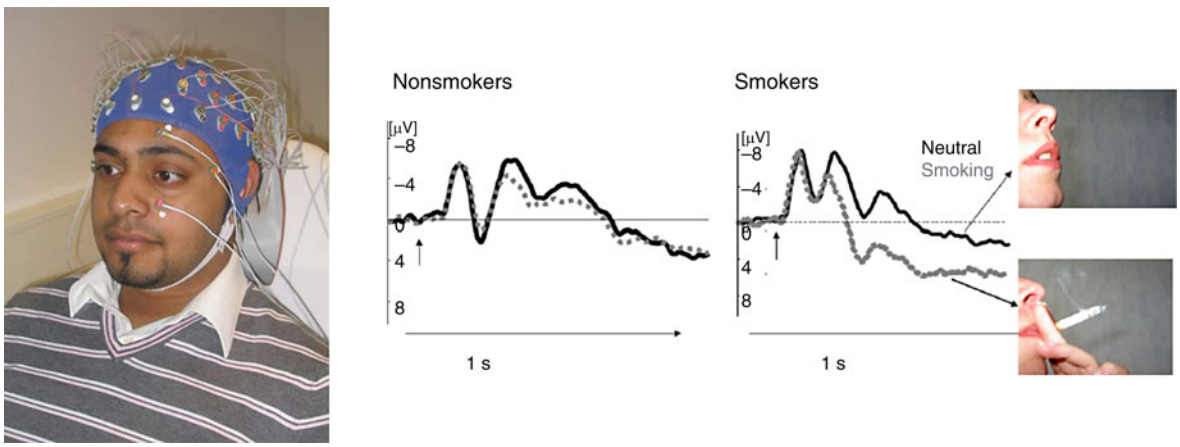
Attentional Bias to Drug Cues. Fig. 2. The visual probe task. Following a centrally presented fixation cross, a drug-related picture and a neutral picture are presented side by side on a computer screen for a brief period. After the pictures disappear, a visual probe is presented, and participants are required to rapidly respond to the probe. In this study, tobacco smokers were faster to respond to probes that replaced smoking-related pictures, than to probes that replaced neutral pictures, but nonsmokers did not show this difference. (Reprinted with permission from Mogg K, Bradley BP, Field M, De Houwer J (2003) Eye movements to smoking-related pictures in smokers: relationship between attentional biases and implicit and explicit measures of stimulus valence. Addiction 98:825–836.)

people maintain their gaze on the drug-related cues. So, it appears valid to use reaction times to visual probes to infer the allocation of attention to drug-related cues that precede those visual probes. A further issue with the visual probe task is that researchers have experimentally manipulated the amount of time that picture pairs are presented on the screen before they are removed and replaced by the visual probe. By varying the stimulus onset asynchrony (SOA), in this way, for example, using very short exposure durations (e.g., 50–200 ms) or longer durations (e.g., 2,000 ms), it is assumed that reaction time can capture the extent to which cues "grab" the attention (with very short SOAs) or "hold" the attention (with longer SOAs). Some studies suggest within-subject and between-group differences in attentional bias when short and long SOAs are used, which is consistent with the notion that these different SOAs can be used to measure different aspects of cognitive processing of drug cues. However, there is currently some controversy over whether reaction times obtained from the visual probe task can ever be used to

index orienting of attention, regardless of how brief the SOA is (Field and Cox 2008).

Given these issues with interpreting results from the visual probe and addiction Stroop tasks, there is a need to use measures of attentional bias that provide more direct readouts of selective attention. Eye movement monitoring is one such measure, because people are usually attending to whatever is currently the focus of gaze. Some researchers have monitored participants' eye movements while they complete a visual probe task in which drug-related and control pictures are presented. It is possible to then look at the orienting of attention to drug-related cues, by measuring which picture (drug-related or control) participants initially direct their gaze toward on each trial of the task. It is also possible to measure the maintenance of attention on, or latency to disengage attention from, drug-related cues, by comparing the amount of time that participants direct their gaze toward drug-related pictures with the amount of time that they direct their gaze toward control pictures. Tobacco smokers, ► cocaine users, and cannabis users (but not control participants) tend to preferentially maintain their gaze on drug-related pictures; however, the evidence for a bias in the initial orienting of attention toward drug-related pictures is currently equivocal (Field and Cox 2008).

Additional laboratory measures have been used in recent years to investigate attentional bias for drug-related cues. These include tasks such as the flicker induced change blindness task and the attentional blink task (see Field and Cox 2008). However, these are not discussed in detail in this section as they are not currently widely used, although both methods may have advantages over existing measures. The final measure that we consider here is ► electroencephalography (EEG), particularly the study of event-related potentials (ERPs) elicited by drug-related cues. EEG recording involves attaching electrodes to various sites on the scalp of participants (see Fig. 3) that measure the electrical activity produced by the brain. Participants are then shown drug-related (or control) pictures, and activity in the cortex can be measured in the form of electrical activity on the scalp in response to presentation of the pictures (ERPs). Although there are many different forms of ERPs, which differ in their latency, magnitude, and brain region of origin (see separate entry), researchers have focused on ERP components such as the P300 (a slow positive wave that typically occurs about 300 ms after stimulus presentation). This particular ERP component has been implicated in selective attention, such that its magnitude (in response to a visually presented stimulus) seems to correlate highly with the degree to which participants attend to that stimulus. This has particularly been observed for motivationally relevant stimuli. In several studies, it has been demonstrated that P300 magnitude in response to drug-related



Attentional Bias to Drug Cues. Fig. 3. Measuring event-related potentials (ERPs) in response to smoking-related cues. Smoking-related and neutral pictures were presented for 2 s, and participants were asked to watch the pictures attentively. The ERP results indicate that both the P300 and the subsequent slow wave amplitudes in response to smoking-related pictures are significantly enhanced in smokers compared to nonsmokers at frontal and central sites, whereas the magnitude of the P300 and SPW amplitudes in response to neutral pictures does not differ between the groups. Accordingly, it can be concluded that smokers show more bias for smoking-related pictures than smokers. (Data published in Littel M, Franken IHA (2007) The effects of prolonged abstinence on the processing of smoking cues: an ERP study among smokers, ex-smokers and never-smokers. J Psychopharmacol 21:873–882.)

cues is significantly larger in drug-users than in control participants (see Fig. 3 for an example). This has been demonstrated in heroin, cocaine, alcohol, and tobacco users (e.g., Franken et al. 2008).

Theoretical Relevance

Arguably, interest in attentional bias in humans originated from animal models of incentive learning processes. It has been known for decades that after ► classical (Pavlovian) conditioning, laboratory animals will direct approach behaviors to conditioned stimuli that are reliable predictors of appetitive rewards, such as food or addictive drugs. This conditioned approach behavior is known as autoshaping. Interestingly, animals show increased interest in conditioned stimuli that predict appetitive rewards, and they orient their attention to them ("sign-tracking") before those cues elicit an overt behavioral approach response. In an influential theory, Robinson and Berridge (1993, cited in Field and Cox 2008) argued that these incentive learning processes are mediated by dopaminergic activity in the ► nucleus accumbens and related structures within the mesolimbic dopamine system. According to the theory, chronic exposure to drugs of abuse leads to sensitization of dopamine activity in this ► dopamine circuit. As a consequence, these incentive learning processes are exaggerated, and drug-related cues acquire very powerful incentive properties, meaning that their capacity to grab the attention and elicit approach behaviors is enhanced. As reviewed by Hogarth and Duka (2006), an emerging body of evidence suggests that a classical conditioning process may be responsible for the development of attentional bias in humans: people tend to direct their attention toward a cue that was previously paired with the availability of ► alcohol or ► nicotine in the laboratory.

Alternative theoretical models are more explicitly grounded in clinical and experimental psychology, yet their predictions are not inconsistent with the aforementioned learning processes. For example, the theory of current concerns (see Cox et al. 2006) suggests that drug users have a dysfunctional motivational structure, such that their goal to use drugs takes precedence over all other goals, leading to a general cognitive hypersensitivity to goal-related (i.e., drug-related) environmental cues. Ryan 2002; cited in Field and Cox 2008) emphasized the need to consider cognitive processes when trying to understand why drug users react to drug-related cues with physiological and subjective changes. In essence, Ryan argued that drug users find it difficult to ignore drug-related cues in their environment, which exacerbates subjective craving in response to those cues; this in turn leads to drug-seeking behavior. Finally, Franken (2003) integrated predictions made by Robinson and Berridge (1993) with some observations of human patients. Franken's (2003) model suggests that attentional bias for drug cues occurs as a consequence of a dysfunctional, dopamine mediated incentive learning process, as discussed above. This causes drug users to be more likely to detect drug-related cues in their environment. Once drug cues have been detected, the drug user experiences subjective ► craving, which leads to a further increase in the salience of drug-related cues (i.e., drug-related cues become even more difficult to ignore). In addition, attentional bias and subjective craving mean that the cognitive resources required for coping strategies (e.g., attempts to resist craving) are further diminished, and the combined effect is that drug-seeking behavior is more likely to occur. All of these theoretical models converge on the common prediction that attentional bias should be positively correlated with subjective craving, and we discuss relevant evidence in the following paragraphs.

Clinical Relevance

The theoretical models discussed above suggest that attentional bias is likely to develop as a consequence of chronic exposure to drugs of abuse, perhaps through a conditioning process. Once established, attentional bias may be long-lasting and difficult to reverse, and this is consistent with results from one study that demonstrated no difference in attentional bias between current tobacco smokers and individuals who had been abstinent from smoking for 6.5 years, on average. These theoretical models also suggest that attentional bias can contribute to the maintenance or escalation of drug-seeking behavior, perhaps because it increases the magnitude of subjective drug craving, or even triggers drug-seeking behavior directly. As such, attentional bias may be clinically relevant, and therefore it could be a viable target for clinical intervention. Two primary clinical applications of attentional bias research can be described. First, if attentional bias causes (or at least indexes the underlying processes that cause) drug-seeking behavior, then individual differences in attentional bias might indicate vulnerability to relapse among drug users who are currently abstinent, possibly in ways that cannot be captured by self-report measures. Consistent with this notion, a number of recent studies demonstrated that individual differences in attentional bias (among tobacco smokers, alcohol abusers, and heroin users) predicted subsequent clinical outcome (either treatment dropout, or time to relapse to drug-seeking after treatment completion; see review by Field and Cox 2008). However, all of these studies used the addiction Stroop task to measure attentional bias; given the problems with interpreting results from this task,

there is a need to replicate these findings with more direct measures of selective attention, such as eye movement measures. The second clinical implication is that attentional bias itself might be a suitable target for treatment intervention: if individuals can be "trained" to reduce the extent to which they get distracted by drug-related cues, they might be less likely to relapse to drug-seeking behavior in the future. There is currently a great deal of enthusiasm for this type of intervention, although it should be noted that the early results are not promising. That is, when attentional bias is experimentally reduced, it does not consistently lead to a reduction in drug-seeking behavior (see Field and Cox 2008).

The association and causal relationship between attentional bias and subjective craving (rather than drug-seeking behavior) is currently more compelling. Among drug users, all measures of attentional bias are positively correlated with subjective drug craving (Field and Cox 2008; Franken 2003), and the association is particularly robust for more "direct" measures of attention, such as eye movement monitoring or the P300 component of ERPs (see Field et al. 2009). As predicted by some of the theoretical models discussed earlier (e.g., Franken 2003; Ryan 2002), there appears to be a reciprocal causal relationship between attentional bias and subjective craving. That is, when subjective craving is experimentally manipulated (e.g., through stress, enforced abstinence), attentional bias seems to increase in line with subjective craving; on the other hand, when attentional bias is experimentally increased, this leads to a small but significant increase in subjective craving (all reviewed by Field and Cox 2008).

So attentional bias may be related to drug-seeking behavior, although the evidence for this is limited at present. The evidence for an association, and mutual causal relationship, between attentional bias and subjective craving is much more compelling. Given that some investigators (e.g., Tiffany 1990; cited in Field and Cox 2008) believe subjective craving to be of little relevance to drug-seeking behavior itself, it remains to be seen whether attentional bias could have a clinically meaningful role in the prediction of treatment outcome in drug abusers, or whether it is a suitable target for treatment.

Pharmacological Modulation

The effects of a variety of pharmacological challenges on attentional bias have been studied. Firstly, administration of small to moderate doses of alcohol seems to increase attentional bias for alcohol- and smoking-related cues in heavy drinkers and tobacco smokers, respectively (see Field and Cox 2008). Alcohol affects a variety of neurotransmitter systems, but its direct effects are to increase ▶ GABA activity and reduce ▶ glutamate activity, which then has knock-on effects on other neurotransmitter systems, such as ▶ dopamine and ▶ serotonin. The precise mechanism of action through which alcohol increases attentional bias is unclear, but it may be related to some of the other effects of alcohol priming doses, such as increased craving or a decreased ability to regulate attention. Investigators have also increased or decreased dopamine and serotonin function before examining the effects on attentional bias (reviewed in Munafo and Albery 2006). In one study, ▶ Haloperidol, a dopamine antagonist, was seen to eliminate Stroop interference produced by heroin-related words in heroin addicts. In another study, researchers depleted dopamine levels by administering an amino acid mixture which was devoid of the amino acids tyrosine and phenylalanine, which are required for dopamine synthesis. Compared to a control manipulation (consumption of an amino acid mixture that did not deplete tyrosine and phenylalanine), this led to reduced Stroop interference for smoking-related words in tobacco smokers. However, these effects were not particularly robust, as they were only seen in female participants, but not in males. In a further study, researchers replicated this effect of tyrosine depletion on Stroop interference, but again the effects were not robust: in this study, effects were moderated by the sequence in which participants consumed the two different amino acid mixtures.

So, there is emerging evidence that a dopaminergic mechanism is involved in attentional bias, with manipulations that reduce dopamine function leading to a reduction or abolition of attentional bias in tobacco smokers and heroin users. This is very important theoretically because it is consistent with the dopamine sensitization theory of addiction, which was discussed previously (Robinson and Berridge 1993; see Field and Cox 2008). To briefly recap, according to the theory, chronic drug use leads to sensitization of dopamine function in the nucleus accumbens and interconnected structures, which leads to an increase in the "salience" of drug-related cues. As predicted by the model, pharmacological manipulations that reduce dopamine function seem to reduce the salience of drug-related cues, i.e., they reduce attentional bias. However, dopamine is unlikely to be the only neurotransmitter involved. One group of investigators were able to increase Stroop interference for smoking-related words in tobacco smokers by depleting levels of ▶ typtophan, an amino acid required for the synthesis of serotonin (5-HT). So, although the evidence is limited, different neurotransmitter systems may have conflicting roles in attentional bias, with some (e.g., dopamine) increasing it and others (e.g., serotonin) reducing it. Finally, we note

that these pharmacological challenge studies used the addiction Stroop task to measure attentional bias. Given that it is difficult to accurately characterize the roles of selective attention versus other cognitive processes (e.g., generic slowdown, thought suppression) in the production of Stroop interference, future researchers should explore the effects of pharmacological challenges on other, more direct measures of attentional bias, such as eye movement monitoring or ERPs.

Cross-References

► Attention
► Classical (Pavlovian) Conditioning
► Event-Related Potentials

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Attentional Effect

Definition

Attentional effect refers to the immediate effect of a drug on the allocation of cognitive resources required for timing. These effects are reflected, for example, in the alteration of the delay in responding that follows a retention interval. Should subjects pay more attention to timing, they would be able to stop timing during the delay and resume timing afterward with little or no loss of accumulated time prior to the interruption. Should subjects pay less attention to timing, they would not be able to stop timing during the delay, and they will restart (reset) timing afterward. In the PI procedure with gaps, an attentional effect is observed by an immediate shift in the response function in trials with gaps (retention intervals), indicative of more or less attention paid to the timing task (see Buhusi 2003).

Attentional Learning

► Blocking, Overshadowing and Related Concepts

Attentional Retraining Intervention

Definition

Attentional retraining interventions involve procedures that are designed to assist individuals in maintaining, focusing, redirecting, and dividing attention. Extrapolated from neuropsychological testing and interventions, attentional retraining utilizes auditory and/or visual stimuli to isolate different areas of attention. Through repeated completion of specific tasks, attentional retraining can lead to increased overall attention, reduced distractibility, and increased ability to shift attention. In relation to drug effects, attentional retraining interventions are designed to redirect automatic attentional bias in order to lessen the impact of drug-related cues. By redirecting attention, these interventions decrease distractibility from drug cues and subsequently disrupt the activation of drug-seeking behavior.

Cross-References

► Attentional Bias to Drug Cues
► Expectancies and Their Influence on Drug Effects

Attentional Set

Definition

Attentional set refers to the bias to attend to restricted perceptual aspects of the environment. Organisms learn to attend to the sensory features and responses that are relevant to performing a task and ignore the features and responses that are irrelevant. When certain features and responses retain their relevance across tasks, an

"attentional set" may develop that bias perception and responses and increases the speed of learning new tasks as long as those features and responses remain relevant.

Atypical Antipsychotic Drugs

Synonyms
Second- and third-generation antipsychotics

Definition
All conventional antipsychotics (also called first-generation antipsychotics) share the central property of dopamine 2 receptor antagonism and, in association with this property, can cause extrapyramidal side effects (EPS). Atypical antipsychotics are so-called because they generally have a lower propensity to cause EPS than the older agents; the exact reason for this is unknown but is believed to be due to the fact that these agents have the additional property of 5HT2A antagonism and/or dopamine 2 partial agonism (as opposed to antagonism).

Cross-References
- ▶ Antipsychotic Drugs
- ▶ Bipolar Disorder in Children
- ▶ Schizophrenia

Atypical Autism

- ▶ Pervasive Developmental Disorder Not Otherwise Specified

Atypical Depression

Definition
A form of depression that is characterized by the presence of mood reactivity (responsiveness to positive events) and two or more of the following: significant weight gain or an increase in appetite, hypersomnia (oversleeping), leaden paralysis, and significant social/occupational impairment resulting from a long-term pattern of sensitivity to interpersonal rejection. Exclusionary criteria include depression with melancholic or catatonic features. Patients with atypical depression are often responsive to MAOIs.

Cross-References
- ▶ Antidepressants
- ▶ Monoamine Oxidase Inhibitors

AUC

- ▶ Area Under the Curve
- ▶ Distribution
- ▶ Pharmacokinetics

AUD

- ▶ Alcohol Abuse and Dependence

Augmentation

Definition
Pharmacological strategy to enhance a therapeutic effect.

Aurorix

- ▶ Moclobemide

Autism

Synonyms
Autistic disorder

Definition
Autism is defined by impairment in social interactions and communication, along with restricted repetitive and stereotyped patterns of behavior, interests, and activities. Delays in social interaction, language, or imaginative play must be noted before the age of 3 years.

Cross-References
- ▶ Autism Spectrum Disorders and Mental Retardation

Autism: Animal Models

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Synonyms
Rodent models of autism

Definition

Autism is a neurodevelopmental disorder characterized by impairments in social interaction, verbal and nonverbal communication, and restricted, repetitive, and stereotyped patterns of behavior, interests, and activities appearing before the age of three (American Psychiatric Association 1994). Its clinical manifestations and severity of impairments vary from mild to severe. The core symptoms are frequently accompanied by a spectrum of neurobehavioral derangements, including: hyperactivity, aberrant sensitivity to sensory stimulation, anxiety, mental retardation, seizures, self injury, sleep disturbances, and upset to change in routine. The etiology of autism is thought to involve an interaction between genetic susceptibility, mediated by multiple genes, and environmental factors. Epidemiological studies find a four times higher incidence of autism in boys than in girls. Because the primary diagnostic criteria of autism are abnormal behaviors, rather than biochemical or neuroanatomical factors, the use of animal models in the study of autism is unavoidable, as this is the only way to study behavioral defects in context of a whole organism.

Current Concepts and State of Knowledge

Concepts for In Vivo Modeling

There is an ongoing discussion about the criteria to be used in the evaluation of animal models. It has been suggested that the only meaningful initial evaluating criterion for an animal model is its ability to lead to accurate predictions (predictive validity). Other authors stressed that the demonstration of construct validity (similarity to the underlying causes of the disease) represents the most important and necessary component in validation of an animal model. Others claim that the modeling of symptoms (face validity) must remain the primary goal of animal models of psychiatric disorders. The resolution of this puzzling controversy depends on the desired purpose of the model that one wishes to validate. Although, regarding complex psychiatric disorders such as autism, a multidimensional approach should be used as an optimal strategy.

Challenges for Animal Models of Autism

In recent years, several rodent models of autism have been developed that reflect some behavioral, genetic, and neuroanatomical alterations associated with this disorder. One of the main problems for the development of a relevant model is to define markers of autism, addressing its complexity and diversity. An ideal rodent model of autism should display symptoms of aberrant social interaction and communication, as well as repetitive behaviors. Tasks that could examine these behavioral symptoms in rodents have been already developed and are summarized in Table 1. However, an animal model of autism based solely on behavioral assays would be incomplete. Animal model should also address a combination of the neuropathological, biochemical and genetic factors implicated in autism. Another challenge lies in the fact that many clinical hallmarks of autism are difficult or almost impossible to replicate in rodents, e.g., theory of mind (ability to intuit the feelings and intentions of others) or speech deficits. It is also important to realize that assumed "core" psychopathological phenomena observed in autism are present as common clinical features in schizophrenia, depression, obsessive-compulsive disorder and other medical and psychiatric illnesses. What is specific for autism is a pattern of socio-behavioral aberrations and their appearance before the age of three, and animal models should try to address this fact.

Behavioral Tests for Autistic-Like Aberrations in Rodents

As an important prerequisite, it is necessary to use appropriate behavioral test batteries for the validation of an animal model of autism. The three core symptoms of autism should be targeted first:

1. Impairment in social interaction is a critical component for such models. Rodents are highly social animals displaying a plethora of different social behaviors. The propensity of animals to spend time with conspecific rather than non-social novel objects shall be used as one of the measures. This can be best done in an automated three-chambered apparatus in which social interactions, social recognition, and social memory can also be scored (Crawley 2007). Measures of the level of social approach should be accompanied by more specific analyses of reciprocal social interactions, including, nose-to-nose contacts, anogenital inspections, aggression, escape behavior, nesting patterns, juvenile rough and tumble play, etc.
2. Impairments in social communication may be meaured in rodents using olfactory and auditory communication tasks. Different kinds of ► ultrasonic vocalizations can be elicited in rodents, starting from separation calls in pups isolated from their mothers, to frequency modulated vocalizations in social situations in adult animals, treated, at least in rats, as indicators of positive and negative affective states (Portfors 2007). Both frequency and time structures of ultrasonic vocalizations should be analyzed. Olfactory social signals, including deposition of ► pheromones,

Autism: Animal Models. Table 1. Rodent behavioral tasks relevant to autism (for references see Crawley 2007).

Tests analogous to core autistic symptoms	Tests analogous to associated symptoms
1. Impairment in social interactions • Reciprocal social interactions (partner grooming, nose-to-nose contacts, anogenital inspections, aggression, escape behavior, juvenile rough and tumble play etc.) • Propensity to spend time with conspecific vs. novel objects • Conditioned place preference to conspecifics • Preference for social novelty • Aggression (resident-intruder test) • Social recognition • Nesting patterns in the home cage 2. Impairments in social communication • Behavioral responses to social olfactory cues from conspecifics • Deposition of social olfactory pheromones • Vocalizations emitted during social interactions • Responses to vocalizations from conspecifics • Parental retrieval of separated pups • Ultrasonic vocalizations by separated pups 3. Repetitive, stereotyped patterns of behavior, interests, and activities • Motor stereotypies • Extinction of a learned response in an operant chamber • Reversal of a position habit in an appetitive T-maze task, aversive Y-maze task or the Morris water maze • Spontaneous responses to errors during reversal tasks	1. Anxiety: elevated plus maze; light-dark box exploration; Vogel conflict licking test; marble burying 2. Theory of Mind deficits: location of buried food following observation of conspecifics; social transmission of food preference; avoidance of aggressive encounters 3. Cognitive aberrations: acquisition of different maze tasks; operant learning tasks; attentional measures in the five choice serial reaction time task; contextual and cued fear conditioning; discriminative eyeblink conditioning and reversal 4. Seizure susceptibility: spontaneous seizure activity; sensitivity to audiogenic and drug-induced seizures 5. Motor clumsiness: balance beam foot slips; rotarod motor coordination and balance; gait analysis 6. Sleep disturbances: circadian running wheels; home cage sleep and activity patterns 7. Responses to sensory stimuli: acoustic startle; tactile startle; hot plate; Von Frey filaments; unresponsiveness to sensory attentional cues (failure to disengage attention) 8. Developmental progression: maturational and developmental milestones; brain weight and volume; size of structures

are another form of rodent communication (Arakawa et al. 2008). Rodents' chemical signals play a particularly important role in determining social dominance and intersexual relationships.

3. Finally, repetitive behavior encompasses both motor stereotypy and self-injury, can be scored using standardized scales, and behaviors reflecting general cognitive rigidity, such as ability to change, resistance to change, and responses to the change in routine can be investigated by exploratory choices and reversal tasks using spatially contingent reinforcers, e.g., reversal learning in T-maze or water maze.

Because autism is accompanied by a plethora of neurobehavioral aberrations, it is important to include a range of additional behavioral tasks assessing, e.g., anxiety, seizure susceptibility, sleep patterns, sensitivity to sensory stimuli, learning and memory, and maturation and development. Finally, both pathological features of autism (e.g., decreased number of Purkinje cells) and biological findings (e.g., increased serotonin levels) should be addressed.

Current Animal Models of Autism

More than a dozen of different rodent models of autism are currently used. They can be classified into three categories: (1) models created by neonatal lesions of brain areas shown to be abnormal in autism, e.g., cerebellum, the ► amygdala, ► hippocampus, or the medial ► prefrontal cortex; (2) models mimicking environmental factors that increase the risk for autism in humans, e.g., prenatal exposure to ► valproic acid (VPA) or pre- and neonatal immunological challenges; and (3) ► genetically modified animals, e.g., targeted mutations in genes associated with autism or localized in chromosomal regions identified by linkage analyses.

Lesion Induced Models

The exact locus of brain dysfunction in autism remains a point of debate (Bauman and Kemper 2005). Many brain regions, ranging from brainstem and cerebellum to association areas of the neocortex, have been suggested as potential candidates. Nevertheless, converging lines of evidence suggest that dysfunctions and morphological abnormalities in the medial temporal lobe, especially

amygdala, and the prefrontal cortex (PFC) might underlie social deficits in autism. On that basis several models of autism have been proposed (Tordjman et al. 2007). For example, neonatal ibotenic acid lesion of the amygdala on PND 7 in rat produces a spectrum of behavioral abnormalities resembling those described in autism: decreased social interaction, increased stereotypic-like activity and decreased exploratory behavior. Similarly, neonatal ventral hippocampus lesion in rats leads to impaired social behaviors, motor hyperresponsiveness to stress, enhanced stereotypies, deficits in pre-pulse and latent inhibitions, and working memory problems. Rats with neonatal PFC lesions display reduced social play and non-play behavior in early adolescence, and reduced amount of self-grooming in adulthood. However, as these injuries destroy entire brain regions they have little relationship to the mild neuroanatomical pathologies observed in autism. Furthermore, abilities to investigate genetic or developmental mechanism in such models are very limited.

Models Created by Environmental and Immune Factors

An exposure during embryogenesis to at least three teratogens appears to be a risk factor for autism: ► thalidomide, VPA, and ► misoprostol (Arndt et al. 2005). Accordingly, one of the best validated animal models of autism is induced by prenatal exposure to VPA on the twelfth day of gestation (reviewed in Markram et al. 2007). VPA rats show several brainstem and cerebellar abnormalities resembling those found in autistic patients. At the behavioral level, VPA rats exhibit decreased social interactions, increased repetitive behaviors, enhanced anxiety, locomotor hyperactivity combined with lower exploratory activity, lower sensitivity to pain, higher sensitivity to non-painful sensory stimulation, impaired pre-pulse inhibition, and faster acquisition of eye-blink conditioning. Interestingly, behavioral aberrations described in VPA rats are observed mostly in males and can be reversed by ► environmental enrichment procedure. These might resemble both disproportion in boys to girls ratio in autism and efficacy of early behavioral-cognitive intervention in some patients with autism. VPA rats express also molecular and immunological aberrations resembling those observed in autism, e.g., increased serotonin level in several brain structures and ► hyperserotoninemia, increased frontal cortex dopamine level, enhanced excitatory transmission, and decreased cellular immune response.

Another factor implicated in the pathogenesis of autism is disturbed functioning of the immune system, especially pre- and/or neonatal immunological challenge. The best characterized model of autism utilizing this approach is induced by neonatal Borna disease virus (BDV) infection in rat (Pletnikov et al. 2005). Infected animals have injured cerebellum, progressive loss of Purkinje cells and dentate gyrus neurons, and cortical shrinkage. Neonatal BDV infection induce abnormal social interaction and communication, increased emotional reactivity, reduced cognitive abilities in spatial memory and learning, hyperactivity, stereotypies, and decreased startle responsiveness. These abnormalities mimic the impaired social interaction and atypical responses to sensory and emotional stimuli characteristic in autism. Similarly, mouse prenatally exposed to maternal infection or inflammation also displays autistic-like phenotype, including deficiencies in social interaction, exploration and sensorimotor gating. The disadvantage of infection models is that they lead to a persistent infection of the brain precluding more precise characterization of the time course and structural specificity of the created neuronal aberrations.

Genetically Induced Models

To date, several genetically induced mouse models of autism have been proposed (Moy and Nadler 2008). They were created using three general approaches. One approach is to induce mutations in genes regulating social behavior. For example, oxytocin gene knockout pups display reduced exploration, less separation distress calls, and later on a diminished social recognition. Reduced social interaction and decreased exploration were also observed in serotonin transporter-null mice.

A second approach uses monogenic aberrations, such as loss of Fmr1 or methyl-CpG-binding protein-2 (Mecp2) function, that underlie syndromes associated with autistic-like behavior. The Fmr1-null mice display increased levels of social anxiety, reduced social interaction, hyperactivity, and deficits in spatial and reversal learning. Interestingly, exposure to an enriched environment can reverse some behavioral deficits in this model. The Mecp2-null mice show deficits in social behavior, hypoactivity, impaired learning and memory, and increased anxiety.

A third approach uses gene mutations relevant to loci for autism susceptibility, identified by association or linkage studies. For example, $Reln^{rl/+}$ mice show lower rates of separation distress calls, impairments in reversal learning, increased anxiety, decreased pre-pulse inhibition, and a progressive loss of Purkinje cells. Similarly, Gabrb3 gene deficient mice exhibit impaired social and exploratory behaviors, deficits in non-selective attention and hypoplasia of cerebellar vermal lobules. Another example, mutants of genes regulating synaptic function may show highly specific deficits in social interaction, like mouse with a loss-of-function mutation in X-linked Nlgn4, or a

combination of symptoms, including social deficits, hyperactivity, reduced spatial learning, impaired motor coordination, smaller cerebellum and reduced numbers of Purkinje neurons, like En2-null mice. An important drawback of a targeted gene disruption in animal models of autism is that the null allele is not what is normally observed in humans, and that autism, as a polygenic disorder, is probably a result of an interaction of several dozens of genes.

Conclusions

The advantage of animal models of autism is to study developmental and behavioral deficits in context of a whole organism. We can use such models to clarify complex relationships between genetic, behavioral and environmental variables to better understand and potentially cure autism. What we need now is to combine these different approaches into multidisciplinary studies determining the consequences of environmental factors (e.g., stress, teratogenic substances, enriched environment) on the development of autistic-like behavioral changes in genetically modified animals, and *vice versa*, to determine the genetic basis of negative and positive effects of environmental factors in animal models. It is also critical to facilitate the process of identifying reliable measures of the human phenomenon, as better understanding of the neuropathology of autism will be essential to continue to build and improve animal models in the future.

Cross-References

- ▶ Animal Models for Psychiatric States
- ▶ Antinociception Test Methods
- ▶ Anxiety: Animal Models
- ▶ Autism Spectrum Disorders and Mental Retardation
- ▶ Behavioral Flexibility: Attentional Shifting, Rule Switching, and Response Reversal
- ▶ Construct Validity
- ▶ Distress Vocalizations
- ▶ Elevated Plus-Maze
- ▶ Face Validity
- ▶ Genetically Modified Animals
- ▶ Open Field Test
- ▶ Operant Behavior in Animals
- ▶ Phenotyping of Behavioral Characteristics
- ▶ Prepulse Inhibition
- ▶ Rodent Models of Cognition
- ▶ Schizophrenia: Animal Models
- ▶ Short-Term and Working Memory in Animals
- ▶ Social Interaction Test
- ▶ Social Recognition and Social Learning
- ▶ Social Stress
- ▶ Spatial Learning in Animals
- ▶ Thalidomide
- ▶ Valproic Acid

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Autism Spectrum Disorders and Mental Retardation

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Synonyms

Amentia; Autism spectrum disorders; Intellectual disability; Mental deficiency; Mental retardation; Oligophrenia; Pervasive developmental disorders

Definition

Autism Spectrum Disorders

Autism spectrum disorders (ASDs) are a group of neurodevelopmental disorders that involve qualitative

impairments in social interaction and communication, and restricted repetitive and stereotyped patterns of behavior (► stereotypical and repetitive behavior), interests and activities. The ASDs include ► autism or autistic disorder, ► Asperger's disorder, and ► pervasive developmental disorder not otherwise specified (PDD NOS). The category of ► Pervasive Developmental Disorders (PDDs) is broader and also includes ► Rett's disorder and ► childhood disintegrative disorder. All these disorders cause significant impairment in functioning.

Mental Retardation

Mental retardation (MR) is described as an IQ of 70 or below, age of onset less than 18 years, and deficits in at least two of the following areas: communication, self-care, home living, social/interpersonal skills, use of community resources, self-direction, functional academic skills, work, leisure, health, and safety. The severity of MR is based on intellectual impairment. Mild MR is described as an IQ of 50–55 to 70, moderate MR 35–40 to 50–55, severe MR 20–25 to 35–40, and profound MR below 20–25 (American Psychiatric Association 2000).

Role of Pharmacotherapy

Autism Spectrum Disorders

In ASDs, there are several symptom domains, some core and some associated, that are common targets of pharmacological therapy. These domains are frequently seen in individuals with ASDs and may interfere with their ability to adapt and function. Among others, these symptom domains include motor hyperactivity and inattention, interfering stereotypical and repetitive behavior, aggression and self-injurious behavior (SIB), and core ► social impairment. We will not discuss all possible pharmacotherapies for ASDs in this entry. For example, mood, anxiety, and sleep disorders are often treated with drugs in individuals with ASDs. However, due to a paucity of randomized controlled trials (RCTs) in these areas, they will not be reviewed.

Although the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition – Text Revision (DSM-IV-TR) precludes individuals with ASDs from being diagnosed with attention-deficit/hyperactivity disorder (ADHD) (American Psychiatric Association 2000), symptoms of hyperactivity, distractibility, and motor restlessness are common in this population. Stimulants such as the norepinephrine reuptake inhibitor ► atomoxetine, and alpha2 adrenergic agonists have all been used to treat these symptoms in individuals with ASDs. Stimulants are the treatment of choice for typical developing children with ADHD. Early trials of stimulants in ASDs concluded they were not effective in this population. Several newer RCTs have suggested that stimulants may in fact be helpful, to some extent, for this group of symptoms in ASDs. A recent RCT sponsored by the National Institute of Mental Health (NIMH) on children with ASDs found that 49% of the subjects responded to ► methylphenidate; 18%, however, discontinued the drug due to adverse events. It was concluded that children with ASDs, compared with typically developing children diagnosed with ADHD, have a decreased response rate and an increased likelihood of side effects when prescribed methylphenidate (McDougle et al. 2006).

Clonidine and guanfacine are two alpha-2 adrenergic agonists that have been studied to treat ADHD symptoms in ASDs (Stigler et al. 2008). Clonidine was investigated in two small, controlled trials in individuals with autism. The results of one study yielded improvement on both a teacher and parent rating scale, but not a clinician rating scale. The other study of transdermal clonidine noted significant improvement in hyperactivity and anxiety. Side effects included sedation, hypotension, irritability, and fatigue.

Guanfacine requires less frequent dosing, may be less sedating and decreases the chance of rebound hypertension due to a longer half-life than clonidine (McDougle et al. 2006). RCTs of guanfacine have not yet been performed in ASDs. However, a systematic review of 80 patients with these disorders found improvement in hyperactivity, inattention, and impulsivity, with a response rate of 24%. Overall, participants tolerated guanfacine well and no significant changes in vital signs were noted (Stigler et al. 2008).

Repetitive thoughts and behaviors (stereotypical and repetitive behavior) are a core component of the ASDs (McDougle et al. 2006). These repetitive phenomena can be intrusive and interfere with day-to-day functioning. Due to the success of treating the repetitive thoughts and behaviors of obsessive–compulsive disorder with serotonin reuptake inhibitors (SRIs), studies have been performed with these agents in ASDs. Controlled trials of ► clomipramine, ► fluvoxamine, and ► fluoxetine have been published. Treatment effects on this symptom domain have also been assessed in controlled trials of the antipsychotics ► haloperidol and ► risperidone in individuals with ASDs.

Clomipramine has been evaluated in individuals with PDDs in multiple open-label and two controlled studies (Stigler et al. 2008). Both of the controlled trials found the drug to be superior to placebo. However, side effects were a significant problem and included the prolongation of the

cardiac QTc interval, tachycardia, grand mal seizure, sedation, and tremor.

Results of three double-blind, placebo-controlled studies of fluvoxamine have yielded mixed results (Stigler et al. 2008). It appears that adults with ASDs are better able to tolerate this drug than young children. Side effects included sedation, nausea, hyperactivity, insomnia, aggression, agitation, and behavioral activation.

There have been multiple open-label and two controlled trials published with fluoxetine (Stigler et al. 2008). The drug was generally found to be effective in the majority of open-label trials and superior to placebo in the two placebo-controlled trials. Side effects included aggression, hyperactivity, and decreased appetite.

RCTs of haloperidol and risperidone have both shown efficacy in decreasing stereotypic behavior (► stereotypical and repetitive behavior) in subjects with ASDs (McDougle et al. 2006).

The overall findings of these studies concluded that prepubertal children with ASDs may not respond to or tolerate SRIs as well as postpubertal adolescents or adults with these disorders (McDougle et al. 2006). There are several factors that could contribute to this. It may be that changes in the serotonin system over the course of development in individuals with ASDs could influence their ability to tolerate and respond to SRIs.

Irritability that can be manifested as aggression, SIB, or severe tantrums is another target symptom domain associated with ASDs that can be amenable to pharmacological management (Stigler and McDougle 2008). The ► atypical antipsychotics are emerging as first-line agents for this purpose. Other classes of drugs that have been studied include typical ► antipsychotics, ► anticonvulsants, and ► mood stabilizers.

Early studies found haloperidol effective for treating maladaptive symptoms in children with ASDs (Stigler and McDougle 2008). However, significant side effects were noted with this drug, including dystonic reactions and dyskinesias (especially on withdrawal of the drug). Due to its side effect profile, haloperidol is normally limited to treatment-refractory patients.

The atypical antipsychotics have replaced the typical antipsychotics as the first-line treatment for irritability in ASDs due to their decreased propensity for dyskinesias and extrapyramidal symptoms (EPS) (Stigler and McDougle 2008). ► Clozapine, ► risperidone, ► olanzapine, ► quetiapine, ► ziprasidone, and ► aripiprazole all have published reports of their use in the ASDs.

There are only three published reports of clozapine in the ASD population describing a total of five patients (Stigler and McDougle 2008). All showed significant improvement with clozapine. The paucity of reports is likely due to clozapine's potential to cause agranulocytosis, its ability to lower the seizure threshold, and the need for weekly to biweekly venipuncture.

Risperidone is a well-studied drug for the treatment of irritability in ASDs (Stigler and McDougle 2008). Multiple case series, open-label trials and double-blind placebo-controlled studies have found risperidone to be effective for treating irritability in individuals with ASDs. Due in part to the results of two RCTs demonstrating the efficacy and tolerability of risperidone for the treatment of irritability in children and adolescents with autism aged 5–16 years, it was approved by the US Food and Drug Administration (FDA).

Olanzapine has been studied in several open-label trials and one small placebo-controlled trial (Stigler and McDougle 2008). It has been shown to be effective for irritability and behavioral symptoms of autism. Side effects noted in the studies included increased appetite and often significant weight gain.

Four open-label reports of quetiapine have been published involving the treatment of ASDs (Stigler and McDougle 2008). The results have been mixed. Side effects reported included increased appetite, weight gain, sedation, agitation, aggression, and sialorrhea.

Two different open-label trials with ziprasidone reported it to be effective in treating irritability and aggression in individuals with ASDs (Stigler and McDougle 2008). Side effects included transient sedation, a clinically insignificant increase in the QTc interval and dystonic reactions. There is an FDA warning regarding the use of ziprasidone in relation to its potential to increase the cardiac QTc interval. It should not be given without consultation with a cardiologist to individuals with a known cardiac history, a long QT syndrome or in those taking other medications that can prolong the QTc interval.

Two open-label studies and one retrospective chart review found aripiprazole to be effective for treating irritability in individuals with ASDs (Stigler and McDougle 2008). Adverse events included transient sedation and weight gain (greater in individuals less than 12 years of age).

Mood stabilizers and anticonvulsants have also been used to treat irritability in ASDs (Stigler and McDougle 2008). Reports have been published for the use of ► lithium, divalproex sodium, ► lamotrigine, ► topiramate, and levetiracetam. However, RCTs supporting the use of mood stabilizers and anticonvulsants for the treatment of irritability in ASDs have not been published. The current literature suggests that atypical antipsychotics are more effective for the treatment of this symptom domain in

ASDs than mood stabilizers or anticonvulsants. Only one report has appeared demonstrating the effective use of lithium in one individual with autism that had significant irritability.

One open-label and one double-blind, placebo-controlled study have been published with divalproex sodium (Stigler and McDougle 2008). The open-label study determined divalproex to be effective. However, the double-blind, placebo-controlled trial found no significant difference between the two groups in irritability after 8 weeks. Adverse events included sedation, weight gain, behavioral activation, hair loss, elevated liver enzymes, increased appetite, skin rash, and hyperammonemia.

A double-blind, placebo-controlled study of lamotrigine did not find a significant difference between drug and placebo on several standardized outcome measures (Stigler and McDougle 2008).

One published report on the use of topiramate in five youths with autism and treatment-refractory severe behavioral problems found most children able to tolerate the drug but did not show notable improvement (Stigler and McDougle 2008).

One double-blind, placebo-controlled study of levetiracetam has been performed in 20 children and adolescents with autism to assess its efficacy in treating aggression and affective instability (Stigler and McDougle 2008). No difference was found between the drug and placebo groups. Adverse events included agitation and aggression.

One fundamental core deficit in ASDs is social impairment that is severe and persistent (McDougle et al. 2006). Social impairment can be seen through deficits in nonverbal behavior, for example, eye contact, facial expression, and body gestures. These children often fail to develop age appropriate relationships. They also may not seek to share achievements or enjoyment with others. Initially, preliminary reports of fenfluramine and naltrexone to treat social impairment were encouraging. However, subsequent placebo-controlled studies of these drugs failed to show any difference between groups for this core symptom deficit.

There has been consideration that ▶ glutamate may have a role in the pathophysiology and treatment of autism (McDougle et al. 2006). Thus, several drugs that affect the glutamate system have been studied for treating the social impairment seen in ASDs.

Two case reports described an improvement in autistic patients' social impairment after being prescribed lamotrigine, an anticonvulsant that slows glutamate release (McDougle et al. 2006). However, a double-blind, placebo-controlled study of lamotrigine in 28 children with autism failed to show a difference between drug and placebo.

▶ Amantadine, an antagonist at the *N*-methyl-D-asparate (▶ NMDA) subtype of glutamate receptor, has also been studied in autism (McDougle et al. 2006). An initial open-label study showed improvement in half the children given the drug. However, a double-blind, placebo-controlled trial failed to show a difference based on a parent rating scale. A clinician rating scale showed significant improvement in hyperactivity and inappropriate speech.

D-cycloserine is an antibiotic used to treat tuberculosis (McDougle et al. 2006). It is a ▶ partial agonist at the NMDA receptor. A small pilot study showed a statistically significant improvement on the Aberrant Behavior Checklist (ABC) Social Withdrawal subscale. Adverse events included transient motor tics and increased echolalia.

Research in the pharmacotherapy of ASDs will continue to pursue treatment for the core and associated symptoms related to this condition. Many individuals with ASDs have interfering symptoms in multiple domains. Thus, coactive pharmacological treatment strategies, involving concomitant treatment with more than one drug at a time, will be a future area of research (Stigler et al. 2008).

Mental Retardation

In the past, there was a belief that individuals with MR could not have co-occurring mental illness. It is now widely accepted that these patients develop such comorbidity at a higher rate than the normal population. Most studies estimate the prevalence of mental illness in the MR population at between 30 and 70% (Szymanski and King 1999). Approximately 20–45% of individuals with MR are prescribed psychotropic medications (Deb et al. 2007). All DSM-IV-TR diagnostic categories are potentially represented in these patients. However, the evaluation and diagnostic determination can be difficult due to inherent limitations, including communication deficits, physical limitations (Szymanski and King 1999), and lack of collateral information regarding the patient and their environment (Madrid et al. 2000). Additionally, due to a lack of capacity to give informed consent, there are relatively few RCTs in individuals with MR (Deb et al. 2007). This leads clinicians to base treatment decisions on a few well-designed investigations or to use studies in individuals without MR to guide treatment (Madrid et al. 2000).

Common reasons for pharmacologic referrals of patients with MR include SIB, aggressive behavior, impulsiveness, and hyperactivity. These symptoms are nonspecific and can be the result of anything from a medical illness to a mood, anxiety, psychotic or impulse control disorder. The context surrounding the onset of symptoms,

associated symptoms, and environmental changes can all be clues to the diagnosis. If there are associated sleep and appetite changes, a mood disorder may be considered. If the symptoms occur only in certain environments, then a psychotic or mood disorder is less likely. If the symptoms are of sudden onset, a medical illness may be contributing to the presentation (Madrid et al. 2000).

The MR population is two times more likely to suffer from a medical disorder than other mental health populations. One study showed 75% of the referrals for psychiatric assessment had undertreated or undiagnosed medical illnesses. In addition, psychiatric symptoms can be caused by several medical illnesses (Szymanski and King 1999). Thus, it is always important to consider a medical illness as a cause of psychiatric symptoms in the differential diagnosis of individuals with MR.

Screening assessments can be used to identify individuals with MR who need psychiatric referral. Some of these instruments can also be used for determining and evaluating symptoms over the course of treatment. The more commonly used scales in the MR population include the Reiss Screen for Maladaptive Behavior, the Reiss Scales, the Psychopathology Inventory for Mentally Retarded Adults (PIMRA), the ABC, and the Diagnostic Assessment for Dual Diagnosis (Madrid et al. 2000; Szymanski and King 1999).

Anxiety disorders can be difficult to diagnosis in MR individuals because of the necessity of subjective complaints. However, by observing patients, symptoms such as avoidance, autonomic arousal, psychomotor agitation, or irritability can help to clarify the diagnosis (Madrid et al. 2000). Specifically, posttraumatic stress disorder should be considered in the differential diagnosis. Individuals with MR are an inherently vulnerable population; they have difficulty reporting events and often want to please their caretaker (Szymanski and King 1999).

Psychotic disorders should be considered in individuals with MR that present with observable hallucinations such as yelling or hitting at empty space, catatonic posturing that appears psychotic in nature, negative symptoms or grossly disorganized behavior. Imaginary friends should not be confused with psychosis (Madrid et al. 2000; Szymanski and King 1999).

Mood disorders are common in individuals with MR. They can be diagnosed when there is a significant change in the baseline affective state. Observations of change in sleep, activity level, and appetite can be obtained from caretakers to help to confirm the diagnosis. Mood disorders can also present atypically in this population. Sometimes aggressive behavior can be a symptom of depression. This is sometimes termed "► behavioral equivalent" in the literature. A recent change in the environment, death of a family member, rejection, or abuse can also cause depression in the MR population (Hurley 2006; Madrid et al. 2000; Stigler et al. 2005).

► Disorders of impulse control may be considered one of the most common justifiable indications for psychotropic use in the MR community. The three most common behaviors include SIB, stereotyped behavior (stereotypical and repetitive behavior), and aggressive behaviors (Szymanski and King 1999). Studies indicate that 14–30% of the MR population receiving psychotropics are prescribed them for these types of behavior problems (Deb et al. 2007).

Pharmacotherapy in the MR population should only be a part of the overall treatment plan. The lowest possible dose of drug that is effective for the patient should be used and should not adversely affect the individual's ability to function. Drug treatment should follow the adage "start low, go slow." Certain drugs are more likely to cause side effects in MR individuals. Some of these patients seem to be more sensitive to the disinhibiting effects of ► benzodiazepines. There has been some evidence to suggest that the combination of stereotypy (stereotypical and repetitive behavior) and SIB may be a significant risk factor for benzodiazepine-induced disinhibition. There is also the potential for benzodiazepines to cause hyperactivity, SIB, or withdrawal-induced manic symptoms in the MR population. Individuals with compromised central nervous system function may be more sensitive to drugs with anticholinergic side effects, as well (Madrid et al. 2000; Szymanski and King 1999).

Antipsychotics are often used in the MR population to target aggressive or stereotyped behavior (stereotypical or repetitive behavior) and SIB, but can also be given for psychotic symptoms. Careful attention to side effects of these drugs should be paid. Patients with MR are more susceptible to tardive dyskinesia, withdrawal irritability, and EPS than other mental health populations. This is one of the reasons for the increasing trend of using atypical antipsychotics over typical antipsychotics (Madrid et al. 2000; Szymanski and King 1999). The RCTs that do exist have demonstrated the efficacy of risperidone for aggressive behavior in individuals with MR. However, most studies found side effects of weight gain and somnolence. To date, studies have not systematically reviewed adverse metabolic issues arising from risperidone. Evidence for the use of the other atypical antipsychotics in the adult MR population is mostly based on case studies. Short follow-up periods were used in these trials, making it difficult to know if the drugs would provide sustained

behavioral effects. In addition, several studies used the antipsychotics as add-on therapy (Deb et al. 2007).

► Antidepressants are used to treat depressive symptoms in individuals with MR as in the general population (Madrid et al. 2000; Stigler et al. 2005). ► Selective serotonin reuptake inhibitors (SSRIs) are frequently the first-line pharmacotherapy for individuals with MR due to their tendency to cause fewer side effects. Tricyclics are not used as often due to their side-effect profile of potentially lowering the seizure threshold, cardiac arrhythmias, and cognitive dulling. However, to date, there have been no published RCTs of antidepressants supporting their use for the treatment of depression in patients with MR (Stigler et al. 2005). One retrospective chart review of treatment with an SSRI or clomipramine for aggression, SIB, destructive/disruptive behavior, and depression/dysphoria showed a significant decline in these symptoms. This study gives support to "behavioral equivalents" being used as signs/symptoms of depression in the MR population (Hurley 2006). Other open-label studies of SSRIs have been conducted for behavioral problems in MR individuals with mixed results. Due to these findings, it is difficult to come to a clear conclusion regarding the use of antidepressants for treating behavioral problems in individuals with MR. The noted favorable outcomes were mostly for SIB and perseverative/compulsive behaviors. In addition, many of the studies used antidepressants as an add-on drug to an existing psychotropic regimen (Madrid et al. 2000; Stigler et al. 2005).

Mood stabilizers and anticonvulsants are often used to treat cyclical mood disorders in the general population. To date, there have been no published RCTs for the treatment of comorbid bipolar disorder in patients with MR (Stigler et al. 2005). Based on open-label reports, first-line options for this purpose in patients with MR include ► carbamazepine and ► valproic acid. Although lithium may be effective, it can cause a magnified cognitive dulling in this population that would make it a less attractive choice. Individuals with MR may also be more likely to develop lithium toxicity due to a change in their fluid intake (Szymanski and King 1999). Some studies have been performed regarding the use of mood stabilizers and anticonvulsants for the management of behavior problems in the MR population. The conclusion from three trials of lithium indicated an improvement in behavioral problems in a large portion of the individuals studied. Lithium toxicity was mostly absent in these studies. Two studies with valproate add-on therapy indicated improvement in SIB and aggression. One retrospective study with topiramate as an add-on therapy also indicated improvement in SIB and aggression. One double-blind, controlled, crossover study with carbamazepine indicated no difference between drug and placebo in decreasing overactivity. Although most of these studies indicate improvement in behavioral problems with these medications, methodological problems compromised many of them (Deb et al. 2007). Side effects that may be more common with carbamazepine in the MR population compared with the general population include the elevation of carbamazepine–epoxide levels during polypharmacy (resulting in seizure exacerbation), hyponatremia, hypovitaminosis D, folic acid and riboflavin deficiency, and irritability. Side effects of concern for valproate include pancreatitis, hepatotoxicity, and myelodysplasia (Szymanski and King 1999).

Even though between 20 and 45% of people with MR are receiving psychotropic drugs, there are very few published RCTs to guide practitioners. Much more research is needed to determine the efficacy and tolerability of psychotropics in individuals with MR for treating the majority of comorbid DSM-IV-TR diagnoses that commonly co-occur with the core intellectual disability.

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Cross-References

► Anticonvulsants
► Antidepressants
► Antipsychotic Drugs
► Atomoxetine
► Attention Deficit and Disruptive Behavior Disorders
► Benzodiazepines
► Bipolar Disorder
► Impulse Control Disorders
► Lithium
► Major and Minor and Mixed Anxiety-Depressive Disorders
► Methylphenidate and Related Compounds
► Mood Stabilizers
► Movement Disorders Induced by Medications
► Muscarinic Agonists and Antagonists

- ▶ Rating Scales and Diagnostic Schemata
- ▶ SSRIs and Related Compounds
- ▶ Traumatic Stress (Anxiety) Disorder
- ▶ Withdrawal Syndromes

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Autistic Disorder

- ▶ Autism

Autoinhibition

Definition

Inhibition of DA release from a neuron mediated by the activation of D_2 receptors on the neuron by endogenous DA or D_2 agonists.

Autonomous

- ▶ Independents

Autoreceptors

Definition

Receptors located on presynaptic nerve terminals sensitive to the neurotransmitter that is released by the same neurons in whose membrane the autoreceptor sits. Somatodendritic autoreceptors, such as serotonin-5-HT_{1A}, dopamine-D_2, and a_2-adrenoceptors, exert an inhibitory effect on the firing activity of the cell. Autoreceptors present on presynaptic nerve terminals usually regulate the synthesis and release of the neurotransmitter without affecting the firing activity of the cell.

Aversive Drug Effects

- ▶ Conditioned Taste Aversions

Aversive Stimuli

Definition

Unpleasant or noxious stimuli or events.

Avoidance

Definition

A conditioning procedure in which the instrumental response, for example, absence of a transfer response, prevents exposure to the context associated with an aversive stimulus.

Avoidance of Feared Places and Situations: Anticipatory Anxiety

- ▶ Agoraphobia

Avoidant Personality Disorder

► Social Anxiety Disorder

Avolition

Definition

Inability to initiate or persist in goal-directed behavior.

AVP

► Arginine-Vasopressin

Aβ

► Amyloid-Beta

B

β-Blockade

Definition
This is the short terminology for beta-adrenoceptor blockade, the attenuation of the effects of adrenaline and noradrenaline on one of the two main classes of adrenal receptor in the body.

B_{avail}

► B_{max}

B_{max}

Synonyms
B_{avail}

Definition
The concentration of the receptor pool available for binding to a radiotracer. Some authors may make a distinction between B_{max} and B_{avail}; the former referring to the total pool of a particular receptor type and the latter to that portion of B_{max} accessible to the radioligand.

Cross-References
► Receptor Binding

BAC

Definition
Blood alcohol concentration.

Balanced Placebo Design

Definition
The balanced placebo design is an experimental method created to simultaneously evaluate expectancy and drug effects. The type of drug (active drug versus placebo) and the instructions (receive active drug versus receive placebo) are used to create four distinct conditions. These conditions are (1) receive active drug and told that they receive active drug, (2) receive active drug and told that they receive placebo, (3) receive placebo and told that they receive active drug, and (4) receive placebo and told that they receive placebo. Condition (1) provides information about combined drug and expectancy effects, whereas condition (4) should result in no effect. Conditions (2) and (3) provide differential information about the strength of placebo and pharmacological effects. In condition (2), expectancies are not activated because the individuals are told that they are receiving a placebo; thus, pure pharmacological effects can be studied. In condition (3), individuals' expectancies are activated but no drug is given, allowing for the isolation of the effects of expectancies.

Cross-References
► Expectancies and Their Influence on Drug Effects
► Placebo Effects

Barbital

Synonyms
Barbitone

Definition
Barbital was the first barbiturate to be developed and is considered a prototype. It is a sedative and hypnotic and was used as a sleeping aid and anxiolytic, although now largely replaced by nonbarbiturate agents. Due to its slow onset of action, fatal overdosing is a risk. Prolonged usage of barbital, like other barbiturates, results in tolerance, abuse, dependence, and withdrawal.

Cross-References
► Anxiolytics
► Barbiturates
► Sedative, Hypnotic, and Anxiolytic Dependence

Ian P. Stolerman (ed.), *Encyclopedia of Psychopharmacology,* DOI 10.1007/978-3-540-68706-1,

Barbitone

► Barbital

Barbiturate Derivatives

► Barbiturates

Barbiturates

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Synonyms

Barbiturate derivatives; Diethyl barbituric acid; Malonylurea

Definition

Barbiturates have been used in addiction medicine for stabilizing inpatients during alcohol detoxification, in psychiatry for long-sleep therapy, phobia desensitization, and as purported "truth serum" in narcoanalysis of patients with stupor, mutism, dissociative fugue, or suspected conversion and malingering. Rapid-acting intravenous barbiturates are used in anesthesizing of patients undergoing electroconvulsive therapy or acute Caesarian section. Intravenous barbiturates are also used for execution by lethal injection, and oral solutions for physician-assisted suicide and euthanasia by consent. Barbiturate tablets and elixirs are still available as sedatives and hypnotics in general medicine. The long-acting phenobarbital is effective in seizure disorders, and barbiturates are used in treatment-resistant status epilepticus and neonatal seizures. Barbiturates are used as an intravenous or intracarotid diagnostic presurgical aid in intractable epilepsy to localize an epileptic focus. In traumatic brain injury, barbiturates have been used to reduce intracranial pressure, cerebral edema, blood perfusion, and metabolism. They have been used in essential tremor, acute migraine, and tension headache. In veterinary medicine, barbiturates are used to tranquilize animals and for euthanasia.

Barbiturates are contraindicated in intermittent porphyria. Their use in outpatients has been more or less eliminated due to the narrow margin of safety, and risk of suicide in overdose.

Barbiturates are by international convention controlled substances to be prescribed, yet are available over the Internet for nonmedical purposes, such as to potentiate the effects of opioids and alcohol, and to alleviate withdrawal from CNS stimulants.

Pharmacological Properties

Pharmacodynamics

Uric acid, discovered in 1776 by Scheele, is the basis for the 2,500 barbiturates synthesized over the years with antimicrobial, antitumor, spasmolytic, anticonvulsant, hypnotic–sedative, anti-inflammatory, analgesic, diuretic, or herbicidal properties. Those with past or current clinical applications are displayed in Table 1.

The parent compound barbital, first synthesized in 1882 and distinguished by an alkyl group on the fifth carbon (CH_3CH_2), was the first barbituric acid recommended for clinical use in 1903 based on its hypnosedative effects. Substitution of sulfur for the oxygen at the second carbon produced thiobarbiturates (thiopental, thioamylal, methohexital) that are highly lipid-soluble with a rapid onset of action and metabolic degradation.

The mechanism of action of pentobarbital has been elucidated. At lower doses, it modulates the GABA-mediated chloride conductance into the neuron, thus inhibiting neuronal activity in the CNS and spinal cord (Mercado and Czajkowski 2008). At intermediate doses, this does not require the presence of ► GABA, and at high doses the chloride channel activity is blocked. ► Pentobarbital binds to the GABA receptor below the binding site of GABA. Furthermore, barbiturates decrease excitatory amino acid release and postsynaptic response, primarily blocking excitatory ► glutamate response. The effect of barbiturates on calcium conductance probably accounts for their anticonvulsant action.

Furthermore, there is a barbiturate binding site on the nicotinic receptor, with specific structural requirements (Nordberg and Wahlström 1992). There are also interactions with cholinergic agonists and antagonists. Cholinergic systems are involved in the barbiturate withdrawal syndrome, and muscarinic receptors in withdrawal convulsions, indicative of a hypersensitivity to acetylcholine that can be prevented by administering atropine. Long-term barbital treatment induces long-term presynaptic cholinergic deficiencies conducive to cognitive decline in experimental animals, and accompanied by a reduction in brain weight. Such effects on cholinergic

Barbiturates. Table 1. Alphabetical list of barbiturate derivatives in international and national conventions on narcotic drugs[a].

Common name, year of synthesis	Trade names	Formulation	Indications	Comment
Allobarbital 1912			Anticonvulsant, insomnia,	
Amobarbital 1923	Amytal, Tuinal, Pentymal	Tablet, capsule, iv	Insomnia, Preanesthesia, anticonvulsant	
Aprobarbital	Alurate	Tablet, Capsule, Elixir	Insomnia	
Barbital (Barbitone) 1903	Veronal			
Brallobarbital				
Butalbital (butalbarbital)	Fiorinal, Butalbital with aspirin	Capsules	Tension headache	
Butobarbital 1922	Butisol Sodium, Neonal	Tablets, Elixir	Insomnia	
Cyclobarbital 1928	Phanodorm	Tablets		
Phenobarbital 1912	Luminal		Anticonvulsant	Long-acting
Heptabarbital	Medapan			
Hexobarbital 1936	Enhexymal, Evipan			
Mephobarbital	Mebaral		Anticonvulsant	Long-acting
Methohexital 1957	Brevital	Iv, rectal	Preanesthesia, e.g., ECT, abortion	Ultrarapid
Methylphenobarbital				
Pentobarbital (pentothal) 1924	Nembutal	Oral, rectal, iv, im	Insomnia, Preanesthesia, anticonvulsant, euthanasia	
Sekbutabarbital				
Secobarbital 1929	Seconal Sodium	Capsule, rectal, iv	Insomnia preanesthesia	
Talbutal	Lotusate	Tablet 120 mg	Insomnia	
Thiamylal	Surital	iv	Preanesthesia	Ultrarapid
Thiopental 1934	Pentothal	iv	Preanesthesia, euthanasia	Ultrarapid
Vinbarbital	Sonuctane			
Vinylbital (butylvinyl)	Speda		Insomnia	
Amobarbital+secobarbital	Tuinal	Capsule	Insomnia, preanesthesia	Fixed combination
Secobarbital, brallobarbital, hydroxyzine	Vesparax	Tablet		Fixed combination
Vinbarbital, aprobarbital	Diminal duplex	Capsule	Insomnia	Fixed combination

[a]UN Convention on Psychotropic Substances, 1971; Single Convention on Narcotic Drugs, 1961; List of Psychotropic Substances under International Control, International Narcotics Control Board, Vienna, 2003; Swedish Medicinal Products Agency Regulation LVFS, 2000:7; United States Drug Enforcement Administration List of Controlled Substances, 2008

neurotransmission have not been noted with ethanol or the ► benzodiazepines. Barbiturates cause a widespread increase in fast activity (20–30 Hz) in the EEG beginning in frontal areas.

Clinically, the effects of barbiturates on neurotransmission translate into raising the threshold for seizures, lessening anxiety, inducing sedation, sleep, coma, and subsequently death. At toxic doses, respiration is inhibited, requiring assisted ventilation in management of overdose.

The ► abuse liability of barbiturates has been studied experimentally by assessing their reinforcing properties and "liking" (Griffiths and Johnson 2005). Notably, reinforcement can be augmented by the subject's perceived risk (nocebo) of precipitating withdrawal symptoms when

the drug is discontinued. In a comparison of 19 hypnotics, pentobarbital ranked highest both with regard to abuse liability and toxicity (idem). In contrast to heroin, ► cocaine, cannabis, and ► alcohol, which cause positive rewarding effects by increasing dopamine release, barbiturates do not release extracellular ► dopamine in the nucleus accumbens. In baboon and rhesus monkey experiments, the reinforcing properties of ► secobarbital were similar to those of cocaine, while the benzodiazepines were frequently indistinguishable from placebo. Secobarbital and pentobarbital caused more subjective "liking" in humans while phenobarbital had a considerably lower liking potential. In experiments with male sedative abusers, subjects consistently preferred pentobarbital over the benzodiazepine ► diazepam.

All hypnotics with abuse liability work on the GABA receptor site. Since hypnotics are widely used, particularly in the elderly, the clinical risk/benefit ratio for barbiturates in outpatient use is unacceptable in comparison with the benzodiazepines.

► Pharmacokinetics

Phenobarbital, a long-acting barbiturate with selective anticonvulsant activity, is absorbed with peak plasma levels after 6–18 h and is clinically active for 24 h. The $t_{½}$ is 86 h in adults and 50 h in children. The short-acting pentobarbital and secobarbital are more lipid-soluble and thus enter the CNS rapidly with effects after 30 min. Anesthetic barbiturates (thiopental and methohexital) administered intravenously cause sleep within 1 min, but only transitorily due to the rapid redistribution.

Barbiturates are mostly metabolized by the liver and excreted in the urine. Elderly patients and those with hepatic disease have a reduced metabolic capacity. Hepatic enzyme induction is a phenomenon occurring with long-term administration. The activity of bilirubin glucuronyl transferase can be enhanced by barbiturate enzyme induction, which is of potential therapeutic use in Gilbert's Syndrome to reduce plasma bilirubin levels. Secobarbital is highly protein-bound and overdoses are thus difficult to treat by dialysis.

Safety

Prolonged administration of barbiturates narrows the safety margin by inducing both pharmacodynamic and pharmacokinetic ► tolerance. As with rapidly acting benzodiazepine hypnotics (► zaleplon, ► zolpidem, and ► zopiclone), lipid-soluble barbiturates can cause a paradoxical excitation or "high" rather than sedation and sleep if the subject is determined to remain awake, or is kept awake by others.

Concurrent use of alcohol aggravates CNS toxicity, sometimes resulting in death due to respiratory depression in intentional or unintentional overdoses. The barbiturates interact not only with alcohol but with commonly used medications such as antihistamines, warfarin, digitoxin, and anticancer chemotherapeutics. Phenobarbital was the first drug shown to induce drug/steroid metabolism by activating the transcription of genes encoding various metabolizing enzymes (Kakizaki et al. 2003).

The ► withdrawal syndrome following long-term barbiturate use was first described in 1914 by von Muralt, and in 1934 by Pohlisch and Panse. Sands at the Psychopathic Service of Bellevue Hospital described the clinical signs of acute and chronic intoxication in detail, stating that "the largest number of chronic barbital patients belong to the emotionally unstable type of constitutional psychopathic inferiority group. . .in his inability to face reality because of the painful effect it might entail". Harry Isbell in 1949 administered barbiturates (secobarbital, pentobarbital, or ► amobarbital) experimentally to five male substance abusers for 100 days and then withdrew the drugs abruptly. A withdrawal syndrome was precipitated that included anxiety, muscle twitching, intention tremor, weakness, hypotension, nausea, and perceptual distortions. It was followed in four subjects by tonic-clonic convulsions and by a delirium that lasted for up to 15 days. This syndrome appeared more severe than morphine withdrawal.

Clinical Uses

The efficacy of using barbiturates for treating *any* psychiatric condition is not evaluable by modern criteria of evidence-based medicine. ► Randomized controlled trials versus placebo or active comparators in anxiety or sleep disorders are generally lacking. In a few comparative studies, the benzodiazepines consistently showed a more favorable risk-to-benefit ratio. Yet, regulatory bodies keep barbiturates on the pharmacopeia, e.g., in the USA. Among 13 hypnotics on the US market in 2008, three were barbiturates: Butisol Sodium^{R} (butabarbital), Carbrital^{R} (carbromal+pentobarbital combination), and Seconal^{R} (secobarbital). There are also fixed combinations of barbiturates with nitroglycerin, ► caffeine, ► amphetamine, theophylline, and various gastrointestinal drugs.

How did the barbiturates become the major drugs in sedating patients in mental asylums and in general medicine? This is only partly elucidated, but the path must have been very different from today's highly regulated process of phase I to phase III studies based on regulatory and industrial conventions such as Good Clinical Practice. The original publication in 1864 of Adolf Baeyer (1835–1917; Nobel Prize in chemistry 1905) described in detail the chemical

synthesis of different malonylureas, one of which was also given the name *Barbitursäure*. In 1903, 49 years later, the chemist Emil Fischer (1852–1919; Nobel Prize in chemistry 1902) and the pharmacologist Josef von Mering (1849–1908) reported studies of 16 dogs that were given two different malonylureas, one of which they recommended as a hypnotic. The body weights and the behaviors of the dogs were observed during 1-day periods. At least two dogs died, and some fell asleep. The authors then moved on to recommendations for clinical doses, stating the hypnotic power of diethyl barbituric acid as four times that of the contemporary sulfonal, and that it was easily synthesized. They proposed the trade name Veronal, supplied by E. Merck in Darmstadt, and recommended a 0.5 g initial dose (in "weaker" persons such as women 0.3 g) and that 1.0 g needed rarely be exceeded. The effect appeared after 30 min, and the drug could be given in a cup of warm tea. Unwanted adverse effects had not been noted according to this seminal paper, but further study of long-term adverse effects should come with continued therapeutic research. The paper does not refer to or include any experiments on humans. Barbital became the name in the USA, and barbitone in the UK as a result of World War I trade negotiations.

► Barbital (Veronal) was subsequently applied to calm manic patients and to promote sleep in melancholic patients, thereby substituting bromide and opium as the drugs of choice. Phenobarbital (Luminal) was introduced in 1912, and was used for "sleep therapy" in psychosis by Giuseppe Epifanio in Turin in 1913, a substitute for "the Bromide Sleep" of 1897. The idea was modified on psychoanalytical grounds by Jakob Klaesi in Zurich in 1922 to facilitate reaching into unconscious material during psychotherapy of patients with ► schizophrenia with a combination drug called Somnifaine (López-Muñoz et al. 2005).

Sleep therapy was also tried in battle neurosis following the Dunkirk evacuation in World War II, in delirium tremens, autism, obsessive-compulsive disorder, and morphine withdrawal. The "Cloetta Mixture" with seven compounds including barbiturates was administered rectally to schizophrenic, manic, hysterical, or psychoneurotic patients to induce continuous sleep for 2–3 weeks under nurse supervision. The sleep therapies were phased out due to the mortality (5%), pulmonary embolism, bronchopneumonia, and other adverse effects, and when insulin shocks were introduced in 1935. Subsequently, chlorpromazine was launched in 1952, its trade name Hibernal stemming from "hibernation therapy." In the 1950s, the Central Intelligence Agency carried out trials to quicken the recovery of "brainwashed" repatriated soldiers in the Korean War with propaganda during barbiturate sleep.

The lethality of a barbiturate overdose was exploited for other means. Alfred Ploetz (1860–1940), father of racial hygiene, had argued in 1895 for an authorized board of physicians to kill children with congenital defects with morphine. When the National Socialist Party came to power in Germany in 1933, such boards were established, and 5,000 children with neuropsychiatric abnormalities were secretly killed by means of phenobarbital (Lauter and Meyer 1982).

Other clinical applications of barbiturates were essential tremor, tension headache, migraine, rheumatic pain, and intractable pain conditions. Barbiturates were added to fixed combination medications for bronchial asthma, hypertension, and functional gastrointestinal complaints. It has been estimated that 408 tons of barbiturates were manufactured in the USA at the peak of usage in 1947, sufficient to treat ten million patients for a year. Only in 1952 did the World Health Organization recommend that they should be prescribed by physicians only.

In the 1970s, there was a shift from barbiturate to benzodiazepine prescribing, partly influenced by campaigns to reduce barbiturate prescribing. Between 1959 and 1974, 27,000 deaths were caused by barbiturates in the UK, based on 225 million prescriptions that peaked in 1965. There were 134 barbiturate combinations on the market. In 1977, the UK Committee on Review of Medicines recommended restricting the use of barbiturates to patients with severe intractable insomnia, owing to the lack of proof of efficacy in any other psychiatric indication, and due to safety concerns. These concerns were primarily the risk of lethal overdoses, but also the risk of addiction, particularly of the fixed combinations of two barbiturates such as Tuinal, Diminal duplex, and Vesparax. Also noted was the risk of enzyme induction upsetting the metabolism of anticoagulants, steroids, phenytoin, and other psychoactive drugs. Studies of elderly people with hip fractures found that most had been prescribed barbiturate hypnotics, implying that they may have fallen due to drug-induced dizziness.

Clinical studies of patients detoxified from dependence and abuse of prescribed medications revealed that they had taken a range of different medications for pain, insomnia, and anxiety, including the barbiturates and their combinations (Allgulander 1986). The risk of suicide was particularly high among physicians, nurses, pharmacists, and their spouses admitted for inpatient detoxification from prescription drug abuse, as they had access to medications and knew how to administer them to die (Allgulander et al. 1987). It was a relief to the medical community when the benzodiazepines were introduced in the 1960s with a negligible risk of death in overdose.

Amobarbital (Pentymal) was used in the 1970s to treat alcohol-dependent patients during detoxification to prevent delirium tremens and seizures. Benzodiazepines (primarily diazepam) have since taken over.

The concept of *truth serum*, a drug to make people speak only the truth, arose in the 1920s, as a substitute for torture in war and religion (e.g., the Catholic Inquisition), mesmerism, and psychoanalysis. Paradoxically, ▶ scopolamine, which caused amnesia during labor, was proposed by a Texas rural obstetrician to extract the truth in criminal proceedings, an idea that was amplified by media at the time. Amytal was first tried in the 1930s to recover memories of sexual abuse, the idea stemming from the Freudian credo of the unconscious. A variant called *narcoanalysis* or Amytal interview (intravenous administration of amobarbital) was used to promote self-disclosure in patients with mutism, psychogenic amnesia, suspected conversion disorder, depression, and dementia. There is no evidence to support this procedure (Kavirajan 1999). In fact, false memories from childhood or adulthood can be implanted in hypnosis, in product marketing, and by a biased psychotherapist.

The *anticonvulsant* property of phenobarbital was discovered serendipitously in 1912 by Alfred Hauptmann in Munich, and it became the first effective medication for epilepsy. Its application was delayed until the 1930s when phenobarbital superseded potassium bromide as a drug of choice. Phenobarbital is effective in adults with partial, complex (motor and sensory) partial, and generalized tonic-clonic seizures, in treatment-resistant status epilepticus, for complex febrile and nonfebrile seizures in children, and for neonatal seizures. It is on the World Health Organization list of essential drugs, and is exempted from international conventions regulating controlled substances, as it is not of interest for nonmedical use.

Thiopental (Pentothal^{R}) became the drug of choice for intravenous *anesthesia* when introduced in 1935 by Ralph M Walters in Wisconsin. Other barbiturates had been used previously, but thiopental had superior pharmacodynamic and ▶ pharmacokinetic properties. Intravenous barbiturate anesthesia combined with muscle relaxant drugs came to be used for sleep induction in electroconvulsive therapy.

Barbiturates have been widely used in acute *traumatic brain injury* in the belief that such treatment can reduce intracranial pressure by suppressing metabolism. Six controlled trials were evaluated with Cochrane methodology. The author concluded that there was no evidence that barbiturates improved mortality or morbidity, and that the hypotensive reaction to barbiturates in one of four patients offset any benefit from reduced intracranial pressure.

A number of fixed combinations of barbiturates (mostly butalbital) and analgesics (acetylsalicylic acid, codeine) and caffeine were marketed to treat various *pain* disorders. A review of controlled studies concluded that there was no evidence that barbiturates enhance analgesic efficacy, and that the safety risks were substantial.

Lethal injections as a means of capital punishment were first applied in the USA in 1982. Most such protocols use a sequence of intravenous thiopental 3–5 g (increased if the subject is still conscious after 60 s), followed by pancuronium bromide 50 mg to prevent movements for the benefit of staff and witnesses, and potassium chloride 100–240 mEq to cause asystole, followed by saline flush. Death usually occurs in 7–10 min. There is controversy over the efficacy of these procedures, partly based on the biphasic pharmacokinetics of thiopental and with lower procedural standards than those developed for euthanasia in veterinary medicine. Between 1977 and 2005, there were 839 such deaths by injections among a total of 1,007 commuted death penalties in the USA.

Euthanasia by consent and *physician-assisted suicides* are illegal in most countries, yet legal in Oregon, Thailand, Canton Zurich, and in the Netherlands. A Dutch study found that over 40 different drugs had been used, most frequently a barbiturate or an ▶ opioid (Willems et al. 1999). Most patients (85%) died within an hour, and physicians were satisfied with the procedure in 90% of cases. However, delayed drug absorption, dehydration, and malnutrition may delay or upset the process. The Royal Dutch Pharmaceutical Association in its 1994 revised guideline recommend that patients are given an antiemetic (metoclopramide 20 mg every 8 h) 24 h before administering an oral 100 mL solution of 9 g of either pentobarbital or secobarbital. Death occurs usually within 1 h, but can take up to 24 h. For parenteral euthanasia by consent, 10 mL intravenous solution of thiopental 20 mg/kg is recommended, followed by pancuronium bromide 20 mg. There were 2,425 such physician-assisted deaths in the Netherlands in 2005, mostly in patients with cancer before the age of 80. Assisted suicides at Dignitas in Zurich by means of pentobarbital were performed in 876 persons from 26 countries in the first 10 years, 59% of whom were women.

Comment

The barbiturates played an important role as sedative–hypnotics for 100 years and were succeeded by the benzodiazepines in the 1960s. Their pharmacodynamic and

pharmacokinetic properties caused unacceptable risk/benefit ratios for use in outpatient care. Phenobarbital is still appreciated for controlling seizure disorders, and intravenous formulations are useful in rapidly inducing sleep prior to ► electroconvulsive therapy and brief surgical procedures. Pentobarbital and secobarbital are effective in euthanasia by consent and physician-assisted suicides in humans, and in mercy killing of animals.

Cross-References

► Abuse Liability Evaluation
► Anticonvulsants
► Drug Interactions
► Ethical Issues in Human Psychopharmacology
► Habituation
► History of Psychopharmacology
► Hypnotics
► Insomnias
► Pharmacodynamic Tolerance
► Pharmacokinetics
► Sedative, Hypnotic, and Anxiolytic Dependence
► Suicide
► Withdrawal Syndromes

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Basal Forebrain Cholinergic Neurons

Definition

These are CNS neurons located in the fairly ventral (basal) and anterior (forebrain) regions of the CNS which display a cholinergic phenotype (i.e., generating and releasing the neurotransmitter ► acetylcholine (ACh)). Two main neuronal nuclei have shown marked dependency on NGF support: the medial septum and the nucleus basalis. The first provides the main cholinergic input to the hippocampal complex and the second to the cerebral cortex. These systems are thought to be very relevant for attention, memory, and learning mechanisms. These neurons are affected by the aging process and they are the earliest compromised and the most vulnerable to the Alzheimer's pathology. In the human species and primates, the nucleus basalis is also referred to as the nucleus magnocellularis of Meynert. This nomenclature does not apply to rodents, given fundamental differences in the nuclear organization.

BDNF

► Brain-Derived Neurotrophic Factor

Bed Nucleus of the Stria Terminalis

► BNST

Behavioral Addictions

► Impulse Control Disorders

Behavioral Allocation Function

Definition

A rule for predicting the vigor or prevalence of reward-seeking behavior on the basis of variables such as the strength, cost, imminence, and likelihood of reward.

Behavioral Augmentation

► Sensitization to Drugs

Behavioral Characterization

► Phenotyping of Behavioral Characteristics

Behavioral Despair

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Synonyms

Forced swimming test; Porsolt test; Tail suspension test

Definition

Tests of behavioral despair are used to measure the effects of ► antidepressant drugs on the behavior of laboratory animals (typically rats or mice). Examples of these tests include the forced swimming test (a.k.a., the FST or Porsolt test) and the tail suspension test (TST).

When forced to swim in a restricted space without the possibility of escape, rats and mice will, after a period of vigorous behavior directed toward escape, adopt a characteristic immobile posture, where they remain passively floating in the water, making only those movements necessary to keep their heads above water. The immobility response is usually measured by the latency until development or the overall duration during the session. The immobility in the forced swim test is thought to indicate resignation to a state of despair, in which the rodent has learned that escape is impossible (Porsolt et al. 1977, 1978a). The immobility response is reduced by administration of antidepressant drugs and other treatments that are therapeutically effective in depression.

The tail suspension test was developed later as a second test for use with mice (Steru et al. 1985). Mice that are hung by their tail from a bar will, after some time spent trying to escape, adopt a characteristic immobile position. The test relies on the same behavioral principle as the forced swimming test, since mice are not able to escape from being attached to the bar. Administration of antidepressant drugs reduces the time spent immobile.

Principles and Role in Psychopharmacology

Procedures

Rats and mice are used most often in tests of behavioral despair, although gerbils and guinea pigs have also been tested. Different procedures are commonly used for rats and mice. It must be emphasized, however, that procedural modifications for particular experimental purposes, e.g., to measure effects following chronic treatment or in genetically modified rodents, are common.

Rats are usually given two trials separated by 24 h. The first trial lasts 15 min and is usually referred to as a pretest. Antidepressant or test drugs are given to rats 2 or 3 times between the trials, as a loading protocol. The second trial lasts only 5 min, because the onset of the immobility is sensitized by the pretest. Antidepressant drug effects are evident in a reduction of duration of immobility during the second test (Porsolt et al. 1977).

Important procedural changes were introduced to the rat forced swimming test because the effects of selective serotonin reuptake inhibitors (► SSRIs) could not be measured using the original testing method (Cryan et al. 2005b; Detke et al. 1995). The modified rat FST measures the frequency of two active behaviors, swimming and climbing, in addition to passive immobility during the second trial. A larger cylinder (at least 20 cm diameter) and higher water level (30 cm depth) was recommended, to keep rodents from positioning themselves to thwart the stressful aspects of the test by using the bottom or sides for support. The new conditions also improved the measurement of swimming behavior produced by the SSRIs. Antidepressant drugs produce different effects on the active behaviors in the modified rat FST. The SSRIs (e.g., ► fluoxetine, ► paroxetine, ► citalopram) reduce immobility and increase swimming behavior, ► tricyclic antidepressants and selective ► NARI antidepressants (e.g., desipramine, maprotiline, reboxetine) reduce immobility and increase climbing behavior, and ► SNRI antidepressants with effects on both, serotonin and catecholamines or ► monoamine oxidase inhibitors reduce immobility and increase both swimming and climbing behavior (Cryan et al. 2005b; Lucki 1997).

Mice are tested in the forced swimming test or the tail suspension test with just a single trial, lasting usually for 6 min. In the forced swimming test, only the last 4 min may be scored. Cylinders of varying sizes have been used, although larger cylinders (>20 cm) may avoid detecting ► false positives and ► false negatives (SSRIs) in the test. Antidepressant drugs usually have to be given only once to produce a behavioral effect. The total duration of immobility, and the duration until an initial bout of immobility, are usually scored. Some studies have measured immobility, swimming, and climbing behaviors in the mouse FST.

Predictive Validity for Antidepressant Treatments

The FST and TST demonstrate good ► predictive validity for measuring the effects in animals of drugs that are used clinically to treat depression. Antidepressant drugs

produce various pharmacological effects on diverse neurotransmitters and have been divided into different structural classes. All clinically effective antidepressant treatments produce reductions of immobility, including tricyclics, monoamine oxidase inhibitors, SSRIs, and atypical ▶ antidepressants. In addition, somatic treatments for depression, such as ▶ electroconvulsive shock, sleep deprivation, chronic exercise, and ▶ transcranial magnetic stimulation, also produce reductions of immobility. Reviews of drugs that have been successfully tested, have appeared for the traditional FST (Borsini and Meli 1988), the modified rat FST (Cryan et al. 2005b) and the mouse TST (Cryan et al. 2005a).

The FST also distinguishes many drugs that are not antidepressants. For example, ▶ anxiolytic drugs with anti-anxiety effects, such as ▶ benzodiazepines, are not active in the FST, with the exception of ▶ alprazolam, the lone benzodiazepine with antidepressant effects. The chief consistent false positives in the FST and the TST are psychomotor stimulants such as ▶ amphetamine, which reduce immobility because of general motor stimulation but are probably ineffective clinically as antidepressants. Most studies of established or novel antidepressants employ secondary tests of locomotor activity to distinguish treatments that produce unambiguous indications of antidepressant activity from those that may be caused by increased motor stimulation. Nearly, all clinically established reference antidepressants produce no effect, or decrease locomotor activity at the same doses that are active in antidepressant tests. Although drugs that decrease immobility in the FST and increase locomotor activity may still be antidepressants, their antidepressant activity would be characterized as ambiguous unless demonstrated to be unaccompanied by motor activating effects. Activity in the FST by anticholinergic or antihistamine drugs, effects that may simulate side effects of tricyclic antidepressants, have been both detected and rejected by different laboratories and may depend on test conditions.

Common Uses of the FST and TST

Antidepressant discovery research. The FST and TST are used primarily as behavioral screens for antidepressant discovery research in the pharmaceutical industry, because the tests are relatively easy to administer and demonstrate good predictive validity for measuring clinically effective drugs. Hundreds of compounds with differing pharmacological mechanisms of action have been tested for potential antidepressant activity, using these behavioral screens. A frequent issue in antidepressant discovery research is whether the tests of behavioral despair that are tuned to measure the effects of the traditional drugs used for treating depression, are able to measure the effects of novel classes. The answer is unknowable until a novel class of antidepressants is discovered. However, a second issue, somewhat incompatible with the first, is that a large number of drugs demonstrate effects in the FST and TST, and it is difficult to know which of these compounds could eventually be developed into effective antidepressants in humans.

Validation of pharmacological effects. The antidepressant response in behavioral despair tests has been used to test a functional role for particular neurotransmitters. For example, brain lesions, receptor antagonists, or inhibitors of neurotransmitter synthesis can produce changes in performance in the FST and TST. Studies have shown that SSRIs are not behaviorally active if synthesis of the neurotransmitter serotonin (see ▶ Indoleamines) is prevented. Tricyclic antidepressants are not behaviorally active if synthesis of the neurotransmitter ▶ norepinephrine is prevented or noradrenergic pathways have been destroyed. However, it is not known whether facilitating monoamine transmission or stimulating monoamine receptor mechanisms is an essential property for all drugs to produce antidepressant-like effects in the FST and TST.

Neural circuitry. The FST has been used in combination with site-specific injections to identify circuits with potential for mediating the effects of antidepressant drugs. Specific injection into brain regions, such as the frontal cortex, ▶ hippocampus, ▶ amygdala, and ▶ nucleus accumbens, have been shown to mediate reductions of immobility in the FST. Other studies have used the FST to measure changes in neurotransmitter release in discrete brain regions or activation of local circuits. However, thus far, the integrated circuitry that identifies the behavioral effects of antidepressant drugs has not been established.

Genetics. Until there is agreement on identified genetic causes of depression, it will not be possible to test rodents generated with a homologous genetic condition. However, a large variety of ▶ genetically modified mice have been examined using tests of behavioral despair to identify genes that produce either an antidepressant-like or a prodepressive effect (Cryan and Mombereau 2004). Genetically modified mice have also been used to identify the functional significance of cell signaling pathways such as CREB, or of ▶ neurotrophic factors such as ▶ BDNF, in the behavioral effects of established antidepressant drugs. Inbred strains of rats and mice demonstrate different baseline levels of response in the FST and TST. Breeding techniques, combined with modern maps of chromosomal structure, have been used to identify genes associated with behavioral despair. Another genetic technique allows for rodents with high or low levels of immobility on tests of behavioral despair to be bred over successive generations. These animals demonstrate rapid genetic separation

into separate populations, and show different responses to antidepressant treatments.

Different inbred rodent strains also vary in their behavioral response to specific types of antidepressant drugs (Porsolt et al. 1978b). Swiss mice and BALB/c mice appear to respond to the greatest variety of antidepressants in the FST, NMRI mice were commonly used in the TST, and Sprague–Dawley or Wistar are the most commonly used strains of rats. However, some rat strains considered as genetic models for depression (Flinders sensitive line (FSL) or Wistar-Kyoto (WKY)) demonstrate higher levels of immobility in the FST and selective responses to different types of antidepressant drugs. The correct detection of antidepressant activity may depend on the selection of the appropriate rodent strain for use.

Models of disease. Although tests of behavioral despair are ordinarily conducted in normal, or otherwise unstressed populations of rodents, this may not always be the case. Baseline performance in the tests is sensitive to changes by conditions or models of diseases that cause depression by showing changes in the opposite direction of antidepressant drugs. ► Chronic mild stress, or acute drug withdrawal, conditions that are highly correlated with depression, produce an increase in the duration of immobility. Depression is economically burdensome because the disease is frequently comorbid with other chronic medical diseases, such as cardiovascular disease, diabetes, and stroke. Models of diabetes, cardiovascular disease, stroke, and ischemia in rodents have been shown to produce increased immobility in the FST and TST, and performance using such tests with these models can be used to detect drug treatments that may be especially effective in treating depression under these conditions. Gonadectomy or models of postpartum depression in rodents also increase immobility in tests of behavioral despair and may be used to study endocrine and neural correlates of depression.

Validity of the FST

There has been debate about the validity of behavior despair tests as good models of depression. There is general agreement that the FST and TST measures the effects of most antidepressant treatments that are currently approved for clinical use (good predictive validity).

The original idea that immobility in the FST emerged from feelings of behavioral despair in the rodents caused many to consider the FST as a model of depression. However, because the FST is a short-term behavior test rather than a condition that attempts to recreate the symptoms of human depression in rodents, the FST lacks ► construct and ► face validity to model clinical depression. Logically, symptoms would be expected to persist for weeks in a valid model of depression, instead of just minutes in the FST. The most efficient use of the FST has been as an indicator test of stress-induced behavior, rather than as a condition that simulates depression as the term behavioral despair implies. FST performance can be interpreted in ways that are behaviorally descriptive, rather than referring to internal motivational factors such as behavioral despair, and still remain relevant to a behavioral state associated with depression. For example, one such scheme stresses the differential behavioral consequences of active (swimming and climbing) versus passive (immobility) coping behaviors in the ambiguous situation of the forced swimming test (Cryan et al. 2005b). Depressed patients are more sensitive to the display of passive behavior. Active and passive coping behaviors is a homologous distinction described for coping behaviors displayed by humans when they are stressed. The FST will also model depressive behavior more effectively if used in combination with genetic and environmental factors that contribute to the development of clinical depression (see above).

Cross-References

► Animal Models for Psychiatric States
► Antidepressants
► Depression: Animal Models

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B

Behavioral Economics

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Definition

Behavioral economics is the study of drug consumption conceived as decision-making behavior under an economic framework. It is the combination of two separate disciplines: economics – the study of rational decision-making – and psychology – the study of human behavior. These two disciplines have been combined to examine actual decision-making behavior under an economic framework. This concatenation of paradigms has identified a number of relationships that have been found to influence the consumption of commodities. We will illustrate how behavioral economics, including the study of demand and temporal discounting, describes these interdependencies using examples from drug research.

The fundamental concept in behavioral economics is ▶ demand, the amount of a commodity consumed at a specific price (Pearce 1989). This relationship between price and consumption has a natural translation to behavioral psychology, where a commodity can be considered as a *reinforcer*, something that increases the likelihood of the response occurring again, and price, which can be considered the *response requirement* to obtain that reinforcer (Lea 1978). The relationship between price and consumption is expressed as a demand curve and typically follows a negative slope – as price increases consumption falls – and is referred to as the "law of demand."

Demand curves are categorized by ▶ elasticity – the degree to which a change in price changes the demand for a commodity. Demand is thought to be *unit-elastic* when increases in price results in proportional decreases in consumption, *elastic* when the change in price produces greater-than-proportional changes in consumption, and *inelastic* when a change in price causes smaller-than-proportional changes in consumption. Thus, the slope of the demand curve represents the elasticity of the price-consumption relationship.

Principles and Role in Psychopharmacology

Price Elasticity and Demand Curves of Goods

MacKillop and Murphy (2007) investigated the relationship between price and demand for ▶ alcohol in college drinkers. They asked subjects the number of drinks they would consume at different prices and found that increasing drink prices decreased the anticipated consumption of heavy drinking episodes for both men and women. Moreover, they found that heavy drinking episodes appeared to be inelastic at low prices and elastic at higher prices, indicating a mixed elasticity demand curve.

Changes in price can also affect the consumption of concurrently available commodities. For example, Nader and Woolverton (1991) trained rhesus monkeys to choose between food and intravenous injections of ▶ cocaine or procaine. When the amount of food available was increased for the same response requirement (i.e., the price of food was decreased) and the doses of both drugs were held constant (i.e., the price of drugs was unchanged), the frequency of drug consumption decreased suggesting positive ▶ cross-price elasticity – a decrease in price for one commodity resulted in the decreased consumption of the alternative.

These results illustrate another feature of behavioral economics, the characterization of the interaction between commodities of qualitatively different goods and services along one continuum. At one end of the continuum, ▶ substitutes exist where increases in the price of one good correlate with increases in the consumption of an alternative commodity. For example, when the increase in the price of cocaine/procaine results in a decrease in consumption of cocaine/procaine and an increase in the consumption of food, the goods, food and cocaine/procaine, are considered substitutes. At the other end of the continuum, ▶ complements exist where increases in the price of one good correlate with decreases in the demand for that good and the alternative good. In the middle of the continuum, where changes in the price of one commodity have no effect on the demand of the alternative, goods are considered ▶ independents. Thus, the price of alternatively available commodities, whether they are substitutes, complements or independents influences demand.

In addition to demand and price, *income*, or the total purchasing power or the overall rate of reinforcement, also influences consumption. This occurs to the degree to which normal and inferior goods can be bought. For example, an increase in income can lead to purchasing a more preferred good, such as smokers who buy a preferred brand of cigarette rather than the less valued alternative with the same nicotine level (DeGrandpre et al. 1993). These items would be *normal* goods and *inferior* goods, respectively. Income can also affect the elasticity of demand, where increases in income can lead to increased consumption of normal goods and decreased

consumption of inferior goods. Thus, the effects of price and income on demand interact, indicating a complex system of interdependencies between goods, prices, elasticities, and incomes.

Effect of Unit Price on Operant Behaviors

These interrelationships can be addressed using the concept of ▶ unit price, or cost per unit of a commodity. Unit price is often represented as the schedule requirement or response effort, divided by reinforcer magnitude (quantity of reward commodity) (Hursh et al. 1988). It is formally expressed as:

$$\text{Unit price} = \frac{\text{Response Requirement}}{\text{Reinforcer Magnitude}} \quad (1)$$

where either decreasing the magnitude of the reinforcer (commodity) or increasing the response requirement (cost) can increase the unit price of a commodity. This simple calculation predicts that when a commodity has the same response requirement and magnitude as another their unit prices will be equal. Thus, when represented in unit prices, commodities can be compared to each other despite different levels of magnitude and cost. Behavioral economic researchers have suggested that unit price may be the single construct that underpins both reinforcer-magnitude and schedule-of-reinforcement effects (DeGrandpre and Bickel 1996). For example, Bickel et al. (1991) assessed cigarette smoking under varying response requirements (fixed-ratio 200, 400, and 1,600 level pulls) and reinforcer magnitudes (1, 2, and 4 puffs per bout). For each subject, Bickel et al. found a positive relationship between unit price and responses per session, and a negative relationship between unit price and consumption of puffs. Moreover, the responses per session and the consumption of puffs were generally comparable among subjects at the same unit price; that is, an increase in response requirement is functionally equivalent to a decrease in the number of puffs. This positively decelerating demand curve appears to be a ubiquitous phenomenon: meta-analysis of smoking studies showed positively decelerating demand curves across all reported data sets (DeGrandpre and Bickel 1996).

The positively decelerating function has an implication when response rate rather than consumption is plotted as the dependent variable. During low prices consumption is typically inelastic, with smaller-than-proportional changes in response rate in relation to changes in price. However, as consumption increasingly decelerates with increases in price, the changes in response rate become elastic and response rate declines at a faster rate than the change in price. This causes the response rate to follow a bitonic function (exhibiting both inverse and direct relationships) where response rate increases at low prices and decreases at higher prices.

Unit price has also been applied in characterizing the interaction between commodities in pharmacology and drug consumption. For example, the effects of agonists and antagonists have been modeled using unit price; that is, unit price can describe the specific drug effects of ▶ methadone and ▶ naltrexone (DeGrandpre and Bickel 1996). DeGrandpre and Bickel reanalyzed the animal self-administration of opioid antagonists (▶ naltrexone) and agonists (▶ methadone) for heroin self-administration. They found, relative to saline, doses of antagonists increased the consumption of heroin at low unit prices, and decreased the consumption of heroin at high unit prices. Similar results have been found using ▶ morphine administration and cigarette smoking (ibid).

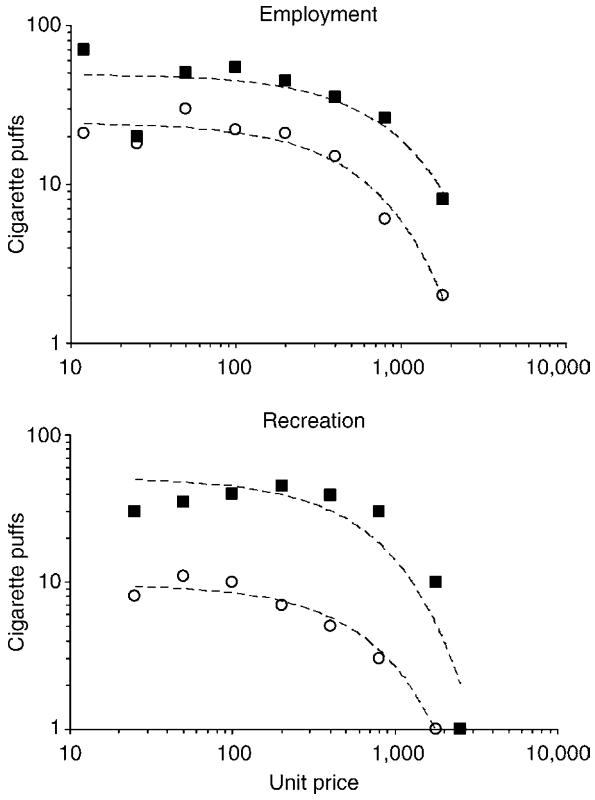
Interrelating Variables Predicting Drug Demand and Consumption

Other behavioral economic concepts also contribute to drug consumption. For example, Bickel et al. (1995) studied the effects of concurrently available alternatives to drug taking. They examined drug consumption using a fixed ratio (FR) response requirement when drug consumption was available and an alternative activity, employment (experiment 1), or another activity such as reading, playing games, etc. (experiment 2), was either available or unavailable. Fig. 1 illustrates these results.

Another variable that affects choice behavior is temporal duration. Elsmore et al. (1980) examined the effects on income when the inter-trial interval, the time between trials, changed. Elsmore et al. found that although there was the same number of choices for heroin and food at low inter-trial intervals, the consumption of heroin decreased to a greater extent than for the food alternative. Thus, temporal effects modify the subjective "value" of a commodity as indicated by choice responses. Similar temporal interactions are also important for another behavioral methodology describing decision-making – temporal discounting.

Discounting of Delayed Reward: Choice and Addiction

Research examining the effect of changing the temporal delay between choice and obtaining the reward has found that ascribed value changes, i.e., the subjective value is discounted. Specifically, the longer the delay that precedes the reward the less the reward is valued. This discounting



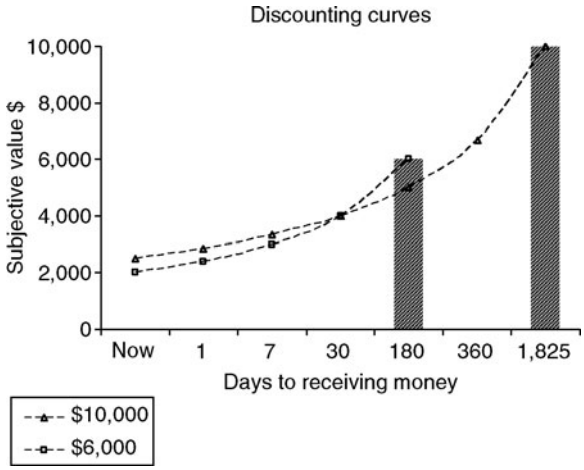
Behavioral Economics. Fig. 1. Consumption (number of cigarette puffs) is plotted as a function of unit price on log–log coordinates. Redrawn from DeGrandpre and Bickel (1996) Figure 10 (two plots only). The top panel shows consumption for one subject when the opportunity to earn money was and was not concurrently available; and the bottom panel show consumption for the same subject when recreational activities were and were not concurrently available. Data points located crossing the *x*-axis represent values of 0.0 on the *y*-axis. Advances in Behavioral Economics Volume 3: Substance Use and Abuse, L. Green and J. H. Kagel. Copyright © 1996 Ablex, Publishing Corporation. Reproduced with permission of ABC-CLIO, LLC. Open circle represents alternative present, filled square represents alternative absent, and dotted line represents best fitting non-linear trend line. The top panel shows the effects of available and unavailable employment, and the bottom panel shows the effects of available and unavailable recreation for one participant (similar curves were obtained for the other participants in these experiments). Drug consumption decreased as a positively decelerating function of unit price in each experiment. Moreover, available alternative reinforcers led to greater decreases in consumption compared to unavailable reinforcers indicating both employment and activities were acting as substitutes to drug consumption.

process can be represented as a hyperbolic curve, most commonly represented by Mazur's (1987) hyperbolic function:

$$V = \frac{A}{1 + kD} \tag{2}$$

where V is value, A is the undiscounted reward value, D is delay, and k is a free parameter describing the ► temporal discounting rate. The hyperbolic discounting relation implies that value decreases based on the total delay rather than a constant decline as suggested by other interpretations.

The hyperbolic function of temporal discounting has been used to describe the behavioral phenomena of ► preference reversal, or "switching" between alternatives when the delay to the outcomes changes. For example, given a choice between $100 now and $50 now most people would choose the larger alternative. However, as delays to obtaining the larger alternative increase the subjective value of this alternative declines, and given a long enough delay to reinforcement, organisms will switch their preference from the larger delayed alternative to the smaller immediate alternative. The switching phenomenon is illustrated in Fig. 2.



Behavioral Economics. Fig. 2. Hypothetical discounting curves. Hypothetical discounting curves for $10,000 and $6,000 delayed 5 years and 6 months, respectively. The dotted lines represent the hyperbolic decay of the subjective value of receiving the money as the delay increases. Delay is represented on the *x*-axis and the two alternatives are represented as vertical bars. The changes in value are represented by the dotted lines for each alternative, and the point where switching occurs is predicted by their intersection.

The methodology of mathematically describing preference reversals requires applying an equation, such as equation 2, to the obtained data. This "fitting" process requires the free parameter in the model, *k*, to change in an attempt to minimize the difference between the prediction and the obtained data across different delays calculated by a computer algorithm, e.g., Microsoft Excel Solver©. The parameter iteration that has the most accurate prediction of the data – the free parameters that achieve the lowest variance from the obtained data – is roughly considered the best estimate of the theorized model to the data.

Advantages and Limitations of Behavioral Economics in Modeling Drug Addiction

Temporal discounting has been found to be an accurate framework for describing preference reversals. For example, Yoon et al. (2007) investigated whether sociodemographic characteristics or discounting of hypothetical money could predict smoking relapse for post partum women. They found that only discounting data predicted smoking status at 24 weeks post partum, and greater baseline discounting rates was also a significant predictor of relapse.

Delay discounting rates have been found to differentiate between nonaddicted and addicted people (see Bickel and Marsch 2001). Research has found that heterogeneous groups of drug addicts discount hypothetical money more steeply than controls, where higher discounting rates are taken for greater preference for more immediate alternatives, suggesting that addicts were more impulsive than controls in their discounting behavior. This preference for immediate alternatives suggests the addicted groups have a "myopic" temporal view when considering alternatives.

Recently, research has suggested that ► temporal myopia appears to extend both toward future outcomes and also to past outcomes. Bickel et al. (2008) examined temporal discounting by cigarette smokers and non smokers. They found relative symmetry between past and future discounting curves, including comparable hyperbolic functions, sign effects, and greater discounting for smokers than nonsmokers. This convergence across temporal epochs suggests similar discounting processes are involved for future and past discounting. Furthermore, as past gains have already happened, subjects receive no reinforcement value from past gains. Thus, the symmetry between past gains and future gains indicates subjects are valuing something other than biological salient cues. A possible explanation is that discounting reflects the width of their temporal window rather than their internal feelings of impulsivity (Bickel et al. 2008). This could explain why addicts have difficulty learning from previous behaviors, even though they recognize their earlier actions have long-term consequences (Franken et al. 2007).

One limitation of these economic models is although they are well suited to describe in parsimonious terms the current behavior of individuals suffering from addiction, they do not suggest the conditions or reasons why an individual becomes an addict or discounts the future. Perhaps, some answers will result from the study of the economics of addiction at the neuroscientific levels. The development and growth of the translational field of neuroeconomics may provide that promise.

Conclusion

In conclusion, behavioral economics, and in particular unit-price and temporal discounting, have been found to describe consumption across a range of commodities, including drugs of abuse. This approach suggests that commodities are valued in a dynamic relationship between the environment and the available reinforcers. Moreover, these relationships appear multifaceted – some commodities exhibit certain characteristics in certain situations and others in different situations. Furthermore, relational understandings appear to describe molecular understandings about drug pharmacology, such as whether a certain substance is acting as an assumed agonist, antagonist, or mixed agonist–antagonist. Thus, behavioral economic methods provide a quantification of demand that seems a broad and coherent description of drug consumption.

Cross-References

► Behavioral Flexibility: Attentional Shifting, Rule Switching, and Response Reversal
► Contingency Management in Drug Dependence
► Delay Discounting Paradigms
► Impulsivity
► Nicotine Dependence and Its Treatment
► Timing Behavior

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Behavioral Equivalents

Definition

Behavioral equivalents are maladaptive behaviors that can be seen in individuals with intellectual disability that have been historically substituted for standard diagnostic criteria when diagnosing mood disorders in this population. These maladaptive behaviors can include, but are not limited to, aggression, self-injury, and destruction.

Cross-References

► Autism Spectrum Disorders and Mental Retardation

Behavioral Facilitation

► Sensitization to Drugs

Behavioral Flexibility

► Behavioral Inhibition

Behavioral Flexibility: Attentional Shifting, Rule Switching and Response Reversal

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Synonyms

Adaptability; Cognitive flexibility; Responsiveness

Definition

Behavioral flexibility refers to the adaptive change in the behavior of an animal, in response to changes in the external or internal environment. Ongoing behavior (which might include inactivity) is stopped or modified and new behavior is initiated. Adaptive changes in behavior can vary by degree, ranging from changes that are little more than reflexes or tropic reactions (i.e., reflecting a change in environmental conditions but without the involvement of cognitive processes) to behavioral changes that are anticipatory of environmental changes. Unlike ► impulsivity, which is responding without inhibitory control and can be maladaptive (see ► impulse control disorders), behavioral flexibility reflects a change in cognitive state in response to the perceived environmental contingencies.

Given that there is a wide range of adaptive responses, it is important to be clear about terminology, particularly if the intention is to make comparisons between different species in order to draw inferences concerning neural mechanisms. The term behavioral flexibility is preferably used to refer only to behavior that reflects a cognitive change, thereby excluding reflexive behaviors. To illustrate this distinction, behavioral change in response to a drop in temperature includes shivering (reflexive), but this is contrasted to cognitive flexibility involved in choosing whether to put on a coat or light a fire (flexible). Cognitive changes might be in response to changes in the internal environment (such as planning how to find food in response to hunger) or changes in the external environment (such as planning a route of escape in response to a threatening stimulus).

Although it is helpful to regard behavioral flexibility and cognitive flexibility as synonymous – indeed the terms are often used interchangeably – it is important to remember the distinction between them. Cognitions are covert and cannot be directly observed, but they can be inferred by observing overt behavior. This means that while it is possible to conceive of cognitive flexibility in the absence of behavioral evidence, in general, whenever

one discusses evidence for cognitive flexibility, the evidence is of behavioral flexibility. On the other hand, the inverse is not necessarily the case: it is possible to observe behavior that appears to be flexible but does not reflect cognitive flexibility. For example, a learned response to alternate presses on two levers in an ► operant chamber may be considered as an example of behavioral flexibility, but, once learned, this behavior may not require cognitive flexibility.

Use in Psychopharmacology

In behavioral neuroscience and psychopharmacology, the most commonly used measures of behavioral flexibility are tests of attentional shifting, rule switching, and reversal learning. In all three cases – whether shifting, switching, or reversing – the key feature is that the behavior is adaptive. For this reason, it is clearly important to ask whether, and to what extent, the behavioral flexibility being measured is the same in each of these three cases and, thus, whether they reflect a common mechanism of cognitive flexibility.

Mental set is a concept that has been used by psychologists for many decades to refer to an acquired cognitive predisposition or bias that influences subsequent behavior (see Gibson 1941 for a useful review). Mental set is manifest in many domains, but of most relevance here are ► attentional set and ► learning set. Attentional set can be formed by prior experience of the relevance of one aspect or ► dimension of a multidimensional stimulus. Thus, repeatedly sorting or selecting stimuli according to their color, while ignoring their shape, is the basis of both the "► Wisconsin Card Sort Task" (WCST) (Berg 1948) and the "Intradimensional–Extradimensional" (ID/ED) task (Lawrence 1949). In both of these tasks, the subject learns which dimension of a stimulus is relevant by trial and error, getting positive feedback for responses that are made in accordance with the relevant dimension. The strength of the attentional set is indicated by the difficulty the subjects have in shifting their focus of attention to a different stimulus dimension. Set shifting is thus the ability to overcome an attentional set. The ease with which a shift is made is indicated by fewer ► perseverative responses in the WCST and by more rapid acquisition, with fewer errors, in the ID/ED task.

Rule switching is the ability to overcome a learning set: the relative difficulty of new learning is indicative of the strength of the learning set. Thus, both set shifting and rule switching represent the dynamic operation of mental set and describe the processes by which the mental set is weakened or altered as circumstances, or reinforcement contingencies, demand. They further have in common that both the perceptual dimensions and the rules by which response might be selected are potentially relevant throughout the task. That is to say, the focus of attention (i.e., attentional set) or the problem-solving strategy (i.e., learning set) are a feature of the respondent and, while they may be elicited by the demands of the task, they are not a feature of the task. Indeed, without the formation of an attentional or a learning set, the tasks could still be performed perfectly adequately. Indeed, sometimes the absence of a "set" would result in better performance, as at the ED stage in the ID/ED task or as demonstrated by the "Einstellung effect," which refers to the retardation of new learning when a previously learned rule or principle does not apply (Luchins 1942).

Thus, mental set might be regarded as cognitive short hand: knowing about contingencies, rules and probability or likelihood, enables an animal to anticipate and prepare for future events, and, by decreasing the range of available options, can improve the speed of processing and likely suitability of a response choice. Mental set is best understood as being an example of preconception (when thinking is influenced by prior experience), and/or predisposition (when responding is influenced by prior experience). The corollary of this is that forming a mental set is the antithesis of cognitive flexibility: the act of "thinking outside the box" means abandoning the preconceptions and predispositions of mental set. Thus, having a mental set is good for predictable events (including predictable changes), but when the unexpected occurs, optimal responding requires that mental set be overridden – that is to say, it requires cognitive flexibility.

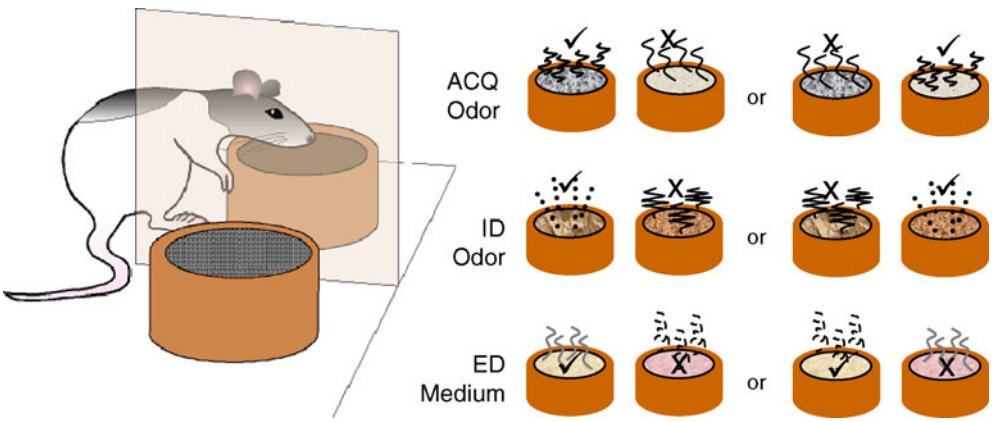
Flexibility and behavioral change are sometimes confused, with new or unpredicted behavior being more likely to be considered flexible than is repeated or predictable behavior. The important point is that any objective assessment of the predictability of behavior is much less relevant than whether the behavior is consistent with the mental set: as long as the required response is consistent with set, cognitive flexibility (the overriding of set) is not required. Thus, response alternation requires no more flexibility than response repetition as long as it is consistent with the response set. It is for this reason that reversal learning poses an interesting case.

Reversal learning refers to the reversal of previously established stimulus-reward contingencies. In its most simple form, it is the reversal of a Pavlovian conditioned response (► Classical (Pavlovian) conditioning), such that the conditioned response (CR) to a CS+ is extinguished. The old-CS is now paired with the US and so, as the new CS+, it comes to elicit a CR. However, the term

"reversal learning" is used much more widely and, particularly in studies of behavioral flexibility, it is most often used to refer to instrumental learning (▶ Instrumental conditioning) of a two-choice discrimination task, such as a T-maze or two lever operant task. In these tasks, there is a reinforced response (R+) and a response that is not reinforced (R−), and it is this response–outcome association that is reversed. Sometimes, reversal learning is used yet more generally, to describe any task in which a previously reinforced response is no longer reinforced, even where there is, strictly speaking, no reversal. For example, in a ▶ water maze the location of a submerged platform might be moved or, in a multiarm maze, the location of food bait might be changed, such that a previously reinforced response (e.g., "swim to the North-East quadrant" or "go to the right") is no longer reinforced but the reward is now associated with a response not previously reinforced (e.g., "swim to the South-West quadrant" or "go to the left"). However, such spatial relocations are not necessarily equivalent to reversal learning of nonspatial discriminations.

Reversal learning is different to tests involving acquisition of new discriminations. As noted above, the formation of a mental set is not required to perform the tasks in which the presence of set is determined: not only is mental set incidental to the task but also the presence of a set is detected due to the detrimental effect it has on performance. This is not true for reversal learning, which involves "unlearning" an old association before a new association is formed.

Ideally, a task will not conflate reversal learning with either response switching or attentional shifting. It is possible to dissociate switch/shift effects from reversal-learning effects, but only if there is a change of stimuli at the critical stages, such that, at these stages of testing, previously rewarded stimuli or responses are no longer presented and the subject must acquire a novel discrimination. One of the challenges in devising suitable tasks to probe attentional set or learning set in animals is finding a sufficient number of suitable stimuli to enable testing in multiple stages with novel stimuli at each. For example, when visual stimuli are used in studies with rats or mice, the stimulus sets are limited by the limited visual acuity of rodents. For this reason, attentional set is often measured in rodents using baited digging bowls, which are distinguishable on the basis of haptic or odor properties, so exploiting the animals' natural tendency to forage (see Fig. 1). In a single session lasting a few hours, a rat learns a series of discriminations between two bowls. The odor and haptic stimuli are both replaced at the ID and the ED



Behavioral Flexibility: Attentional Shifting, Rule Switching and Response Reversal. Fig. 1. Rats are presented with a pair of bowls on either side of a divider. Both bowls contain a different digging medium filling the bowl and they smell differently (odors are represented by lines above the bowls), but only one of the bowls is baited with food. In an initial acquisition phase (ACQ), either the odor (as shown in the illustration) or the medium indicates which bowl is baited. At the intradimensional (ID) stage, the media and the odors are replaced with novel stimuli. The relevant dimension (in the illustration, the odor) remains relevant for finding the food. At the extradimensional (ED) stage, the media and odors are again replaced with novel stimuli. The previously relevant dimension no longer indicates the location of the food. The animal must change its attentional focus to the other dimension – the medium. Typically, animals require more trials to learn new discriminations when they must reorient their attention (ED stage) compared to when their attention is already appropriately focused (ID stage).

stages, but, at the ED stage, the characteristic of the bowl that is relevant to solve the discrimination is also changed. The additional trials required to learn the discrimination are indicative of the strength of attentional set. The fact that the rodent can discriminate between a very large number of odors and haptic stimuli overcomes the limitations of using visual stimuli.

In the case of rule-switching tasks, it is not stimuli, but responses that must be novel; however, it is not trivial to devise a task for a rodent in which a rule will be extrapolated to form a learning set, which will then benefit new learning, while not being "the same" discrimination. With foraging animals, spatial discriminations are powerful tools as a variety of rules (e.g., egocentric ("turn right"), visual ("approach the light"), and allocentric ("head South")) can be generated to solve them. However, it is problematic to prevent the partial reinforcement of the application of a previously correct rule because there are not a similar variety of responses to express the learning of those rules. If there is still the possibility of making a previously rewarded response by applying an old rule, then the previously learned discrimination will be unintentionally partially reinforced and this might retard learning of the new rule, rather than an attentional switch-cost *per se*.

Impact of Psychoactive Drugs

Impairments in behavioral flexibility have been reported in many different psychiatric and neurological conditions, including ▶ schizophrenia, ▶ attention deficit hyperactivity disorder, ▶ Parkinson's disease, ▶ mild cognitive impairment, Alzheimer's disease, and ▶ bipolar disorder. Most of our current understanding of impairment in behavioral flexibility derives from studies of these conditions, or animal models of these conditions (▶ Primate models of cognition, ▶ Rodent models of cognition, ▶ Dementias: animal models, ▶ Depression: animal models, ▶ Animal models for psychiatric states, ▶ Schizophrenia: animal models), compared to control subject performance. Thus, (dorso)lateral prefrontal cortex of primates (medial prefrontal cortex of rodents) has been implicated in both attentional shifting and rule switching, while impairments in reversal learning are associated with orbital prefrontal cortex. Investigations of the effects of psychoactive drugs on behavioral flexibility have served either to model human pathological conditions by inducing neurochemical imbalance, or to ameliorate the effects of those models. In particular, dopamine (DA), serotonin (5-HT), norepinephrine (NE), and acetylcholine (ACh) have all been implicated in shifting/switching and/or reversal learning.

Dopamine (DA)

Most of the evidence, from patients and experimental animals, implicates prefrontal cortical, and not striatal, ▶ dopamine in shifting/switching performance while striatal dopamine has been implicated in reversal learning.

Impairments in attentional shifting are consistently reported in patients with schizophrenia, a disorder long associated with dopamine overactivity. However, while ▶ first-generation antipsychotic treatments, which block striatal dopamine D_2 receptors, are effective treatments for positive symptoms of schizophrenia, they do not improve and may further impair cognitive (including shifting) impairments. ▶ Second-generation antipsychotics, such as clozapine, olanzapine, and risperidone, do offer some cognitive benefits, perhaps deriving from their actions on prefrontal cortical function and perhaps mediated by effects on receptors other than dopamine.

Parkinson's disease is associated with both frontal and striatal dopamine depletion, either of which could account for the shifting deficits reported in these patients. Nevertheless, converging data suggest that it is prefrontal, rather than striatal, dopamine that is responsible.

Shifting and/or switching impairments in rats have been reported in a variety of animal models of schizophrenia). Subchronic ▶ phencyclidine (PCP) impairs shifting and second-generation, but not the first, antipsychotics ameliorate the deficits. Similarly, ▶ amphetamine sensitization (▶ Sensitization to drugs) impairs shifting and reversal learning. Infusion of the D_1 receptor agonist 1-phenyl-2,3,4,5-tetrahydro-(1H)-3-benzazepine-7,8-diol hydrochloride (SKF38393) into medial prefrontal cortex ameliorates the effect of amphetamine sensitization on shifting, without improving the impairment in reversal learning.

Antagonism of the D_1 receptor by 7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride (SCH 23390) impairs switching, with the D_1 agonist 6-chloro-2,3,4,5-tetrahydro-1-phenyl-1H-3-benzazepine hydrobromide (SKF 81297) having no effect. Switching is also impaired by the D_4 agonist, *N*-(Methyl-4-(2-cyanophenyl)piperazinyl-3-methylbenzamide maleate (PD168077), and improved by the D_4 antagonist, 3-[{4-(4-chlorophenyl)piperazin-1-yl}methyl)-1H-pyrrolo[2,3-*b*]pyridine (L745870).

Serotonin (5-HT)

▶ Serotonin is implicated in various forms of behavioral flexibility, including shifting, switching, and reversal learning. There may be a direct effect in the orbital prefrontal cortex on reversal learning. For example, serotonergic depletion of frontal cortex with 5,7-dihydroxytryptamine

(5,7-DHT) has been reported to impair reversal learning without impairing rule-switching.

A variety of serotonergic compounds improve shifting, but the serotonergic action might be indirect, via a modulation of levels of dopamine, norepinephrine, and/or acetylcholine. For example, the 5-HT_6 receptor antagonist *N*-[3,5-dichloro-2-(methoxy)phenyl]-4-(methoxy)-3-(1-piperazinyl)benzenesulfonamide (SB399885T) improves shifting in normal rats and both the selective 5-HT_6 antagonist 5-chloro-*N*-(4-methoxy-3-piperazin-1-yl-phenyl)-3-methyl-2-benzothiophenesulfonamide (SB271046A) and the antipsychotic, sertindole, ameliorate PCP-induced impairment in shifting. Asenapine (a second-generation antipsychotic, which has higher affinity for 5-HT_{2A}, 5-HT_{2C}, 5-HT_6, and 5-HT_7, as well as α_2-adrenergic receptors than it does for D_2 receptors) ameliorates shifting impairments following a lesion of the prefrontal cortex.

Norepinephrine (NE)

Increasing prefrontal cortical ▶ norepinephrine in normal rats has been reported to improve shifting. However, increasing norepinephrine also increases prefrontal cortical dopamine and this co-modulation means that it is difficult to separate their effects on behavioral flexibility (for review see Arnsten and Li 2005). Nevertheless, there may be specific and selective effects: noradrenergic-specific lesions have been reported to result in impairments in shifting/switching in rats, which can be reversed by the selective NE reuptake inhibitor ▶ atomoxetine, at doses reported to have no effect on prefrontal cortical dopamine.

Acetylcholine (ACh)

Scopolamine (▶ Muscarinic agonists and antagonists) impairs shifting and switching in rats and there have been reports of beneficial effects of nicotine (▶ Nicotinic agonists and antagonists). However, selective lesions of prefrontal or basal forebrain cholinergic neurons impact reversal learning and not shifting (for review see Robbins and Roberts 2007).

Conclusion

Specifying the neurochemical profile of behavioral flexibility is made complex by the co-modulatory effects of the monoaminergic systems in frontal cortex. Nevertheless, there is little doubt that the prefrontal cortex and the innervating neurochemical projection systems are important for executive control, of which behavioral flexibility is a key component.

Cross-References

▶ Animal Models for Psychiatric States
▶ Atomoxetine
▶ Attention Deficit Hyperactivity Disorder
▶ Bipolar Disorder
▶ Classical (Pavlovian) Conditioning
▶ Dementias: Animal Models
▶ Depression: Animal Models
▶ First-Generation Antipsychotics
▶ Impulse Control Disorders
▶ Impulsivity
▶ Instrumental Conditioning
▶ Mild Cognitive Impairment
▶ Muscarinic Agonists and Antagonists
▶ Nicotinic Agonists and Antagonists
▶ Primate Models of Cognition
▶ Rodent Models of Cognition
▶ Schizophrenia
▶ Schizophrenia: Animal Models
▶ Second Generation Antipsychotics
▶ Sensitization to Drugs

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Behavioral Inhibition

Synonyms

Action inhibition; Behavioral flexibility; Impulse control; Motor inhibition

Definition

In cognitive neuroscience, behavioral inhibition is an active inhibitory mechanism that allows us to withhold unwanted or prepotent responses. These responses could be actions or movements and be triggered by either internal or external stimuli. The ability to exert inhibitory

control over automatic reflexes and conditioned responses has been suggested to have evolved in higher mammals to allow slower cognitive processes to guide behavior in certain circumstances. Deficient behavioral inhibition is one of the most prominent symptoms in ADHD.

Cross-References

- ▶ Attention Deficit and Disruptive Behavior Disorders
- ▶ Attention Deficit Hyperactivity Disorder
- ▶ Impulse Control Disorders
- ▶ Impulsivity

Behavioral Models of Psychopathology

- ▶ Animal Models for Psychiatric States

Behavioral Pathologies and Comorbidities

- ▶ Addictive Disorder: Animal Models

Behavioral Phenotyping

- ▶ Phenotyping of Behavioral Characteristics

Behavioral Sensitization

Synonyms

Sensitization to drugs

Definition

An increase in drug effect with repeated drug administration.

Cross-References

- ▶ Sensitization to Drugs
- ▶ Sex Differences in Drug Effects

Behavioral Tests

- ▶ Primate Models of Cognition

Behavioral Tolerance

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Synonyms

Conditioned tolerance; Contingent tolerance

Definition

▶ Behavioral tolerance describes the diminution of a drug-induced disruption of a goal-oriented behavior that is dependent upon learning processes, i.e., performance of the behavior while intoxicated.

Impact of Psychoactive Drugs

Behavioral Tolerance

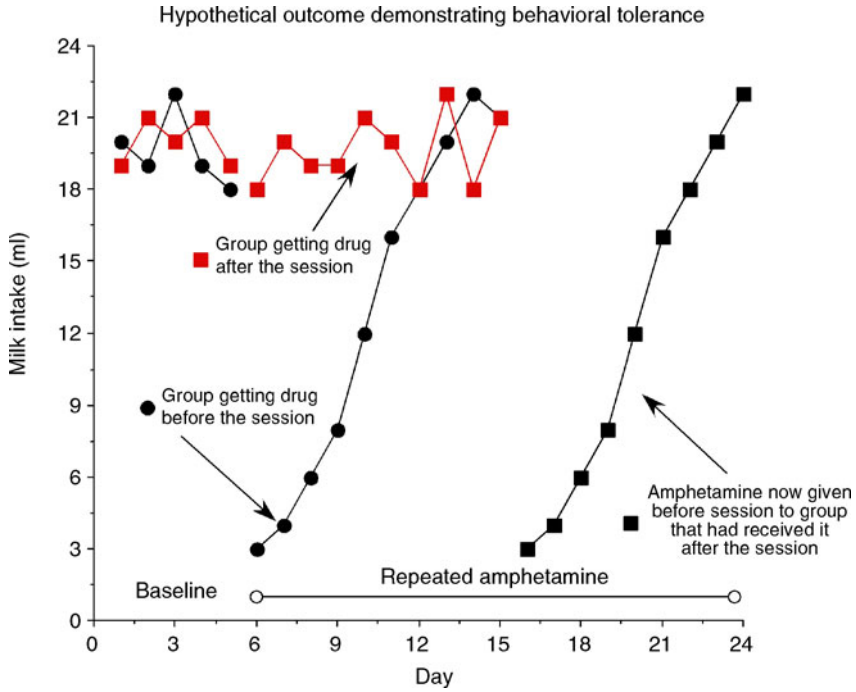
▶ Tolerance refers to the diminution of a drug's effect with repeated dosing. In controlled laboratory settings, tolerance is measured by giving a drug repeatedly, and assessing a dependent measure as a function of drug history. In clinical settings, tolerance is inferred when a person reports that she/he thinks it currently takes a greater amount of drug to achieve an effect than it did when use of the drug first started. A modifier is often used to indicate a type of tolerance or a mechanism responsible for tolerance. Some modifiers are used to further describe the conditions under which tolerance is observed. For example, ▶ acute tolerance refers to a diminution of effect during a single drug taking episode such that the drug produces greater effects as blood concentration increases, i.e., on the ascending limb, compared to when blood concentration decreases, i.e., on the descending limb of the drug concentration curve. Other modifiers are used to describe the mechanism by which tolerance occurs. For example, ▶ pharmacodynamic tolerance describes a diminution of a drug effect due to a more rapid elimination of the drug from the body. Behavioral tolerance actually combines both types of meanings; descriptive and mechanistic. Behavioral tolerance describes the diminution of a drug-induced disruption of a goal-oriented behavior with repeated dosing that is dependent upon learning processes, i.e., performance of the behavior while intoxicated. Given the use of many words to modify the term tolerance, it is not surprising that some terms related to tolerance are poorly used. Behavioral tolerance does not simply mean tolerance to a behavioral effect of a drug.

While scientists and drug users alike had long noticed that practicing a behavior while under the influence of a drug helped one overcome disruptions in behavior, the basic tenets of behavioral tolerance were well demonstrated by Schuster et al. (1966). For years, it had been noticed that tolerance developed at different rates to different behaviors, and that some drug effects became greater with time, i.e., ► sensitization. A key issue was what factors determined the development of tolerance versus sensitization. It was well-known that ► amphetamine and other stimulants commonly increased rates of responding (rate-dependency). Schuster and colleagues hypothesized that tolerance would develop to responding that was disrupted by the rate-increasing effects of amphetamine, but tolerance would not develop to responding that was *not* disrupted by the rate-increasing effects of amphetamine. What was needed was an operant schedule of responding that reinforced low rates of behavior and one that did not. Thus, the effects of acute and repeated amphetamine administration in rats responding under a multiple response schedule were examined: responding during 1 component was reinforced under a DRL, or differential reinforcement of low rates of responding schedule in which reinforcement is based on time since last response, and responding during another component was reinforced under an FI, or fixed interval schedule in which reinforcement is based on time since last reinforcer. Using these schedules, an increase in response rate will disrupt DRL performance, but have minimal effects on FI performance. Tolerance should develop specifically to the effects of amphetamine on DRL performance which decrease reinforcer deliveries.

As expected, amphetamine increased the rate of responding and the increases were associated with a decrease in food pellet deliveries during the DRL component, but *not* during the FI component. During repeated amphetamine dosing, tolerance developed to the rate-increasing effects of amphetamine on DRL responding such that after 30 days, rats earned as many food pellets as they did during baseline. There was no evidence of tolerance to the rate-increasing effect of amphetamine during the FI component; an action that did not decrease food pellet deliveries. Tolerance development was dependent upon the environmental contingencies. Hence, behavioral tolerance is also sometimes referred to as contingent tolerance. Schuster et al. (1966) proposed the reinforcement-loss hypothesis to account for behavioral tolerance. "Behavioral tolerance will develop in those aspects of the organisms' behavioral repertoire where the action of the drug is such that it disrupts the organism's behavior in meeting the environmental requirement for reinforcements. Conversely, where the actions of the drug enhance, or do not affect the organism's behavior in meeting reinforcement requirements we do not expect the development of behavioral tolerance." p. 181

While Schuster et al. (1966) used a within-participants design to show differential development of tolerance, other researchers, e.g., Carlton and Wolgin (1971) used a between group design to assess the role of behavioral experience in tolerance development. In order to demonstrate that behavioral factors played a role in tolerance development, it is important to have a group of animals who have the same drug history, but a different behavioral history. This can be accomplished by giving one group of animals drug before the experimental session so that these animals can experience the drug effect in combination with the behavioral requirement, while another group of animals receive the drug after the behavioral session so that they do *not* experience the drug–environment interaction (before vs. after design; see Fig. 1). A popular approach for examining the effect of repeated dosing with the anorectic drug amphetamine on milk drinking involves one group of rats given amphetamine before the session and one group of rats given amphetamine after the milk-drinking session. Thus, drug exposure is matched between the two groups. In this case, amphetamine substantially decreases milk drinking when given before the session, but tolerance developed rapidly and milk drinking is back to baseline levels in less than 10 days. If drug exposure alone was sufficient to induce tolerance then the animals who had received amphetamine after the session should also have be tolerant to the effect of amphetamine when it is then given before the session. This is not the case. Amphetamine exposure alone is not sufficient to induce tolerance. In fact, when the group that had received amphetamine after the session is given repeated amphetamine before the session it takes as long to develop tolerance as it did in the other group of rats; amphetamine experience after the session did not increase the rate of tolerance development. Clearly, drinking milk under the influence of amphetamine was necessary in order to develop tolerance to the anorectic effect of amphetamine.

Data collected using similar procedures support the idea that reinforcer loss and instrumental learning of behaviors that remediate the loss are a key component in the development of behavioral tolerance, i.e., tolerance occurs because new compensatory behaviors are learned. One mechanism by which stimulants can decrease food intake is by eliciting behavior, such as stereotypy that is incompatible with milk drinking that requires organized licking and spout contact. Stereotypy is not incompatible



Behavioral Tolerance. Fig. 1. Hypothetical data, based on Chen (1968) and Carlton and Wolgin (1971) showing how behavioral tolerance can be measured using one group of animals that initially receives a drug (in this example amphetamine) that disrupts reinforcement (milk drinking in this example) before daily access to the reinforcer, and a second group of animals that initially receives a drug that disrupts reinforcement after daily access to the reinforcer. The appetitive behavior decreases in the group that received drug before the session, but tolerance develops over time with performance returning to baseline levels. If behavioral factors were not involved then when the animals in the after group were given drug before the session they too should also show tolerance, i.e., intake would be at baseline levels. If experience with the behavior and reinforcement while under the influence of drug were necessary then behavior would be disrupted as if they had not received any drug yet. Furthermore, if behavior recovers at the same rate as it did in the group first exposed to drug before the session then this indicates that the prior pharmacological drug experience produced no savings or increase in the rate of tolerance development.

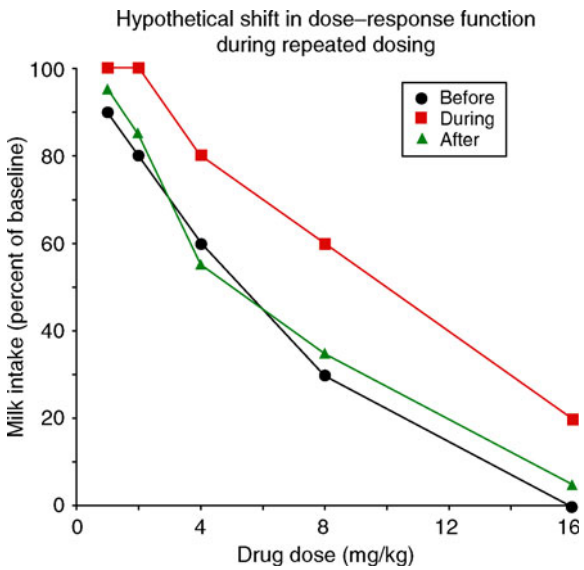
with milk drinking that only requires swallowing milk that is delivered intraorally. One approach for testing the learning hypothesis of behavioral tolerance is to compare the effects of an anorectic stimulant drug on milk swallowing versus milk drinking, e.g., Wolgin and Munoz (2006). You would hypothesize that stereotypy induced by a stimulant would disrupt milk drinking, but not milk swallowing such that tolerance would only be observed in the rats that must learn to approach and lick the fluid spout in the presence of drug-induced stereotypy. This is indeed the case. When the animals that received drug and drank milk intraorally were switched to licking the fluid spout, the previous exposure to the stimulant did not provide savings in the rate of tolerance development. Thus, tolerance development required the contingency between licking and fluid delivery to suppress stereotypic movements.

These data are exciting in that they clearly showed a role for environmental contingencies in modulating the response to long-term drug administration. The development of tolerance only in the animals drinking milk after drug administration strongly argues that dispositional and pharmacodynamic factors alone cannot account for tolerance development, and also strongly supports the reinforcement-loss hypothesis to account for behavioral tolerance. The demonstration of behavioral tolerance does not rule out a contribution for dispositional tolerance or some other factor related to the environment modulating tolerance development. For example, the increase in food deprivation due to reinforcement loss or some motor component of behaving could alter the physiological response to a drug, and in turn alter drug disposition.

An ideal study on behavioral tolerance would determine complete dose–response functions for a drug effect

on behavior before, during, and after a period of repeated administration in one group of animals receiving drug prior to the session, and another group of animals receiving drug post session. In this way tolerance development could be clearly quantified and defined as a shift to the right in the dose-response function during the period of repeated administration (see Fig. 2). Behavioral tolerance would be defined as a shift to the right in the dose-response function during the period of repeated administration only in those animals receiving drug prior to the session. Although ideal, many studies do not determine dose-response function during the period of repeated administration. In the absence of a shift to the right in the dose-response function one must be cautious in assuming tolerance development. It is possible that the animals may have learned the compensatory behavior only under the influence of the dose given repeatedly. In that case, the repeated drug dose may be functioning as a discriminative stimulus for responding.

Behavioral tolerance, i.e., tolerance to a behavioral effect of a drug that is dependent upon experience with reinforcement while intoxicated, has been well documented. Although the reinforcement-loss hypothesis that requires instrumental responding for tolerance to develop has received much support, the exact biological mechanisms accounting for the drug–environment interaction have not been identified. Future work in neuroscience may wish to take advantage of the specificity of behavioral tolerance development to examine the central nervous system changes associated with learning including analysis of neural pathways and cellular mechanisms. Such work will not only provide valuable insight into the central mechanisms underlying behavioral tolerance, but also elucidate mechanisms associated with learning in general.



Behavioral Tolerance. Fig. 2. Hypothetical data showing how complete dose–response functions are used to demonstrate the development of tolerance. During repeated administration the effect of each dose is less than observed before the period of repeated administration, i.e., there is a shift to the right in the dose–response function. After repeated administration the effect of each dose is similar to what was observed before the period of repeated administration, i.e., the dose–response function has shifted back to baseline.

Cross-References

- ▶ Appetite Suppressants
- ▶ Drug (dose)-Effect Function (Curve)
- ▶ Instrumental Conditioning
- ▶ Operant Behavior in Animals
- ▶ Rate-Dependency Theory
- ▶ Schedule of Reinforcement
- ▶ Sensitization to Drugs

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Benperidol

Definition

Benperidol is an older antipsychotic belonging to the ▶ butyrophenone class that blocks dopamine D2 receptors with high affinity. While it has similar properties to ▶ haloperidol, benperidol has been used primarily for the treatment of deviant antisocial sexual behavior. Potential side effects, as with other neuroleptics, include extrapyramidal symptoms (EPS), QT prolongation, and hyperprolactinemia.

Cross-References

- ▶ Antipsychotics
- ▶ First-Generation Antipsychotics
- ▶ Sexual Disorders

Benserazide

Synonyms

2-amino-3-hydroxy-N'-[(2,3,4-trihydroxyphenyl) methyl] propanehydrazide; Ro 4-4602; Serazide

Definition

Benserazide is a peripherally acting aromatic l-amino acid decarboxylase or DOPA decarboxylase inhibitor and as such inhibits the early degradation of L-DOPA, the dopamine precursor in blood. Benserazide is always used in combination with L-DOPA in the management of ► Parkinson's disease. Benserazide does not cross the blood–brain barrier and has no anti-Parkinson's effects in its own right, nor does it treat ► dyskinesias. It is also used in the treatment of restless leg syndrome.

Cross-References

► Anti-Parkinson Drugs
► DOPA Decarboxylase Inhibitor
► L-DOPA

Benzatropine

Synonyms

Benztropine; Endo-3-(diphenylmethoxy)-8-methyl-8-azabicyclo[3.2.1]octane methanesulfonate

Definition

Benztropine is a centrally acting anticholinergic drug. It is primarily used as an adjunct in the treatment of drug-induced Parkinsonism and other forms of Parkinsonism, and ► akathisias. Benztropine can also be used as second line treatment of ► Parkinson's disease; it improves tremor, but not rigidity. Benztropine may also be used to treat acute dystonia, which results in abnormal muscle contractions with twists in limbs, trunk, or face. Anticholinergics are generally less effective than ► L-DOPA, but are of use in all forms of Parkinsonism as their side effect profile is rather mild.

Cross-References

► Anti-Parkinson Drugs

Benzedrine

► Amphetamine

Benzodiazepine Dependence

► Sedative, Hypnotic, and Anxiolytic Dependence

Benzodiazepines

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Definition

BZs are used for a number of indications in general practice, neurology, anesthesiology, and psychiatry:

Insomnia
Adjuvants in anesthesia
Anxiety disorders (GAD, specific phobias, panic disorder, social anxiety disorder)
Adjustment disorders
Organic brain syndrome (acute, e.g., delirium tremens, and chronic, e.g., dementia)
Anxiety in depression (as an adjunct at initiation of antidepressant therapy)
Schizophrenia (catatonic type, and for rapid tranquillization)
Acute mania
Avoidant personality disorder
Alcohol and sedative withdrawal
Suicidal patients with prominent anxiety symptoms
Status epilepticus
Tardive dyskinesia, akathisia
Spasticity (e.g., spastic paraplegia), acute torticollis
Contraindications: Myasthenia gravis, sleep apnea, severe pulmonary disease

Intolerance of SSRIs/SNRIs is another important reason to prescribe benzodiazepines. SSRIs/SNRIs sometimes cause a paradoxical increase in anxiety at initiation of treatment that calls for adjunct prescribing of a BZ. Although anxiety is not a DSM-IV criterion for a major depressive episode, clinicians should be aware of the frequent anxiety component in depression that needs to be addressed, as anxiety may precipitate suicidal acts.

BZ anxiolytics are recommended for short-term (<1 month) relief of anxiety and insomnia and as an adjunct

to initial antidepressants, according to a 1997 guideline of the Royal College of Psychiatrists. It is stated that "dose escalation in uncomplicated cases is rare," and that "The decision to allow dependence to develop is sometimes defensible, but it must be appreciated that, once dependence has become established, it is often extremely difficult to treat and may become a long-term or even permanent state."

Another guideline emanating from the Psychopharmacology Unit at the University of Bristol in 1995 advises that patients with panic, generalized, or social anxiety disorder be started on an SSRI/SNRI and given adjunct BZ for 3–4 weeks. If the SSRI/SNRI turns out to be ineffective, BZs are used as single therapy after careful discussion with the patient. BZs are also used to alleviate acute (trauma-induced) anxiety on the grounds that it would by unethical to deny patients with severe anxiety the benefits of immediate relief.

A 2007 survey among specialists found that BZs were the last resort for a minority of complicated patients, also pointing to the value of using BZ in rapid tranquillization. A 2008 task force for the World Association of Societies of Biological Psychiatry issued similar recommendations.

Pharmacological Properties

Pharmacodynamics

Early work on central monoaminergic mechanisms concluded that the reduction of fear-motivated behavior and aggressiveness in rats could be due to reductions of noradrenaline, serotonin, and dopamine turnover. Later, it was shown that the principal effect of ▶ chlordiazepoxide and diazepam is by enhancing the action of the inhibitory transmitter ▶ GABA on the GABA-A receptors. The hypnotics ▶ zopiclone, eszopiclone, ▶ zolpidem, and ▶ zaleplon, although structurally different from the BZs and different from each other as well, also act on the same site on the GABA-A receptor as the effects of all these drugs are blocked by the antagonist ▶ flumazenil. Many other substances act on the GABA-A receptor but at different modulatory sites, such as ▶ neurosteroids, anesthetics, and ▶ alcohol. If taken together, these can all potentiate the actions of the benzodiazepines, leading to dangerous levels of sedation (Nutt and Malizia 2001).

There are 14 genes identified encoding GABA-A receptor subunits, and 5 of these come together to make a functioning receptor. BZs may produce their anxiolytic effects by stimulating certain GABA-A receptor subunits (especially $\alpha 2$ and $\alpha 3$) in limbic structures such as the ▶ amygdala and the septum. Deficits in inhibitory neurotransmission may increase anxiety-related behavior, and increased inhibitory GABAergic activity causes behavioral inhibition in mice, a proxy for anxiety-related behavior. When the BZ antagonist flumazenil is administered, human subjects on maintenance benzodiazepine treatment react with a withdrawal state characterized by anxiety, dizziness, nausea, sweating, and perceptual distortions. Recent work shows that the ▶ hypothalamic pituitary axis activity is modulated by effects of BZs on the ▶ corticotropin-releasing factor.

Pharmacokinetics

There are two key ▶ pharmacokinetic elements to the BZs; speed of onset and speed of offset. In general, faster onset is better for BZ hypnotics and those used for status epilepticus. In the former case, more rapid uptake from the gut is obtained using drugs with certain physicochemical properties such as zolpidem. For seizures, the fastest route for a clinical effect is intravenous or rectal. There are also formulations for nasal administration, e.g., of midazolam.

Speed of offset is determined by several factors of which the most important is the metabolic ▶ half-life of the drug. The first-generation BZs had half-lives of more than 24 h, with active metabolites with even slower clearance rates. While this was useful in conditions such as epilepsy, drug accumulation was an issue when they were used for anxiety and insomnia as it might cause sedation with a risk of fall hip fractures, especially in the elderly. To reduce this problem, ▶ lorazepam and ▶ alprazolam with a shorter half-life were developed. For hypnotic use, ▶ temazepam and ▶ triazolam were developed followed by the Z-drugs. All these have short half-lives with low risk of daytime sedation (Table 1).

Safety

Heritability and Pharmacodynamics of Addiction and Dependence

The heritability for addictions is the focus of intense research efforts. A set of 89 genes has been identified for phenotypes of alcohol, methamphetamine, nicotine, and barbiturate addiction that regulate explicit memory systems. This long-term effect on memory may be more important than the initial drive for euphoria, turning an individual into compulsive drug use, and to drug craving being precipitated by social reminders of drug use for many drugs, especially cocaine and metamphetamine. ▶ Dopamine release is an important determinant of reinforcing drug experiences and increased self-administration. However, in contrast to these substances that cause positive rewarding effects by increasing

Benzodiazepines. Table 1. Key kinetic properties of commonly used benzodiazepines.

Drug	Free fraction (%)	T_{max}	$T_{1/2}$
Midazolam	2		
Diazepam	2		28.0
Zopiclone	20	3.0	4.4
Zolpidem	8	1.2	1.9
Zaleplon	40	1.4	1.0
Triazolam	80	1.4	2.8
Flunitrazepam	20	0.5	4.0
Clobazam	11		47.0
Nitrazepam	15	1.6	24.0
Temazepam	4	1.1	9.1
Lorazepam			
Lormetazepam	8	2.0	10.0
Alprazolam	20	1.3	9.5
Alprazolam slow release	20	10.0	28.0

dopamine release, BZs have not been shown to enhance extracellular dopamine in the ▶ nucleus accumbens, but actually *reduce* dopamine levels (Licata and Rowlett 2008). Thus, the BZs are not capable of inducing dependence by the same mechanism as addictive drugs. The connecting mechanism between GABA-A receptors and the reduction in dopamine appears to be by a modulation in the glutamatergic transmission of ▶ ventral tegmental area dopamine neurons (Heikkinen et al. 2009). Recent evidence points to a role for extrasynaptic GABA receptors regulating intake and dependence development, although these mechanisms are not clearly identified. ▶ Barbiturates have three distinct effects on GABA-A receptor activity, but little is known about the structural rearrangements underlying these functional effects.

BZ Discontinuation Symptoms

BZ ▶ discontinuation symptoms appear in some patients upon rapid cessation of therapeutic dose treatment, first called low-dose dependence by Malcolm Lader in 1981. Such symptoms occur at rates varying between 5 and 75% after therapeutic use for at least 1 year, probably reflecting selection bias in different study populations. Only a fraction of patients experience major distress. The discontinuation symptoms reportedly manifest themselves as a rebound of anxiety/insomnia, agitation, dysphoria, fatigue, nausea, tremor, tinnitus, muscle twitches, paraesthesias, perceptual distortions, and confusion. The partial BZ agonist flumazenil significantly reduces withdrawal symptoms and craving in patients in comparison with ▶ oxazepam tapering over a 7-day period, and with placebo. The mechanism is believed to normalize and upregulate BZ receptors by restoring GABA receptor allosteric structure.

Several other classes of psychoactive and other drugs cause discontinuation or rebound phenomena: SSRIs, SNRIs, antipsychotics, lithium, corticosteroids, beta-blockers, beta-stimulants and other medications that are rapidly discontinued in humans. The type of discontinuation symptoms is related to the pharmacodynamics of the medication, pharmacokinetics, and negative expectations (*nocebo*) (Nutt 2003).

Tolerance

Acquired ▶ tolerance to the effects of a substance is a complex mechanism based on the pharmacogenetic make-up of an individual, the duration and amount of substance administered, and other unknown factors. BZ tolerance to the anticonvulsant action may develop with chronic exposure as a consequence of regulatory changes in the expression of GABA-A receptor subunits in specific brain areas. Tolerance develops quickly to the sedative and motor coordination effects of BZ anxiolytics, but not necessarily to the anxiolytic or memory impairing effects, and therapeutic drug doses are rarely increased with time (Licata and Rowlett 2008). Some patients develop tolerance to the hypnotic effects of BZs including the Z-drugs, as evidenced by rebound insomnia on withdrawal, and there are reports of abuse (Hajak et al. 2003).

Problem Patients

Several individual components other than the affinity with which a drug binds to the benzodiazepine modulatory site have been identified in discontinuation symptoms: dependent (harm avoidant) personality traits, negative expectations (*nocebo*), and relapse and rebound of the anxiety or sleep disorder for which treatment was instituted. Studies of the medical files of patients claiming iatrogenic BZ-induced neuropsychiatric symptoms found that the symptoms attributed to BZ treatment were present before it was instituted (Mattila-Evenden et al. 2001).

In 1990, a task force appointed by the American Psychiatric Association issued a report on the potential hazards of BZs. The report stopped short of concluding that all criteria for dependence occurred. It further stated that

- Physiologic dependence on benzodiazepines, as indicated by the appearance of discontinuance symptoms, can develop with therapeutic doses. . . . Benzodiazepines

do not strongly reinforce their own use, and are not widely abused drugs. When abuse does occur, it is almost always among persons who are also actively abusing alcohol, opiates, or other sedative hypnotics.

The Scottish pharmacologist LF Prescott stated in 1983 that

- In contrast to the enormous general consumption of benzodiazepines, their abuse "for kicks" by young drug takers is distinctly uncommon and they have no street value. Unlike barbiturates, methaqualone, and ethanol, the benzodiazepines do not normally cause disinhibited behavior and excitement. They are not "fun" drugs and have a deadening rather than stimulating effect. In Edinburgh, chemists' shops (drug stores) are often broken into; the thieves are very discriminating and clear out all the narcotics, barbiturates, methaqualone, and amphetamines but leave the benzodiazepines behind.

The founder of the Haight-Ashbury free medical clinic for the flower-power generation in San Francisco, David E. Smith was of a similar opinion in 1985:

- . . . most benzodiazepine abuse is secondary drug abuse: self-medication of adverse effects of other drugs (e.g., to reduce the nervousness induced by cocaine, or self-medication of heroin withdrawal symptoms). Because of benzodiazepines' effectiveness in ameliorating symptoms induced by other drugs or withdrawal, benzodiazepines have drug value in the illicit drug marketplace. . .The amount of primary abuse of the benzodiazepines in the drug culture is minimal. . .

Is it possible to identify risk factors for BZ abuse in patients? Individual risk factors for BZ abuse include antisocial, borderline, and histrionic personality disorders, alcohol and stimulant abuse, somatization, and familial sociopathy. Another typical behavior of such sedative–hypnotic abusers is "doctor shopping" – seeing multiple doctors to acquire BZs to potentiate effects of street opioids or alcohol, or to facilitate getting out of a period of a CNS stimulant high (Allgulander 2000). Such antisocial behavior violates the bond of trust, yet can be done with impunity in most countries. It can also include forging and manipulating of prescriptions, smuggling in used, labeled pill bottles, and prescribing by proxy (colluding with a spouse or a friend posing as patient with simulated symptoms). The internet has become a major source of BZs, anabolic steroids, opioids, and other drugs for nonmedical uses. The risk of suicide in such patients is extremely high, partly because many of them are doctors, nurses, or pharmacist with access to lethal drugs and with the skills to use them (Allgulander et al. 1987). Still, some argue that there is no reason to exclude patients with a history of substance abuse and dependence from BZ treatment, while others see a need to preclude such patients.

Memory Impairment

One important adverse effect of long-term benzodiazepine use is memory impairment. In a meta-analysis of tested subjects after a mean of 10 years of BZ treatment, significant impairment was found in all cognitive domains (Barker et al. 2004). Restoration of cognitive function was also noted, although impairment persisted for up to 6 months in comparison with controls or normative data in 11 of 12 tested domains, most notably verbal and working memories, psychomotor speed, and motor control/performance. No neuroimaging abnormalities have been noted in long-term users of BZs.

Clinical Uses

Historical Notes

From the early 1900s and for 60 years, barbiturate derivatives were the sedative–hypnotics of choice, in spite of their narrow safety margin (see ▶ Barbiturates). Following the breaking news of chlorpromazine as an antipsychotic in 1952, several new sedative–hypnotics were developed, such as methaqualone, ▶ meprobamate, ▶ clomethiazole, and gluthetimide. They had all been overtaken by ▶ diazepam and chlordiazepoxide by the mid-1960s. Hoffman-La Roche patented the first benzodiazepine chlordiazepoxide in 1959, and it was approved by the FDA under the trade name Librium in 1960, soon followed by diazepam, oxazepam, and ▶ nitrazepam. The more potent alprazolam was introduced in the early 1980s. The United Nations Convention on Psychotropic Substances Schedule IV lists 34 BZs for the purpose of restricting import and export, to require licenses for manufacture and trade, and to be available by prescription only. Diazepam is the only benzodiazepine on the WHO list of essential medicines.

The BZs were enthusiastically marketed in the 1960s, their use peaking in the mid 1970s. They were accepted by clinicians as being safe, effective, and predictable, much more so than the barbiturates. The prominent psychopharmacologist, Malcolm Lader, reacted to the increasing sales of BZs in the 1970s with social explanations (Lader 1978). He argued that BZ prescribing had become a solution to emotional problems in the lower social classes; a substitute for counseling that initiated a self-perpetuating treatment for fear of precipitating discontinuation

symptoms. Lader argued that this use of BZs medicalized social problems:

> It is much cheaper to tranquilize distraught housewives living in isolation in tower blocks with nowhere for their children to play than to demolish these blocks, and to rebuild on a human scale, or even to provide playgroups. . . An educational campaign to make doctors realize the more nebulous dangers of our present scale of use of the benzodiazepines is urgently needed.

Malcolm Lader then appeared on the BBC; an activist group was formed in the UK, lawyers got involved, and legal class actions were set up.

When the BZs became an ethical, social, and political target, prescribing was substantially reduced, precipitating a need for new evidence-based treatments of anxiety disorders. This coincided with the emerging DSM-III nosology for ▶ anxiety and ▶ mood disorders. ▶ Buspirone was readily accepted by regulatory bodies for anxiety symptoms. In the 1990s, the SSRIs/SNRIs became a substitute for the BZs as the primary drugs of choice, approved by regulatory authorities for the new DSM-III anxiety disorders: generalized, social, and ▶ panic anxiety, ▶ posttraumatic stress disorder, and ▶ obsessive-compulsive disorder. Although much slower in anxiolytic response, these medications had the advantage of acting both as antidepressant and anxiolytic, and with no street value for nonmedical use. These drugs became the drugs of choice in the absence of comparative trials with BZs, and in spite of a considerable side effect burden such as sexual dysfunction, sweating, nausea, and headaches (Baldwin et al. 2005). The "Z-drugs," zopiclone, eszopiclone, zaleplon, and zolpidem, were subsequently approved for insomnia.

BZs in Public Health and Inpatient Surveys

The Pharmacy Corporation, Sweden, analyzes prescriptions that have been issued to the patient, using the mean therapeutic dose per 1,000 inhabitants per day as an index (DDD/TID). In 2006, there were 50 DDD/TID of BZs in the Swedish general population, 60% of which were Z-drugs (zopiclone, zolpidem, zaleplon), 28% daytime BZ anxiolytics (diazepam, oxazepam, lorazepam, alprazolam), and 12% BZ hypnotics (flunitrazepam, nitrazepam). Z-drugs were mostly prescribed to elderly patients. For comparison, SSRI/SNRI prescribing in 2006 in Sweden was 65 DDD/TID, and the rates of BZ prescribing in other European countries varied between 43 and 62 DDD/TID (Petitjean et al. 2007).

In the Swedish public health survey in 2007, 5% of men and 8% of women aged 16–84 years, reported use of anxiolytics (including BZs) during the last 3 months. Antidepressant use was reported by 6 and 9% of men and women, respectively. For both drug classes, much higher rates were reported by those unemployed or on disability pension, and by immigrants from non-EU countries, corresponding to higher rates of reported mental health problems among these subgroups.

Although utilization rates of anxiolytics and other psychotropic drugs differ markedly between European countries, there were generally strong associations between the severity of mental health problems and reported treatment with such medications. A Swiss survey found that 44% of patients received only one BZ prescription, while those who continued treatment used lower than recommended doses except in 1.6% of patients who used more than twice the recommended therapeutic dose (Petitjean et al. 2007). It was projected from the data that 0.16% of the adult Swiss population abused or were dependent on benzodiazepines.

Admissions with a diagnosis of ▶ sedative/hypnotic dependence were studied in a national hospital data registry on random samples of adult Swedes (Allgulander 1989). There were 38 such admissions in 15 years among 32,679 Swedes, 21 of which were in polydrug users taking street drugs and/or alcohol as well. This result yielded a risk of 3.5 per 100,000 person years. In another inpatient registry analysis covering a 14-year period in Stockholm County (pop. 1.6 million), substance use disorders on prescribed medications (sedatives, hypnotics, and analgesics) were diagnosed in 676 inpatients, yielding a risk of 3.0 per 100,000 person years.

Two Dutch studies of first-time BZ users found an overall improvement in health-related quality of life over a 6 month period, compared to a matched reference group, and no increase in long-term utilization compared to community controls during a 4 year follow-up, respectively.

Appendix

The DSM-IV states in section 304.10 Sedative, Hypnotic, or Anxiolytic dependence

> There may be evidence of tolerance and withdrawal in the absence of a diagnosis of Substance Dependence in an individual who has abruptly discontinued benzodiazepines that were taken for long periods of time at prescribed and therapeutic doses. A diagnosis of Substance Dependence should be considered only when, in addition to having physiologic dependence, the individual using the substance shows evidence of a range of problems (e.g., an individual who has developed drug-seeking behavior to the extent that important activities are given up or reduced to obtain the substance. . . Sedative, Hypnotic,

or anxiolytic Dependence and Abuse may often be associated with Dependence on, or Abuse of, other substances (e.g., alcohol, cannabis, cocaine, heroin, amphetamines). Sedatives are often used to alleviate the unwanted effects of these other substances... Antisocial behavior and Antisocial Personality Disorder are associated with Sedative, Hypnotic, or Anxiolytic Dependence and Abuse, especially when the substances are obtained illegally... Most of these individuals take the medication as directed, without evidence of misuse... The more usual course involves young people in their teens or 20s who may escalate their "recreational" use of sedatives, hypnotics, and anxiolytics to the point at which they develop problems that might qualify for a diagnosis of Dependence or Abuse... Although the great majority of those who are prescribed a medication from this class do not develop problems, a small proportion do... substance-seeking behavior becomes more prominent and the person may seek out multiple physicians to obtain sufficient supplies of the medication.

With regard to benzodiazepines, the DSM-IV states that

- It should be noted that there are individuals who continue to take benzodiazepine medication according to a physician's direction for a legitimate medical indication over extended periods of time. Even if physiologic dependent on the medication, many of these individuals do not develop symptoms that meet the criteria for Dependence, because they are not preoccupied with obtaining the substance and its use does not interfere with their performance of usual social or occupational roles.

Cross-References

- ▶ Abuse Liability Evaluation
- ▶ Alprazolam
- ▶ Anticonvulsants
- ▶ Bromazepam
- ▶ Chlordiazepoxide
- ▶ Clobazam
- ▶ Cloxazolam
- ▶ Diazepam
- ▶ Drug Interactions
- ▶ Ethical Issues in Human Psychopharmacology
- ▶ Flurazepam
- ▶ Habituation
- ▶ History of Psychopharmacology
- ▶ Hypnotics
- ▶ Insomnias
- ▶ Lorazepam
- ▶ Midazolam
- ▶ Nitrazepam
- ▶ Pharmacodynamic Tolerance
- ▶ Pharmacokinetics
- ▶ Sedative, Hypnotic, and Anxiolytic Dependence
- ▶ Temazepam
- ▶ Triazolam
- ▶ Withdrawal Syndromes

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Benztropine

- ▶ Benzatropine

Beta Amyloid

► Amyloid-Beta

Beta-Adrenoceptor Antagonists

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Synonyms

Beta-adrenoceptor blocking drugs; Beta-blockers

Definition

Beta-adrenoceptor antagonists (β-blockers), created by Sir James Black after research in the 1950s and 1960s, are well-known drugs in cardiology and circulatory diseases, and their role in psychiatry is limited. As their name implies, they inhibit the effects of adrenaline and ► noradrenaline on β-receptors, but the members of the drug class vary in their affinity for the two main types of β-receptor and in the extent to which they have stimulant (i.e., partial agonist) effects on these receptors. Stimulation of β_1-receptors by adrenaline has its main effects on the heart with increased speed of cardiac conduction velocity and cardiac output, with a lesser effect on the kidney in stimulating the release of renin. Stimulation of β_2-receptors induces tremor in striated muscle but relaxation in smooth muscle, and by increasing glycogenolysis in both liver and striated muscles, it promotes the production of glucose for increased pumping action. There are also β_3-receptors involved in the breakdown of fat (lipolysis), which may also have a role in smooth muscle and cardiac function, but their effects are minor compared with the other β receptors.

Pharmacological Properties

β_1-Adrenoceptor antagonists act on the receptors in heart and kidney and their blockade reduces the demands on cardiac muscle, and by concomitant reduction of renin secretion in the kidney, blood pressure is lowered. They also act on β_1-receptors in the eye and may be used to reduce glaucoma. β_2-blocking drugs act on receptors in skeletal muscle, smooth muscle in the gastrointestinal tract, liver, uterus, and lungs, and thereby reduce tremor in voluntary musculature, reduce the opening of bronchi in the respiratory tract, and lessen the breakdown of glycogen. It has also been suggested that β-adrenoceptor antagonists may block ► serotonin autoreceptors, and thereby have a role in the augmentation of antidepressant therapy with selective serotonin reuptake inhibitors, and one β-blocking drug, pindolol, has been used specifically for this purpose. However, this pharmacological action is far from being confirmed and remains a speculative suggestion. In general, the β_1-blocking effects are regarded as therapeutically valuable and β_2-blockade as unhelpful with a tendency to create adverse effects, of which reduced bronchial dilation, provoking asthma in susceptible subjects, is one of the most prominent. In higher doses, β-adrenoceptor antagonists have some central nervous system effects including drowsiness, insomnia, and impairment of reaction time, but it seems unlikely that these are due to β-blockade. As some drugs (e.g., sotalol, atenolol) are water soluble and do not penetrate the central nervous system easily, they may reduce the incidence of such effects. As some of the more peripheral indications for β-adrenoceptor antagonists (e.g., reduction of aggression) are likely, if confirmed, to be due to central nervous system action, this is relevant to the choice of drug. One of the well-documented adverse effects of β-adrenoceptor antagonists in general medicine is depression; it is not clear how this is generated.

Mechanisms of Action

There are many β-adrenoceptor antagonists; the main ones and their indications are summarized in Table 1. It is noted that very few of them are used for psychiatric purposes. The possible action of pindolol in promoting the effect of ► SSRI antidepressants mentioned earlier has not been tested with other drugs in this group; its value remains to be determined.

The β_1-blocking effects that are so helpful in cardiology have a potential use in the treatment of various forms of anxiety. There has been considerable argument over the mechanism whereby such effects are mediated. Most available data support the hypothesis that the action is a direct consequence of peripheral ► β-blockade, not of any central effects. This is based on several lines of reasoning: the fact that water-soluble β-blocking drugs are as effective as lipid-soluble ones in anxiety, the evidence that the specific somatic symptoms of tremor and palpitations are helped most by treatment, the lack of efficacy of the d-isomer of ► propranolol, which has no β-blocking activity, and the relatively low doses of drug necessary to reduce anxiety symptoms when compared with the higher doses normally associated with central nervous system effects.

Some studies have suggested that many other symptoms found in ► generalized anxiety, completely

Beta-Adrenoceptor Antagonists. Table 1. Beta-adrenoceptor antagonists in common use.

Type of receptor blockade	Intrinsic sympathomimetic activity present	Approved name	Main therapeutic use in medicine	Main therapeutic use in psychiatry
Nonselective (i.e., mixed blockade)	No	Propranolol	Hypertension, angina prophylaxis of myocardial infarction	Generalized anxiety, specific social anxiety disorders. Tremor (all causes)
	Yes	Acebutalol[a]	Hypertension, angina, and arrhythmias	As for propranolol but rarely used
	Yes	Celiprolol	Hypertension	
	No	Esmolol	Supraventricular arrhythmias	
	No	Nebivolol	Hypertension	
	No	Nadolol	Hypertension, angina, cardiac arrthythmias	As for propranolol but rarely used
	No	Carvedilol	Hypertension, angina, cardiac failure	
	Yes	Oxprenolol	Hypertension, angina	As for propranolol and occasionally used
	No	Pindolol	Hypertension, angina	Augmentation of SSRI treatment of depression
	No	Sotalol	Cardiac arrhythmias	As for propranolol but rarely used
	No	Timolol	As for propranolol	
β_1 Selective blockade	No	Atenolol	Hypertension, angina and arrhythmias	
	No	Bisoprolol	Hypertension, heart failure	
	No	Metoprolol	As for atenolol, also used in migraine	
	No	Betaxolol	Hypertension	
	No	Nebivolol	Hypertension	
Combined α and β receptor blockade	Yes	Labetalol	Hypertension and angina	

[a]Shows a small degree of β_1 selective blockade

unconnected to β-blockade such as sweating, irritability, nausea, and frequency of micturition, can also be helped by β-adrenoceptor antagonists. This may be true, but it does not follow that these are direct consequences of β-blockade. If a cardiac symptom such as palpitations is prominent in the expression of anxiety, its alleviation will reassure and help the patient so that other symptoms of anxiety are reduced as well.

The need for selection in β-blockade is less relevant in the treatment of anxiety unless the patient has cardiac comorbidity. The reduction of tremor is a result of β_2-blockade, and so nonselective β-adrenoceptor antagonists are preferred for this indication. Tremor is reduced at all frequencies and irrespective of its pathology, so the tremor accompanying treatment with lithium, the syndrome of parkinsonism, whatever its cause, and essential tremor are all equally influenced by the tremor reducing effects of propranolol and similar drugs. Exactly the same is true of anxious tremor, and the efficacy of nonselective β-adrenoceptor antagonists is most marked when tremor is a highly important and sensitive adverse or troublesome effect. Thus, the public speaker who is afraid of tremor affecting vocal performance, the snooker player who wishes to keep his cue direction absolutely still, and the violin player who wishes to confine tremulo and vibrato playing to only selected parts of public performance will all receive benefit from the effects of nonselective β-blockade. Indeed, such is the concern of the advantages gained by these drugs in competitive sports such as snooker and archery that they are now generally banned. The main clinical usage is in specific forms of ▶ social anxiety (phobia), in which blushing and tremor are prominent symptoms.

Other potential uses of β-adrenoceptor antagonists include the reduction of aggressive and challenging behavior, the treatment of schizophrenia (now virtually abandoned), and the management of movement disorders such as ► akathisia and ► tardive dyskinesia. Here, both the evidence and the ways in which β-adrenoceptor antagonists might assist in reducing the symptoms are very limited. It appears unlikely that peripheral β-blockade is relevant here, except possibly with the more simple movement disorders, but no other good explanation of action is forthcoming.

Value in Psychiatry and Psychology

The clinical usage of β-adrenoceptor antagonists drugs is discussed elsewhere in this volume (► generalized anxiety disorder, social anxiety disorder), and although there has been very little research into their efficacy in most recent years, they are still frequently prescribed for up to 10% of patients presenting with various forms of anxiety in primary care. In general, it is reasonable to consider the use of a β-blocking drug at least on a temporary basis, for patients who are especially troubled by symptoms such as blushing, tremor, palpitation, and general concern about excessive cardiac activity. They may also be helpful in reducing some of the withdrawal symptoms associated with cessation of benzodiazepines and similar drugs when they are accompanied by marked somatic accompaniments (► benzodiazepines, ► withdrawal syndromes). Most of the drugs are best given on an as required basis rather than regularly.

Cross-References

► Benzodiazapines
► Generalized Anxiety Disorder
► Nonselective Blockade
► Social Anxiety Disorder
► Withdrawal Syndromes

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Beta-Adrenoceptor Blocking Drugs

► Beta-Adrenoceptor Antagonists

Beta-Blockers

► Beta-Adrenoceptor Antagonists

Biased Agonism

► Functional Selectivity

BIM-23014

► Lanreotide

Binding

Definition

In general, the term binding refers to signaling molecule binding to target receptors. More specifically, binding represents an assay used both in vivo (PET studies) and in vitro for the characterization of receptor density and for the assessment of the affinity of a ligand versus a target receptor. This method is based on the use of radioligands (radioisotope-labeled compounds) specific for a target biding site.

Cross-References

► Receptor Binding

Binding Potential

Synonyms

BP; BP_1; BP_2; BP_F; BP_{ND}; BP_P; V_3''

Definition

A composite parameter used in ▶ PET and ▶ SPECT imaging that is proportional to the product of receptor density and affinity of the radioligand for the receptor, or B_{max}/K_D. The binding potential is also equal to the limiting value of the ratio of receptor-bound to free radioligand as the free concentration approaches zero. The nature of the constant of proportionality depends on the free pool being referred to. When the binding potential is measured relative to a reference tissue, the constant of proportionality is f_{ND}, the free fraction of the free plus nonspecifically-bound ligand in brain, and the binding potential is termed BP_{ND}. When measured relative to the radioligand concentration in arterial plasma, the constant is f_P, the fraction of radioligand in arterial plasma that is not protein bound, and the binding potential is termed BP_P. Finally, if f_P is measured and accounted for so that the true free concentration in arterial plasma is known, the constant of proportionality is 1 and the binding potential is called BP_F. These naming conventions have been agreed upon relatively recently in the imaging community. In older literature, BP_{ND} was variously referred to as BP, BP_2, or V_3'' BP_P as BP or BP_1; and BP_F as BP.

Binge

Synonyms

Binge eating

Definition

An episode of binge eating, known as a binge, is a period of rapid food intake during which a person consumes more than would be expected of a normal individual over the same time period. To qualify as a binge, this episode must also be accompanied by a subjective loss of control and inability to stop eating. Binges most commonly involve foods high in fat or sugar, but this is not a requirement. Recurrent binge eating is a core symptom of bulimia and binge eating disorder.

Cross-References

▶ Eating and Appetite
▶ Hunger
▶ Palatability

Binge Eating

▶ Binge

Binge-Eating Disorder

▶ Eating and Appetite
▶ Eating Disorders: Animal Models

Bioavailability

Definition

The fraction of the dose of a drug that is absorbed and that reaches the systemic circulation or target organ unaltered by a biotransformation. By convention, drugs administered intravenously have 100% bioavailability since 100% of the drug has reached systemic circulation. Bioavailability is one of the essential tools in pharmacokinetics and must be considered when calculating dosages for therapeutic use.

Cross-References

▶ Absorption
▶ Distribution
▶ First-Order Elimination
▶ Pharmacokinetics

Biogenic Amines

Definition

Naturally occurring amines produced by enzymatic decarboxylation of amino acids. These include neurotransmitters such as epinephrine, norepinephrine, dopamine, serotonin, and histamine. Synthetic analogues (such as amphetamine) are useful in pharmacology.

Biologic Rhythms and Medicine

▶ Circadian Rhythms

Biological Clock and Drugs

▶ Circadian Rhythms

Biological Clock and Pharmacology

► Circadian Rhythms

Biological Half-Life

► Elimination Half-Life
► Half-Life

Biotransformation

► Metabolism

Bipolar Disorder

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Synonyms

Bipolar illness; Manic-depressive illness

Definition

The unique phase of ► bipolar disorder is ► mania. In many ways mania is the opposite of depression and is characterized by elevated mood or euphoria, overactivity with a lack of need for sleep, and increased optimism that usually becomes so severe that judgment is impaired. Other drives such as sexual desire are also enhanced: manic patients are disinhibited in their speech about sexual matters, making jokes or talking about subjects not normally allowed in their culture. Manic patients are sometimes disinhibited in their sexual actions as well, and may endanger their marriages or relationships as a result. A key point is that manic behavior is distinct from a patient's usual personality, but may have a gradual onset over weeks or months before the syndrome is full-blown. In the absence of effective treatment, manic episodes could last months and years, although ultimately most are self-limited. Even after a long manic episode in the era before effective treatments, patients were known to recover to a state closely approximating, if not identical with, their premorbid personality.

The depression that alternates with manic episodes (bipolar depression) is characterized by the familiar symptoms of depression. A single manic episode is sufficient to diagnose bipolar illness. Some patients might have one manic episode at a young age and frequent depressive episodes for the rest of their life; others might have alternating manias and depressions on a yearly basis; still others might have manic episodes every 5 years and never a single depression.

Mild episodes of mania without psychotic symptoms and without symptoms dangerous to self or others are called hypomania. Hypomanic episodes can occur in patients with diagnosed full-blown bipolar illness, but they can also occur in patients with histories of depression only. This syndrome of major depressive episodes and hypomanic episodes has been called bipolar II and distinguished from the full-blown bipolar illness called bipolar I. However, the reliability of the diagnosis of bipolar II disorder is lower than for bipolar I disorder, and drug response and family history do not convincingly demonstrate that it is truly a milder version of full-blown bipolar disorder. Bipolar I illness affects approximately 1% of the population. Bipolar II disorder is reported to be much more prevalent, and a spectrum of bipolar disorders has been described that includes states of chronic mild hypomanic personality. However, the risks of the wide spectrum concept for the clinician include drug overprescribing and medicalization of psychosocial issues.

Patients who have four or more episodes of mania or depression a year are called rapid cyclers and are difficult to treat. However, life course studies are few and many clinicians find that a patient may have a period of a few years of rapid cycling and then go to much less frequent episodes, or vice versa.

The lifetime incidence of about 1% for bipolar disorder contrasts by an order of magnitude with the range of estimates of the prevalence of unipolar (i.e., nonbipolar) depression, which is a much more common phenomenon in the population. However, bipolar disorder, especially in its manic phase, is so destructive to work and family function that it constitutes a substantial public health problem even in comparison to the more common unipolar depression. The genetic and biochemical causes of bipolar disorder are still unclear.

Role of Pharmacotherapy

Management decisions for the bipolar patient include decisions on voluntary or involuntary hospitalization, achievement of a workable treatment setting for regular and affordable follow-up, and establishment of communication

with significant others to provide collateral history and warning of affective relapse. Without proper management, no pharmacotherapy can be effective. Many bipolar patients can be best managed in specialty clinics, once called "lithium clinics," but which now have a large armamentarium of effective treatments. Moreover, pharmacotherapy of bipolar disorder is now known to be best supplemented by one or more proven psychotherapies such as psychoeducation or social rhythms therapy (Osher et al. 2010).

Treatment of Acute Mania

Acute mania is a medical emergency. If not treated rapidly, a manic patient is likely to engage in activities that will endanger his or her marriage, job, and possibly, life. Acutely manic persons may seem rational one moment yet out of control the next. For example, a manic patient driving at 110 miles an hour through the city may have just had a rational conversation with his family physician in which he or she denied delusions or hallucinations and seemed pleasant, if speaking rapidly. It is critical to obtain collateral information from relatives, friends, or coworkers about such a patient's behavior in recent days to supplement the clinical interview.

Numerous effective treatments exist for acute mania (see Table 1). The neuroleptic drugs, also known as ► antipsychotics, are clearly effective in acute mania. These drugs are not recommended for long-term prophylaxis because of the danger of ► tardive dyskinesia. In the acutely manic patient, these medications have the advantage of readily available parenteral as well as oral forms, as well as rapid onset of psychomotor inhibition that may be lifesaving in the violent or psychotic patient. These medications are generally disliked by patients with milder disease, who are more compliant. The newer ► atypical antipsychotic medications are effective in these more compliant patients and may also pose lower risks of inducing depression as compared to classical neuroleptic drugs. Parenteral preparations of some atypical antipsychotic drugs are available. Some worrisome side effects of the atypical antipsychotic drugs include weight gain, lipid changes and glucose tolerance abnormalities. Thus, a patient who responded well in the past to a classic neuroleptic should probably be treated similarly for a recurrent manic episode (Belmaker 2004).

Research studies have demonstrated that ► lithium, ► valproate, and ► carbamazepine have proven efficacy in acute mania and are effective as monotherapy in clinical practice for occasional episodes of mild mania in the unusually compliant patient. Practice surveys, however, suggest that these drugs work too slowly for the great majority of patients with acute mania. Treatment should generally be initiated, then, with a typical or atypical neuroleptic and the addition of a mood stabilizer such as lithium, valproate, or carbamazepine as soon as oral

Bipolar Disorder. Table 1. Pharmacotherapies of bipolar disorder.

Treatment	Side effects	Indications	Effectiveness
Classical oral neuroleptics	Extrapyramidal syndrome, hypotension	Moderate to severe mania with good compliance	Highly effective, risk of depression
Clozapine	Agranulocytosis	Severe nonresponse	Highly effective
Atypical neuroleptics	Diabetes and weight gain (olanzapine) Hyperprolactinemia (risperidone) Q-T prolongation (ziprasidone) Sedation (quietiapine)	Replacing classical neuroleptics	Definite for moderate mania, not proven for severe mania
IM neuroleptics	As for oral neuroleptics	Noncompliance	Highly effective, risk of depression
Lithium	Polyuria, hypothyroidism, weight gain, nephropathy	Good compliance	Highly effective, slow onset, low risk of depression
Valproate	Rare hepatotoxicity, tremor, weight gain	Good compliance	Highly effective, slow onset, low risk of depression
Lamotrigine	Rare Stevens-Johnson Syndrome	Predominant depression	Good in depression, poor in mania
Carbamazepine	Rare hepatotoxicity, rash	Good compliance	Only small studies available
Clonazepam and lorazepam	Excessive sedation	Anxiety, psychomotor tension, insomnia	Questionable for core syndrome, useful adjunct

compliance is assured. The newer anticonvulsant lamotrigine is useful in prophylaxis of bipolar depression (see below) but its value in acute mania is unlikely (Cousins and Young 2007; Fountoulakis and Vieta 2008).

Treatment of Bipolar Depression

Bipolar depression (depressive episodes in a patient with bipolar illness) may respond to ► tricyclic antidepressants, serotonin-specific reuptake blockers, and ► monoamine oxidase inhibitors. The time course for response in a patient with bipolar depression is similar to that seen in unipolar depression. However, treatment for bipolar depression must be carried out with the knowledge that antidepressants may induce a switch from depression to mania. A patient with a history of at least one dangerous episode of mania that endangered family or work should probably avoid antidepressants, even if residual low mood or low energy continues. However, patients who have had one diagnosable moderate episode of mania in which neither self-injury nor damage to family occurred but who have had recurrent crippling depressions following the single manic episode may benefit from an antidepressant without sustaining undue risk (Belmaker 2007).

Some studies suggest that newer antidepressants such as ► selective serotonin uptake inhibitors (SSRIs) or bupropion are less likely to induce mania in persons with bipolar depression, but the relevant data are often restricted to patients with very mild manias ("bipolar II") and should not be extrapolated to all patients with bipolar illness. Omega-3 fatty acids are experimentally reported to be antidepressant in preliminary studies and might potentially be a new direction for treatment of bipolar disorder. Inositol is another natural compound that has been experimentally studied in bipolar depression (Belmaker and Agam 2008).

Mood Stabilizers and Prophylaxis

Lithium is the quintessential and classic mood stabilizer. ► Lithium was developed in an era in which drug regulatory agency standards were less stringent, and the newer agents used for mania may be promoted as the only treatments that meet particular methodological standards. However, over a 50-year period, lithium has been shown to have antimanic efficacy, prophylactic efficacy in bipolar disorder, and some efficacy in prophylaxis of bipolar depression. Lithium has a narrow therapeutic index and must be monitored with blood levels. Severe toxicity and sometimes death can occur when renal excretion is impaired even by such apparently innocent changes as initiation of diuretic treatment for hypertension. Progressive renal failure after decades of lithium use has been reported, though some have questioned the specificity of lithium as the causative agent in these cases (Lepkifker et al. 2004).

► Carbamazepine was the major anticonvulsant drug reported to treat bipolar illness through the 1980s. In the 1980s it was estimated that as much as one half of the sales of carbamazepine were for bipolar illness. Throughout the 1980s large numbers of small studies reported therapeutic efficacy for carbamazepine in mania, bipolar depression, and bipolar disorder prophylaxis, sometimes as monotherapy but often as an add-on to other treatment. This literature has lately been reevaluated critically in the light of the standards required for licensing of new anticonvulsants for bipolar disorder by the US Food and Drug Administration (FDA), and sometimes found wanting. However, the clinician must include the relative long and successful clinical experience with this compound in his judgment.

► Valproate was the next anticonvulsant reported to have anti-bipolar properties. As with carbamazepine, the first reports were from outside the USA and these early reports were criticized by Americans as poorly controlled. However, when an American pharmaceutical company, Abbott, reached agreement with the FDA to patent a new formulation of valproic acid, a large-scale controlled study was carried out, leading to a profitable compound on the American market, divalproex sodium. Some feel that divalproex sodium is of dubious pharmacologic advantage over valproic acid, and despite heavy advertising and promotion of divalproex sodium, lithium still controls a large market share of treatment of bipolar disorder in the US and elsewhere. A large study suggests that lithium prophylaxis is more effective than valproate prophylaxis in the prevention of suicide in bipolar disorder (Goodwin et al. 2003).

The success of carbamazepine and valproate and the recent development of newer anticonvulsant drugs for epilepsy have led to their use in bipolar disorder as well. Case reports and small studies suggest that ► topiramate is effective in bipolar illness, although a large study sponsored by Janssen-Cilag failed, perhaps because of a large number of mild, antidepressant-induced manias that subsided in the placebo group. ► Lamotrigine has also been reported to exert a positive effect in bipolar illness, particularly in the depressive phase of the disorder. Clinicians for many years have felt that lithium, valproate, and carbamazepine more successfully control the manic phase as compared to the depressive phase of bipolar disorder, and a clear need exists for a depression-oriented drug in bipolar disorder. A large company-sponsored study suggested that lamotrigine was effective in prophylaxis in bipolar

depression as compared to lithium and placebo. However, the actual size of the effect was small, and criticism has been raised as to whether an excessive number of lithium non-responders are attracted to such a study.

► Benzodiazepine drugs, which act on the benzodiazepine receptor component of the GABA-benzodiazepine complex, are effective in status epilepticus, and these drugs may be useful adjuncts for the treatment of mania, reducing tension, and improving sleep as discussed above; however, they do not seem to have true "antimanic" efficacy. ► Gabapentin has been studied in a well-designed fashion and is not antimanic despite earlier reports suggesting this. ► Zonisamide and felbamate are also new anticonvulsants for which efficacy in bipolar disorder has been suggested in some case reports, but they have not yet been studied in a controlled fashion.

Dopamine receptor-blocking drugs (neuroleptics) that are used in schizophrenia are therapeutic in acute mania (American Psychiatric Association 2002). A few studies have found them efficacious in bipolar prophylaxis as well, but the risk of tardive dyskinesia limited their use in bipolar disorder. More recently, atypical neuroleptic drugs such as ► clozapine, ► quietiapine, ► olanzapine, ► risperidone, and ► ziprasidone have been found to have efficacy in at least some phases of bipolar disorder. Such efficacy blurs the distinction between antischizophrenic therapy with neuroleptics and mood stabilizer therapy, and future prophylactic studies with atypical antipsychotics in bipolar disorder will perhaps lead to an entirely new diagnostic system for psychoses (Aubry et al. 2007).

While lithium or an anticonvulsant provide many bipolar patients remarkable prophylaxis over many years, referral centers see large numbers of patients with breakthrough manias and even more commonly, breakthrough depression. The effectiveness of using a polypharmacy approach – lithium plus anticonvulsant, two anticonvulsants, lithium plus atypical neuroleptic, and occasionally lithium plus antidepressant – are all supported by research data (Post et al. 1996).

The ethics of future trials of anti-bipolar drugs are controversial. A manic episode can be a life-threatening condition and many psychiatrists and physicians feel that bipolar patients, given the existence of effective treatment, should not be recruited for placebo-controlled trials. The FDA, however, continues to demand in most cases placebo-controlled monotherapy trials for registration of new compounds in psychiatry. Some statisticians support the FDA position, calculating that more patients will be exposed to poor treatment if no placebo control is used, since it may take a much higher number of subjects to prove lack of efficacy of a new treatment as compared to a standard control medication such as lithium. These statistical calculations do not take into account the distortions induced by unrepresentative patient populations in placebo-controlled studies, since only a very select group of patients consent to participate in such studies. The clinician must not only consider, in deciding on treatment, the results of randomized placebo-controlled trials but also the history of smaller trials and clinical experience with a specific compound. Moreover, bipolar disorder is likely a heterogeneous illness with early-onset forms, late-onset forms, forms with mostly depressions and forms with mostly mania, forms with mild mania, and forms with severe psychotic mania. Studies of large numbers of patients meeting criteria for bipolar disorder do not always provide clear guidance to the physician regarding specific cases. For instance, patients with mostly depressions may have a favorable risk-benefit ratio for prophylactic treatment with a lithium-antidepressant combination even if this is not indicated for all, or even most bipolar patients. In addition, many patients do not respond to treatments that are evidence based on the strict criteria of large ► randomized placebo-controlled studies (2002). At that point in treatment the physician must rely on smaller studies and pharmacologic extrapolation to plan individualized, creative treatment. This often works and can make the difference between severe disability and a useful life for bipolar patients who do not respond to standard treatment guidelines.

Cross-References

► Carbamazepine
► Clozapine
► Depression
► Lamotrigine
► Lithium
► Olanzapine
► Topiramate
► Valproate

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Bipolar Disorder in Children

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Synonyms

Manic-depression

Definition

Bipolar disorder (BD) is a chronic psychiatric condition that occurs throughout the life cycle. It is characterized by several different mood states (► bipolar disorder). Pediatric BD (PBD) is oftentimes associated with psychiatric comorbidity. When bipolarity does occur in children and adolescents, it is usually serious, chronic, and debilitating (McClellan et al. 2007). Therefore, treatment research has considered means by which to reduce the symptomatology and suffering associated with BD in the young.

Role of Pharmacotherapy

For adults, pharmacotherapy is the cornerstone of intervention for BD. However, agents that may be safe and effective for the treatment of BD in older patients may not be associated with similar outcomes in juveniles. For that reason, treatment studies of methodological stringency that consider medication response in youths with BD are needed in order to make scientifically informed treatment decisions. Unfortunately, very less is known about the pharmacotherapy of BD in youths when compared to what is known in adults.

It should be noted that the overwhelming majority of pharmacotherapy studies in BD have examined the acute treatment of manic or mixed episodes, rather than depressed states. This is likely due to the observation that youths with BD appear to suffer from depressive episodes substantially less frequently than adults (Findling 2008). There is an unfortunate paucity of data regarding intervention in juvenile BD's psychiatric comorbidities, its maintenance treatment, and intervention studies in symptomatic genetically at-risk youths. Thus, this summary will focus on what is known about the acute treatment of manic and/or mixed states in this patient population.

Lithium

► Lithium is a benchmark treatment for the pharmacotherapy of BD in adults. It was the first treatment approved by the United States Food and Drug Administration (FDA) for use in adolescents of ages 12 and older with BD. However, it should be noted that this approval was not based on definitive, well-controlled studies of adolescent patients. While there have been multiple studies on the use of lithium for the treatment of BD in children, most have lacked methodological rigor (Findling and Pavuluri 2008). As a result, the lithium treatment for youths suffering from BD is oftentimes based upon extrapolation from adult research.

Lithium has been shown to have a narrow therapeutic window (0.6–1.2 mEq/L). For that reason, dosing is a key consideration for this drug in order to maximize clinical benefit while minimizing potential risks and toxicities. In the absence of data specifically considering this topic, it has been assumed that therapeutic levels of lithium in children and adolescents are the same as in adults. As a result of this assumption, dosing strategies that yield "adult" therapeutic levels of lithium have been developed for youths. One possible strategy is to initiate lithium at a dose of 20 mg/kg/day, or 900 mg/day (whichever is less) divided into two or three daily doses. The initial dose is then gradually increased to achieve a target blood level of 0.6–1.2 mEq/L. Doses are generally not increased if (1) blood levels of the drug exceed 1.2 mEq/L, (2) side effects preclude dose increases, or (3) adequate symptom reduction has already occurred (Findling and Pavuluri 2008).

In regard to effectiveness, lithium has been reported to be associated with reductions in symptomatology as a drug monotherapy in multiple reports pertaining to its use in young people suffering from manic or mixed states. However, it has been repeatedly noted that while many patients benefit from lithium monotherapy, a substantial number of young patients do not fully achieve remission when prescribed lithium alone. For that reason, lithium is a drug that has been examined under the auspices of combination drug studies. In such clinical trials, benefit

from drug combinations that include lithium as an agent has been described.

As far as safety is concerned, the side effects that can occur in adults treated with lithium may also occur in young patients who are administered this agent. Although it has been asserted that younger children may be more vulnerable to lithium-related side effects than older adolescents, this assertion has yet to be definitively confirmed or refuted.

In summary, despite the lack of definitive efficacy studies, lithium appears to be a reasonably safe and generally effective treatment of acute mixed and manic states in pediatric patients, both as monotherapy and when co-administered with other mood stabilizers. Definitive studies pertaining to the dosing, short-term efficacy, maintenance treatment, and safety (both acute- and long-term) are currently underway.

Anticonvulsants

Several medications originally marketed as ▶ anticonvulsants have been shown to be beneficial in treating BD in adults. As a result, it was believed that these medications may have mood-stabilizing properties in PBD as well. What follows is a summary of what is known about this class of medication in PBD.

Carbamazepine

While there have been studies demonstrating the efficacy of ▶ carbamazepine in the treatment of adults with mania, there are limited data regarding the safety and efficacy of this drug in the treatment of PBD. In an open-label study in which patients were randomly assigned to receive lithium, divalproex, or carbamazepine, clinically meaningful benefit was reported for all three study groups. In addition, carbamazepine was reasonably well tolerated in the study with no serious adverse outcomes reported. Some case reports have suggested that carbamazepine can be effective in adolescents with mania that have been nonresponsive to lithium. In addition, it has been suggested that the combination of lithium and carbamazepine may be a reasonable treatment option. On a cautionary note, there have been case reports that suggest that carbamazepine may actually worsen mania. Despite these preliminary observations, there are no randomized placebo-controlled studies on the use of carbamazepine in the treatment of BD in children and adolescents, and definitive proof of its safety, tolerability, and efficacy, both as monotherapy and as an agent used in combination with other compounds, remains to be established (Danielyan and Kowatch 2005).

Divalproex (▶ Valproate)

Divalproex sodium has demonstrated efficacy in the treatment of adults with acute mania. However, much of the data on the use of divalproex in the pediatric population are from case reports. One randomized, double-blind, industry-sponsored study investigating the use of divalproex in 150 children and adolescents with BD found no statistically significant improvement in acute manic symptoms when compared with placebo. However, another randomized, NIMH-supported double-blind trial investigating 153 youth found that divalproex was superior to placebo for treating children and adolescents with BD during a mixed or manic episode. A possible explanation for the discrepant results of these two studies may be due to issues related to between-site variability. The NIMH-supported study was conducted at substantially fewer sites than the industry-supported trial. Furthermore, there have been combination studies that suggest that divalproex may be beneficial when co-administered with lithium, quetiapine, or risperidone (Findling and Kuich 2008).

Common side effects of divalproex in children are weight gain, nausea, sedation, and tremor. In addition, particular concern has been raised regarding the relationship between divalproex and the development of polycystic ovarian syndrome (PCOS) in girls. Therefore, it is recommended that clinicians should monitor female patients treated with divalproex for any signs of PCOS, including weight or menstrual abnormalities, hirsutism, or acne.

Topiramate

Preliminary data has indicated that ▶ topiramate may be effective for PBD. These data come primarily from a study that was discontinued prematurely secondary to early evidence that topiramate was not beneficial in treating BD in adults. However, when these preliminary data were analyzed from the pediatric study, it was found that topiramate would have likely proven beneficial had the study continued (DelBello et al. 2005). Key side effects of topiramate include anorexia, weight loss, and sedation. It should be mentioned that although there are no methodologically rigorous data on this topic, some clinicians appear to utilize topiramate's weight loss properties and prescribe this drug as an adjunctive treatment for youth with BD who have gained weight as a result of treatment with other psychotropic agents.

Oxcarbazepine

A randomized, double-blind placebo controlled study by Wagner and colleagues investigated the use of ▶ oxcarbazepine versus placebo in 116 youth with BD. The

authors found that the response to oxcarbazepine was no different than the response seen with placebo. As a result, these findings do not support the use of oxcarbazepine as monotherapy in the treatment of the manic phase of PBD (Wagner et al. 2006).

Gabapentin

► Gabapentin has not been found to be effective for the treatment of BD in adults, and there is currently no evidence to support its use in the treatment of PBD (Smarty and Findling 2007).

Lamotrigine

► Lamotrigine has been shown to be efficacious for the maintenance treatment of bipolar disorder in adults, and data support its use in the long-term treatment of bipolar depression in adults. There have been open studies indicating that lamotrigine may be beneficial for adolescents with bipolar depression as well. However, randomized, controlled studies are still needed. The risk of potentially lethal cutaneous reactions, such as Stevens–Johnson syndrome and toxic epidermal necrolysis, is greater in youth younger than 16 years old than in adults. However, dosing guidelines using a more conservative dose titration lower the risk of such serious rashes.

Antipsychotics

► Atypical antipsychotics (► antipsychotic drugs) have been shown to be efficacious in treating bipolar disorder in adults. Evidence from recently completed placebo-controlled trials provide evidence that atypical antipsychotics may be beneficial for the acute treatment of manic and/or mixed states in youths suffering from bipolarity. However, as with adults, the possible metabolic complications of these drugs are important considerations, particularly over the long term. Unfortunately, there is a paucity of information about the long-term effects of these agents in juveniles. In addition, there are no methodologically stringent studies that have specifically compared the safety and efficacy of one atypical to another. Moreover, there are almost no data about the use of ► typical antipsychotics in this patient population.

Clozapine

There is some evidence from open trials and case reports that ► clozapine may be beneficial in the treatment of PBD patients who have not shown adequate response to other agents. However, the side effects of clozapine, which may include sedation, weight gain, increased salivation, seizures, and myocarditis, as well as potentially lethal agranulocytosis, limit the usage of this medication. For these reasons, clozapine is generally recommended only for children and adolescents who have not responded to multiple treatment courses with other medications.

Risperidone

► Risperidone, either as monotherapy or in combination with a mood stabilizer, has been reported to be effective in the treatment of juvenile bipolarity in case reports and open-label studies. Of note, one randomized, placebo-controlled study of youth with bipolar disorder found that risperidone was efficacious and relatively well tolerated at doses as low as 0.5–2.5 mg per day in the acute treatment of manic or mixed episodes in youth ages 10–17.

Olanzapine

One double-blind, randomized, placebo-controlled trial in adolescents 13–17 years of age with a manic or mixed episode found that ► olanzapine, at doses between 2.5 and 20 mg per day, was superior to placebo in the treatment of these adolescent patients. However, the study also found that youths treated with olanzapine had significantly greater weight gain and increases in the levels of hepatic enzymes, prolactin, fasting glucose, fasting total cholesterol, and uric acid when compared to those treated with placebo (Tohen et al. 2007).

Quetiapine

Quetiapine was one of the first atypical antipsychotics to be studied in a double-blind, placebo-controlled trial for the treatment of mania in adolescents. This study found that combination therapy with ► quetiapine and divalproex was more effective than divalproex and placebo in the acute treatment of adolescents suffering from manic or mixed episodes (DelBello et al. 2006). In addition, a randomized, placebo-controlled study of 277 participants, ages 10–17, concluded that quetiapine, at doses of 400 and 600 mg/day, was significantly more effective than placebo in treating acute manic symptoms in children and adolescents with bipolar disorder.

Ziprasidone

Ziprasidone has been shown to be effective in treating mania in adults. In addition, ► ziprasidone is typically associated with less weight gain than risperidone and olanzapine. One randomized, double-blind, placebo-controlled study of 150 youth ages 10–17 years old with bipolar disorder found that ziprasidone at doses of 80–160 mg per day was effective and generally well tolerated.

Aripiprazole

One randomized, double-blind, placebo-controlled study has shown ► aripiprazole, at doses of 10 and 30 mg, to be superior to placebo in the acute treatment of manic and mixed episodes of children and adolescents with bipolar disorder.

Conclusion

Historically, the pharmacological treatment of pediatric bipolar disorder in clinical practice was based on data collected from the treatment of adults with this disorder. More recently, clinical trials have been conducted in PBD and new data are now available, particularly concerning the efficacy of the atypical antipsychotics in treating children and adolescents. However, some medications that have been shown to be useful in treating adult patients remain unstudied in children. In addition, long-term safety and efficacy data are lacking for many drugs. Thus, unknown risks to this vulnerable population may exist. However, with continued research and forthcoming data from ongoing trials, clinical decisions predicated on scientifically stringent evidence will become increasingly feasible.

Cross-References

► Anticonvulsants
► Antipsychotic Drugs
► Bipolar Disorder
► Lithium

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Bipolar Illness

► Bipolar Disorder

Black Box Warning

Definition

A black box warning, also called a boxed warning or black label warning, is an FDA requirement for drugs that require close monitoring or are associated with potentially dangerous side effects that must be clearly disclosed in product labeling.

Blocking, Overshadowing and Related Concepts

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Synonyms

Attentional learning; Selective learning

Definition

Blocking is a reliable cross-species learning effect. It has been studied primarily using ► Classical (Pavlovian) Conditioning in which animals come to show their learned anticipation of a biologically significant outcome, typically food or foot shock, through a behavioral conditioned response. This conditioned response often resembles the unconditioned response for the outcome (► unconditioned stimulus, UCS) – for example, in Pavlov's original studies, the salivation response to food came to be elicited by a bell, termed the ► conditioned stimulus (CS), that preceded food delivery. This anticipatory responding allows us to quantify the strength of the conditioned association.

Importantly, classical conditioning is selective to the best predictors of outcomes, raising the possibility that

here is a mechanism allowing animals to build up a representation of the causal structure of the environment. In any event, in the absence of selectivity, the learning mechanism would be overloaded and inefficient. The blocking effect, discovered by Kamin in 1968, is an example of selectivity based on the redundancy of a potential CS (B). This redundancy arises because there already exists a reliable CS (A) for the outcome in question.

Impact of Psychoactive Drugs

The impact of psychoactive drugs on blocking can only be evaluated with respect to the behavioral controls in place, and these vary from study to study. Blocking in its simplest form is demonstrated in a two-stage procedure: (Stage 1) present A followed by the UCS; (Stage 2) present A in combination with B, followed by the same UCS. Ideally, several controls are needed: For example, because A might be intrinsically more salient than B, the best designs counterbalance the stimulus identities; most importantly, because conditioning to B might be reduced due to competition with A, the Stage 2 conditioning is also compared with that seen in a separate group of animals conditioned to the compound. This control group is given equivalent Stage 2 training in the absence of any Stage 1 pre-training with A. Thus, we can separate out the reduced conditioning to B, which results from direct cue competition through ► Overshadowing as distinct from the pre-training with A to establish B as redundant. Overshadowing refers to the attenuation of learning to B as a consequence of conditioning in compound with A, relative to a group who are conditioned to B in isolation. The most essential experimental comparison groups to demonstrate blocking and overshadowing are shown in Table 1.

Thus, blocking is typically examined together with overshadowing in the same procedure. The fact that the blocking effect is reliably demonstrated over and above the reduction in learning to B produced by overshadowing in the control group suggests that it may rely on additional mechanisms (beyond direct cue competition). At the psychological level, the prior learning in Stage 1 is most likely an important factor.

Related Selective Learning Effects

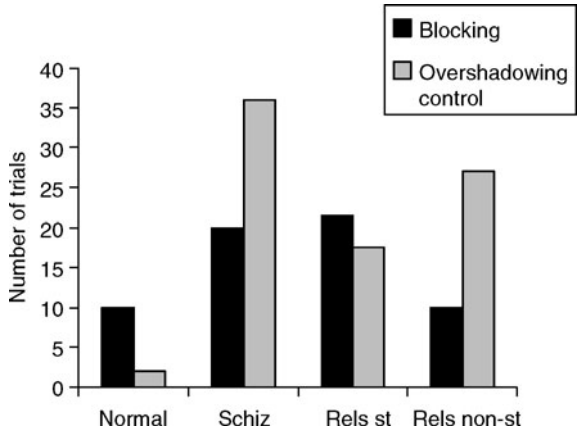
There exist a number of other selective learning phenomena, likely to be related to blocking or overshadowing in terms of underlying mechanisms. Like blocking, ► Latent Inhibition is a two-stage procedure in which Stage 1 experience reduces subsequent Stage 2 conditioning. A variety of mechanisms have been proposed to contribute to this effect (Escobar et al. 2002; Gray et al. 1991; Hemsley 1993; Weiner 2003). For example, selectivity in learning could arise from changes in the effective salience of less predictive cues or interference between competing associations. Like overshadowing, ► Relative Validity procedures show the superiority of one available CS at the expense of another. In this case, the best predictor is established on a probabilistic basis over a number of conditioning trials. All of these selective learning effects reflect competition between the range of experimental cues available, including those provided by the context.

Blocking as an Endophenotype for Schizophrenia

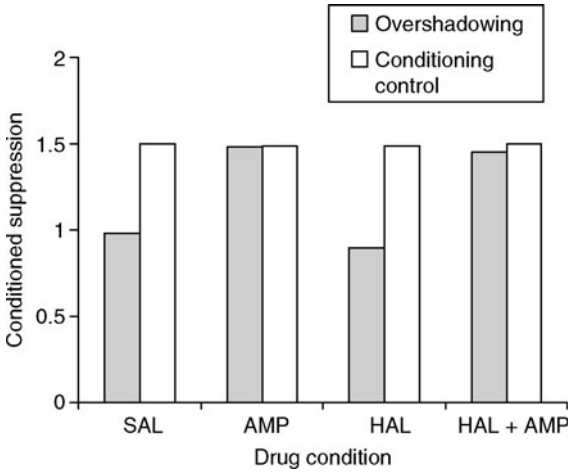
Selective learning effects like blocking have become targets for translational research. Overconditioning to cues that would normally be treated as irrelevant or redundant provides an ► Animal Model of disorder. First, when selectivity in learning fails, the animal is flooded with a profusion of potential conditioning cues and aberrant associations will be formed. Second, the neural substrates implicated in selective learning effects point to a key role for the dopamine system known to be dysfunctional in ► schizophrenia (Gray et al. 1991; Hemsley 1993; Kapur 2003; Weiner 2003). Furthermore, studies with human participants show that the normal blocking effect is abolished in schizophrenia (Fig. 1). Thus, like impaired latent inhibition, impaired blocking shows excellent validity, both at the behavioral and the neurochemical level, as an ► Endophenotype for schizophrenic attention deficit (Gottesman and Gould 2003).

Blocking, Overshadowing and Related Concepts. Table 1. Basic design to show a blocking effect (learning in group 2 minus learning in group 1) and overshadowing (learning in group 3 minus learning in group 2). A and B represent the alternative CSs.

Experimental group	Stage 1	Stage 2	Learning test
1. Blocking	A → Shock	[A + B] → UCS	Weak conditioning to B
2. Overshadowing		[A + B] → UCS	Moderate conditioning to B
3. Conditioning control		B → UCS	High conditioning to B



Blocking, Overshadowing and Related Concepts. Fig. 1. Blocking in human participants shown in normal participants as an increased number of trials (to the learning criterion) required in the blocking condition relative to the overshadowing controls. This blocking effect was abolished or even reversed in schizophrenic participants (Schiz) and their relatives (Rels), irrespective of levels of schizotypy (st) as measured by questionnaire. (Adapted from Jones et al. (1997) Behav Brain Res 88:103–114, see text for full details.)



Blocking, Overshadowing and Related Concepts. Fig. 2. Overshadowing shown as reduced learning relative to the conditioning control group in a standard fear conditioning (lick suppression) procedure. The dependent variable is the log transform of the time taken to complete 10 licks in the presence of the CS. Overshadowing was shown in the saline- (SAL) and haloperidol- (HAL) injected groups. Overshadowing was abolished by treatment with amphetamine (AMP) and the amphetamine-induced abolition of overshadowing was not reversed by treatment with haloperidol, suggesting that dopamine D2-like receptors do not mediate the amphetamine-induced abolition of overshadowing. (Adapted from O'Tuathaigh and Moran (2002) Psychopharmacology 162:225–231, see text for full details.)

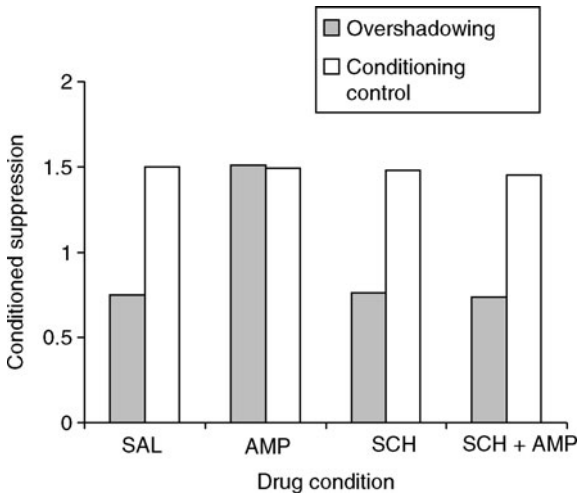
Animal Studies of Blocking and Overshadowing

In animals, psychopharmacological studies have shown that treatment with indirect ▶ dopamine agonists given systemically (typically ▶ amphetamine at around 1.5 mg/kg in rats) abolishes blocking and overshadowing. In every case, abolition of the normal effect results in overconditioning, with the consequence that the CS that would normally be treated as uninformative, whether because of redundancy in the case of blocking or relatively low intensity in overshadowing, accrues more associative strength than in non-drug-treated groups (Cassaday and Moran 2010).

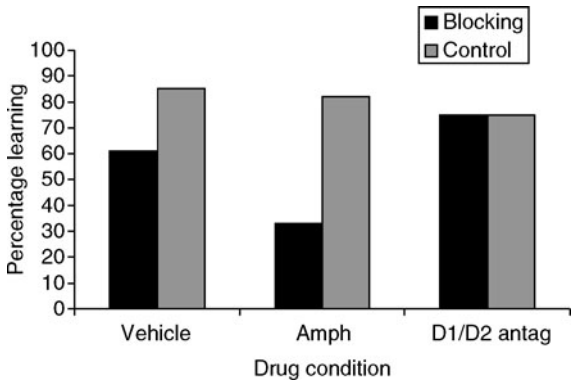
In part for practical reasons, because of the need to test for dose-related effects, psychopharmacological studies are not always run with full behavioral controls. In the case of blocking, further reduction in learning produced by the Stage 1 pre-training can be a relatively small effect when compared to that seen in an overshadowing group. In some studies, apparent amphetamine-induced abolition of blocking may be entirely attributable to impaired overshadowing under amphetamine (Fig. 2).

However, patients with schizophrenia have been reported to show impaired blocking, over and above any change in overshadowing (Fig. 1) and in animal studies blocking and overshadowing may be dissociable in terms of their differential sensitivity to dopamine D2-like (Fig. 2) vs. dopamine D1-like (Fig. 3) receptor agents.

With respect to the neural mediation of the systemic effects of amphetamine, dopamine activity in part of the ventral striatum, specifically ▶ nucleus accumbens, has been reported to modulate blocking in the absence of any effect on overshadowing in the control group (Fig. 4). Similarly, the evidence for a pivotal role of nucleus accumbens and related structures is overwhelming in the case of latent inhibition (Gray et al. 1991; Weiner 2003). However, it is important to note that the nucleus accumbens is a heterogeneous structure and opposing effects of drug treatments and lesions can be seen in relation to very small differences in the laterality of the cannula placement. Moreover, the evidence with respect to the neural substrates of other selective learning phenomena is patchy, in part because of the poor selectivity of the lesion methods used to date. Techniques in neuro-psycho-pharmacology such as lesions selective to dopamine and precisely targeted microinjection studies are required to delineate the underlying substrates of



Blocking, Overshadowing and Related Concepts. Fig. 3. Overshadowing shown as reduced learning relative to the conditioning control group in a standard fear conditioning (lick suppression) procedure. The dependent variable is the log transform of the time taken to complete 10 licks in the presence of the CS. Overshadowing was shown in the saline- (SAL) and SCH23390- (SCH, dopamine D1-like antagonist) injected groups. Overshadowing was abolished by treatment with amphetamine (AMP) and the amphetamine-induced abolition of overshadowing was reversed by treatment with SCH23390, suggesting that dopamine D1-like receptors mediate the amphetamine-induced abolition of overshadowing. (Adapted from O'Tuathaigh and Moran (2002) Psychopharmacology 162:225–231, see text for full details.)



Blocking, Overshadowing and Related Concepts. Fig. 4. Blocking shown as a low percentage of baseline learning in a contextual fear conditioning procedure. The comparison group controls for overshadowing by context which it can be seen was unaffected by any of the drug treatments. Blocking was increased by injection of amphetamine in n.acc and decreased by combined D1 and D2 receptor antagonism produced either by injection of cis-(z)-flupenthixol or combined treatment with SCH23390 and sulpiride. In isolation, SCH23390 and sulpiride were without effect, suggesting that a combined action at dopamine D1-like and D2-like receptors mediates the amphetamine-induced abolition of blocking. (Adapted from Iordanova et al. (2006a) Eur J Neurosci 24:3265–3270, see text for full details.)

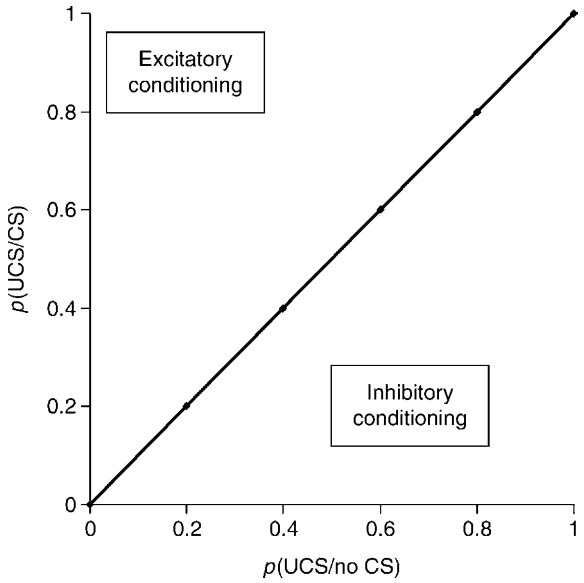
blocking, overshadowing, and related effects. To date, the role of dopamine has been an understandable focus for pharmacological studies, principally of latent inhibition, though also of blocking and other selective learning effects, due to the fact that established ► antipsychotics are dopamine antagonists. The modulation of these effects by other neurotransmitter systems remains to be established. For example, based on the known effects of serotonergic treatments on latent inhibition (Weiner 2003), ► serotonin would similarly be expected to modulate blocking and related effects.

Blocking and Prediction Error

The blocking effect has been targeted, to understand the biological basis of attentional abnormality, to a large extent without a full consideration of its underlying psychological mechanisms. This situation may soon be remedied in that blocking has recently assumed prominence as a tool to investigate the neural basis of ► Prediction Error. Prediction error is fundamental to normal associative learning because it provides the basis on which to learn when there is a discrepancy between what is expected, and what actually occurs. Thus, uncertainty is an important factor in determining attention in learning and dominant learning theories propose that new learning requires that an association is not already at full strength. Positive prediction error generates excitatory conditioning; negative prediction error generates inhibitory conditioning (Fig. 5).

Electrophysiological studies show the pivotal role of ► dopamine as a neurochemical substrate of prediction error (Schultz 2006; Schultz and Dickinson 2000). Blocking was the key paradigm that drove our understanding of associative learning in terms of prediction error: the Stage 1 pre-training means that the UCS is fully predicted by the time that the competing cue is introduced in Stage 2. Thus, there can be no prediction error and thus no additional conditioning to the redundant cue. However, prediction error can be systematically manipulated by changing the UCS delivered. If the UCS is other than expected, ► Unblocking occurs. This can take the form of additional excitatory conditioning to the additional CS

if the UCS is more than expected (e.g., a higher intensity foot shock is delivered in upshift unblocking) or inhibitory conditioning to the additional CS if the UCS is less than expected (e.g., a lower intensity of foot shock is delivered in downshift unblocking). Electrophysiological studies have confirmed that some of the same populations of dopamine neurons that show increased activation following the presentation of excitatory CSs, that signal "more than expected," show depressed neuronal firing following the presentation of inhibitory CSs, that signal "less than expected" (Schultz 2006). These neurons show no change in neuronal firing when there is zero prediction error, in other words when things remain "as expected." Such a case is provided in the blocking procedure. Pretraining with CS A normally blocks learning about CS B because the prediction error is small. The standard blocking procedure is readily adapted to study the neural bases of excitatory and inhibitory learning (Fig. 5) by manipulating the UCS delivered (Table 2).



Blocking, Overshadowing and Related Concepts. Fig. 5. Positive prediction error when the probability (*p*) of the UCS is increased on presentation of the CS in question generates excitatory conditioning. Negative prediction error when the probability of the UCS is decreased on presentation of the CS in question generates inhibitory conditioning. When *p*(UCS/CS)=*p*(UCS/no CS) along the diagonal trend line, there can be no new learning.

Thus, blocking and unblocking variants provide target tasks to identify the neuropharmacological substrates of prediction error, for example, using microinjections into the nucleus accumbens (Fig. 6).

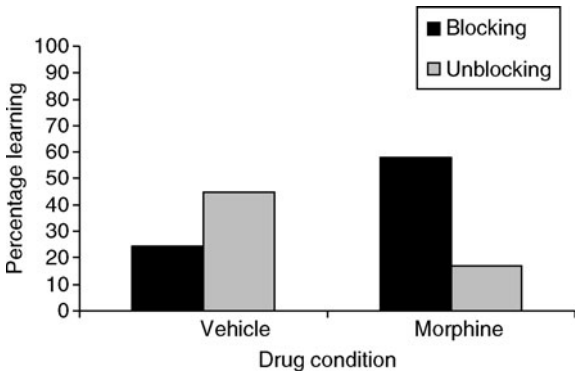
Thus, analysis of blocking from an associative learning theory perspective has identified the same underlying neural substrates that are the target of translational studies of blocking as an endophenotype for schizophrenia. At the behavioral level, abnormalities in the processing of prediction error may be the cause of the formation of inappropriate associations in schizophrenia. In other words, studies of prediction error, known from electrophysiological studies to depend on the dopamine system, also further our understanding of dopaminergic disorders such as schizophrenia. Deficits in blocking, seen both in schizophrenia and under amphetamine, represent a paradigm instantiation of abnormalities in the processing of prediction error. Future studies of the relevant neural substrates of prediction error should include, but are not restricted to, those identified in blocking procedures. Downstream from these Pavlovian effects, abnormal processing of prediction error has been linked to abnormalities of action, including drug addiction where overconditioning in hyperdopaminergic states could promote cue-driven relapse because of the increased representation of drug-related cues (Montague et al. 2004; Schultz and Dickinson 2000).

Advantages and Limitations of Blocking and Overshadowing

Latent inhibition, now well established as a model for schizophrenia, shows the predicted sensitivity to psychoactive drugs, and human participants with schizophrenia

Blocking, Overshadowing and Related Concepts. Table 2. Basic comparison groups to show unblocking due to upshift when the UCS is more than expected (UCS) and downshift when the UCS is less than expected (ucs). A and B represent the alternative CSs.

Experimental group	Stage 1	Stage 2	Learning test
Blocking	A → UCS	[A + B] → UCS	Weak conditioning to B
Upshift unblocking		[A + B] → UCS	Excitatory conditioning to B
Downshift unblocking		[A + B] → ucs	Inhibitory conditioning to B



Blocking, Overshadowing and Related Concepts. Fig. 6. Blocking shown as a low percentage of baseline learning in a fear conditioning procedure. Unblocking was produced by halving the UCS (shock intensity) and was demonstrated as relatively increased percentage learning. The control level of learning was around 50%. Blocking and unblocking were affected in opposite ways by injection of opioid compounds in nucleus accumbens. (Adapted from Iordanova et al. (2006b) J Neurosci 26: 4036–4045, see text for full details.)

show impaired latent inhibition (though this demonstration depends on medication status). Similarly, there is good evidence for impairments in blocking in schizophrenia; hence blocking provides a potential animal model in which to assess the effects of psychoactive drugs; for example, to distinguish the role of dopamine D1 and D2 receptor families in this aspect of attentional learning, as distinct from overshadowing (Figs. 2–4). Much of this work has yet to be done, in part because reliable parameters to demonstrate blocking can be difficult to establish. An additional disadvantage in the use of blocking arises because a fully controlled study necessitates the use of an overshadowing comparison condition and overshadowing is itself affected by some of the same dopaminergic treatments. Future studies should address this confound. However, overshadowing remains of interest in its own right as a procedure to present stimuli that should normally show reduced salience for learning, to test for overconditioning to weak cues in hyper-dopaminergic states (Cassaday and Moran 2010; Gray et al. 1991; Kapur 2003).

In principle, blocking has an additional attraction in that it relates an issue of fundamental importance in normal associative learning, namely the role of surprise, encapsulated in the study of prediction error. Through unblocking manipulations, we can study the liberation of attention by surprise and drug effects thereon. However, the reliable demonstration of unblocking can require extensive behavioral pilot work. Moreover, attention is only half the story in that successful associative learning should reflect the direction of change when the outcome is more or less than expected. Aficionados have noted that inhibitory learning is not consistently demonstrated in aversively motivated downshift unblocking procedures – on the contrary, a weaker UCS than expected can result in excitatory conditioning to the additional CS B (Fig. 6).

Cross-References

- ▶ Aminergic Hypotheses for Schizophrenia
- ▶ Animal Models for Psychiatric States
- ▶ Antipsychotic Drugs
- ▶ Attention
- ▶ Attentional Bias to Drug Cues
- ▶ Classical (Pavlovian) Conditioning
- ▶ Cognitive Enhancers
- ▶ Latent Inhibition
- ▶ Schizophrenia
- ▶ Schizophrenia: Animal Models
- ▶ Translational Research

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Blonanserin

Synonyms
AD-5423

Definition
Blonanserin is a second-generation (atypical) antipsychotic drug indicated for the treatment of schizophrenia. It belongs to a series of 4-phenyl-2-(1-piperazinyl)pyridines and acts as an antagonist at D_2, D_3, and 5-HT_{2A} receptors. Its affinity for D_2 receptors is approximately six times greater than that for 5-HT_{2A} receptors. It has low affinity for α_1, 5-HT_{2C}, H_1, and M_1 receptors, but displays relatively high affinity for 5-HT_6 receptors. Its safety profile compared favorably with haloperidol, particularly with respect to prolactin elevation and the frequency of extrapyramidal motor side effects.

Cross-References
► Extrapyramidal Motor Side Effects
► Haloperidol
► Schizophrenia
► Second-Generation Antipsychotics

Blood–Brain Barrier

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Synonyms
Hematoencephalic barrier; Neurovascular unit

Definition
Regions of the brain where capillary endothelial cells express unique anatomical properties such as high-resistance tight junctions and selective biochemical properties of metabolism and transport, allowing the regulation of solute exchange between blood and brain.

Current Concepts and State of Knowledge

Basic Properties of the Blood–Brain Barriers

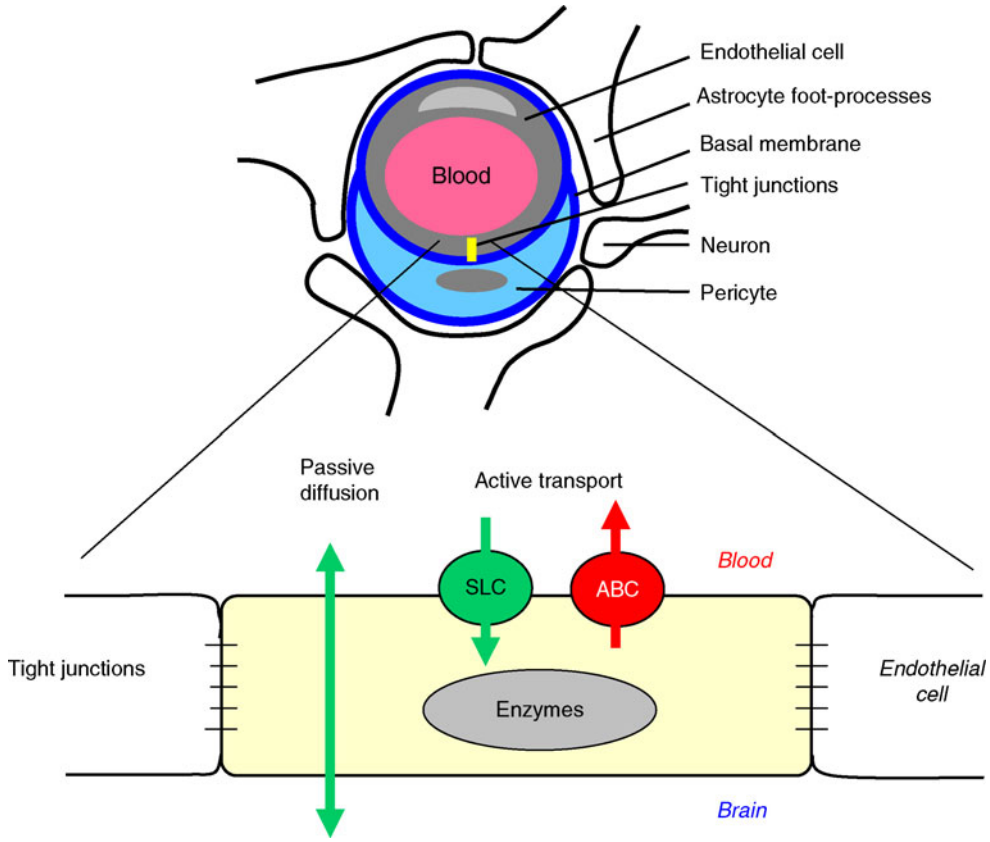
The Two Barriers
The general concept of a restricted passage of solutes out of the blood into the brain dates from the early studies of Lewandowsky and Ehrlich in the 1900s who described that dyes injected intravenously were not taken up by the brain (Goldstein and Betz 1986). Only a few small regions of the brain, collectively known as the ► circumventricular organs making up less than 1% of the cerebrovascular bed have no barrier, enabling substances in the blood to reach the brain extracellular fluid.

There are two physiological barriers separating the brain from its blood supply; they control the entry and exit of endogenous and exogenous compounds. This allows the body to maintain a constant internal milieu in the brain, protecting it from fluctuations in circulating hormones, amino acids, ions, and other nutrients, thereby preventing uncontrolled disturbances of the central nervous system (CNS). One is the blood–brain barrier (BBB), and the other is the ► blood–cerebrospinal fluid barrier (BCSFB). In 1919, Goldmann carried out experiments with trypan blue injected directly into the cerebrospinal fluid. These studies helped to differentiate the two barriers, as the dye left only the blood vessels of the choroid plexuses. The BCSFB is located at the choroid plexuses. These plexuses float freely in the brain ventricles and are formed by epithelial cells held together at their apices by tight junctions (junctional complex between two cells whose membranes join together forming an impermeable barrier to fluid). Beneath the epithelial cells is a stroma containing the blood vessels, which lack tight junctions. Thus, the fenestrated blood vessels of the choroid plexus allow large molecules to pass, but the tight junctions at the epithelial cell surfaces restrict their passage into the CSF (Spector and Johanson 1989).

Since the surface area of the human BBB is estimated to be 20 m or around a thousand times greater than that of the BCSFB, the BBB is considered to be the main region controlling the neuronal environment and the uptake of drugs into the brain parenchyma. It is also the main target for delivering drugs to the brain via carrier-mediated strategies (Scherrmann 2002).

From BBB to the Neurovascular Unit
The BBB is defined by the microvasculature of the brain, which consists of a monolayer of polarized endothelial cells connected by complex tight junctions having a high

electrical resistance (>1,000–3,000 Ω/cm). This structure prevents paracellular transport across the brain endothelium. These endothelial cells are separated from the astrocyte foot processes and pericytes by a basement membrane (Fig. 1). The astrocyte foot process are about 20 nm from the abluminal (the layer of plasma membrane of polarized cells that is adjacent to the basement membrane, also called basolateral membrane) surface of the endothelial cells and this space is mainly filled with the microvascular basement membrane and the brain extracellular fluid. The endothelial cells actively regulate vascular tone, blood flow, and barrier function in the brain microvasculature. Endothelial cells are thin, about 0.1 µm thick, and thus occupy about 0.2% of the volume of the whole brain. They are polarized, like epithelial cells; the luminal (the layer of plasma membrane on the side toward the lumen of polarized cells, also called apical membrane) and abluminal endothelial membranes each segregate specific transcellular transport across the brain endothelium (Zlokovic 2008). This cell polarity is well illustrated by the distribution of several enzymes. Alkaline phosphatase is equally distributed between the luminal and the abluminal membranes but Na, K-ATPase and 5′-nucleotidase are present primarily on the abluminal side, and gamma-glutamyl transpeptidase is found mainly on the luminal side. Goldmann first postulated that the brain capillaries provide the anatomical basis of a barrier in 1913, but this was not conclusively demonstrated until the 1960s, when electron microscope studies revealed that the endothelial cells of a brain capillary form electron-dense junctional contact between two adjacent cells. There are no gap junctions (specialized intercellular connections



Blood–Brain Barrier. Fig. 1. Anatomical and functional definition of the blood–brain barrier (BBB). The cross-sectional scheme shows that the brain capillary endothelial cell is sealed by tight junctions which are surrounded by the pericyte and astrocyte foot processes. All these cellular components are separated by a basal membrane and constitute the neurovascular unit. Solutes can cross the cerebral endothelial cells by passive diffusion or active transport involving influx and efflux transporters from the solute carrier (SLC) and ATP-binding cassette (ABC) superfamilies. Enzymes can also metabolize solutes.

between cells allowing solute exchanges between adjacent cells) in brain capillaries and postcapillary venules and the tight junctions are responsible for sealing adjacent cells and maintaining cell polarity. Tight junctions are membrane microdomains made up of many specific proteins engaged in a complex membranar and intracytosolic network. Continuous tight junctions are not the only feature that makes the blood vessels of the brain different from those of other tissues. There are no detectable fenestrations or single channels between the blood and interstitial spaces. They contain fewer pinocytotic vesicles (cytoplasmic vesicles resulting from a mechanism by which extracellular fluid is taken into a cell following the invagination of the cell membrane) than do endothelial cells in the peripheral microvasculature and there is evidence that the majority of what appear to be independent vesicles in the endothelium cytoplasm are part of membrane invaginations that communicate with either the blood or the perivascular space. The endothelial cells that form the BBB also contain many mitochondria. They occupy 8–11% of the cytoplasmic volume, much more than in brain regions lacking a BBB and tissues outside the CNS. This indicates that the BBB also functions as a metabolic barrier, in addition to its physical barrier properties (Ballabh et al. 2004). There are highly specific transport systems carrying nutrients at the luminal or abluminal sides, or at both sides of the endothelial cell membrane. These carrier-mediated transport systems regulate the movement of nutrients between the blood and the brain. The brain capillary endothelium also bears specific receptors for circulating peptides or plasma proteins and these mediate the ► transcytosis of peptides or proteins through the BBB. More recently, the discovery of active carrier-mediated transporters which are not involved in transporting substrate from the blood to the brain, but from the brain to the blood, has greatly reinforced the barrier properties of the BBB. Most of these transmembrane proteins are located at the luminal or abluminal membranes of the endothelial cells and restrict the uptake of numerous drugs by the brain. Thus a large number of amphipathic cationic drugs are effluxed by one ATP-binding cassette (ABC) protein, the ► P-glycoprotein (P-gp) which is present at the luminal surface of the BBB. Brain vessels also have more classical types of receptors, including α-and β-adrenergic receptors and receptors for serotonin, adenosine, histamine, angiotensin, and arginine vasopressin. The brain capillaries are also almost completely surrounded by other cells, like pericytes and the astrocyte foot processes. Pericytes lie periendothelially on the abluminal side of the microvessels (Fig. 1). A layer of basement membrane separates the pericytes from the endothelial cells and the astrocyte foot processes. Pericytes send out cell processes which penetrate the basement membrane and cover around 20–30% of the microvascular circumference. Pericyte cytoplasmic projections encircling the endothelial cells provide both a vasodynamic capacity and structural support to the microvasculature. CNS pericytes can be viewed as housekeeping scavenger cells and a second line of defense in the BBB. The blood capillaries of the CNS of vertebrates are also enveloped by a perivascular sheath of glial cells, mainly astrocytes (Fig. 1). Immunohistochemical and morphometric studies on astrocytes and the microvasculature of the human cerebral cortex have shown that the astrocyte perivascular processes form a virtually continuous sheath around the vascular walls. While the astrocytes themselves do not form the barrier, they have an important role in the development and maintenance of the BBB. Astrocytes release factors that can induce the BBB phenotype and/or the angiogenic transformation of brain endothelial cells in vitro and in vivo. All these cellular components of the brain capillaries are joined by junctional systems. Zonal and extensive tight junctions seal the endothelial cells and gap junctions connect the endothelium to the subjacent pericyte layer, allowing their functional coupling and also weld them to the astrocyte processes (Abbott et al. 2006). The last component of the neurovascular unit is the nerve fibers, which may be seen close to the cerebral blood vessels; these may be noradrenergic and peptidergic nerves (Fig. 1). They influence the cerebrovascular tone and blood flow by secreting classical transmitters and a number of peptides, including substance P and vasoactive intestinal peptide. This neurogenic influence could also explain the circadian variation in the permeability of the BBB under noradrenergic influence. The intimate relationships between these cells make the BBB a pluricellular interface between the blood and the brain extracellular fluid.

Role of the Neurovascular Unit in Psychopharmacology

This overview points out the complexity of the BBB, as at least four types of cells plus the basement membrane are implicated in its structure and function. Thus many genes and the proteins they encode play a critical role in the broad pharmacological spectrum of activities carried out by the BBB. As psychoactive drug responses depend on numerous proteins in the body, including metabolizing enzymes, transporters, receptors, and all signaling networks mediating the response, it is very likely that gene–protein-mediated events at the BBB can play a role in the efficacy and safety of psychopharmacotherapies. For example, polymorphisms in genes encoding drug-metabolizing enzymes or transporters expressed at the

BBB could affect the transport of a drug across the BBB and consequently the patient's response to it.

Drug-Metabolizing Enzymes in the BBB

Although the absence of paracellular transport across the BBB impedes the entry of small hydrophilic compounds into the brain, low molecular weight lipophilic substances may pass through the endothelial cell membranes and cytosol by passive diffusion. While this physical barrier cannot protect the brain against chemicals, the metabolic barrier formed by the enzymes from the endothelial cell cytosol may transform these chemicals. Compounds transported through the BBB by carrier-mediated systems may also be metabolized. Thus, L-DOPA is transported through the BBB and then decarboxylated to dopamine by the aromatic amino acid decarboxylase.

This metabolic barrier was first postulated for amino acid neurotransmitters in the 1960s. The presence of enzymatic systems suggests that a battery of enzymes may modulate the entry of neuroactive molecules into the brain. Several phase 1 enzymes, such as cytochromes P450 (CYP), monoamine oxidases (MAO-A and -B), flavin-containing monooxigenases, reductases and oxidases and phase 2 enzymes catalyzing conjugation, such as UDP-glucuronosyltransferases (UGTs) and glutathione and sulfotransferases have been found in the rat and human CNS, as well as in isolated brain microvessels and cerebrovascular endothelial cells, which constitute the BBB (El-Bacha and Minn 1999).

Drug-Carrier Transporters in the BBB

A second type of drug pharmacokinetic event at the BBB is mediated by proteins on the luminal and/or the abluminal membranes of the endothelial cells (Ohtsuki and Terasaki 2007). These proteins can mediate influx or efflux transport from the blood to the brain or vice versa. They belong to two superfamilies, the solute carrier (SLC) and the ABC. This type of active transport was first discovered for nutrients that are not lipid soluble and cannot cross the barrier by simple diffusion. Most of these transporters are SLC members and like the glucose carrier, the carrier for large neutral branched and aromatic amino acids, the so-called L-system – now designated LAT – 1 (Large Neutral Amino acid Transporter) is present at both sides of the endothelial cell membranes and transports at least ten essential amino acids. ► L-DOPA used to treat ► Parkinson's disease and other CNS pharmaceuticals, such as baclofen and ► gabapentin, cross the BBB via the L system.

The monocarboxylic acid transporter (MCT1) is present on both the luminal and abluminal membranes of the BBB and seems to transport substrates in both directions. MCT1 is responsible for the transport of several substances, including the gamma-hydroxybutyrate sleeping and anesthetic agent, which can be also used as a recreational drug at higher doses. Interestingly, the anticonvulsant, ► valproic acid, is more efficiently transported from the brain to the blood than the other way round because an organic anion transport counterbalances the uptake mediated by MCT1 at the BBB.

The BBB also has sodium and pH-independent transporters of organic cations. They are important for the homeostasis of choline and thiamine in the brain and for the permeation of cationic drugs like, ► fentanyl, H_1-antagonists and choline analogs. These organic cation transporters are mainly located at nerve terminals, glial cells and in the BBB.

The identification of the ABC brain-to-blood efflux transporter, P-glycoprotein (ABCB1, P-gp), in 1992 has added a novel property to the concept of the BBB (Scherrmann 2005). P-gp decreases the permeability of the BBB to lipophilic drugs by actively impeding their crossing of the luminal membranes or by transporting them out of the endothelial cells to the bloodstream. P-gp was originally found as an over-produced membrane protein in multidrug resistance tumor cells, and was found to be responsible for reducing the intracellular accumulation of several anticancer drugs. Transport mediated by P-gp is coupled with ATP hydrolysis and affects many substrates that have a planar structure, neutral, or cationic charge and are hydrophobic. While humans have only one gene (MDR1) encoding the drug-transporter P-gp, rodents have two genes, mdr1a and mdr1b, that encode P-gps with overlapping substrate specificities. The availability of mice with disrupted mdr1 genes has helped to demonstrate that the P-gp in the BBB limits the entry of many drugs into the brain by actively pumping them back into the blood. Most light-microscope and electron-microscope immunochemical experiments using several specific antibodies to P-gp indicate that the luminal membrane of the brain endothelial cells normally has a high concentration of P-gp (Fig. 1). Its role as a barrier to the entrance of small lipophilic compounds across the luminal membranes of the brain capillary endothelial cells is now clearly established.

One such is the dopamine antagonist, domperidone, which only produces an antiemetic effect in P-gp competent mice due to its selective peripheral activity. The antipsychotic effect of domperidone becomes its main effect when it is given to mice lacking P-gp, indicating its distribution and activity in the CNS. Similarly, the antinociceptive effect of ► morphine and other opioids

is increased in mice lacking P-gp and the brain distribution of risperidone, its active metabolite 9-hydroxyrisperidone and metoclopramide is affected by P-gp.

Several functional polymorphisms of the human MDR1-gene were recently described and correlated with the synthesis and activity of P-gp in vivo and this might be an extremely important factor influencing between-subject variations in the uptake of a large number of pharmaceuticals by the CNS.

There is always a risk of interaction between P-gp-mediated drugs at the BBB. Any resulting modulation of P-gp transport activity may also give rise to variations in the response of the CNS to drugs, both between individuals and within the same individual, depending on the other drugs being administered. The interaction of loperamide, an antidiarrheal drug that is transported by P-gp, with quinidine has been evaluated in healthy volunteers. Loperamide had several side effects on the CNS phenotype, including respiratory depression, demonstrating that the inhibition of BBB P-gp by quinidine allowed loperamide to be transported across the BBB.

There seem to be several other transporters that exclude drugs from the brain, in addition to P-gp such as the breast cancer resistance protein (BCRP, ABCG2) which is also expressed at the luminal side of BBB.

Conclusion

The functional characterization and identification of the proteins and genes of so many nutrient and drug enzymes and transporters at the BBB over these last 25 years has led to a change in our understanding of the way psychoactive drugs are transported across the BBB. This has opened an important avenue for the development of attractive strategies for delivering drugs to the brain using some of these enzymes or transporters. This new information may also shed light on the factors involved in inter- and intra-subject variations in the uptake of drugs by the CNS.

Cross-References

► ABC Transporters

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Blood–Cerebrospinal Fluid Barrier

Definition

Regions of the brain ventricles where choroid plexus epithelial cells, the anatomical site of BCSFB, produce the cerebrospinal fluid (CSF). These cells are connected by tight functions that restrict solute exchange between blood and CSF. Unlike capillaries of the blood–brain barrier, capillaries enveloping the epithelium are fenestrated and have no tight junctions allowing free movement of solutes.

Blood Oxygenation Level-Dependent Contrast

► BOLD Contrast

BMI

► Body Mass Index

BNST

Synonyms

Bed nucleus of the stria terminalis

Definition

The brain region partially responsible for regulation of the HPA axis. The BNST receives input from the ► prefrontal

cortex, ► amygdala, and ► hippocampus and projects to the paraventricular nucleus of the ► hypothalamus. Stimulation of CRF receptors in this area can lead to ► social anxiety in animal models. Lesion studies have also shown that BNST lesions aggravate behavioral despair in rats.

Cross-References
► Behavioral Despair

Body Mass Index

Synonyms
BMI

Definition
The body mass index (BMI), or Quetelet index, is a statistical measurement that compares a person's weight and height. It is a useful tool to estimate a healthy body weight based on how tall a person is. It is the most widely used diagnostic tool to identify weight problem within a population including: underweight, overweight, and obesity. Body mass index is defined as the individual's body weight divided by the square of his height.

BOLD

► Cerebral Perfusion

BOLD Contrast

Synonyms
Blood oxygenation level-dependent contrast

Definition
BOLD contrast has emerged as one of the most potent noninvasive tools for mapping brain function and has been widely used to explore physiological, pathological changes and mental activity in the brain. The physiological basis underlying the BOLD contrast is based on the neurovascular coupling. Neuronal activity leads to a hemodynamic response resulting in a concentration change of oxygenated and deoxygenated hemoglobin. As oxygenated and deoxygenated hemoglobin have different magnetic properties, this concentration change can be detected using MRI. Thus, the MR image contrast depends on the blood oxygenation level.

Cross-References
► Functional MRI
► Pharmacological fMRI

Bolus

Definition
An injection of a substance given in its entirety over a short period of time, generally less than 1 min. In most ► PET studies, radiotracer is administered as a single intravenous bolus.

Bolus Plus Constant Infusion

Definition
A method of administration of a substance intended to introduce a steady state concentration in plasma. An initial bolus is given, followed by an extended infusion at a much slower rate. An optimal ratio of bolus to infusion rate is chosen to induce steady state as rapidly as possible. For PET imaging, the resulting steady state allows investigators to infer equilibrium constants from concentration ratios. The pharmacokinetics of many radioligands, relative to the decay rate of the isotope, are too slow for this method to be practical. But for those radioligands amenable to it, the bolus plus constant infusion method has several advantages, including robust parameter estimates and less vulnerability of outcome measures to errors produced by changes in cerebral blood-flow rates than the bolus approach.

BP

► Binding Potential

BP_1

► Binding Potential

BP_2

► Binding Potential

BP_F

► Binding Potential

BP_{ND}

► Binding Potential

BP_P

► Binding Potential

BPSD

Definition

The term "behavioral and psychological signs and symptoms of dementia" (BPSD) describes the spectrum of noncognitive manifestations of dementia that include seven phenomenological categories: paranoid and delusional ideation, hallucinations, activity disturbances, verbal and physical aggression, diurnal (sleep) rhythm disturbances, affective disturbances, and anxieties and phobias. BPSD are common, present a major risk factor for caregiver burden, are associated with a worse prognosis, and add significantly to the direct and indirect costs of care.

Cross-References

► Dementia

Bradykinesia

Definition

Slowed movements.

Brain Abnormalities

Definition

Already in the early 1900s, imaging techniques were available to investigate the human brain *in vivo*. In 1970, a first CT study was published, which showed brain abnormalities in patients with ► schizophrenia and in 2000 a cross-sectional meta-analysis convincingly showed that brain volume changes are present in schizophrenia. Nowadays, schizophrenia is generally known as a disease associated with changes in brain morphology.

Brain Atrophy

► Neuroprotectants: Novel Approaches for Dementias

Brain-Derived Neurotrophic Factor

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Synonyms

BDNF

Definition

Brain-derived neurotrophic factor (BDNF) is a polypeptide factor that binds to and activates ► TrkB, which is a receptor protein tyrosine kinase (Soppet et al. 1991). There is considerable interest in BDNF as a pharmacological agent for the treatment of neurodegenerative diseases [► Neurodegeneration and Its Prevention]. In addition, contemporary data indicate that BDNF may be required for the action of ► Antidepressants (Kozisek et al. 2007). The role BDNF may have in the mechanism of action of other psychotropic drugs, such as opiates, ► Benzodiazepines and ► Antipsychotic Drugs is less clear, but remains a subject of considerable research.

Pharmacological Properties

Introduction

History. Brain-derived neurotrophic factor (BDNF) is a member of a family of neurotrophins related by sequence homology and was originally identified as a factor that promoted the survival of cultured embryonic chick sensory neurons. ► Nerve Growth Factor is the prototypic member of this neurotrophin family, which also includes

Neurotrophin-3 (NT-3) and Neurotrophin 4/5 (NT-4/5). Pro-BDNF (~28 kDa) is processed into BDNF (14 kDa), both of which may have biological activity. BDNF is known to promote activity-dependent synaptic plasticity, axonal guidance, and neuronal survival. BDNF is required for the normal development of several areas of the nervous system.

Physiological role in plasticity. Following early evidence that BDNF was important for the survival of hippocampal and motor neurons, data have been accumulating demonstrating that BDNF has a major role in the physiological processes underlying the plasticity and development of the nervous system. BDNF and TrkB are required for normal hippocampal ►Neurogenesis in the adult rodent (Li et al. 2008). Moreover, BDNF is required for long-term potentiation [►Long-Term Potentiation and Memory], which involves BDNF regulating both presynaptic and postsynaptic mechanisms. It may be that antidepressant drugs regulate synaptic plasticity by inducing the expression of BDNF, which in turn may underlie some of the behavioral effects of these drugs (Brunoni et al. 2008; Kozisek et al. 2007).

Cellular signaling pathways activated by BDNF. In addition to activating the receptor protein tyrosine kinase TrkB (Soppet et al. 1991), BDNF also binds to the p75 low affinity neurotrophin receptor. The expression of the TrkB gene results in a full-length receptor protein tyrosine kinase (gp145 kDa) and truncated receptors (~gp90 kDa) (Middlemas et al. 1991). BDNF activates several signaling pathways that are involved in both mitogenesis and survival of cells as well as in regulating synaptic function and adult hippocampal neurogenesis. Neurogenesis in the adult ►hippocampus involves mitogenesis, migration, differentiation, and survival of neural precursor cells. Whether the role of BDNF in neurogenesis is mitogenic or trophic is hotly debated. BDNF could also be involved in differentiation or migration of these newborn cells.

BDNF, via its receptor, TrkB, activates major signaling pathways requiring phosphatidylinositol 3-phosphate kinase and the microtubule-associated kinases (MAPKs). With regard to putative roles for these signaling pathways in hippocampal neurogenesis, the phosphatidylinositol 3-phosphate kinase pathway is a cellular survival pathway whereas the MAPK pathway is the major mitogenic pathway activated by growth factors. Notably, BDNF activates multiple pathways leading to MAPK activation (Easton et al. 2006), which may underlie some of the physiological differences between BDNF and traditional growth factors such as the epidermal growth factor. The phospholipase C-gamma (PLC-gamma) pathway, which is also activated by BDNF, is involved in the regulation of long-term potentiation.

There is keen interest in BDNF, both as a possible pharmacological agent and for its potential role in the therapeutic action of psychotropic drugs. BDNF is required for survival of some populations of neurons during development. These neurotrophic properties of BDNF led to testing BDNF for amyotrophic lateral sclerosis (ALS). Unfortunately, the phase III clinical trial of BDNF failed to demonstrate a significant effect for treating ALS. Although there has been research directed at a possible role for BDNF in the treatment of other neurodegenerative diseases, there is now significant interest in the role BDNF may have in the treatment of major depressive disorder [►Major & Minor & Mixed Anxiety-Depressive Disorders]. Antidepressants increase BDNF expression in the adult rodent hippocampus and considerable evidence indicates that BDNF is required for the therapeutic action of these agents.

All antidepressant drugs acutely increase the levels of monoamine neurotransmitters in the CNS. One class of antidepressants, the ►Monoamine Oxidase Inhibitors, blocks catabolism of norepinephrine, serotonin, and dopamine. Other classes of antidepressant drugs inhibit the transporters required for the reuptake of monoamines from synaptic cleft. These drugs can be classified as serotonin-specific reuptake inhibitors (SSRIs [►SSRIs and Related Compounds]) or norepinephrine reuptake inhibitors [►NARI Antidepressants]. Some antidepressant drugs inhibit the reuptake of several of the monoamine neurotransmitters. Notably, there is a delay, on the order of days to weeks, in the therapeutic effect following the start of chronic treatment with antidepressant drugs. This delayed action gives rise to at least two distinct hypotheses for the cellular basis of antidepressant drug action. These drugs may induce changes in synaptic efficacy and synaptogenesis, or the antidepressants may induce hippocampal neurogenesis. BDNF has a putative role in both of these physiological processes.

The neurotrophic hypothesis for depression. It is proposed that deficits in BDNF expression underlie major depression disorder [►Major & Minor & Mixed Anxiety-Depressive Disorders], and, moreover, that chronic antidepressant treatment increase BDNF levels in the hippocampus. The initial finding that implied a role for BDNF in depression was that antidepressants increase the expression of BDNF, both mRNA and protein, in the adult hippocampus (Nibuya et al. 1995). Additional findings supporting the neurotrophic hypothesis include the demonstration that BDNF mRNA expression is decreased by stress and glucocorticoids in the hippocampus. Both

stress and increased cortisol levels are thought to have a causal role in major depression.

A few key experiments suggest an actual requirement for BDNF in antidepressant action. BDNF infusion directly into the midbrain of rats produces an antidepressant-like effect. Furthermore, heterozygous BDNF knockout mice do not respond to antidepressants in the forced-swim test (Saarelainen et al. 2003), which is a model used to test for antidepressant activity. The implication is that antidepressant drugs increase BDNF levels, which leads to changes in neuronal circuitry underlying an antidepressant effect.

Evidence suggesting that neurogenesis may be required for antidepressant drug action. An ingenious experiment implied a role for hippocampal neurogenesis in the action of antidepressant drugs. Because neurogenesis is acutely sensitive to radiation, it was used to block neurogenesis. Radiation treatment also blocked the action of antidepressant drugs (Saarelainen et al. 2003). Consistent with this finding, antidepressant drugs also induce hippocampal neurogenesis in the adult rat hippocampus (Sairanen et al. 2005). In addition, exercise also induces neurogenesis, which correlates well with the established antidepressant effect of exercise. Taken together, the data suggest increases in neurogenesis may underlie some of the antidepressant effects of these drugs. There may well be other effects of antidepressant drugs such as changes in synaptogenesis or synaptic efficacy.

A role for BDNF in hippocampal neurogenesis. Evidence is growing that BDNF has a direct role in hippocampal neurogenesis. In knockout mice with heterozygous BDNF expression, hippocampal neurogenesis was decreased compared to wild-type BDNF mice. Neurogenesis was decreased in both heterozygous BDNF mice and mice expressing a dominant negative TrkB receptor (TkB.T1) (Sairanen et al. 2005). These studies point to a role for BDNF promoting both increased mitogenesis and survival of newborn neurons.

To get at the precise role of TrkB in neurogenesis, actual neural precursor cells have been used for experiments (Li et al. 2008). Initially, using Nestin-GFP mice, where neural precursor cells were fluorescently marked, it was demonstrated that hippocampal neural precursor cells do indeed express TrkB. Because TrkB knockout mice die shortly after birth, TrkB conditional knockout mice were then used to show that the ablation of TrkB impairs the normal development of the dentate gyrus granule cell layer (Li et al. 2008). This was correlated with a direct decrease in the number of granule neurons. In these studies, the role of TrkB was shown to be in proliferation rather than survival. Most importantly, TrkB expression is required for neural precursor cell proliferation and neurogenesis induced by antidepressant drugs. In a striking extension of these experiments, it was shown that TrkB is also required for the behavioral effects of antidepressant drugs in the novelty-suppressed feeding test paradigm using the conditional knockout mice (Li et al. 2008). This is a conflict paradigm where latency to feed in a novel environment is an indicator of anxiety level in mice. The extensive groundwork that has now been laid indicating a role for BDNF and TrkB in antidepressant action may lead to novel targets for antidepressant discovery and development.

Developmental differences in antidepressant efficacy. There is a distinct difference in the efficacy of different classes of antidepressant drugs in children and adolescents [► Depressive Disorders in Children] compared to adults (Bylund and Reed 2007). Children and adolescents respond to some SSRIs [SSRIs and Related Compounds], but do not respond to tricyclic antidepressants [► Adolescence and Responses to Drugs]. The reason for this underlying difference in antidepressant drug class efficacy between adolescents and adults is not known. Because the serotonergic neurotransmitter systems mature earlier during development than do the adrenergic neurotransmitter systems, earlier maturation of the serotonergic system may explain why SSRIs are effective in adolescents, whereas noradrenergic selective drugs lack efficacy (Bylund and Reed 2007). In a juvenile rodent model, the SSRI ► escitalopram, but not desipramine (a tricyclic which is highly selective for inhibiting ► norepinephrine as compared to ► serotonin reuptake), increases levels of hippocampal BDNF and TrkB (Kozisek et al. 2008). The failure of desipramine to increase BDNF and TrkB levels in juvenile rats is consistent with the lack of efficacy of desipramine in children and adolescents.

This is a truly exciting era in psychotropic drug research. There remains a tremendous need for both more effective treatments and a reduction in the adverse effects of treatment for most mental disorders, including major depression. The delineation of the mechanism of action of fascinating psychotropic drugs, such as the antidepressant drugs with their delayed action, continues at a brisk pace. Further delineation of the precise role BDNF has in hippocampal neurogenesis and the cellular signaling pathways activated by BDNF that are required for antidepressant action may well identify novel targets for antidepressant drug discovery. The role BDNF signaling has in the physiological process underlying the antidepressant effect of drugs could well lead to strategies for novel therapies. This offers the prospect of more effective

antidepressant drugs or perhaps effective cell-based antidepressant therapies.

Cross-References

- ▶ Adolescence and Responses to Drugs
- ▶ Antidepressants
- ▶ Antipsychotic Drugs
- ▶ Benzodiazepines
- ▶ Depressive Disorders in Children
- ▶ Long-Term Potentiation and Memory
- ▶ Major & Minor & Mixed Anxiety-Depressive Disorders
- ▶ Monoamine Oxidase Inhibitors
- ▶ NARI Antidepressants
- ▶ Nerve Growth Factor
- ▶ Neurodegeneration and Its Prevention
- ▶ Neurogenesis
- ▶ SSRIs and Related Compounds

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Brain Imaging

- ▶ Neuroimaging

Brain Mapping

- ▶ Neuroimaging

Brain Microdialysis

- ▶ Microdialysis

Brain Reward Systems

- ▶ Mesotelencephalic Dopamine Reward Systems

Brain Stimulation Reward

Synonyms

BSR

Definition

The effect of electrical brain stimulation that causes the recipient to seek reinitiation of the stimulation.

Breaking Point

- ▶ Breakpoint

Breakpoint

Synonyms

Breaking point; Final ratio

Definition
Breakpoint is used as a dependent variable in experiments using a ▶ progressive ratio (PR) schedule of reinforcement. A breakpoint is said to have been reached when the response output falls below a predefined level. In self-administration experiments, the breakpoint is often defined as the final ratio in effect (i.e., response requirement) when the last injection was delivered. Alternatively, the breakpoint can be defined as the total number of reinforcing events during the session.

Cross-References
▶ Progressive Ratio

Brexiaceae

▶ Celastraceae

Bromazepam

Synonyms
Benzodiazepines

Definition
Bromazepam is a classical benzodiazepine drug with an intermediate-short half-life (12–20 h). It produces anxiolytic, sedative, hypnotic, and anticonvulsant effects by increasing GABAergic neurotransmission via ▶ allosteric modulation at ▶ $GABA_A$ receptors, that is, it binds to a distinct site within the $GABA_A$ receptor Cl-ion channel complex causing a conformational change that increases the efficacy of ▶ GABA. It is used clinically to treat anxiety and panic disorder and also as a premedication before surgical procedures. Adverse effects of bromazepam include cognitive impairments such as memory, attention, psychomotor activity, reaction time, and vigilance performance, and these effects are particularly evident in the elderly. It is also subject to misuse and abuse and is often involved in drug overdoses.

Cross-References
▶ Benzodiazepines
▶ Sedative, Hypnotic, and Anxiolytic Dependence

2-Bromo-Alpha-Ergocryptine

▶ Bromocriptine

Bromocriptine

Synonyms
2-bromo-12′-hydroxy-2′(1-methylethyl)-5′-(2-methylpropyl) ergotoman-3′,6′,18-trione; 2-bromo-alpha-ergocryptine; CB-154

Definition
Bromocriptine is a centrally acting dopamine D2 receptor agonist used to treat ▶ Parkinson's disease. There are indications that direct agonists may have beneficial effects with respect to the onset of treatment-induced side effects such as dyskinesias. Bromocriptine is also used in the treatment of hyperlactation by suppressing prolactin secretion, pituitary tumors/acromegaly, and neuroleptic malignant syndrome. Bromocriptine and other direct dopamine receptor agonists may help in reducing ▶ L-DOPA dosing (thus reducing side effects such as dyskinesias and "on-off" motor function). They may also be of help for patients experiencing the L-DOPA "wear-off" effect.

Cross-References
▶ Anti-Parkinson Drugs
▶ Neuroleptic Malignant Syndrome

2-Bromo-12′-Hydroxy-2′(1-Methylethyl)-5′-(2-Methylpropyl) Ergotoman-3′,6′,18-Trione

▶ Bromocriptine

Bromovalerylurea

Definition
Bromovalerylurea is a non-benzodiazepine sedative and hypnotic of the bromoureide class that contains bromide. It produces barbiturate-like sedative and hypnotic effects, such as dose-related drowsiness, confusion, and impairs motor coordination. Chronic intake of excessive amounts can produce bromide intoxication (bromism), which in some instances is prolonged or permanent. Bromide intoxication may cause variable symptoms, particularly psychiatric, cognitive, neurological, and dermatologic. It is subject to dependence and abuse.

Cross-References
▶ Abuse
▶ Barbiturates

- ▶ Benzodiazepines
- ▶ Dependence
- ▶ Hypnotics
- ▶ Substance Abuse

Bromperidol

Definition

Bromperidol is an antipsychotic drug used to treat the symptoms of schizophrenia. It is a first-generation drug and does therefore have a stronger tendency to induce motor side effects than many newer antipsychotics. Bromperidol can be administered as a depot given intramuscularly every few weeks, which gives long-term antipsychotic treatment and improves compliance.

Cross-References

- ▶ Antipsychotic Drugs
- ▶ First-Generation Antipsychotics
- ▶ Schizophrenia

Brotizolam

Synonyms

Benzodiazepines

Definition

Brotizolam is a benzodiazepine medication that has anxiolytic, sedative, and anticonvulsant properties. It is a short-acting compound (i.e., elimination ▶ half-life 5 h) and does not have active (i.e., benzodiazepine) metabolites. The relatively short duration of action of brotizolam has resulted in its use as a hypnotic, although it is also used as an anxiolytic. Like most similar compounds, brotizolam is subject to ▶ tolerance, ▶ dependence, and ▶ abuse.

Cross-References

- ▶ Anxiolytics
- ▶ Benzodiazepines
- ▶ Hypnotics

BSR

- ▶ Brain Stimulation Reward

Bulimia Nervosa

- ▶ Eating Disorders: Animal Models

Buprenorphine

Definition

Buprenorphine is a long-acting ▶ opioid analgesic that is 25–50 times more potent than morphine. It is a partial μ-opioid-receptor agonist and a κ-kappa-receptor antagonist and is used as a medication in ▶ opioid maintenance therapy. Because of its partial antagonist property, a submaximal ceiling effect is seen. Unlike other opioids, in some circumstances buprenorphine does not seem to produce ▶ tolerance. It has less severe withdrawal effects than ▶ methadone, making detoxification easier.

Cross-References

- ▶ Analgesics
- ▶ Opioids

Buprenorphine–Naloxone

Definition

The buprenorphine–naloxone combination contains ▶ buprenorphine with ▶ naloxone at a ratio of 4:1 and was invented with the intention of reducing intravenous misuse of the medication. Naloxone has a low oral bioavailability thus not influencing the mechanisms of action of buprenorphine when taken sublingually. However, when buprenorphine/naloxone combinations are dissolved and injected intravenously, opioid agonist actions are blocked by naloxone and can precipitate unpleasant and dysphoric symptoms of opioid withdrawal.

Bupropion

Definition

Bupropion is an atypical ▶ antidepressant that acts on noradrenaline and dopamine transporters to enhance extracellular levels of ▶ catecholamines, which may account for its antidepressant action. In addition, bupropion has been shown to block some ▶ nicotinic receptors, an effect that may explain its efficacy as a smoking cessation aid. Bupropion reduces the severity of nicotine cravings and

withdrawal symptoms. Treatment with bupropion approximately doubles the chance of quitting smoking successfully for 3 months. Trials have shown that 1 year after the treatment, the odds of sustaining smoking cessation are still 1.5 times higher after bupropion than after placebo. Slow release formulations have been prescribed for clinical depression, particularly those cases not responding to SSRI. The metabolites of bupropion are pharmacologically effective and may contribute to the clinical efficacy. The common adverse effects include dry mouth, nausea, insomnia, tremor, excessive sweating, and tinnitus.

Cross-References

► Nortriptyline

Buspirone

Definition

An azapirone anxiolytic acting as a ► partial agonist at 5-HT_{1A} receptors, with efficacy in GAD. Many of those who have previously been treated with a ► benzodiazepine find it to be of little value in relieving anxiety symptoms, and treatment can be compromised by increased nervousness and dizziness, particularly in the first few weeks of treatment.

Butyrophenones

Definition

A group of drugs that includes key members of the first generation of antipsychotic substances that brought about major changes in the treatment of schizophrenia. The most prominent member of this category is ► haloperidol.

Cross-References

► Antipsychotics
► First-Generation Antipsychotics

C

Cabergoline

Synonyms

FCE21336; N-[(3-dimethylamino)propyl]-N-[(ethylamino)carbonyl]-6-(2-propenyl)-ergoline-8b-carboxamide

Definition

Like bromocriptine, cabergoline is a centrally acting dopamine D2 receptor agonist used to treat Parkinson's disease in its early phase. Cabergoline can be used in combination with L-DOPA and carbidopa in the progressive phase of Parkinson's disease (see also L-DOPA and carbidopa). Cabergoline is also used in the treatment of hyperlactation by suppressing prolactin secretion, pituitary tumors (prolactinomas), and dysfunctions related to hyperprolactinemia. Cabergoline and pergolide are contraindicated in patients with evidence of heart valve problems due to activation of 5-HT_{2B} receptors.

Cross-References

► Anti-Parkinson Drugs

Cachexia

Definition

Cachexia is a wasting syndrome involving reduced appetite, loss of body weight, and muscle atrophy. In contrast to other causes of weight loss such as anorexia nervosa or dieting, weight loss due to cachexia is involuntary. Individuals with cachexia are not actively attempt to lose weight. These symptoms are commonly observed in cancer patients undergoing chemotherapy treatment.

Cross-References

► Anorexigenic
► Eating Disorder: Anorexia Nervosa

Caffeine

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Synonyms

1,3,7-Trimethylpurine-2,6-dione; Trimethylxanthine; 1,3,7-Trimethylxanthine

Definition

Caffeine is a natural xanthinic alkaloid consumed worldwide for its ability in exerting psychostimulant effects of a mild extent usually devoid of severe unwanted consequences.

Pharmacological Properties

History and Sources

Caffeine is contained in several vegetal species, the most famous being *Coffea arabica, Thea sinensis*, and *Theobroma cacao*. The most ancient documentation on the consumption of caffeine-containing plants and their derivatives dates back to the China of the third century, where caffeine was consumed as tea. However, it is believed that consumption of caffeine-containing plants began far earlier, perhaps even during the Stone Age.

Coffee as a beverage was first imported in Europe by the Venetian Prospero Alpino in 1570, while in 1573 Léonard Rauwolf, a German physician and botanist was the first European to describe the preparation and drinking of coffee and in 1819 Friedrich Runge first isolated caffeine. Social appreciation of caffeine dates to the seventeenth century when "coffee houses" were established in Costantinople and Venice. Nowadays, caffeine can be found in dietary products like coffee, tea, mate, and

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chocolate as well as an additive to soft drinks, particularly in the so called "energy drinks." Moreover, caffeine is a component of certain over the counter medications and of several dietary supplements.

Biological Effects: General Overview

Caffeine is capable of targeting several body organs and of influencing complex physiopathological phenomena (Table 1). Although psychostimulation is envisioned as "the" effect of caffeine, other effects may be associated with caffeine intake whose nature and intensity considerably vary among consumers. This depends, on one hand, on the existence of a different inter-individual responsiveness to caffeine and, on the other, on the rate and duration of caffeine consumption. Some of caffeine effects are manifested only after its intake at very high doses, while ► tolerance to certain effects may occur after prolonged caffeine consumption. Furthermore, ► effect inversion can take place after either the intake of high doses or prolonged consumption of caffeine.

Biological Effects: Central Effects

As mentioned earlier, psychostimulation is the most popular among the central effects exerted by caffeine. Caffeine-induced psychostimulant effects include increased wakefulness, delayed need for sleep, reduced fatigue perception, and augmented alertness. Caffeine also elicits rewarding effects associated with a beneficial influence on mood, and interferes with the perception of stimuli bearing, in addition, discriminative properties (► drug discrimination) towards other psychostimulants. Furthermore, nootropic properties have been suggested for caffeine based on its beneficial effects in tests measuring memory function. However, it is debated whether this result reflects a genuine effect on memory or rather stems from caffeine-induced increase in alertness. Then, the existence of a neuroprotective potential (► neuroprotection) for caffeine has been observed in experimental animal models of Parkinson's and Alzheimer's disease and suggested in humans based on epidemiological evaluation of ► Parkinson's disease incidence (Fig. 1). Finally, caffeine-mediated psychoactive effects may powerfully influence those of other centrally active substances, leading to either their amplification (► amphetamines) or attenuation (► alcohol).

Mechanisms of Action: General Overview

A wealth of experimental evidence indicates that the most commonly manifested biological effects of caffeine arise from its action on ► adenosine receptors. Such receptors are the only ones among the known biological targets of caffeine to be sensitive to the plasmatic concentrations of the substance attained upon its recreational consumption (Table 2). One cup of coffee may contain from 60 to 100 mg of caffeine (~ 5 μM plasma levels); up to 10 cups of coffee, caffeine acts as an antagonist of adenosine A1/A2A receptors. At higher concentrations (100 μM) caffeine inhibits cyclic nucleotide ► phosphodiesterases, whereas at toxic concentrations (1 mM) it stimulates the release of Ca^{2+} through the ryanodine receptor.

Four subtypes of adenosine receptors, namely A1, A2A, A2B, and A3, have been characterized. Caffeine is an antagonist towards these receptors: in humans it preferentially blocks A2A receptors (KD = 2.4 μM), displays a good affinity towards A1 (KD = 12 μM) and A2B receptors (KD = 13 μM), while A3 receptors are bound with lower affinity (KD = 80 μM). All adenosine receptors are G protein-coupled receptors, and their stimulation leads to modifications involving the activity of adenylyl cyclase, phospholipase C, phospholipase D as well as changes in the gating state of Ca^{2+} and K^{+} channels, eventually triggering the biological effects of adenosine (Fredholm et al. 1999). Caffeine effects can, therefore, be considered as resulting from the counteraction of such neurochemical cascade (Fig. 1). The participation of non-adenosinergic mechanisms in caffeine effects, particularly upon intake of high doses, may however exist.

Mechanisms of Action: Central Effects

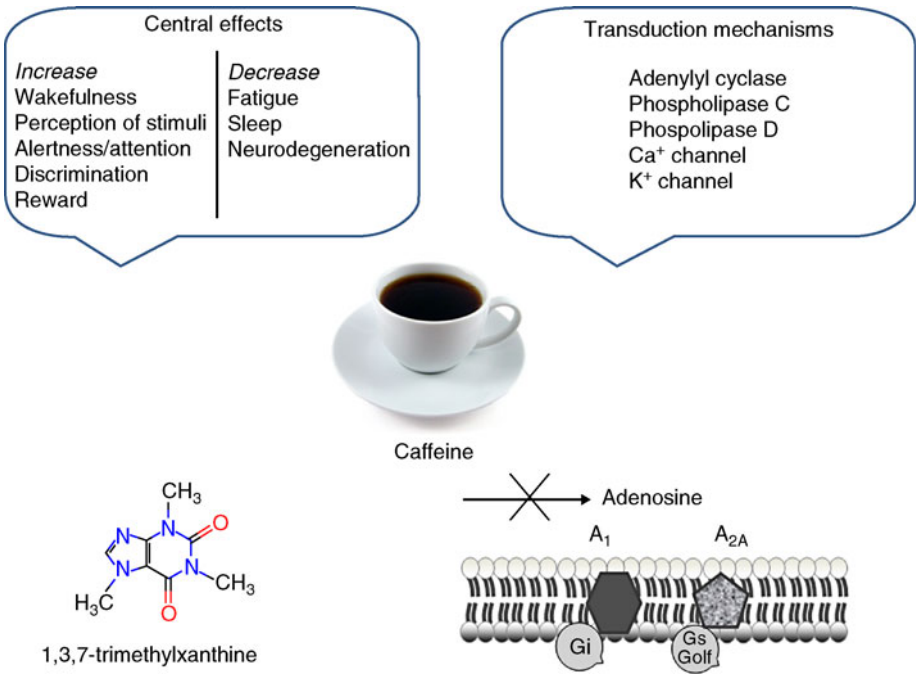
The A1 and A2A receptors are those mainly involved in mediating caffeine-induced central effects, since next to bearing a good affinity for caffeine, they are also highly enriched in the brain. In this regard, experimental evidence has suggested that, although caffeine leads to a combined A1/A2A receptor blockade, either receptor subtype may acquire particular importance in mediating a specific effect of caffeine. Caffeine discriminative effects appear mostly dependent on A1 receptors, while A2A receptors seem to govern caffeine-induced arousal, increased alertness, and neuroprotection (Higgins et al. 2007; Schwarzschild and Ascherio 2004). Adenosine receptor subtypes other than A1 and A2A appear scarcely relevant to caffeine central effects, as A3 receptors display a poor affinity for caffeine (see above) and A2B receptors are negligibly stimulated by brain adenosine under physiological conditions.

The existence of profound functional interactions between adenosine and other neurotransmitters appears of paramount importance to the manifestation of the central effects of caffeine. In particular, the cross-talk between adenosine and the dopaminergic transmission, whose

Caffeine. Table 1. Overview of the effects of caffeine on different organs and physiopathological functions.

Organ or physiopathological function	Effects of caffeine
Central and peripheral nervous system	Analgesia
	Modification in EEG activity
	Neuroprotection[a,b]
	Pro-convulsant effects[c]
	Psychostimulation and rewarding effects
	Psychiatric-like effects[c]
	Stimulation of catecholamine release
	Stimulation of respiration
Eye	Elevation in intraocular pressure[c]
HPA axis	Stimulation of the secretion of adrenocorticotropin and cortisol
Cardiovascular system	Acceleration of heart rhythm
	Increase in blood pressure
	Pro-arrhythmogenic activity[c]
	Vasocostrinction and/or vasodilation[i]
Lung	Relaxation of bronchial smooth muscle
Gastrointestinal tract	Depression of lower esophageal sphincter pressure
	Stimulation of gastric acid secretion
	Stimulation of intestine motility[c]
Liver	Modifications in the activity of ALT, AST and GGT enzymes[b]
Kidney	Increase in renin secretion
	Stimulation of diuresis
Skeletal Muscle	Increased muscular endurance
	Stimulation of muscular contraction[d]
Bone	Detrimental influence on bone mass[c]
Gonads and gametocytes	Modulation of circulating levels of sexual hormones[a,b]
	Interference with oocyte maturation[d,f]
	Interference with spermatozoa motility and capacitation[d,f]
Immune system	Modulation of the production of antibodies, cytokines and other mediators of inflammation[a,d,e]
	Modulation of leukocytes count and function[a,d,e]
Metabolic effects	Stimulation of thermogenesis and lipolysis
	Increase in the levels of cholesterol[a,b]
	Influence on glucose tolerance and insulin sensitivity[e,g]
Carcinogenesis	Modulation of carcinogenesis[a,b,d,h,j]
Mutagenesis	Interference with DNA repair mechanisms[d]
Teratogenesis	Teratogenetic effects[a]

[a]Effect observed in experimental animals
[b]Effect hypothesized in humans based on epidemiological studies
[c]Effect observed at very high doses, or in individuals bearing either a pre-existing susceptibility or a pre-existing condition (disease, unbalanced diet) favoring the manifestation of the effect
[d]Effect observed in vitro
[e]Both a facilitation and an impairment of this effect have been described in the literature, and results may differ between acute and chronic intake
[f]Interspecies differences in this effect have been described
[g]An inverse association between caffeine consumption and type II diabetes has been suggested by epidemiological studies
[h]An inverse association between caffeine consumption and different type of tumors has been suggested by epidemiological studies
[i]Effects may vary according to the vascular district examined
[j]Both anti- and pro-carcinogenetic effects have been described at the preclinical level according to the type of the tumor considered



Caffeine. Fig. 1. Summary of caffeine chemical structure, receptor binding, transduction mechanisms and central effects.

activation is critically involved in promoting psychomotor stimulation, seems crucial to caffeine-elicited psychostimulant effects (Cauli and Morelli 2005). Thus, opposite functional interactions between adenosine receptors and ► dopamine receptors have been demonstrated in both animal and human brain (Fredholm and Svenningsson 2003). Stimulation of adenosine receptors depresses dopaminergic transmission while adenosine receptor blockade amplifies it (Ferré et al. 1997). Caffeine, by antagonizing adenosine receptors, boosts dopaminergic transmission, and rodent studies have substantiated the relevance of such a mechanism to caffeine's neurobehavioral effects. In this regard, an attenuation in caffeine-elicited psychomotor stimulation has been described in mice bearing a genetic deletion of either the D2 receptor or the phosphoprotein ► DARPP-32, a key second messenger in dopamine receptor-mediated signal transduction (Fisone et al. 2004; Zahniser et al. 2000). Interactions between adenosine and neurotransmitters other than dopamine, such as ► glutamate, ► serotonin, ► acetylcholine, and histamine, also exist in the brain which may be important to caffeine-induced central effects. In particular, adenosine–glutamate interactions have been suggested to participate in caffeine-elicited psychostimulant effects and to underlie the neuroprotective effects of caffeine (Schwarzschild and Ascherio 2004).

Experimental Paradigms

Several experimental models exist that are suited to the investigation of the biological effects of caffeine. These may involve either in vitro paradigms, widely used to evaluate the effects of caffeine on cell cycle, or in vivo models, employed to study caffeine-induced effects at both the peripheral and central level. The latter models can address the influence of caffeine on phenomena such as diuresis, metabolic and heart function, and neurotoxicity. The majority of the studies concerned with caffeine, however, use models aimed at investigating its effects on brain function. Such paradigms evaluate the capability of caffeine in modifying the behavioral performance of animals, mainly rodents, and they can be paired with complementary techniques (e.g., ► microdialysis) aimed at elucidating the changes in brain neurochemistry triggered by caffeine.

Thus, the magnitude of caffeine-elicited motor activity, whose increase is an index of psychostimulation, is largely measured as parameter reflecting the gross psychostimulant effects of caffeine. Next to this, caffeine influences ► conditioned place preference and ► intracranial self-stimulation, two paradigms useful to investigate drug-induced positive rewarding effects. Furthermore, caffeine affects animals' performance in different ► drug discrimination and taste preference paradigms, reflecting caffeine's influence on the perception of stimuli. Finally,

Caffeine. Table 2. Biological targets of caffeine.

Target	Action	Range of effective concentrations (mM)[a]
Adenosine A1 and A2A receptors	Antagonism	0.01–0.1
GABAA receptors	Antagonism	0.1–10
Glycogen phosphorilase enzymes	Inhibition	0.25–2[b,c]
Na^+/K^+ Pump	Stimulation	0.1–10
Phosphodiesterases isoenzymes	Inhibition	0.1–6[d]
Phosphoinositides	Inhibition of metabolism	0.5–5
Ryanodine sensitive Ca^{2+} receptor	Activation of Ca^{2+} release	1–10

[a]Plasmatic concentrations of caffeine attained after recreational consumption of moderate amounts of the substance are estimated to be considerably below 0.1 mM
[b]May significantly drop in the presence of glucose
[c]Differences may exist between liver and muscle enzymes
[d]May significantly vary among different isoforms

the ability of caffeine in influencing the execution of tests aimed at evaluating either memory or attention can be used to study the effects of caffeine on cognitive performance (► rodent models of cognition). Either acute or chronic changes in animals' behavior as measured by means of the above paradigms can also be used to ascertain whether, and to what extent, exposure to caffeine modulates the effects elicited by other psychoactive substances. Finally, the study of the conditions favoring the instatement and maintenance of a caffeine consumption habit (► caffeinism) is also possible in animals. This can be performed in either rodents or primates by means of the ► drug self-administration paradigm (Fredholm et al. 1999).

Human Paradigms

The majority of the investigations dealing with the effects of caffeine in humans are concerned with its ► psychostimulant and rewarding effects. The conditions under which caffeine delays the need for sleep and promotes alertness in sleep-deprived individuals are extensively investigated and so are the effects of caffeine on mood and on the execution of mental tasks. Such investigations usually employ a single administration or a brief multiple exposure to caffeine, and are often paired with electroencephalographic analysis (► electroencephalography) to examine the pattern of caffeine-induced neuronal activation. Moreover, investigations can be conducted to address either the features of ► caffeine withdrawal syndrome (► withdrawal syndromes) or the influence of caffeine intake on the neurobehavioral effects of other centrally active substances. Peripheral effects of caffeine can be evaluated in humans as well, and consumption of caffeine is usually included as a variable in epidemiological studies, in light of the widespread diffusion of this habit (Fredholm et al. 1999).

Pharmacokinetics

Caffeine is rapidly and nearly completely absorbed after oral intake. In adult healthy humans, caffeine reaches its plasmatic concentration peak within 0.5–2 h from ingestion. Plasmatic ► half-life of caffeine is estimated for 2–10 h in young adults and elders, while it is higher in neonates and infants, due to the incomplete development of metabolic pathways in these subjects. As it displays lipophilic properties, caffeine crosses the ► blood–brain barrier and can reach the brain at high concentrations. Furthermore, caffeine penetrates the placenta, thus reaching the fetus. Significant levels of caffeine can be also detected in milk and saliva.

Caffeine is mainly metabolized by the ► cytochrome P-450 hepatic enzymes. Several active caffeine metabolites have been isolated, the major being theophylline, theobromine, and paraxanthine, and interspecies differences in caffeine metabolism exist. Many of caffeine metabolites display a pharmacological profile close to the one of their parent compound, and can participate in caffeine effects. In humans, the main metabolic pathway of caffeine involves its degradation to paraxanthine which is catalyzed by the CYP1A2 subform of the P-450 enzymes.

Conditions influencing the function of P-450 enzymes can profoundly impact the metabolism and, accordingly, the ► pharmacokinetics of caffeine. Caffeine plasmatic half-life is increased by diseases depressing hepatic metabolic activity (e.g., cirrhosis) and by agents that are metabolized by, or that inhibit, the CYP1A2 (e.g., cimetidine, ► disulfiram, estrogens). Conversely, a reduction in caffeine half-life is caused by agents capable of inducing P-450 enzymes (e.g., ► carbamazepine, rifampicin, cigarette smoke) (Fredholm et al. 1999; Magkos and Kavouras 2005).

Toxicological and Adverse Effects

Consumption of caffeine is considered a safe habit, since the lethal dose of the substance is very high (at least 100 mg/kg). Nevertheless, cases of either poisoning or anaphylaxis induced by caffeine have been reported, and adverse effects may be associated with recreational caffeine consumption. Irritability, anxiety, psychotic-like symptoms, and increased susceptibility to seizures have been described in caffeine consumers. These effects are likely manifested in the presence of a pre-existing individual susceptibility; hence, their incidence is negligible though it can increase when caffeine is consumed at high doses. In addition, caffeine elevates blood pressure and can, at times, trigger alterations in heart rhythm (Higdon and Frei 2006). Rodent studies have suggested that caffeine consumption during pregnancy might promote teratogenesis, but this hypothesis has not been proven conclusively in humans. Similarly, neither has caffeine intake been convincingly demonstrated to increase the risk of abortion. However, moderation in caffeine consumption is advisable in pregnant women to prevent the fetus from being reached by caffeine which could exert adverse effects on it.

Caffeine can influence the pharmacological effects of several drugs. This may happen through mechanisms involving metabolism (see above), clearance (e.g., lithium), absorption (e.g., oral iron supplements), or pharmacodynamic amplification of other drugs' effects (e.g., ephedrine). In its recreational use, caffeine is often associated with other psychostimulants, as amphetamine analogs, to increase their effects, or to alcohol, to counteract alcohol depressive effects and hangover. In both cases, use of caffeine may produce severe side effects by raising the toxicity of amphetamine analogs (e.g., ▶ MDMA) or letting the alcohol consumer to increase the assumption of alcohol up to toxic doses.

Use as a Medication

The major uses of caffeine as a medication are as analgesic for the treatment of headache and as a respiratory stimulant for the management of postpartum apnea in premature neonates. Furthermore, due to its lipolitic and thermogenetic properties, caffeine is an adjuvant in topic anti-cellulite preparations and its use has been suggested for the treatment of obesity. The use of caffeine to counteract some aspects of ▶ akinesia and tremor associated with Parkinson's disease has also been proposed.

Use as a Research and Diagnostic Tool

Caffeine is widely employed in biomedical research. Thus, caffeine is a standard molecule in studies investigating the pharmacology of adenosine receptors, due to its reduced cost and good solubility in physiological mediums. Furthermore, activation of the ryanodine receptor, which modulates Ca^{2+} release from intracellular stores, by caffeine is exploited to investigate muscular physiopathology and mechanisms of cellular Ca^{2+} turnover. Caffeine is also used in biopharmaceutical studies evaluating the permeability of the skin and artificial skin-like membranes, due to its well-characterized biophysical properties. Measurement of the clearance of caffeine and/or its metabolites is employed to estimate hepatic and/or renal functionality, while quantification of caffeine degradation to paraxanthine is used as a phenotypic marker for the CYP1A2 enzyme. Moreover, changes in the susceptibility of the skeletal muscle to caffeine-induced contraction are evaluated as a diagnostic parameter for malignant hyperthermia.

Conclusion

Caffeine is one of the most popular psychostimulant substances in the world. Although caffeine consumption is generally not associated with harmful consequences, moderation in caffeine intake is advisable to selected categories of individuals, such as pregnant women or persons particularly susceptible to its adverse effects. Finally, the ability of caffeine in interfering with the effects of centrally active substances, including addictive psychostimulants, may represent a further risk factor associated with its consumption.

Cross-References

- ▶ Caffeinism
- ▶ Conditioned Place Preference and Aversion
- ▶ Conditioned Taste Aversion and Preference
- ▶ Drug Discrimination
- ▶ Electroencephalography
- ▶ Intracranial Self-Stimulation
- ▶ Microdialysis
- ▶ Neuroprotection
- ▶ Pharmacodynamic Tolerance
- ▶ Psychomotor Stimulants
- ▶ Rodent Models of Cognition
- ▶ Self-Administration of Drugs
- ▶ Withdrawal Syndromes

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Caffeine Abstinence

► Caffeine Withdrawal Syndrome

Caffeine Intoxication

► Caffeinism

Caffeine "Jitters"

► Caffeinism

Caffeine Withdrawal Syndrome

Synonyms

Caffeine abstinence

Definition

Condition that follows the discontinuation of caffeine intake and that is characterized by symptoms such as fatigue, headache, irritability, depressed mood. Symptoms of caffeine withdrawal syndrome are not necessarily manifested all at the same time and their intensity may considerably vary among different individuals. Caffeine withdrawal syndrome is usually not harmful; it is self-limiting and can be manifested by both moderate and heavy caffeine consumers.

Cross-References

► Caffeine
► Caffeinism
► Withdrawal Syndromes

Caffeinism

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Synonyms

Caffeine intoxication; Caffeine "jitters"; Coffee nerves

Definition

Caffeinism is a complaint encompassing a variety of unpleasant mental and physical symptoms associated with the consumption of excessive amounts of ► caffeine. Symptoms primarily result from exaggerated stimulation of the central nervous system or other organ systems and are not due to a general medical condition or another mental disorder. Symptoms can cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. Symptoms resolve when caffeine ingestion is discontinued, and caffeine is metabolized and eliminated from the body.

Role of Pharmacotherapy

Caffeine is generally accepted as the most widely consumed drug in the world. It is naturally present in coffee and tea, the most popular beverages in the world, and in cocoa, chocolate, and a number of other plants consumed around the world. It is added to a variety of soft drinks, especially "cola" drinks, and is a major component of the growing category of "energy drinks" sold as dietary supplements. Caffeine is also a component of many over-the-counter and prescription drugs. Its consumption and use is so widespread, and caffeine-containing beverages are so much a part of social culture around the world, that caffeine is seldom thought of as a drug. However, it is a drug with widespread effects throughout the body.

In its many forms this drug is most often consumed for its properties as a central nervous system stimulant

(► Psychomotor Stimulants). In moderate doses, it is used to reduce physical fatigue, to prevent drowsiness and sleep, and to maintain and restore mental alertness and wakefulness. However, at higher doses, these stimulatory effects can become excessive and lead to an unpleasant and dysphoric physical and mental state that is labeled caffeinism and is also known colloquially as "coffee nerves" or "caffeine jitters."

Symptoms

The common symptoms of caffeinism are essentially exaggerations of the effects that are sought after by those who ingest caffeine and are similar to the effects of overdose of other stimulant drugs. Caffeine overdose results in a state of central nervous system overstimulation, with symptoms that include restlessness, nervousness, excitement, and irritability. People may report feeling jittery or "wired" with "racing thoughts" and have difficulty falling asleep or returning to sleep if awakened. Physical symptoms can include flushing of the face, increased urination, gastrointestinal disturbances, muscle twitching, and irregular or rapid heart beat. These symptoms can result either from acute overdose or from chronic consumption of high doses over extended periods of time.

The acute form is perhaps best described as "caffeine intoxication," which occurs following consumption of an unusually large caffeine dose within a short period of time. This could occur when an individual who is inexperienced with caffeine ingests several cups of coffee, energy drinks, or caffeine tablets, perhaps in an effort to stay awake and alert and to ward off sleep, or to "get a buzz." Acute intoxication can also occur in habitual caffeine consumers, when the doses of caffeine ingested are much higher than normal. A few extra cups of coffee consumed to meet a deadline can produce symptoms of intoxication even in a regular coffee drinker.

Chronic ingestion over long periods of time can also produce symptoms that are labeled caffeinism. Heavy coffee drinking has been associated with symptoms that were initially diagnosed as generalized anxiety or ► panic attacks (James 1991; Lane 1987). Later examination of the patients' histories indicated that anxiety or panic symptoms began after the patient started drinking 10–12 cups of coffee or more every day. In each case, symptoms disappeared shortly after caffeine intake was discontinued. Another report described long-term low-grade fever accompanied by ► insomnia, anorexia, and irritability in a woman who drank 15–18 cups of coffee every day, whose symptoms disappeared after she severely restricted her caffeine intake. Caffeinism associated with chronic ingestion also includes the symptoms that result from the ► physical dependence on caffeine that develops over time. In the habitual heavy consumer, symptoms of caffeine ► withdrawal, including headache, fatigue and sleepiness, mental fogginess and difficulties concentrating, depression, and irritability can appear when regular patterns of caffeine ingestion are disrupted, in as little as 12 h after the last dose (of caffeine).

Mild or occasional symptoms of caffeine overdose may cause few disruptions to the quality of life for the caffeine consumer. However, the American Psychiatric Association currently recognizes several mental health disorders related to caffeine in the ► Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR), which can be clinically significant to mental health. Of these, "Caffeine Intoxication" is the disorder most closely related to caffeinism as described here. According to the DSM-IV-TR, the essential feature of Caffeine Intoxication is the recent consumption of caffeine. This diagnosis requires the presence of at least five signs or symptoms, from a list of 12, that develop during or shortly after caffeine use. (American Psychiatric Association 2000) The signs and symptoms are divided into one group that can appear after an intake of as little as 100 mg of caffeine (roughly the amount contained in a cup of brewed coffee) and another group of symptoms that appear at higher levels of intake (more than 1 g per day). Low-dose symptoms include "restlessness, nervousness, excitement, insomnia, flushed face, diuresis (increased urination), and gastrointestinal disturbance." Symptoms associated with high doses of caffeine include "muscle twitching, rambling flow of thought and speech, tachycardia and cardiac arrhythmia, periods of inexhaustibility, and psychomotor agitation." In order to meet the diagnosis of caffeine intoxication, these symptoms must cause "clinically significant distress or impairment in social, occupational, or other important areas of functioning." Symptoms cannot be due to a general medical condition or be better explained by another mental disorder. This diagnosis does not distinguish between symptoms of acute overdose and of chronic ingestion.

DSM-IV-TR includes two other caffeine-related diagnoses associated with chronic ingestion of caffeine. The diagnosis of "Caffeine-Induced Anxiety Disorder" recognizes that consumption of large amounts of caffeine over time induces in some individuals symptoms that are indistinguishable from anxiety sufficiently severe to warrant clinical attention. This disorder can take many forms, including generalized anxiety disorder, panic attacks (Panic), obsessive–compulsive symptoms (► Obsessive–Compulsive Anxiety Disorders), and phobic symptoms. The diagnosis of "Caffeine-Induced Sleep Disorder"

recognizes that the sleeplessness associated with caffeine ingestion at high doses over time can produce significant disruptions of sleep (Insomnia). Although insomnia may be the typical complaint, some individuals present with a complaint of excessive daytime sleepiness related to caffeine withdrawal. Here again, symptoms must be associated with recent or ongoing caffeine ingestion and cannot be explained by other medical conditions or mental disorders. The World Health Organization (1993) also recognizes the potential for caffeine-related mental disorders in the ▶ ICD-10, although caffeine is grouped with all stimulants other than cocaine. As a result, no caffeine-specific symptoms are mentioned in the diagnostic criteria. The signs and symptoms that are associated with the diagnosis of "Acute intoxication" include most of those listed in the DSM-IV, but also include many that have not commonly been associated with caffeine ingestion. The ICD-10 does recognize that physical dependence on caffeine and caffeine withdrawal are potential mental disorders that can disrupt daily living. However, the diagnostic criteria are general and do not include the specific symptoms known to be caffeine-related.

Risk Factors

Although many of the symptoms of caffeinism are dose-dependent, the dose of caffeine consumed is not the only factor that determines whether symptoms appear or not. There is no consensus about what constitutes an "overdose" of caffeine, and there is no accepted minimum dose that is certain not to produce symptoms in any individual. As the DSM-IV-TR (American Psychiatric Association 2000) states, some symptoms of caffeine intoxication can appear after acute doses of only 100 mg (one cup of coffee), yet other sources suggest that doses of 300–500 mg are necessary.

Caffeine can be consumed in many beverages, foods, medications, and dietary supplements. These vary widely in the amount of caffeine present in a "standard serving." Not all sources are equally likely to promote the development of caffeinism. Coffee is probably the beverage most often associated with symptoms of acute and chronic caffeine overdose, because it provides the highest dose of all foods and beverages. A typical 8-ounce cup of coffee might contain 125 mg of caffeine, although the dose varies widely. By contrast, a cup of brewed tea contains less than half as much caffeine, and 12-ounce servings of caffeinated soft drinks contain roughly one-third the caffeine. In amounts normally consumed, cocoa and chocolate contain even smaller doses. Coffee is also the most likely cause of caffeinism because of its growing popularity and its place as a primary social beverage in many settings. The fact that serving sizes have increased over the years from 5 or 6 ounces in a cup to 24 ounces or more at neighborhood coffee houses and convenience stores only serves to increase the likelihood that coffee drinking will lead to symptoms of overdose. However, consumption of the so-called "energy drinks" sold as dietary supplements is a growing risk factor, as the popularity of these drinks increases. Unlike soft drinks, the caffeine content of these beverages is not commonly restricted, and some brands contain over 350 mg of caffeine per serving. Manufacturers are not required to put the caffeine dose on the label. This can create special problems for the adolescents targeted by marketing, who often have little prior experience with caffeine.

At least three other factors interact with dose to determine vulnerability to caffeinism. The first is individual sensitivity to caffeine. Chronic ingestion of caffeine leads to the development of tolerance to the drug (▶ Pharmacodynamic Tolerance), as the nervous system and body adapt to the continued presence of the drug. When tolerance develops, the same dose has less effect, which should reduce the risk of caffeine intoxication. However, tolerance provides little protection when caffeine doses are acutely increased. Caffeine sensitivity also varies as a function of how quickly caffeine is eliminated from the body (▶ Pharmacokinetics). For example, genetic differences are known to produce slow and fast eliminators. Concurrent use of some other common medications, including oral contraceptives, has been shown to interfere with caffeine metabolism and slow elimination. Those who eliminate the drug more slowly experience higher drug concentrations for longer periods of time after consuming caffeine , which increases the risk of symptoms. A second factor is the presence of other psychiatric conditions (James 1991). The risk for caffeine intoxication is thought to be much greater in those individuals who are already susceptible to anxiety, panic disorder, or other mood disorders. In these individuals, caffeine appears to aggravate an underlying susceptibility. Finally, exposure to stress may increase the risk of caffeinism (Lane 1987). In some studies, increased stress in daily life was associated with increases in the consumption of caffeine. Furthermore, caffeine has been shown to exaggerate the impact of stress on mood and physiology, which could aggravate the symptoms that define the disorder (Lane et al. 1990).

Epidemiology

Little is known about the prevalence of caffeinism in the general population (Iancu et al. 2007). Although most people are familiar with the disorder, it probably remains underdiagnosed, because patients are rarely questioned

about the use of caffeine. Few surveys have been drafted to determine the proportion of the general population who have experienced caffeinism symptoms. These limited results suggest that 10–20% of the general population met the criteria for Caffeine Intoxication (DSM-IV-TR) in the previous year. Surveys also suggest that those who use caffeine to enhance academic or professional performance or to maintain alertness for extended periods of time will tend to use more of the drug and be at greater risk of caffeinism.

Prevention and Treatment

Both the prevention and treatment of caffeinism depend simply on reducing the levels of caffeine present in the body, either acutely or chronically. This depends on reduction of caffeine ingestion and the passage of sufficient time for metabolic elimination of caffeine in the body.

Control of caffeine intake requires awareness of the caffeine content of caffeinated beverages, over-the-counter drugs, and other sources of caffeine in the diet. Such information is not easy to obtain. The content of brewed beverages such as coffee and tea varies greatly based on the method of preparation (James 1991). There can be no standard value for "a cup of coffee." The caffeine content of soft drinks and energy drinks can be difficult to determine, because the labels do not indicate the dose per serving. Caffeine doses in these beverages range from 20 to 30 mg in some soft drinks, up to 350 mg or more in some energy drinks. Although some Internet web sites report caffeine content for beverages, official lists are not available and the number of brands continually grows.

It is possible to eliminate caffeine from the diet by abruptly quitting all consumption of caffeine-containing products ("going cold turkey"). This approach is not recommended, because the resulting symptoms of caffeine ► withdrawal (► Withdrawal syndromes), including headache, fatigue, and difficulty concentrating, can be so unpleasant that the attempt fails. Gradual reductions in caffeine use are recommended to avoid withdrawal. Because caffeinated beverages are often a regular part of daily life, it is essential to break the habits associated with caffeine ingestion and consciously substitute with uncaffeinated alternatives. Programs based on techniques of behavior management have proved successful, although few clinical trials have been conducted to determine the best procedures (James 1991).

Cross-References

► Caffeine
► Insomnia
► Obsessive–Compulsive Anxiety Disorders
► Panic
► Pharmacodynamic Tolerance
► Pharmacokinetics
► Psychomotor Stimulants
► Withdrawal Syndromes

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Calcium Acetylhomotaurinate

► Acamprosate

CAM

► Confusion Assessment Method

Camazepam

► Benzodiazepines

Cambridge Neuropsychological Test Automated Battery

► CANTAB

cAMP

Synonyms
Cyclic-adenosine monphosphate

Definition
Cyclic-adenosine monphosphate (cAMP) is a major intracellular second messenger generated by adenylate cyclase. Many GPCRs either stimulate or inhibit adenylate cyclase, depending on the specific G-proteins they interact with. cAMP stimulates activation of protein kinase A and also directly binds to other proteins, including some ionic channels to modulate their function in the cell.

Campral

► Acamprosate

Cannabinoid Receptors

Definition
A family of receptors (with two current members) that a part of the ► G-protein-coupled receptor superfamily. They are activated by the cannabinoids and endocannabinoids.

Cannabinoids

Definition
Refers to a group of substances or compounds that are structurally related to tetrahydrocannabinol (THC), the primary psychoactive compound in cannabis.

Cross-References
► Cannabinoids
► Classification of Psychoactive Drugs

Cannabinoids and Endocannabinoids

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Synonyms
Cannabinoids

Definition
In the strictest sense, ► cannabinoids are alkaloids that are present in the *Cannabis sativa* plant. However, the word cannabinoid is often used to refer to all chemicals (synthetic and natural) that bind to ► cannabinoid receptors. Endocannabinoids are cannabinoid receptor ligands that are present in biological tissues and function as endogenous agonists of the cannabinoid receptors.

Pharmacological Properties

History
The unique pharmacological properties of the preparations of *Cannabis sativa* plant have been recognized for thousands of years. There is evidence that *Cannabis* was cultivated in China as early as 4,000 B.C. for multiple purposes, including its use as a food and medicinal agent. In India, the use of *Cannabis* for medicinal purposes began approximately 1,000 BC. C*annabis* extracts were used by these cultures to reduce pain, seizures, anxiety, mania and muscle spasms, and to stimulate appetite.

The introduction of *Cannabis* to Western medicine occurred in the mid-19th century through the writings of William B. O'Shaughnessy, an Irish physician, who became aware of indigenous use of *Cannabis* plant during his service under the British in India. O'Shaughnessy reported the beneficial therapeutic effects of *Cannabis* for convulsions and muscular spasms caused by rabies and tetanus. Jacques-Joseph Moreau, a French psychiatrist, also discovered *Cannabis* during his travel in the Far East and studied its psychological effects in himself and his students. Moreau published his observations regarding the use of *Cannabis* as an experimental psychotomimetic in Du Hachisch et de l'Alientation Mentale: Etudes Psychologiques (1840).

The beginning of the modern era of cannabinoid pharmacology is ascribed to the 1964 publication by Gaoni and Mechoulam of the structure of the psychoactive chemical in *Cannabis*, Δ^9-tetrahydrocannabinol (THC), together with a method for its isolation from the plant. A body of scientific literature was published between 1965 and 1986 that focused on the pharmacological and cellular effects of THC. Among the important contributions of this era was the codification of a tetrad of THC effects in rodents (analgesia, reduction in body temperature, catalepsy, and spontaneous activity) that was used to characterize the cannabinoid activity of an extensive library of THC structural analogs. Levonantradol was found to mimic the effects of THC, although with higher potency, it was used to provide the first biochemical evidence that THC-like molecules inhibit adenylyl

cyclase activity with characteristics that indicated the involvement of a ► G-protein coupled receptor (GPCR). In 1990, the cloning and sequencing of the cannabinoid receptor was reported, confirming both its membership in the GPCR superfamily of receptors and its identity as a high-affinity binding site for THC. This receptor, now referred to as the CB1 ► cannabinoid receptor (CB1R), is the protein product of the *Cnr1* gene. Biochemical studies of the ability of THC to activate the CB1R indicated that THC had surprisingly low efficacy at the CB1R. In other words, although THC binds to the CB1R with high affinity, the THC-bound receptor has a limited ability to activate signaling. As a consequence, THC functions as an antagonist at CB1R that are activated by endogenous ligands and as an agonist at CB1R that are not endogenously activated.

Devane, Mechoulam, and colleagues isolated and identified *N*-arachidonylethanolamine (AEA, also called anandamide) as an endogenous ligand of the CB1R. Several years later, 2-arachidonoylglycerol (2-AG) was identified as a second endogenous ligand of the CB1R. The term "endocannabinoid" is used to refer to these two endogenous, cannabinoid receptor ligands. AEA is the ethanolamide of arachidonic acid, whereas 2-AG is the glycerol ester of arachidonic acid. Both are found in the brain and in the circulation; both bind and activate the CB1R at a binding site that overlaps with that of THC. AEA is a partial agonist of the CB1R and 2-AG is a full agonist.

Mechanisms of AEA Biosynthesis and Catabolism

AEA is a minor member of a family of ethanolamides of fatty acids (*N*-acylethanolamines; NAEs). The immediate precursor of AEA and other members of the NAE family is *N*-acylphosphatidylethanolamine (NAPE), a low-abundance membrane phospholipid that is most likely synthesized via the actions of a poorly understood transacylase. NAPE is subsequently hydrolyzed to NAE via either a single enzymatic step (NAPE-phospholipase D; NAPE-PLD) or via a two-step process recently described by Simon and Cravatt (2008). Very little is currently known about the regulation of these enzymatic processes. There is evidence that increased intracellular calcium can increase AEA biosynthesis; however, whether this is of biological significance is not clear.

AEA is degraded in the brain by ► fatty acid amide hydrolase (FAAH). FAAH-mediated catabolism is a primary mechanism by which brain AEA concentrations are regulated. FAAH is largely constitutively active; the major mechanism for the regulation of FAAH appears to be at the level of its expression. For example, FAAH expression is increased by progesterone and leptin and decreased by ► estrogen and glucocorticoids. Since FAAH is constitutively active, its inhibition would be expected to increase AEA concentrations and, thus, activate CB1R signaling. FAAH inhibitors would be expected to function as indirect agonists of the CB1R.

Mechanisms of 2-AG Biosynthesis and Catabolism

2-AG is synthesized from diacylglycerol (DAG) by an sn-1-acting DAG lipase (DGLα). DAG is a product of phospholipase C (PLC) hydrolysis of phosphorylated phosphoinositides. All isoforms of PLC produce DAG and, thus, could result in 2-AG synthesis. In particular, mGluR activates PLC$ß_1$ and both mGluR and PLC$ß_1$ are co-localized with DGLα in dendrites in proximity to CB1R-expressing axons. This places 2-AG signaling downstream and under the control of ► glutamate signaling.

The primary mechanism of 2-AG inactivation in the brain is via hydrolysis by monoacylglycerol lipase (MGL). MGL is present in brain regions in which the CB1R is also expressed, supporting the hypothesis that MGL regulates the amount of 2-AG available to activate the CB1R. A selective inhibitor of MGL increases the brain 2-AG content by eightfold and produces cannabinoid-like behavioral effects (Long et al. 2009), supporting the notion that catabolism as well as synthesis regulates 2-AG concentrations and, thus, CB1R function. These data suggest that inhibitors of MGL function as indirect agonists of the CB1R.

Localization of CB1 Receptors in the Nervous System

The CB1R is present in the CNS but exhibits a heterogeneous expression pattern. The CB1R is present at extremely high density in the cingulate gyrus, frontal cortex, ► hippocampus, cerebellum, and the basal ganglia. Moderate receptor densities are found in the basal forebrain, ► amygdala, ► nucleus accumbens, periaqueductal gray, and ► hypothalamus; low density is seen in the midbrain, pons, and medulla. Relatively little receptor is found in primary motor cortex or thalamus. Comparison of the expression profiles for CB1R protein and CB1R mRNA reveals several important distributional characteristics that have functional consequences. In the forebrain, CB1Rs are expressed at very high density in restricted number of neurons. These CB1R-expressing neurons project widely, resulting in a dense network of CB1R-positive processes. Double-labeling studies demonstrate that these highly expressing cells are GABAergic interneurons that also express the neuropeptide ► cholecystokinin (CCK). Other neurons express the CB1R at lower densities; these neurons are more heterogeneous and consist of non-CCK, GABAergic interneurons, and glutamatergic terminals.

Functional or anatomical evidence demonstrates that CB1R are also expressed by neurons in other regions of the nervous system. Within the spinal cord, CB1R are expressed by interneurons within the dorsal horn and on axon terminals of descending inputs into the dorsal horn. Primary sensory afferents express the CB1R at their terminals in the spinal cord and in the innervated tissues. CB1R are distributed throughout the enteric nervous system and their activation inhibits both intestinal motility and secretion – effects that are consistent with reports stating that *Cannabis* use reduces some of the signs and symptoms of irritable bowel disorder. CB1R agonists inhibit neurotransmitter release from neurons in the ileum and vas deferens through a presynaptic mechanism.

The CB1R is also expressed by non-neuronal cells in the CNS, including astrocytes, oligodendrocytes, and by endothelial and smooth muscle cells of the cerebral circulation.

CB1R Signaling

Activation of the CB1R results in the inhibition of adenylyl cyclase activity in most tissues and cells via activation of Gi-mediated signaling. In addition, CB1R activation is coupled with the activation of p42/p44 and p38 mitogen-activated kinases and Jun N-terminal kinase. CB1R activation has also been linked to the activation of PLC and Akt signaling in some cells; through these pathways, CB1R activation can influence intracellular calcium concentrations, protein kinase activities, and other signaling cascades that regulate cell growth and differentiation.

Pertinent to its role in psychopharmacology, CB1R activity regulates short-term signaling in the brain. Activation of CB1R present on axonal terminals results in an inhibition of the opening of voltage-operated calcium channels. This results in a reduction in calcium influx in response to an action potential or other depolarization and underlies the role of ► endocannabinoid signaling in the regulation of synaptic strength. This property of the CB1R underlies an important role for endocannabinoid/CB1R signaling in the retrograde regulation of synaptic transmission. Sustained glutamate release results in the mobilization of endocannabinoids from postsynaptic neurons, through increased intracellular calcium or activation of mGluR. The released endocannabinoids act on presynaptic CB1R leading to short-term inhibition of neurotransmitter release. There are two versions of this type of synaptic inhibition: depolarization-induced suppression of excitation (DSE), which is characterized by a reduction in the release of glutamate and DSI, which is the reduced release of GABA. Though endocannabinoid-mediated DSI and DSE are transient, endocannabinoid signaling also underlies more persistent forms of synaptic plasticity. For example, long-term depression of inhibition is mediated by endocannabinoid mobilization and activation of CB1R; it most likely involves a kinase signaling cascade, as CB1R activation results in long-lasting changes in neurotransmitter release.

CB1R Pharmacology

There are currently two preparations of CB1R agonists available in the US and a third preparation is in Phase III clinical trials. Marinol® is a synthetically prepared THC (also called ► dronabinol) that is used as an oral formulation. Nabilone, which is marketed in North America under the trade name Cesamet®, is structurally very similar to THC, but binds to the CB1R with higher affinity and efficacy than THC. In the USA, dronabinol and nabilone have been approved to treat chemotherapy-induced nausea and vomiting and to stimulate appetite in AIDS-related anorexia and weight loss. In addition, nabilone is often prescribed off-label as a treatment for chronic pain, particularly neuropathic pain. A third preparation, Sativex®, is a 1:1 combination of plant-derived THC and a second plant-derived cannabinoid, cannabidiol (CBD). There is good evidence that the presence of CBD in this preparation results in a reduction of adverse effects, particularly anxiety that can occur with the use of THC alone. Sativex is formulated as an oral spray and is currently approved in Canada and rapidly approaching approval the UK for the treatment of pain and spasticity of multiple sclerosis and for cancer pain. Sativex is currently in Phase III trials in the US for the same indications.

Several antagonists of the CB1R have been developed; the prototype is ► rimonabant (previously named SR141716 and SR141716A). Rimonabant is a reversible, competitive antagonist of the CB1R; it also has some ► inverse agonist efficacy. Until late-2008, rimonabant was approved in Europe and the UK for the treatment of obesity, diabetes, and metabolic disorder under the trade name Acomplia®. In November 2008, Acomplia was withdrawn from the market because its use resulted in an unacceptable number of adverse psychiatric events. These events included depression, anxiety, and sleep disturbances. Rimonabant has not received US FDA approval, largely because of its profile of adverse effects.

Potential Therapeutic Uses of Cannabinoids in Psychiatry

Preclinical and human data support a possible therapeutic role for cannabinoid receptor ligands in the treatment of ► anxiety, ► mood disorders, ► schizophrenia, and addictive behaviors. In addition, evidence has accumulated that dysregulation of endocannabinoid/CB1R signaling

could contribute to the risk of the development of psychiatric disorders. The therapeutic promise of cannabinoid-based therapeutics is hampered by adverse psychiatric effects; for ▶ agonists, these are cognitive impairment and for ▶ antagonists, the effects are depression and anxiety. Unfortunately, most of the adverse effects of CB1R agonists and antagonists result from the activation or inhibition of CB1R signaling, not from an off-target mechanism. The CB1R does not exhibit subtypes that would be amenable to the development of drugs selective for the desired over-adverse effects. Although not currently available for use in humans, indirect agonists, including inhibitors of FAAH and MGL, will be arguably more selective as they will only enhance signaling through CB1R that are engaged by endocannabinoids. Preclinical studies with inhibitors of FAAH support this hypothesis.

Anxiety

There is considerable evidence that the activation of CB1R results in decreased ▶ anxiety in humans. This evidence includes the data that the most commonly cited reasons for recreational *Cannabis* use are relaxation and reduction in tension. Although *Cannabis* can also induce anxiety and panic in some individuals, anxiety reactions are more common in stressful environments, with high doses and in inexperienced users. A recent meta-analysis of four large clinical trials indicated that patients taking rimonabant had a significantly greater increase in anxiety symptoms while taking the drug than patients taking placebo (Christensen et al. 2007). Therefore, human experience with a cannabinoid receptor agonist (THC) and antagonist (rimonabant) support the hypothesis that endocannabinoid signaling regulates anxiety in humans and suggest that activation of the CB1 receptor by endocannabinoids could produce anxiolytic effects. A functional single nucleotide polymorphism (SNP) in FAAH (C385A; rs 324420) is associated with reduced FAAH stability and, therefore, has been hypothesized to result in increased AEA-mediated CB1R activation. Individuals who are homozygous for this SNP, exhibited decreased threat-related activation of the amygdala in a recent imaging genetics study (Hariri et al. 2008). This study suggests that genetic variation in endocannabinoid signaling could underlie individual risk for the development of anxiety-related disorders.

Data from animal models of unconditioned anxiety support the hypothesis that activation or enhancement of endocannabinoid/CB1R signaling can produce a reduction in anxiety. This aspect of endocannabinoid signaling appears to be tonically "on" or easily activated since treatment of rodents in mildly aversive environments with CB1R antagonists enhances anxiety behaviors, whereas FAAH inhibition is anxiolytic. ▶ Conditioned fear is a model for certain types of anxiety disorders including post-traumatic stress disorder (PTSD). It has been conclusively demonstrated that inhibition of CB1R signaling impairs the extinction of conditioned fear responses, whereas activation of CB1R signaling enhances extinction of fear responses (Lafenetre et al. 2007). Taken together, these preclinical studies suggest that activation of CB1R signaling could be very useful in the treatment of disorders in which recurrent, fearful memories occur, such as PTSD.

Drug Addiction

Current understanding of drug addiction strongly suggests that drugs with abuse liability share an interaction with brain circuits involved in motivated behavior and reward. In particular, drug-induced plasticity in the mesocorticolimbic circuit contributes to addiction by consolidating reward-driven behavior. CB1R are abundant in the reward circuit and endocannabinoids contribute to ▶ synaptic plasticity in these regions through the mechanisms described above. While the CB1R in these regions certainly contribute to the rewarding effects of THC itself, there is also strong evidence that endocannabinoid signaling is involved in the rewarding and addictive properties of all abused substances (Maldonado et al. 2006). In particular, data suggest that endocannabinoids are released within the ▶ ventral tegmental area (VTA) and that they enhance the activation of dopamine neurons, resulting in potentiation of drug seeking behavior. In agreement with this mechanism, clinical trials with CB1R antagonists show modest efficacy in smoking cessation, particularly when combined with nicotine replacement therapy.

Schizophrenia

Epidemiological evidence indicates that *Cannabis* use can induce psychotic states in healthy individuals, worsen psychotic symptoms of schizophrenic patients, and precipitate ▶ schizophrenia in otherwise susceptible individuals (Ujike and Morita 2004). Examination of CB1R density postmortem reveals that the density of CB1R is higher in the ▶ prefrontal cortex of schizophrenic patients than controls; AEA is also increased in the cerebrospinal fluid of schizophrenic patients. Genetic studies have found that individuals with a repeat polymorphism in the *Cnr1* gene have a 2.3-fold higher risk for the development of schizophrenia than those without this sequence. Taken together, these results suggest that hyperactive CB1R signaling, particularly in the prefrontal cortex, is involved in the pathogenesis of schizophrenia. This hypothesis is supported by preclinical studies as well.

The hypothesis that hyperactive CB1R signaling contributes to the symptoms of schizophrenia led to a limited trial of rimonabant in schizophrenics. The results of this trial were not remarkable; rimonabant did not provide efficacy over that of placebo. While these findings indicate that reduced CB1R activation is not globally effective as a treatment for schizophrenia, it is possible that it would be effective in a subpopulation of patients.

Depression

Elevation of mood is a commonly cited motivation for the use of *Cannabis*. Several clinical trials in the 1970s designed to determine the anti-depressant efficacy of THC found that it failed to improve the symptoms of depression and produced unacceptable adverse effects. A similar hypothesis, that depressed individuals self-administer *Cannabis* because it elevates mood, predicts that depressed people use *Cannabis* to elevate mood more frequently than nondepressed users. This prediction was not upheld in a recent study (Arendt et al. 2007); in fact, depressed subjects experienced more depression, aggression, and sadness when intoxicated with *Cannabis* than when they are not intoxicated.

Cannabis dependence and depression are co-morbid diagnoses more than being expected by chance and available evidence suggests that a common factor or factors predispose individuals to both depression and *Cannabis* dependence. There is evidence that common genetic and environmental factors contribute to both diagnoses.

Bipolar Disorder

People with ▶ bipolar disorder have a 30–61% life-time likelihood for abusing *Cannabis*, compared with 6% in the general population. It is very likely that the co-occurrence of bipolar disorder and *Cannabis* use results from a combination of patients in whom bipolar disorder initiates *Cannabis* abuse and others in whom *Cannabis* abuse initiates bipolar disorder. The first subgroup of patients includes those who use *Cannabis* either in an attempt of self-medication or as a direct result of the mania, which evokes excessive involvement in pleasurable activities such as substance abuse. Evidence supporting this type of relationship between bipolar disorder and *Cannabis* abuse is sparse. In fact, the available data suggest the opposite, that many patients initiate *Cannabis* use prior to the onset of bipolar symptoms. A third option, which has not been studied at all in detail, is that bipolar disorder and substance abuse are both triggered by a common mechanism. An interesting possibility is that early life stress is a precipitating factor for both substance abuse and mood disorders.

Conclusion

Endocannabinoid activation of CB1R in the brain is involved in the modulation of limbic circuitry. It is not surprising that changes in endocannabinoid signaling, either as a result of *Cannabis* use or treatment with CB1R antagonist, affect mood, motivated behavior, learning, and fear responses. These data lead to the possibility that therapeutic agents that target endocannabinoid signaling for the treatment of psychiatric disorders, could be developed. However, current literature leads to the conclusion that this could be a difficult, although possible, goal. The most possible goals are the treatment of anxiety with indirect CB1R agonists, particularly inhibitors of FAAH, and substance abuse with CB1R antagonists.

Cross-References

- ▶ Adolescence and Response to Drugs
- ▶ Analgesics
- ▶ Antidepressants: Recent Developments
- ▶ Appetite Stimulants
- ▶ Bipolar Disorder
- ▶ Cannabis Use and Dependence
- ▶ Driving and Flying Under Influence of Drugs
- ▶ Eating and Appetite
- ▶ Emotion and Mood
- ▶ Generalized Anxiety Disorder
- ▶ Herbal Remedies
- ▶ Schizophrenia
- ▶ Social Anxiety Disorder
- ▶ Synaptic Plasticity
- ▶ Traumatic Stress (Anxiety) Disorder

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Cannabis Abuse and Dependence

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Synonyms

Cannabis addiction; Marijuana abuse; Marijuana addiction; Marijuana dependence

Definition

Cannabis abuse and dependence are disorders similar to the other ►substance abuse and ►dependence disorders. Problems related to misuse or overuse of cannabis can include social, psychological, and medical consequences. A subset of cannabis users meet the DSM or ICD diagnostic criteria for abuse or dependence which reflect an impairment of daily functioning, repeated use that puts them at risk of harm, failed attempts to cut down or quit, loss of controlled use, or development of tolerance or withdrawal.

Role of Pharmacotherapy

Controversy Over Cannabis Dependence

Controversy regarding the addictive potential of cannabis has propagated since the early 1900s. Advances in the clinical, neurobiological, and behavioral sciences over the last 20 years have provided an empirical base to resolve the major aspects of this enduring controversy. Epidemiological, laboratory, and clinical studies have demonstrated that cannabis dependence occurs, is relatively common, is clinically significant, causes harm, and is difficult to treat. As with other drugs, the majority of people who have tried cannabis do not develop a problem with addiction. However, in the USA, approximately 4% of those older than 12 years, at some time in their lives, have met criteria for cannabis dependence disorder, as defined in the *Diagnostic and Statistical Manual of Mental Disorders* (►*DSM*). This prevalence rate is more than double the lifetime dependence rate for any other illicit drug, reflecting the widespread use of cannabis. ►Conditional dependence rates, that is, the percentage of persons who have ever used a drug who go on to become dependent, suggest that cannabis use is less likely to lead to dependence relative to use of most other illicit drugs. In the USA, approximately 9% of those who try cannabis become dependent compared with lifetime dependence rates of 15% for people who try cocaine and 24% for those who try heroin. Although lower in relative terms, the fact that 9% of cannabis users become dependent is cause for concern given the large number of users. Indeed, the number of people who seek treatment for cannabis abuse and dependence has been steadily increasing in the USA, Europe, and Australia, and is now comparable to the number seeking treatment for cocaine or opiates in some countries.

Two related areas of scientific discovery have provided additional evidence for the addictive potential of cannabis. First, a neurobiological basis for dependence was uncovered with the discovery of the endogenous cannabinoid system in the central nervous system. Specifically, scientists have identified ►cannabinoids that occur naturally in the brain (anandamide, 2AG) and localization of cannabinoid receptors that serve as the sites of action for the direct effects of cannabis and other cannabinoids. Second, human and nonhuman research has established the reliability, validity, time course, and pharmacological mechanism for a true cannabis ►withdrawal syndrome that appears similar to tobacco withdrawal in magnitude and severity (Budney and Hughes 2006; Lichtman and Martin 2002). Prior to these findings, the existence of a clinically significant cannabis withdrawal syndrome was questioned as evidenced by its omission from the DSM. This growing body of research will prompt strong consideration for the inclusion of cannabis withdrawal in the upcoming revision of the DSM.

Epidemiological and controlled treatment evaluation research indicates that the Cannabis Dependence syndrome shares most of the same phenomenology as other types of substance dependence, and the DSM-IV dependence criteria items appear to capture all aspects of the syndrome (cf. Budney 2006). Though the phenomenology of

cannabis dependence is similar, there appear to be some differences in severity relative to dependence typically associated with substances like alcohol, cocaine, or opiates. On average, individuals with cannabis dependence do not meet as many DSM dependence criteria, the withdrawal experience causes discomfort but is not associated with major health risks, and the associated health and psychosocial consequences, although substantial, are typically not as severe. Despite this milder dependence syndrome, quitting cannabis once addicted does not appear any easier than trying to quit other substances. Many of those dependent on cannabis typically use it multiple times per day; they may be ambivalent about its negative effects; they acknowledge multiple perceived positive effects; and the cost is relatively low. All these factors make quitting difficult. Note that the same types of behavioral treatments that are efficacious for other substances (cognitive-behavioral, motivational, and contingency management) have proven effective for cannabis dependence, but the majority of cannabis users who enroll in treatment fail to achieve sustained abstinence (Budney et al. 2007; Roffman et al. 2006).

This body of research suggests that continued debate over whether or not cannabis use can lead to dependence or addiction is obsolete. Cannabis misuse and addiction are relatively common and are associated with significant negative consequences. Moreover, cannabis-related problems reflect a significant public health issue that requires continued attention and action towards developing more effective treatment and prevention interventions.

Neurobiology of Cannabis and the Potential Role of Pharmacotherapy

The increased recognition of the need for effective treatments for cannabis dependence, and the important advances in the understanding of the neurobiology of its actions, has recently led researchers to develop and evaluate potential pharmacotherapies. Delta-9-tetrahydrocannabinol (THC), the primary psychoactive component of cannabis, is a ▶ partial agonist of the CB1 receptor, a G-protein-coupled receptor that is expressed in the brain at the highest concentrations in the basal ganglia (motor control), cerebellum (sensorimotor coordination), hippocampus (memory), and cortex (higher-order cognition) (Cooper and Haney 2009). In addition to direct action on the CB1 receptor, cannabis alters the functioning of several other neurotransmitter systems including those associated with dependence on other drugs such as ▶ alcohol, ▶ cocaine, and ▶ opiates. Specifically, THC and other CB1 receptor agonists have been shown to increase dopamine (DA) release in the mesolimbic-dopamine reward pathway and enhance electrical ▶ brain-stimulation reward. These effects are associated with appetitive drug-seeking and drug-taking behaviors. Also, abrupt cessation of chronic cannabinoid exposure increases ▶ corticotropin releasing factor and decreases dopamine in the ▶ mesolimbic-dopamine reward pathway. These neurobiological changes have been linked to the dysphoric effects associated with ▶ withdrawal from addictive drugs and are thought to contribute to ▶ relapse.

Because chronic cannabis use is associated with neurobiological features similar to those observed with dependence on other drugs, pharmacological approaches successfully applied in the treatment of other drug-use disorders might be similarly effective in the treatment of cannabis-use disorders. One such approach is the use of agonist medications, compounds that have a similar mechanism of action as the abused drug or involve administration of a key component of the abused drug via a different route (e.g., ▶ methadone for opiate dependence, nicotine patch for tobacco dependence). Agonist pharmacotherapies are attractive because they typically attenuate symptoms of withdrawal, are generally well tolerated, and may blunt the reinforcing effects of the abused substance in the case of relapse. Clinical laboratory studies have demonstrated that dronabinol (orally administered THC) reliably and dose-dependently attenuates cannabis withdrawal symptoms and the subjective reinforcing effects of smoked cannabis, but to date there is no evidence that it reduces rates of self-administration. Published case reports and anecdotal reports suggest that dronabinol, when combined with psychosocial counseling, might be an effective ▶ pharmacotherapy for the treatment of cannabis-use disorders. Placebo-controlled clinical trials are currently testing this possibility.

Another pharmacological approach to drug dependence is the use of medications that suppress the reinforcing effects of the abused drug. Examples of this include use of receptor ▶ antagonists (e.g., ▶ naltrexone for opiate dependence) or ▶ vaccines (e.g., nicotine conjugate vaccine for tobacco dependence), which prevent/reduce binding to target receptors in the CNS. Several compounds have been synthesized that exhibit antagonist-like (inverse agonist) effects at the CB1 receptor in non-human species (e.g., suppress self-administration of cannabinoids or precipitate withdrawal). One of these compounds, rimonabant (SR141617A), has been shown to partially attenuate the subjective reinforcing effects of smoked cannabis in humans. In a small open-label clinical trial, administration of rimonabant was associated with a

reduction in cannabis use. While these results indicate some degree of clinical utility, present concerns regarding the safety of rimonabant have resulted in the medication being pulled off the market in most countries. Other neutral CB_1 antagonists that do not inhibit agonist-independent activity of CB_1 receptors and are therefore hypothesized to have a more acceptable side-effect profile compared to CB_1 inverse agonists like rimonabant are under development and may show promise in future studies. To our knowledge, no vaccine for THC or other cannabinoids has been developed.

A third pharmacotherapy approach is to identify medications with pharmacological mechanisms that are different from that of the abused drug, but that may provide clinically desirable effects (e.g., alleviate specific withdrawal symptoms or reduce desire for or liking of the substance). A number of medications typically used to treat affective disorders or other substance use disorders have been investigated as potential adjunct treatments for cannabis use disorders with very limited positive findings (Benyamina et al. 2008; Vandrey and Haney, 2009). ▶ Bupropion and divalproex significantly worsened mood compared with placebo during periods of cannabis abstinence. Nefazodone significantly decreased ratings of anxiety and muscle pain during abstinence, but did not alter other prominent features of cannabis withdrawal. ▶ Lofexidine significantly reduced several symptoms of withdrawal and improved sleep during periods of abstinence, but was associated with significantly increased sedation during the day. The combination of lofexidine and dronabinol significantly reduced withdrawal, improved multiple measures of sleep, and reduced cannabis self-administration during a laboratory relapse test. The combination of dronabinol and lofexidine also increased sedation and drug effect ratings during the day, but it is uncertain whether these effects occurred at a magnitude that would warrant concern in clinical use. A low dose of the opioid naltrexone decreased the intoxicating effects of 20 mg but not 40 mg of dronabinol, whereas higher doses either failed to attenuate or enhanced the subjective effects of dronabinol and smoked cannabis. Another laboratory study showed that pre-dosing with clonidine, a medication used to treat symptoms of opioid withdrawal, reduced cannabis-induced tachycardia, but did not reduce subjective effects.

Several small clinical studies of other commonly used psychiatric medications have recently been tested as treatments for cannabis dependence with few positive findings. ▶ Atomoxetine did not significantly reduce cannabis use and was associated with a high rate of adverse events. An initial trial with ▶ buspirone reported decreased cannabis use, craving, and irritability, but these effects were not replicated in a larger placebo-controlled trial. Two open-label studies of ▶ lithium suggested that it may have some positive effect on withdrawal and cannabis use, but side effects were frequent and the positive effects have not been replicated in controlled studies. The atypical antipsychotic ▶ quetiapine reduced cannabis use in a small study of cannabis-dependent patients with a diagnosis of either ▶ schizophrenia or ▶ bipolar disorder, but this effect has not been replicated in a controlled study and quetiapine has not been assessed in a more general population of cannabis users. Maintenance on the antidepressant ▶ mirtazapine improved subjective measures of sleep compared to placebo, but did not improve other clinical outcomes, including cannabis use, in a controlled clinical trial. Finally, one clinical trial of ▶ fluoxetine for the treatment of alcohol dependence and depression reported that cannabis-dependent participants in that study reported using less cannabis, and using cannabis on fewer days; however, prospective tests examining the effect of fluoxetine on cannabis use have not been reported. A summary of pharmacotherapy research is provided in Table 1.

Summary

Cannabis abuse and dependence pose a significant public health problem. Relatively large numbers of adolescents and adults enroll in treatment programs with cannabis as the primary substance of concern. Unfortunately treatment response rates for cannabis dependence are not substantially better than those observed for most other substance-dependence disorders. ▶ Empirically based behavioral treatments have been identified. Most recently, significant research efforts have focused on the development of pharmacological adjuncts to improve treatment outcomes. To this end, laboratory studies that target the CB1 receptor have demonstrated the most clinically desirable and promising effects (suppressed withdrawal, reduced effects of cannabis). However, results of controlled clinical trials of agonist or antagonist medications have yet to be completed, and there are significant concerns about side effects of each. The medications with pharmacological mechanisms other than the cannabinoid receptor system have thus far exhibited limited clinical benefit, but there is recent laboratory evidence that combinations of these medications and CB1-receptor-specific medications may hold promise. Ongoing research efforts include expanded medication assessments in humans (controlled clinical trials; laboratory studies of hypnotic and anticonvulsant medications), and preclinical development of new

Cannabis Abuse and Dependence. Table 1. Summary of medications tested for potential therapeutic benefit in cannabis users.

Medication tested	Current indication	Mechanism of action	Outcome
Atomoxetine	ADHD	Norepinephrine reuptake inhibitor	No effect on cannabis use, concerning side effects (GI)
Bupropion	Depression, smoking cessation	Norepinephrine and dopamine reuptake inhibitor	Reduced effects of smoked cannabis, but exacerbated cannabis withdrawal symptoms
Buspirone	Anxiety	Serotonin $5HT_{1A}$ receptor partial agonist	Reduced cannabis use, craving, and irritability in pilot study; effects not replicated in placebo-controlled clinical trial
Clonidine	Hypertension, opiate dependence	α_2 adrenergic agonist	Reduced tachycardia, but not subjective effects
Divalproex	Bipolar disorder, epilepsy, migraines	Unknown	No effect on cannabis use; increased withdrawal and effects of smoked cannabis
Dronabinol	Nausea/vomiting, excessive weight loss associated with AIDS wasting	Cannabinoid CB1 receptor agonist	Reduced cannabis withdrawal and subjective effects of smoked cannabis, but had no effect on reinforcement of cannabis and did not prevent relapse in laboratory studies, aided long-term cannabis cessation in 2 case studies
Fluoxetine	Depression, OCD, eating disorders, panic disorder	Selective serotonin reuptake inhibitor	Reduced self-reported cannabis use among a treatment sample of depressed alcoholics
Lithium	Bipolar disorder	Unknown	2 open-label studies suggest reduced withdrawal and cannabis use
Lofexedine	Opiate dependence	α_2 adrenergic agonist	Reduced withdrawal and relapse alone and in combination with dronabinol
Mirtazapine	Depression	α_2 adrenergic antagonist, $5HT_2$ and $5HT_3$ antagonist	Improved subjective sleep during abstinence, no effect of cannabis use outcomes
Naltrexone	Alcohol and opiate dependence	Mu-opioid receptor antagonist	Low dose (12 mg) decreased subjective effects of 20 mg, but not 40 mg oral THC; high doses ($\geq$50 mg) increased or had no effect on the subjective effects of oral THC or smoked cannabis
Nefazodone	Depression	Norepinephrine and serotonin reuptake inhibitor, $5HT_2$ receptor antagonist	Reduced select withdrawal effects but had no effect on total withdrawal severity or the subjective effects of smoked cannabis
Quetiapine	Schizophrenia and bipolar disorder	Antagonism of $5HT_2$ D_2 α_1 α_2 and H_1 receptors	Reduced cannabis use in small sample with schizophrenia or bipolar disorder
Rimonabant	Obesity	Cannabinoid CB1 receptor antagonist	Attenuated subjective and physiological effects of cannabis in laboratory studies. Reduced cannabis use in small open-label clinical study. Side-effect concerns.

medications that target the CB1 receptor system (e.g., second-generation agonists and antagonists, inverse agonists, and FAAH inhibitors) (Janero et al. 2009).

Cross-References

- ▶ Agonist
- ▶ Antagonist
- ▶ Cannabinoid
- ▶ Cannabinoid Receptors
- ▶ Cannabinoids
- ▶ Cannabinoids and Endocannabinoids
- ▶ Cognitive Behavioral Therapy
- ▶ Dronabinol
- ▶ Endocannabinoid
- ▶ Fatty Acid Amide Hydrolase
- ▶ Inverse Agonist

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Cannabis Addiction

► Cannabis Abuse and Dependence

Canotiaceae

► Celastraceae

CANTAB

Synonyms

Cambridge neuropsychological test automated battery

Definition

A battery of tests for human cognition that are partly derived from tests of cognition in animals. The battery includes tests of spatial working memory, paired visuospatial associate learning (PAL), recognition memory, set-shifting, and a human analogue of the five-choice serial reaction time (http://www.cantab.com/camcog/default.asp). There is also a CANTAB battery for nonhuman primates.

Capacitation Function of Spermatozoa

Definition

The process that enables spermatozoa to undergo the acrosomal reaction, whose endpoints consist in the hyperactivated motility and the exocytotic release of enzymes, which are considered of major importance for the fertilization of the oocyte.

Capgras Syndrome

► Delusional Disorder

Carbamazepine

Definition

Carbamazepine is an antiepileptic drug that is also used in treating bipolar disorder, although clinically it has been extensively used in various patient populations since it has been in clinical use for over 50 years. Although its mechanism of action is not fully understood, its main action is at sodium channels leading to reduced excitability in nerve cells.

Cross-References

► Anticonvulsants
► Bipolar Disorder

Carbidopa

Synonyms

MK486; S-alpha-hydrazino-3,4-dihydroxy-α-methyl-bensemonopropanoic acid monohydrate

Definition

Carbidopa is a peripherally acting aromatic L-amino acid decarboxylase or DOPA decarboxylase inhibitor. Carbidopa does not cross the blood–brain barrier, but increases the plasma half-life of ► L-DOPA, the dopamine precursor, thus increasing brain dopamine concentrations while reducing peripheral dopamine side effects, such as cardiac arrhythmias. Like other DOPA decarboxylase inhibitors, carbidopa is always used in combination with L-DOPA in the management of ► Parkinson's disease. It can also be combined with entacapone and L-DOPA in a triple combination.

Cross-References
► Anti-Parkinson Drugs
► Entacapone
► L-DOPA

Carbon-Fiber Amperometry

Definition
Carbon-fiber amperometry is used to study the exocytosis of certain hormones and neurotransmitters from target tissues and cells. It measures the concentration of such substances by the measurement of the electrochemical current caused by the transfer of electrons after oxidation (or reduction). Detailed analysis of the shape of the amperometric spike can provide valuable information regarding the events surrounding exocytosis.

Carpipramine

Definition
Carpipramine is a first-generation (typical) antipsychotic drug that belongs to the iminodibenzyl class indicated for the treatment of schizophrenia, particularly for negative symptoms. It has been found that carpipramine, and its pharmaceutically acceptable salts, possess antagonist properties with respect to D_2 and 5-HT_2 receptors, and are also useful in the treatment of depression, anxiety, and sleep disorders. It can induce insomnia, agitation, and extrapyramidal motor side effects, but it displays generally low toxicity.

Cross-References
► Extrapyramidal Motor Side Effects
► First-Generation Antipsychotics
► Negative Symptoms
► Schizophrenia

Caspases

Definition
Caspases are cysteine proteases that play an essential role in apoptosis by cleaving key cellular proteins. They are synthesized as inactive pro-caspases that become sequentially activated upon cleavage by upstream caspases in a cascade-like manner. Caspases that cleave other caspases are referred to as "initiator" or "apical" caspases; caspases that cleave other cellular proteins are known as "effector" or "executioner" caspases.

Catalepsy

Definition
A state seen in schizophrenia, other disorders of the nervous system and drug-induced dissociated states, in which unusual postures or facial expressions are maintained, regardless of external stimuli.

Cross-References
► Schizophrenia

Catalytic RNA Molecule

► Ribozyme

Catathrenia

► Parasomnias

Catatonia

Definition
Catatonia includes both psychic and motor disturbances and is classically associated with psychiatric conditions (such as ► schizophrenia, ► bipolar disorder, ► posttraumatic stress disorder, and ► depression). It can also be caused by dissociative agents, abuse of other drugs, and many medical conditions including encephalitis, autoimmune disorders, strokes, metabolic disturbances, and benzodiazepine withdrawal.

The DSM-IV criteria for catatonia include at least two of the following: motor immobility as evidenced by catalepsy and waxy flexibility or stupor; excessive and purposeless motor activity not influenced by external stimuli; extreme negativism (motiveless resistance to all instructions or maintenance of a rigid posture against attempts to be moved) or mutism; peculiarities of voluntary movement as evidenced by posturing, stereotyped movements, prominent mannerisms, or prominent grimacing;

echolalia (repetition of the words or phrases of another person) or echopraxia (involuntary repetition or imitation of the observed movements of another person).

Catecholamine Depletion

► Amine Depletors

Catecholamine Hypothesis

► Aminergic Hypotheses for Depression

Catecholamine Toxins

► Neurotoxins

Catecholamines

Definition

Neurotransmitters derived from the amino acid tyrosine that contains both a catechol and an amine component. Examples include ► dopamine, ► norepinephrine, and epinephrine.

CATIE

Synonyms

Clinical Antipsychotic Trials of Intervention Effectiveness; Clinical Antipsychotic Trials of Intervention Effectiveness Study

Definition

A study that compares perphenazine with the SGA in the treatment of schizophrenia. General conclusion was that perphenazine was as effective and well tolerated as SGA.

Cross-References

► Perphenazine
► Second Generation Antipsychotics (SGA)
► Schizophrenia

CB-154

► Bromocriptine

CBF

► Cerebral Perfusion

CBIT

► Habit Reversal Therapy

CBT

► Cognitive Behavioral Therapy

CBV

► Cerebral Perfusion

Celastraceae

Synonyms

Brexiaceae; Canotiaceae; Chingithamnaceae; Euonymaceae; Hippocrateaceae; Salaciaceae; Siphonodontaceae; Stackhousiaceae

Definition

A plant family, which includes about 98 genera and 1,210 species, that is native to both the New and the Old world. They generally grow as small trees, bushes, or lianas and have resinous stems and leaves. The traditional medicine attributed a wide variety of properties to the crude extracts of these plants.

Cell Type-Specific Knockout

► Conditional Knockout

Central Catecholamine Systems

Definition

The cell bodies of ► dopamine (in the ventral tegmental area and substantia nigra) and ► norepinephrine (in the locus coeruleus located in the ventral brain stem) and their projections to the forebrain.

Central Sensitization

Definition

Enhanced responsiveness of central nervous system neurons after injury which arises from augmentation of central pain signaling neurons to input from low-threshold receptors (typically mechanoreceptors). At least some proportion of this phenomenon may be subserved by ► NMDA receptors.

Cerebral Blood Flow

► Cerebral Perfusion

Cerebral Blood Volume

► Cerebral Perfusion

Cerebral Perfusion

Synonyms

BOLD; CBF; CBV; Cerebral blood flow; Cerebral blood volume

Definition

Cerebral perfusion describes the amount of blood passing the brain capillary bed in a certain time period to deliver, that is, oxygen and glucose. Brain perfusion is defined by three quantities: cerebral blood flow (CBF), cerebral blood volume (CBV), and mean transit time (MTT). Brain activity is accompanied with an increase in cerebral energy consumption and consequently prompts changes in cerebral perfusion, thus changes in CBF, CBV, and concentration changes of oxy- and deoxygenated hemoglobin. To assess these processes, different functional MRI methods such as CBF-fMRI, CBV-fMRI, or BOLD-fMRI are applied as indirect measure for brain activity.

Cross-References

► BOLD Contrast
► Functional MRI

Cerebrovascular Accident

► Stroke

CFFF

► Critical Flicker Fusion Frequency

CGI

► Clinical Global Impression Scales

Characteristic

► Trait

Chat

► Khat

ChAT

► Choline Acetyltransferase

Chemical Modifications of Antisense Oligonucleotides

Definition

In order to increase efficiency, the cellular uptake and intracellular stability can be improved by chemical modification of antisense oligonucleotides. The most common chemical

modifications of antisense oligonucleotides are replacing an oxygen group of the phosphate-diester backbone with either a methyl group (methyl phosphonate oligonucleotide) or a sulfur group (phosphorothioate oligonucleotide). Methylphosphanates have high intracellular stability, the absence of charge, however, reduce their solubility and intracellular uptake. The phosphorothioates are the most widely used oligonucleotides, because of their relatively high nuclease stability, relative ease of synthesis, good solubility, and superior antisense properties. Importantly, phosphorothioated antisense oligonucleotides activate RNase H activity both in tissue culture and *in vivo*. Disadvantages include sequence-independent effects making well-designed controls essential. In order to increase specificity as well as efficacy of phosphorothioates, chimeric oligonucleotides are developed in which the RNase H-competent segment (the phosphorothioate moiety) is bounded on both termini by a higher-affinity region of modified RNA.

Other chemical modifications include 2′-OH modifications, locked nucleic acids (LNAs), peptide nucleic acids, morpholino compounds, or hexitol nucleic acids. Although high RNA affinity and high stability have been reported, they do not support RNase H activation. Nevertheless, they can exert their antisense activity via translational arrest or modulation of splicing.

Cross-References

► Antisense Oligonucleotides

Childhood Depression

► Depressive Disorders in Children

Childhood Disintegrative Disorder

Definition

Childhood disintegrative disorder is defined by a normal period of development for the first 2–10 years of life. Between the ages of 2 and 10, there is a regression of 2 of the following: language skills, social skills, bowel/bladder control, play or motor skills. There is also a disruption in functioning in at least two of the following three areas: social interaction, communication and restricted and repetitive patterns of behavior, interests and activities.

Cross-References

► Autism Spectrum Disorders and Mental Retardation

Childhood-Onset Obsessive-Compulsive Disorder

► Obsessive-Compulsive Anxiety Disorders in Childhood

Childhood-Onset Schizophrenia

► Pediatric Schizophrenia

Childhood Schizophrenia

► Autism Spectrum Disorders
► Autism Spectrum Disorders and Mental Retardation

Chimera

Synonyms

Mosaic

Definition

An animal where individual cells contain genetic material from only one of two potential lineages. These animals are often produced in the creation of knockout mice where a mutated ES cell is introduced into the blastocyst containing wild-type ES cells.

Cross-References

► Genetically Modified Animals

Chingithamnaceae

► Celastraceae

ChIP

► Chromatin Immunoprecipitation

Chloral Hydrate

Definition

Chloral hydrate is an obsolescent ► hypnotic medication used in the treatment of severe insomnia. Unwanted

effects include sedation, headaches, gastrointestinal upset, paradoxical excitement, confusion, cognitive and psychomotor impairment, and confusion in the elderly. It interacts with alcohol. Long-term use may be habit forming with marked ► dependence and ► withdrawal reactions. Chloral is a scheduled substance. In overdose, it can depress respiration.

Cross-References
► Insomnias

Chlorazepate

Synonyms
Tranxene

Definition
Chlorazepate is a benzodiazepine-derived anxiolytic with anticonvulsant, sedative-hypnotic, and skeletal muscle-relaxant action. It is used for short-term relief of more severe forms of anxiety as well as adjunctive therapy in the management of partial seizures and alcohol withdrawal. The most common side effect is drowsiness while other, less-commonly reported effects include dizziness, blurred vision, headache, confusion, insomnia, irritability, depression, and tremor. As with other antiepileptic drugs, chlorazepate increases the risk of suicidal thoughts or behavior, thus patients receiving this therapy need to be monitored closely by their physicians and family. Like other ► benzodiazepines, it has a significant potential for abuse and dependence and abrupt cessation after prolonged use causes withdrawal symptoms which include anxiety, insomnia, dizziness, nausea and vomiting, tremor, irritability, tachycardia and postural hypotension, memory impairment and, in extreme cases, convulsions and delirium. It was withdrawn from the U.K. market in 2006.

Chlordiazepoxide

Definition
Chlordiazepoxide is ► benzodiazepine with anxiolytic, anticonvulsant, hypnotic, amnestic, and muscle-relaxant properties. Its medium to long ► half-life is exceeded by that of its active metabolite. The metabolites are largely responsible for its pharmacological activity. Clinical indications for chlordiazepoxide include the short-term treatment of severe ► anxiety and the management of acute ► alcohol withdrawal syndrome. Like most similar compounds, its long-term use is subject to ► tolerance, abuse, ► dependence, and withdrawal.

Cross-References
► Sedative, Hypnotic, and Anxiolytic Dependence

Chlormethiazole

► Clomethiazole

Chlorpromazine

Definition
Chlorpromazine was the first drug developed with a specific antipsychotic action. It is considered to be the first of the first-generation (typical) antipsychotics. Chlorpromazine is the prototype for the phenothiazine class antipsychotic and has relatively low potency at dopamine D_2 receptors as well as antagonism of muscarinic, histaminergic, and adrenergic receptors.

Cross-References
► Antipsychotics
► First-Generation Antipsychotics
► Phenothiazines

Cholecystokinins

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Definition
Cholecystokinins (CCKs) are a group of peptides that possess a common C-terminal sequence and elicit various biological effects after binding to specific G protein coupled receptors termed CCK receptors. CCKs are defined as peptides that elicit gallbladder contraction and have the C-terminal sequence Tyr-Met-X-Trp-Met-Asp-Phe-NH_2,

where X is glycine in most mammals. CCKs can act as a hormone, growth factor or neurotransmitter.

Pharmacological Properties

Physiology

CCK peptides belong to a family of neuroendocrine peptides. CCK was discovered in extracts of the small intestine as a substance that elicits the hormonal gallbladder contracting effect and that can stimulate pancreatic secretion. That these two effects are mediated by the same substance was revealed in 1961 by Viktor Mutt, who also identified its chemical identity (Reeve et al. 1994). CCK also acts as a growth factor for the pancreas and as a neurotransmitter.

Only one CCK mRNA molecule is produced from the CCK gene, and its translational product, preproCCK, consists of 115 amino acid residues. This product is the source of all CCKs. The bioactive CCK peptides include those with 83, 58, 39, 33, 22, and 8 amino acid residues and these are produced in a cell-specific manner. CCK peptides share a common C-terminal sequence with another peptide, gastrin, which has recently also been found in multiple molecular forms (Rehfeld et al. 2007). Modification of this tetrapeptide amide sequence strongly reduces biological activity.

CCK peptides bind to CCK_A and CCK_B (alternatively, CCK_1 and CCK_2, respectively) receptors that are both coupled to G proteins. As ligands, CCK_A receptors require CCKs that are amidated at the C-terminal, and sulfated on a tyrosine in the seventh position from the terminal. These receptors mediate contraction of gallbladder and relaxation of the sphincter of Oddi, and pancreatic growth and enzyme secretion. These receptors are also expressed in the peripheral nervous system and in the anterior pituitary; expression in the brain is less prevalent than of the CCK_B receptors. The latter are identical to the gastrin receptor, and besides brain, are abundantly expressed on gastric ECL-cells and parietal cells, and in the pancreas. CCK_B receptors also bind non-sulfated CCK, CCK-5, and CCK-4 with high affinity. Importantly, the peripheral physiological responses mediated via CCK_B receptors are elicited by gastrin, because the plasma levels of gastrin are much higher than those of CCK (Rehfeld et al. 2007). In brain, CCK_B receptors are expressed with the highest density in the striatum, cerebral cortex, and the olfactory nuclei; moderate levels have been found in the ► hippocampus, substantia nigra, periaqueductal grey matter, and pontine nuclei.

CCK in circulation originates mainly from the intestinal endocrine cells that release the peptide in response to food rich in protein and fat. Since the satiety-inducing ability of CCK was discovered in 1973, many studies on animals and humans have shown it to serve as an endogenous satiety factor (Reeve et al. 1994). This satiety signal appears to be mainly mediated by the vagus nerve and subsequently the nucleus tractus solitarius and area postrema to the hypothalamus. CCK also inhibits gastric acid secretion, directly via CCK_B receptors and indirectly via CCK_A receptors stimulating ► somatostatin release.

Neuronal CCK

Neurons mainly synthesize and release CCK-8. At variance with many ► neuropeptides, expression of CCK is highest in the neocortex. Other brain regions enriched with CCK are caudate-putamen, hippocampus, and ► amygdala, and significant levels are present in thalamus, hypothalamus, olfactory bulb, ventral tegmental area and periaqueductal grey matter. CCK-8 release is, characteristically to neurotransmitters, evoked by potassium-induced depolarization and dependent upon calcium. CCK has been shown to elicit both excitatory and inhibitory postsynaptic potentials. CCK interacts with several other neurotransmitter systems, most notably ► dopamine, ► GABA, ► endogenous opioids and endocannabinoids (Harro 2006).

For both CCK receptors, a plethora of selective ligands of distinct chemical classes have been synthesized (Berna et al. 2007). This has strongly facilitated detailed studies on physiology of the CCK systems. Several of the drugs are chemically not peptides and are active when administered via enteral route.

Panicogenic Properties

Intravenous administration of CCK C-terminal tetrapeptide (CCK-4) or pentapeptide (CCK-5 or pentagastrin) elicits ► panic attacks in patients with panic disorder and in healthy volunteers. This effect is dose dependent. The most common symptoms in response to a bolus injection of CCK-4 are dyspnea, palpitations, chest pain or discomfort, faintness, dizziness, paresthesia, hot flushes or cold chills, nausea or abdominal distress, anxiety or fear or apprehension, and fear of losing control. In panic disorder patients the attacks are not distinguishable to them from their spontaneous panic attacks. The panic disorder patients are more sensitive to the CCK-4 challenge than healthy subjects, but patients with other anxiety disorders do not differ in this regard from healthy volunteers. In panic disorder patients, a few alterations in CCK levels or cellular responses to CCK have been reported, but all findings remain waiting for independent replication. CCK-4-induced anxiety is accompanied by a robust activation in a broad cerebral network including anterior cingulate cortex, middle and superior frontal gyrus, precuneus, middle and superior temporal gyrus,

occipital lobe, sublobar areas, cerebellum and brainstem (Dieler et al. 2008).

The panicogenic effect of administered CCK-4 can be prevented by treatment with ▶ benzodiazepines or CCK_B receptor antagonists, or chronic administration of tricyclics. However, attempts to cure panic disorder or generalized anxiety disorder with non-peptide CCK_B antagonists of different chemical classes have been unsuccessful. It has been proposed that the failure of attempts to prevent panic attacks in panic disorder with CCK_B antagonists used in published studies is due to limitations of these treatments (poor bioavailability and/or insufficient brain penetration of the compounds), but while such a suggestion is not entirely in contradiction with the efficacy of these drugs against CCK-induced panic in humans, it is certainly weakened by this evidence (Harro 2006).

CCK Receptor Agonists and Antagonists in Animal Models of Anxiety

Both systemic and intracerebral administration of CCK peptides has been found to elicit anxiogenic-like effects in ▶ animal models of anxiety, including ▶ elevated plus-maze and ▶ open field test, and several others. These effects are usually antagonized by CCK_B but not CCK_A receptor antagonists. It should be noted that the efficacy of low, non-sedating doses of CCK peptides is not universally reproduced across laboratories and may require presence of unknown environmental factors. CCK_B receptor antagonists as a single treatment have been reported to possess anxiolytic properties, but several thorough studies have not supported such a claim and it seems possible that the anxiolytic-like effect is mimicked by enhancement of locomotor activation by these drugs (Harro 2006).

Behavioral tests that are most sensitive to anxiety-related effects of CCK receptor ligands include potentiated startle, and particularly those that are based on exploratory activity. Effects of CCK receptor ligands on defensive behavior are weak and on social behavior rather contradictory. Conflict tests based on ▶ punishment procedures are not sensitive to CCK, and when exploratory behavior is punished as in the four plate test, CCK antagonists fail to show anxiolytic-like action.

Neurobiology of CCK in Animal and Human Anxiety

Studies that have examined levels of CCK or CCK receptors in anxiety have not found consistent alterations in CCK expression, but increases in CCK_B ▶ receptor binding have been described in animal models of anxiety and in human postmortem studies. CCK_B receptor binding sites are upregulated in cerebral cortex and cerebellum of persistently anxious or stressed rats, and in transgenic mice that overexpress CCK_B receptors anxiety levels are higher, this increase being sensitive to ▶ benzodiazepine anxiolytics. CCK receptor binding has been found increased in frontal and cingulate cortex of human ▶ suicide victims, and by measuring mRNA levels with quantitative PCR this has been confirmed and attributed to CCK_B subtype.

Brain regions in which neuronal CCK appears to play a role in anxiety-related behavior include cortex, amygdala (particularly basolateral), periaqueductal grey matter, cerebellum, septum, hippocampus (particularly areas CA1 and CA2), and paraventricular thalamus (Harro 2006). In some brain regions the anxiety-related effects of CCK are known to occur with some specificity: CCK in amygdala prevents ▶ extinction learning, and CCK-mediated activation of periaqueductal grey by anticipatory anxiety elicits hyperalgesia. In several brain regions such as cortex, hippocampus and amygdala, anxiety-related effects of CCK may interact with changes in GABA-ergic activity. In several brain regions ▶ GABA and CCK coexist in a population of interneurons that also express ▶ endocannabinoid CB_1 receptors. Serotonin, noradrenaline, and opioids also modulate the anxiety-related effects of CCK. The anxiogenic effect of CCK-4 can be blocked with a ▶ CRF receptor antagonist. This suggests that CCK-elicited anxiety is dependent upon the activation of the HPA stress axis.

Stressful events have been associated with changes in CCK levels and CCK mRNA expression. Direct examination of extracellular levels of CCK after a stressful event as measured using in vivo ▶ microdialysis has suggested increased release of the peptide in the frontal cortex (Becker et al. 2001). Importantly, such an increase was observed in rats that had repeatedly been submitted to social defeat in the form of being placed first into a protected smaller environment within an aggressive resident's cage and subsequently allowed a physical contact, but not in animals that could after initial protected exposure explore the whole cage as the resident had been removed. Because ▶ microdialysis was conducted after protected exposure to the resident, the findings suggest that either in frontal cortex CCK is released only after sensitization by severe stressors or that learning of safety can prevent cortical CCK release. Adaptive or maladaptive changes in brain that underlie such differential reactions to threat may also cause the individual to react to drugs dependent upon stressfulness of the situation, as this has been reported for the effects of administered CCK peptides (▶ *Stress: Influence on drug action*). Several other studies also suggest that the role of CCK release in adapting with environmental signals depends upon the previous experiences of the subject, and these may determine whether the net effect of CCK release is anxiety, panic, or instead, perceived safety (Harro 2006).

Implications to Other Psychiatric Symptoms and Disorders

CCK is found in mesetelencephalic dopaminergic neurons that are implicated in ▶ schizophrenia. CCK inhibits dopaminergic activity, changes in the number of CCK expressing neurons have been reported in patients, and thus CCK peptides have been tested in clinical studies as adjuncts to standard antipsychotic treatment (Reeve et al. 1994). It is now known that the interaction between CCK and dopamine neurons takes place at several sites in the brain, involves both CCK receptor subtypes, and is thus very complex, which together with the differences in design in clinical studies may explain why unequivocal results have not been obtained. Alteration in cortical expression of CCK mRNA in schizophrenia could be specific to GABA-ergic circuits and relevant to working memory dysfunction in schizophrenia (Hashimoto et al. 2008).

CCK plays a significant role in cognition (Hebb et al. 2005). The ability of CCK to enhance fear-potentiated startle may be related to its anxiogenic properties, but also to an additional increase in vigilance or memory retention. CCK_B receptor deficient mice have increased locomotor activity and an impairment of spontaneous alternation behavior suggestive of deficiency of ▶ attention or memory. There appears to be a double dissociation between the anxiogenic and pro-cognitive effects of CCK: while many anxiogenic drugs can enhance learning and memory, CCK can be pro-cognitive even when no effect on emotion is observed, and yet in other paradigms reduce memory both in non-anxious and anxious subjects. Decreases in CCK levels that accompany aging have been associated with age-related memory loss.

CCK receptor antagonists modulate effects of ▶ psychomotor stimulants. Low doses of CCK_A antagonists reduce the locomotor enhancing effects of ▶ amphetamine, and such a coadministration prevents amphetamine sensitization from developing. Conversely, CCK_B receptor blockade enhances the psychomotor stimulant effect of amphetamine, and further increase sensitization. Thus, release of CCK occurs during the amphetamine-induced psychomotor response, and this release has opposite effects that are mediated simultaneously via CCK_A and CCK_B receptors and physiologically cancel each other out. Interference with this balance may be important in drug addiction. It seems that to be expressed in full, especially the synergistic effects of psychostimulants and CCK_B receptor antagonists require drug administration to be contingent with exposure to the testing environment.

CCK affects opioid-dependent pain perception (Berna et al. 2007; Hebb et al. 2005). Both CCK_A and CCK_B antagonists potentiate μ- and ∂-opioid receptor dependent analgesia. Disrupting CCK_B mediated neurotransmission by administration of antisense oligonucleotides or knocking the receptor out in mice also potentiates the effects of ▶ morphine and endogenous opioids. CCK acts as a mediator in the periaqueductal grey matter serving both as a positive feedback loop between spinal cord and brainstem that potentiates spinal transmission of nociceptive afferent input, and a suppressor of the opioid-driven anti-nociceptive descending pathway (Lovick 2008). Because ovarian hormones modulate the response of periaqueductal grey neurons to CCK, physiological fluctuations in pain sensitivity and responsiveness to opiates in females could involve changes in sensitivity to CCK. Whether drugs acting at CCK receptors could have a major effect on ▶ opiate dependence is less clear, but CCK_A antagonists have been reported to prevent the development of tolerance to morphine analgesia. Interestingly, CCK antagonists enhance the analgesic ▶ placebo effect and attenuate anxiety-induced ▶ hyperalgesia (Colloca and Benedetti 2007).

CCK is an obvious target in studies on obesity and eating disorders, and impaired CCK response to a meal has been reported to occur in bulimia nervosa patients. CCK receptors undergo complex regulation and can be rapidly desensitized and also resensitized. Continuous minipump infusion of CCK loses its behavioral, including anorectic efficacy in animal models, suggesting that CCK_A agonists may in principle not be sufficient as monotherapy. However, subchronic once daily administration of a peptide CCK_A receptor agonist has been found not to lead to tolerance in an operant feeding test. Nevertheless, in clinical studies CCK_A agonist monotherapy has so far failed to show any beneficial effect in obese subjects (Berna et al. 2007).

Therapeutic Potential

Many subtype-selective CCK receptor agonists and antagonists of different chemical classes are available, but there is no established therapeutic use (Berna et al. 2007). Regarding the CNS disorders of the few trials that have failed to show superiority of these drugs over placebo, the schizophrenia studies have been methodologically too limited to draw conclusions. Selective CCK_B antagonists have not been effective in ▶ panic disorder. However, animal research suggests that CCK ligands deserve investigation as adjunctive medications in anxiety and addictive disorders if applied together with appropriate behavioral therapies. CCK receptor antagonism may also prove beneficial when combined with other neurochemical actions.

Cross-References

- ► Anxiety: Animal Models
- ► Attention
- ► Benzodiazepines
- ► Corticotropin Releasing Factor
- ► Elevated Plus-Maze
- ► Endogenous Cannabinoids
- ► Microdialysis
- ► Open Field Test
- ► Opiate Dependence and its Treatment
- ► Opioids
- ► Panic
- ► Placebo Effect
- ► Psychomotor Stimulants
- ► Punishment Procedures
- ► Receptor Binding
- ► Schizophrenia
- ► Somatostatin
- ► Stress: Influence on Drug Action
- ► Suicide

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Choline Acetyltransferase

Synonyms

ChAT

Definition

Choline acetyltransferase (ChAT) is an enzyme that is synthesized within the body of a neuron. It is then transferred to the nerve terminal via axoplasmic flow. The role of choline acetyltransferase is to join acetyl-CoA to choline, resulting in the formation of the neurotransmitter ► acetylcholine.

Cholinergic

Definition

Cholinergic means related to the neurotransmitter ► acetylcholine. The parasympathetic nervous system is entirely cholinergic. Neuromuscular junctions, preganglionic neurons of the sympathetic nervous system, the basal forebrain, and brain stem complexes are also cholinergic. There are also significant numbers of cholinergic nuclei in the mammalian brain.

Cholinesterase Inhibitors

Definition

Cholinesterase inhibitors are a group of medications used in the treatment of ► Alzheimer's disease. They inhibit CNS acetylcholinesterase in the synaptic cleft, thus preventing the degradation of endogenously released acetylcholine. There are three cholinesterase inhibitors that are marketed for treatment of the cognitive symptoms of Alzheimer's disease including ► donepezil, ► galantamine, and ► rivastigmine.

Chromatin

Definition

The major components of chromatin are DNA and histone proteins, although many other chromosomal proteins have prominent roles too. The functions of chromatin are to package DNA into a smaller volume to fit in the cell, to strengthen the DNA to allow mitosis and

meiosis, and to serve as a mechanism to control expression and DNA replication. The structure of chromatin (whether it is open or closed) around a gene determines the rate at which that gene is transcribed.

Cross-References
► Gene Expression and Transcription
► Histone Deacetylase Inhibitors

Chromatin Immunoprecipitation

Synonyms
ChIP

Definition
Chromatin immunoprecipitation (ChIP) is a method used to determine the location of DNA binding sites on the genome for a particular protein of interest. This technique gives a picture of the protein–DNA interactions that occur inside the nucleus of living cells or tissues. The principle underpinning this assay is that DNA-binding proteins (including transcription factors) in living cells can be cross-linked (often using formaldehyde) to the DNA to which they are binding. By using an antibody that is specific to a putative DNA binding protein, one can immunoprecipitate the protein-DNA complex out of cellular lysates.

Cross-References
► Gene Expression and Transcription
► Histone Deacetylase Inhibitors

Chromatin Remodeling

Synonyms
Epigenetics

Definition
Changes in the structure of chromatin due to posttranslational modifications, such as histone acetylation, methylation, phosphorylation, and DNA methylation may lead to chromatin remodeling. These changes are also referred as epigenetic modifications that are responsible for changes in gene activity and expression without altering the DNA sequence.

Cross-References
► Epigenetics

Chronic Disappointment Reaction

Synonyms
Demoralization syndrome

Definition
A syndrome involving lowered or dysphoric mood that occurs in response to a perceived unpleasant situation or set of experiences that is repetitive or enduring. The offending experience typically represents an assault on the individual's self-concept or self-esteem. The person experiencing a chronic disappointment reaction may feel overmatched by the circumstances and may feel helpless and/or hopeless in terms of prospects for improving the situation. Such a person may engage in any of a number of attitudes or behaviors to protect his or her feeling state from further adverse impact – such as avoidance, disinterest, or psychosocial withdrawal. The person having the chronic disappointment reaction may or may not be fully aware of, or fully able to explain, the issue or issues to which the reaction is in response. A chronic disappointment reaction can continue with an open-ended duration.

Cross-References
► Depressive Disorder of Schizophrenia

Chronic Hairpulling

► Trichotillomania

Chronic Low-Grade Depression

► Dysthymic Disorder

Chronic Mild Stress

Definition
A model of depression that has been extensively validated, in which rats or mice are subjected to a constant barrage of mild stressors, such as decreased availability of food or water, and changes in housing or lighting conditions. This procedure produces many symptoms comparable to

those seen in ► depression, including anhedonia, the core symptom of the major subtype of depression, melancholia.

Cross-References

► Animal Models of Psychiatric States
► Depression: Animal Models

Chronomedicine

► Circadian Rhythms

Chronopharmacology

► Circadian Rhythms

Circadian Rhythm Sleep Disorders

Definition

Sleep disorders resulting from a misalignment between the timing of the individual's circadian rhythm of sleep propensity and the 24 h social and physical environment.

Circadian Rhythms

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Synonyms

Biologic rhythms; Biological clock

Definition

Introduction: The Biological Clock

Living organisms are continuously influenced by external stimuli, many of which have rhythmic patterns. Environmental rhythms in daily and seasonal patterns of light, food availability, and temperature are predictable, and animals – including humans – have the ability to anticipate these environmental events with periodically and predictably changing internal conditions. These rhythmic patterns of anticipation have clear advantages and survival value. Thus, rhythmicity is the most ubiquitous feature of nature. Rhythms are found from unicellular to complex multicellular organisms in both plants, animals, and men. The frequencies of rhythms in nature cover nearly every division of time. There are rhythms that oscillate once per second (e.g., in the electroencephalogram), once per several seconds (respiratory rhythm, heart rate), up to rhythms that oscillate once per year (circannual rhythm).

The most evident environmental change that results from the regular spin of the earth around its central axis and resulting in the alternation between day and night seems to have induced the predominant oscillation, the circadian rhythm (the about-24-h rhythm; circa = about, dies = day, as proposed by Halberg (1959). There is sound evidence that living systems including humans are not only organized in space but are also highly organized in time.

Circadian rhythms have been documented throughout the plant and animal kingdoms at every level of eukaryotic organization. Circadian rhythms by definition are endogenous in nature, driven by oscillators or clocks (Aschoff 1965), and persist under free-running conditions. In various species (*Drosophila melanogaster, Neurospora, Mouse, Golden hamster*), the genes controlling circadian rhythms have been identified (genes: *per, frq, clock, tau*). In 1971, Konopka and Benzer (1971) were able to identify on the X chromosome of *Drosophila* a region, which controlled the period in the eclosion rhythm of three mutants (*per* clock gene). This data provided the first evidence that the biological clock is genetically determined and can even be transplanted from one animal into another, thereby inducing the rhythmicity of the donor into the recipient.

Circadian clocks are believed to have evolved in parallel with the geological history of the earth, and have undergone selection pressures imposed by cyclic factors in the environment. These clocks regulate a wide variety of behavioral and metabolic processes in many life forms. They enhance the fitness of organisms by improving their ability to efficiently anticipate periodic events in their external environments, especially periodic changes in light, temperature, and humidity.

The mammalian circadian clock, located in the neurons of suprachiasmatic nuclei (SCN) in the brain and in the cells of peripheral tissues, is driven by a self-sustained molecular oscillator, which generates rhythmic gene expression with a periodicity of about 24 h. This molecular oscillator is composed of interacting positive and negative transcription/translation feedback loops as

well as clock-controlled output genes. It is interesting to note that clock genes have been also found in single cells of human skin and mucosa (Bjarnason et al. 2001), furthermore, it has been shown that about 8–10% of all genes are regulated in a circadian fashion.

In general, the human endogenous clock does not run at a frequency of exactly 24 h, but tends to be somewhat slower. The rhythm in human body temperature, which is timed by the biological clock has a period of about 25-h under free-running conditions, i.e., without environmental time-cues or Zeitgebers (e.g., light, temperature). The term "Zeitgeber" introduced by Jürgen Aschoff (1954), is now part of the international scientific language. Mammals such as rodents or humans can entrain their activity to regular light cycles not shorter than 22 but not longer than 26 h. Zeitgebers entrain the circadian rhythm to a precise 24-h period. Zeitgebers are, therefore, necessary to entrain a living subject to a "normal" period of 24 h!

In experimental animals and in humans, however, most rhythmic fluctuations still cannot be studied under free-running conditions, leaving the answer open to what degree they are really "circadian." Purely exogenous rhythms are better termed as "24-h" or "daily" rhythms. Thus, an overt 24-h rhythm in a given parameter can be endogenous or predominately exogenous in nature. Within the published clinical literature, however, the term "circadian" is not always used in the above mentioned correct sense (as used by chronobiologists).

Circadian Rhythms in Man

It is a common paradigm in clinical pharmacology that pharmacokinetic parameters are considered not to be influenced by the time of day of drug administration. Concerning drug concentrations-versus-time profiles, "*the flatter the better*" is also a common aim in drug targeting. However, there is convincing evidence that this paradigm cannot be held any longer. The reason is that it is now well established that nearly all functions of the body, including those influencing ▶ pharmacokinetic parameters, display significant daily variations. Circadian or 24-h rhythms exist in heart rate, body temperature, blood pressure, blood flow, stroke volume, peripheral resistance, parameters of ECG recordings, in the plasma concentrations of hormones, neurotransmitters, and second messengers (e.g., cortisol, melatonin, insulin, prolactin, atrial natriuretic hormone, noradrenaline, cAMP), in the renin-angiotensin-aldosterone-system, in blood viscosity, aggregability and fibrinolytic activity, in the plasma concentrations of glucose, electrolytes, plasma proteins, enzymes, in the number of circulating red and white blood cells and blood platelets, etc. Moreover, various functions of the lung such as minute volume, peak flow, FEV_1, dynamic compliance, functions of the liver (metabolism, estimated hepatic blood flow, first-pass effect) and of the kidneys (glomerular filtration, renal plasma flow, pH, urine volume, electrolyte excretion) vary with time of day. Also gastric acid secretion, gastrointestinal motility, gastric emptying time, and GI-tract perfusion exhibit pronounced circadian variation (see Lemmer 1989, 2005, 2006; Reinberg and Smolensky 1983).

Chronoepidemiology

In man, the organization in time can also be seen in certain states of disease in which the onset and symptoms do not occur at random within 24 h of a day: Asthma attacks are more frequent at nightly hours than at other times of day as already observed about 300 years ago by John Floyer (1698) when stating "I have observed the fit always to happen after sleep in the night…."

Similarly, the occurrences of coronary infarction as well as of angina pectoris attacks and of pathologic ECG-recordings are unevenly distributed over the 24 h span of a day with a predominant peak in the early morning hours. Moreover, subtypes of a disease entity such as forms of vasospastic and stable angina pectoris

Circadian Rhythms. Table 1. Biological rhythms and oral pharmacokinetics (Lemmer 2005).

Liberation	Absorption GI-tract	Distribution	Metabolism liver	Elimination kidney
(Time-specified release, programmable)	Perfusion	Perfusion	Perfusion	Perfusion
	Gastric pH	Blood distribution	First-pass-effect	Renal plasma flow
	Acid secretion	Peripheral resistance	Enzyme activity	Glomerular filtration rate
	Motility	Blood cells	Transporter proteins	Urine excretion
	Gastric emptying	Protein binding		Urine pH
	Rest-activity	Rest-activity		Electrolytes

or of primary and secondary hypertensions may exhibit pronouncedly different 24-h patterns in their symptoms. The occurrence of stroke, fatal pulmonary embolism, the onset of gastrointestinal bleeding, etc., does also not occur at random within 24 h of a day.

Current Concepts and State of Knowledge

Chronopharmacology

Having in mind the organization in time of living systems including man, it is easy to conceive that not only must the *right* amount of the *right* substance be at the *right* place, but also this must occur at the *right* time. This is even more important when an organism or individual itself has to act or react in favorable biotic or environmental conditions, which by themselves are highly periodic. Thus, it is easy to understand that exogenous compounds, including drugs, may differently challenge the individual depending on the *time* of exposition.

Chronopharmacokinetics and Chronopharmacodynamics

In the last decade, numerous studies in animals as well as clinical studies, have provided convincing evidence that

Circadian Rhythms. Table 2. Chronopharmacokinetic studies in man.

Cardiovascular active drugs	Antiasthmatic drugs
Beta-Blockers Propranolol Atenolol Arotinolol (α-,β-blocker)	Aminophylline Theophylline Terbutaline Prednisolone Pranlukast
Calcium Channel Blockers Diltiazem Nifedipine Verapamil Nitrendipine	NSAIDs, local anesthetics Acetylsalicylic acid Indomethacin Ketoprofen Diclofenac Pronaprofen Naproxen Phenacetin Paracetamol Lidocaine Bupivacaine Sulindac Ibuprofen
Organic Nitrates Isosorbide-dinitrate Isosorbide-5-mononitrate	
ACE Inhibitors Enalapril	Opioids Dihydrocodeine Tramadol
Others Digoxin Methyldigoxin Potassium chloride Dipyridamol Tiracizine	Anticancer drugs Cisplatin Doxorubicine 5-Fluorouracil Cyclosporine Vindesine Methotrexate Busulfan Mercaptopurine
Psychotropic drugs Benzodiazepines Diazepam Lorazepam Midazolam Temazepam Melatonin Hexobarbitone Amitriptyline Nortriptyline Lithium Haloperidol Carbamazepine Diphenylhydantoine Valproic acid Levodopa	Antibacterial agents Amikacin Cefprozil Ampicillin Gentamycine Griseofulvin Sulphasymazine Sulphisomodine Vancomycin
Miscellaneous Ethanol Coffein Mequitazine Dexamethasone 5-Methoxysporalene	Gastroenterology Cimetidine Omeprazole Pravastatine

Circadian Rhythms. Table 3. Chronopharmacodynamic studies in man.

Cardiovascular active drugs *Beta-blockers* Acebutolol Metoprolol Atenolol Nadolol Bevantolol Oxprenolol Bopindolol Pindolol Labetolol Propranolol Mepindolol Sotalol Bisoprolol Carvedilol Nebivolol Timolol (IOP)	Antiasthmatic drugs Theophylline Aminophylline Orciprenaline Terbutaline Bambuterol Metacholine Methylprednisolone Dexamethasone Fluticasone Budesonide Ciclesonide Adrenaline Isoprenaline Terbutaline + Budesonide
Beta-agonists Xamoterol Midodrine Terbutaline (IOP) Adrenaline (IOP)	Psychotropic drugs Diazepam Clomipramine Haloperidol Phenylpropanolamine Caffeine Desipramine
Calcium channel blockers Amlodipine Nitrendipine Nifedipine Verapamil Nisoldipine Lacidipine Diltiazem Isradipine Nicardipine	
ACE inhibitors Captopril Enalapril Quinapril Lisinopril Perindopril Spirapril Benazepril Delapril Trandolapril	H_1-antihistamines Clemastine Terfenadine Cyproheptadine Mequitazine
AT_1-receptor antagonists Irbesartan Losartan	Ophthalmology Terbulatine Timolol Adrenaline Isoprenaline
Diuretics Hydrochlorothiazide Indapamide Xipamide Piretanide Torasemide Furosemide	NSAIDs, general and local anesthetics and opioids Acetylsalicylic acid Flurbiprofen Ibuprofen Ketoprofen Indomethacin Metamizole Pranoprofene Paracetamol Tenoxicam Piroxicam Mepivacaine Carticaine Lidocaine Halothane Morphine Fentanyl Narcotic analgesics
Organic nitrates Glyceryl-trinitrate Isosorbide-dinitrate Isosorbide-5-mononitrate	Endocrinology/Gastroenterology Prednisone ACTH Methylprednisolone Insulin Tolbutamide Glucose Bezafibrate Clofibrate Simvastatine
Others Clonidine Prazosin Phentolamine Indoramine Potassium chloride Sodium nitroprusside	*Proton pump inhibitors* Omeprazole Lansoprazole
Anticancer drugs Cisplatin Oxaliplatin THP FUDR Folinic acid Doxorubicin Methotrexate Busulfan Combinations	*H_2-blockers* Cimetidine Famotidine Nizatidine Ranitidine Roxatidine
Miscellaneous Tuberculin Ethanol Heparin Nadroparine Placebo Bright light	

the ▶ pharmacokinetics (Lemmer and Bruguerolle 1994) and/or the drugs' effects/side effects can be modified by the circadian time and/or the timing of drug application within 24 h of a day (see Lemmer 1989, 2005, 2006; Redfern and Lemmer 1997; Reinberg and Smolensky 1983).

Functions involved in the pharmacokinetic steps – from drug absorption to drug elimination – can be circadian phase dependent (Table 1). Thus, gastric emptying time of solids is faster in the morning than in the afternoon. Also, the perfusion of the gastrointestinal tract varies with time of day, being more pronounced at midnight and early morning hours than around noon and in the late afternoon. These observations would nicely explain that – in general – drugs are more rapidly absorbed and do more rapidly reach the systemic perfusion when taken in the morning. Accordingly, clinical studies showed – mainly for lipophilic drugs – that Tmax (time to peak drug concentration) can be shorter and/or Cmax (peak drug concentration) can be higher after morning drug dosing than evening drug dosing.

In Tables 2 and 3, drugs are compiled for which the pharmacokinetics and –dynamics were studied "around the clock" in order to get information whether a circadian time-dependent effect is present. This observation was corroborated for a number of compounds resulting in recommendations for a time-specified drug dosing. These findings have greatly contributed to the fact that now "*time-of-day*" plays an increasing role in drug treatment (see Lemmer 1989, 2006; Redfern and Lemmer 1997; Reinberg and Smolensky 1983). Unfortunately, psychotropic drugs were only scarcely studied in this respect (see Tables 2 and 3).

Conclusion

The chronopharmacological studies published in recent years gave evidence that both the pharmacokinetics and the effects of drugs can be circadian phase dependent. In the light of the circadian organization of the onset and 24-h pattern of various diseases, the knowledge about possible chronokinetics and a circadian phase dependency in the dose response relationship are of utmost importance for increasing drug efficacy and/or reducing side effects.

Cross-References

▶ Analgesics
▶ Anticonvulsants
▶ Antidepressants
▶ Antipsychotic Drugs
▶ Barbiturates
▶ Benzodiazepines
▶ Beta-Adrenoceptor Antagonists
▶ Caffeine
▶ Drug Interactions
▶ Histaminic Agonists and Antagonists
▶ Hypnotics
▶ Lithium
▶ Opioids
▶ Pharmacokinetics
▶ Placebo Effect

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Circumventricular Organs

Definition

Regions of the brain where capillaries lack a blood–brain barrier, thus rendering possible direct and rapid solute exchange between blood and brain. These regions are the median eminence, neurohypophysis, pineal gland, organum vasculosum of the lamina terminalis, subfornical organ, subcommissural organ, area postrema, and the choroid plexus.

Cross-References

▶ Blood–Brain Barrier

Citalopram

Definition

Citalopram is a selective serotonin reuptake inhibitor (SSRI). It is commonly used in the treatment of depression and some of the more severe anxiety disorders (e.g., obsessive–compulsive disorder, panic disorder, social anxiety disorder). As with other SSRIs, the most troublesome side effect of citalopram is sexual dysfunction (dysorgasmia and erectile dysfunction); mild side effects include drowsiness, headache, and nausea. Escitalopram, the *S*-enantiomer of racemic citalopram, is also marketed as an antidepressant.

Cross-References

- ▶ Antidepressants
- ▶ Escitalopram
- ▶ Selective Serotonin Reuptake Inhibitors (SSRIs)

CL

- ▶ Clearance

Classical Anticonvulsants

- ▶ First-Generation Anticonvulsants

Classical Antipsychotics

- ▶ First-Generation Antipsychotics

Classical Conditioning

Synonyms

Pavlovian conditioning

Definition

Classical conditioning results when a stimulus that initially does not elicit a response comes to do so by association with a stimulus that does elicit a response. For example, a drug can serve as the unconditional stimulus (US) and produces an unconditional response (UR). Pairing of an initially neutral stimulus with the drug leads to acquisition by that stimulus (the conditional stimulus or CS) of the ability to produce a response like the US, termed the conditioned response (CR). The new property of the CS is conditional by its association with an established stimulus–response relationship of US–UR.

Classical Fear Conditioning

- ▶ Pavlovian Fear Conditioning

Classical Neuroleptics

- ▶ First-Generation Antipsychotics
- ▶ Typical Antipsychotics

Classical (Pavlovian) Conditioning

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Synonyms

Associative learning; Respondent conditioning

Definition

Pavlovian conditioning is a form of learning in which an association is formed between two stimuli. The Russian physiologist Ivan P. Pavlov (1849–1936) was the first to describe and codify this form of learning (Pavlov 1927). In its most basic form this requires the presentation of a novel stimulus (conditioned stimulus, CS) just prior to a second, biologically significant stimulus (unconditioned stimulus, US) that is capable of eliciting a reflexive response. As a result of this stimulus pairing, the CS acquires the ability to elicit a conditioned response (CR) that is identical to the reflexive response (unconditioned response, UR) elicited by the US. The CS also acquires the aversive or appetitive properties of the US. There are a number of related forms of Pavlovian conditioning that are used to examine drug effects (see ▶ Pavlovian fear conditioning; ▶ Conditioned drug effects; ▶ Conditioned taste aversion).

Impact of Psychoactive Drugs

Examination of drug effects on Pavlovian conditioning has employed only a limited number of target responses with the conditioned eyeblink response being the most widely used. Eyeblink conditioning is carried out by presenting a tone or light CS just prior to delivery of an airpuff US to the cornea or a shock US to the cheek. These USs elicit a spectrum of responses but the eyeblink UR elicited by the airpuff or shock is the identified target response. Various components of the eyeblink can be measured including external eyelid closure in humans, rabbits, and rodents; retraction of the eyeball and the associated passive extension of the nictitating membrane in the rabbit; and the electrical signal generated by the muscles involved in the eyeblink. Three other target responses have also been employed. Acquisition of the conditioned skin conductance CR in humans is accomplished by the pairing of a tone CS and an aversive white noise US. Appetitive conditioning of the rabbit's jaw movement response involves the pairing of a tone or light CS with presentation of an appetitive US such as water to a thirsty animal or a highly palatable solution of sucrose to a nondeprived animal. The US is delivered directly into the oral cavity and jaw movements as the animal swallows are recorded by direct measurement. Drugs have also been examined for their effects on the acquisition of a conditioned heart rate response (bradycardia) resulting from the pairing of a tone CS with delivery of a shock US. The popularity of the eyeblink response is due to several factors. Eyeblink conditioning is abnormal in various neuropathologies that impair associative processes in humans such as ▶ schizophrenia, ▶ Alzheimer's dementia, amnesic ▶ Korsakoff syndrome, ▶ fetal alcohol syndrome, ▶ autism, and ▶ obsessive–compulsive disorder (Steinmetz et al. 2001), and this provides the opportunity to employ both humans and experimental animals to examine the potential therapeutic effects of drugs in these disorders (see ▶ Dementias: animal models; ▶ Schizophrenia Animal Models). This comparison has been shown to be valid since the eyeblink response in nonhuman subjects, such as the rabbit, has been extensively characterized with respect to parametric variations in stimulus scheduling, and has been shown to demonstrate all of the associative phenomena seen in humans (Gormezano et al. 1983). The effects of drugs on learning have been measured during acquisition of CRs to a single stimulus, experimental extinction, acquisition or reversal of a discrimination, and serial compound conditioning. Drug effects have been measured after acute or chronic drug administration, after parenteral or central injection, in progeny after prenatal drug exposure, and during early postnatal development. Drugs employed have been hormones, toxins, and the major classes of pharmaceutical agents including ▶ hallucinogens, ▶ antipsychotics, ▶ antidepressants, ▶ opioids, ▶ benzodiazepines, cognition enhancers, and ▶ psychostimulants (Schindler and Harvey 1990).

Two basic schedules are employed in Pavlovian conditioning, delay and trace. In delay conditioning the CS is presented in close contiguity with the presentation of the US either by simultaneous offset of CS with onset of US or by an overlap of CS and US. In trace conditioning, the offset of the CS is followed by a period of time (the trace interval) before US onset. Learning during delay and trace conditioning is mediated by different neuronal circuits. In both rabbits and humans, trace conditioning requires the integrity of the limbic cortex while delay conditioning depends on the integrity of brain stem circuits. Human subjects are aware of the relationship between CS and US during trace conditioning, while delay conditioning proceeds without awareness (Clark and Squire 1998; LaBar and Disterhoft 1998). These schedules of Pavlovian conditioning also generate different rates of learning depending on the CS–US interval defined as the time between onset of the CS and US and/or the duration of the trace interval defined as the time between CS offset and US onset. For both delay and trace conditioning the rate of acquisition and final asymptotic performance of CRs decreases with increasing CS–US intervals, and within a fixed CS–US interval, increases in the trace interval also decrease rates of learning and asymptotic performance. As would be expected, the highest rates of acquisition occur with short delay intervals. The percentage enhancement or retardation of associative learning by drugs is an inverse function of the rate of CR acquisition in vehicle controls. Consequently, the ▶ ED_{50} for the effects of a drug on learning can vary by more than tenfold depending on the schedule employed. There are several control procedures used to determine the behavioral process through which a drug may be affecting CR acquisition. For example, one can distinguish between associative learning that results from the explicit pairing of CS and US, and nonassociative learning often referred to as pseudo conditioning or sensitization that can occur when the CS and US are presented at temporal intervals that do not support learning in normal controls (Gormezano et al. 1983). Using explicitly unpaired presentations of CS and US, one can determine whether a drug enhances the production of CRs to the CS and/or URs to the US. The increase in CRs might be due to an enhanced baseline rate of responding and this can be determined by measuring the response during the interval prior to the presentation

of the US, the period when a CS would have been presented during paired trials. One can also determine whether the drug had altered motoric function by examining the topography of the CR and UR in terms of their onset latencies, peak amplitude, and rise time (time between the onset of a response and its achievement of peak amplitude). Finally, if the drug has produced its effects by altering the rate of associative learning, one can further determine whether the effect is due to a change in sensory processing of the CS or US by measuring the percentage of CRs as a function of CS intensity and URs as a function of US intensity in animals that had reached asymptotic performance of CRs.

One of the characteristics of Pavlovian conditioning is its precise temporal resolution. For example, in eyeblink conditioning there is no evidence of conditioning at CS–US intervals at or below 75 ms. With increasingly longer intervals there is a proportionate increase in conditioning that reaches its peak sometime between 200 and 400 ms. At longer intervals conditioning declines and is totally absent at intervals of approximately 1–2 s. Similar CS–US functions are generated in other organisms from aplysia to humans. Thus, this CS–US function has been highly conserved during evolution and represents two constraints on associative learning. First, an association cannot be formed if the CS cannot elicit a CR before the occurrence of the US, an interval of approximately 75 ms. Second, the probability that a CS is predictive of the delivery of a US, becomes increasingly less likely as the CS–US interval becomes longer. Drugs have a differential effect on learning depending on the CS–US interval employed (Harvey et al. 1985). Both the enhancement of learning produced by LSD and the retardation of learning produced by scopolamine are the greatest at short and long ISIs and are barely detectable at the optimal ISI of 200 ms.

The use of Pavlovian eyeblink conditioning has revealed the involvement of a number of drug classes and their receptors in learning (Schindler and Harvey 1990). Hallucinogens enhance the rate of associative learning as agonists at the 5-HT_{2A} receptor at doses comparable to those that elicit hallucinations in humans (Table 1) (see ► Hallucinogens). The enhancement of associative learning by d-lysergic acid diethylamide occurs during aversive Pavlovian conditioning of the eyeblink response and the appetitive jaw movement response. Antipsychotics act as ► inverse agonists at the 5-HT_{2A} receptor to retard the rate of learning and thus block the effects of hallucinogens (see ► Antipsychotic drugs; ► Inverse Agonists). Finally, ► antagonists such as d-bromolysergic acid and ketanserin have no effect on learning but do block the effects of ► agonists and ► inverse agonists. The existence of antagonists and inverse agonists at the 5-HT_{2A} receptor indicates that this receptor is ► constitutively active (Harvey 2003). The cholinergic system has been of special interest as a target for drugs effective in Alzheimer's and other forms of dementia. Since eyeblink conditioning has been shown to be impaired in Alzheimer's dementia, a number of studies have examined the effects of putative cognitive enhancers on acquisition of the eyeblink response in humans and experimental animals. Muscarinic and nicotinic agonists as well as ► cholinesterase inhibitors enhance the rate of learning (Li et al. 2008; Weiss et al. 2000) while antagonists at these two receptors retard learning (Harvey et al. 1985) (see ► Acetylcholinesterase inhibitors as cognitive enhancers; ► Muscarinic agonists and antagonists). Both μ- and κ-opiod receptor agonists retard learning during eyeblink conditioning. The opioid antagonist ► naloxone has no effect on learning when given alone, but does block the retardation of learning produced by opioid agonists. A more detailed summary of these results has been published (Schindler and Harvey 1990) (see ► Opioids). Inhibitors of neuronal nitric oxide synthase enhance learning while peripheral or central administration of nitric oxide donors retards learning (Du et al. 2000). Finally, NMDA channel blockers (dizocilpine, ketanserin) retard learning (Du and Harvey 1997).

Classical (Pavlovian) Conditioning. Table 1. Enhancement of eyeblink conditioning in rabbits is correlated with production of hallucinations in humans.

Hallucinogens	Rabbit (μg/kg[a])	Human (μg/kg[b])
LSD	0.8	1.0
DOM	52	50
MDMA	500	250
MDA	800	1,000
BOL	No effect	No effect

[a]ED_{50} for enhancement of eyeblink conditioning in rabbits
[b]Threshold dose for elicitation of ► hallucinations in human subjects
LSD D-Lysergic acid diethylamide; *DOM* BOL, D-2-Bromolysergic acid diethylamide; D,l-2,5-dimethoxy-4-methylamphetamine; *MDMA*, D,l-methylenedioxymethamphetamine; *MDA* D,l-methylenedioxyamphetamine

Cross-References

► Acetylcholinesterase Inhibitors as Cognitive Enhancers
► Antipsychotic Drugs
► Conditioned Drug Effects
► Conditioned Taste Aversion
► Dementias: Animal Models
► Hallucinations
► Inverse Agonists
► Muscarinic Agonists and Antagonists

► Opioids
► Pavlovian Fear Conditioning
► Schizophrenia Animal Models

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Classification of Psychoactive Drugs

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Definition

Psychopharmacology may be defined as the study of drugs that affect the mental state.

Current Concepts and State of Knowledge

Introduction

By convention, the term psychopharmacology is applied to drugs that are used to treat psychiatric disorders. Such drugs are termed psychotropic drugs. Psychopharmacology is usually grouped with the discipline of neuropharmacology which is concerned with the application of drugs for the treatment of neurologically based disorders. In reality, these areas often overlap. For example, several antiepileptic drugs are used in the treatment of bipolar disorder. Perhaps a more general term should be used to cover all pharmacologically active substances that directly influence brain function.

What is the historical basis for the classification of psychotropic drugs? The link between psychotropic drugs and modern psychiatry can be traced back to the father of European psychiatry, Emil Kraepelin who, in 1882, undertook a research program in the University of Leipzig with Wilhelm Wundt "On the influence of some medicinal drugs on single mental processes." In the publication that arose from this research, Kraepelin and Wundt surveyed the effects of the ► Hypnotics paraldehyde, chloral hydrate, ether, chloroform, the stimulant caffeine and the opiate morphine (Kraepelin 1899). Together with alcohol, these substances were the main components of the pharmacopeia at that time. In the publication, Kraepelin and Wundt established methods for measuring the reaction time and tests of memory function. In addition evaluating the effects of the different psychoactive drugs on these behavioral parameters, the placebo effects were also recognized. Such research led to one of the first attempts to classify psychoactive drugs, according to their clinical effects, under three headings: Narcotics that were medicaments with a calming action comprising opium (for anxiety and manic states), morphine, hyoscine/scopolamine (for inducing a rapid and deep sleep in manic patients) and hashish (a hypnotic with an unreliable action according to Kraepelin). Hypnotics included chloral hydrate, paraldehyde, sulphonal and trional, alcohol (to treat hysteria), and chloroform (for very excited states) The third category of psychoactive drugs comprised the bromides and were used in epilepsy, neurasthenia, and insomnia; bromism was recognized as a serious side effect. Eugen Bleuler, also an important founder of European psychiatry, published a similar classification to Kraepelin but added a barbiturate to the list of hypnotics (Bleuler 1916). It is worthy of note that the pharmacopeias that were available until the 1950s did not contain any drugs for the treatment of depression and schizophrenia. Non drug therapies available in the 1920s and 1930s included the shock therapies (insulin- and leptazol-induced

seizures) and ► electroconvulsive shock (ECT). Amphetamine was first synthesized in 1927 but its use was confined to the treatment of narcolepsy. It was noted that ► amphetamine was ineffective in the treatment of major depression! As is apparent from this group of drugs, until the latter part of the twentieth century the psychoactive drugs that were available to the psychiatrist were extremely limited and mainly used to calm or sedate disturbed patients.

The Revolution in Pharmacopsychiatry

There is a commonly held view that coincidence and chance have played the major role in the discovery of the first therapeutically effective drugs for the treatment of the major psychiatric disorders. This view is only partly true. Take, for example, the discovery of the first effective neuroleptic, ► chlorpromazine. The discoverers, Delay and Deniker. had long been interested in discovering drugs for the treatment of psychotic disorders and their studies of chlorpromazine followed a series of studies of different types of sympatholytic and anticholinergic compounds (see Swazey 1974). In Australia at approximately the same time, John Cade was trying to find a treatment for mania. Having discovered that the urine of manic patients contained a high concentration of uric acid and that lithium carbonate (which formed a lithium salt with uric acid) could protect guinea pigs from the toxic effects of uric acid. Subsequently Cade found that, despite its toxicity, lithium carbonate had an antimanic effect.

The discovery that the major psychiatric disorders were amenable to drug treatment gave a stimulus to the pharmaceutical industry to extend the research to produce new therapeutically active drugs. Thus ► imipramine, a tricyclic compound related to chlorpromazine, showed little benefit in the treatment of schizophrenia. Roland Kuhn, in Switzerland, did show that imipramine was the first effective tricyclic antidepressant. Thus imipramine was added to the first ► monoamine oxidase inhibitor antidepressant iproniazid, a drug that was a spin-off from a series of hydrazide derivatives used to treat tuberculosis. Readers are referred to an excellent history of psychopharmacology by Ban et al. (2000).

The last major breakthrough in psychotropic drug development came with the discovery of ► meprobamate for the treatment of generalized anxiety disorder (GAD). Meprobamate was a "central" muscle relaxant and based on the structure of the antispasmodic mephenesin. It was soon realized that the efficacy of meprobamate was limited and, in addition, could cause dependence. This discovery occurred at a time that the anxiolytic activity of ► chlordiazepoxide, the first benzodiazepine in therapeutic use, was discovered thereby leading to the introduction of a large range of benzodiazepines that were used for the treatment of anxiety, insomnia, epilepsy, and also as anesthetic agents (► midazolam). The term "serendipity" is used to describe the discovery of modern psychotropic drugs and implies that the drugs were discovered by chance. However, this does not take into account the background to the research, the "prepared mind," that recognizes the importance of the unexpected discovery when it occurs (see Jeste et al. 1979).

Thus the developments in different areas of neuroscience (neurochemistry, neurophysiology, neuroanatomy and neuropharmacology) at the time of the discovery of the first effective psychotropic drugs influenced the way psychiatrists and psychologists viewed brain function. If aberrant behavior was somehow based on disrupted neurotransmitter function then mental disorders could be considered from a biological perspective. Drugs could therefore be used to treat mental disorders in the same way that they are used to treat any other disease.

However, despite the progress that has been made in psychopharmacology since the 1950s, progress in the past decade has been limited with very few genuinely novel compounds (rather than "me-too" drugs with marginally improved profiles to those already available!) being discovered. Perhaps a better understanding of the pathophysiological basis of the major psychiatric disorders is required before the next advance in the development of more effective psychotropic drugs can take place.

Classification of Psychotropic Drugs

Psychotropic drugs may be classified (1) according to their chemical structure, (2) by their pharmacological actions on specific biological processes such as receptors, transporter, or ion channels, or (3) by their therapeutic actions. Theoretically, all three approaches form a continuity, as the chemical structure should indicate how the drug affects a specific biological process that is dysfunctional in the disease under consideration. However, as the pathophysiological basis of the psychiatric disorders is unknown, it is currently impossible to predict what the therapeutic profile of a novel compound based on its chemical structure or even on its in vitro and ex-vivo biological activities would be. For this reason, psychoactive drugs are largely classified according to their therapeutic actions into seven major classes:

1. ► Antipsychotics for the symptomatic treatment of schizophrenia, psychotic states that may have a psychiatric or neurological basis and severe agitation associated with acute mania. Such drugs are

sometimes called "neuroleptics" or, in the older literature, "major tranquilizers" (see Table 1).

2. ► Antidepressants for the symptomatic treatment of depression. In the older literature, antidepressants were called "thymoleptics" (Table 2).
3. ► Anxiolytics, sometimes called "minor tranquillers," for the treatment of GAD. Hypnotics are essentially sedative anxiolytics used for the treatment of insomnia. The psychopharmacology of the anxiety disorder is complex because of the diverse nature of the disorders that include panic disorder, phobic disorders, post traumatic stress disorder and obsessive compulsive disorder in addition to GAD. True anxiolytics are effective in the treatment of GAD and are of only limited efficacy, or lack efficacy, in the treatment of the other disorders (Table 3).
4. ► Mood Stabilizers are drugs used for the treatment of mania, hypomania and bipolar disorders (mixed mania and depression) (Table 4).
5. ► Psychostimulants are a group of drugs whose therapeutic use is largely confined to the treatment of narcolepsy and attention deficit hyperactive disorder (ADHD). In the older literature, psychostimulants are called "analeptics" (Table 5).
6. ► Nootropics are classified as a group of drugs that may improve cognitive function without having a stimulant profile. Despite the initial therapeutic claims that nootropics improve cognitive impairment in the elderly (evidence for which was partly based on improved cognitive function in rodents) such drugs are seldom used in Europe, North America or Australasia because they lack proven efficacy.

Classification of Psychoactive Drugs. Table 1. Classification of typical and atypical antipsychotics.

Typical antipsychotics		
D2 antagonists	Phenothiazine type	Main therapeutic action on positive symptoms. EPS side effects related to D2 blockade in basal ganglia
	Chlorpromazine	
	Fluphenazine	
	Perphenazine	
	Prochlorperazine	
	Thioridazine	
	Thioxanthine type	Similar potency and side effects to phenothiazines
	Chlorprothixene	
	Flupenthixol	
	Butyrophenone type	Potent D2 antagonists
	Haloperidol	
	Trifluperidol	
	Pimozide	
	Benzamides	Least potent of typicals but least likely to cause EPS
	Sulpiride	
Atypical antipsychotics		
Multireceptor antagonists	Clozapine	All atypicals have less EPS side effects than typicals. Show some improvement in negative symptoms. Drugs of first choice for treatment of schizophrenia
	Olanzapine	
	Quetiapine	
5-HT2/D2 antagonists	Risperidone	
	Paliperidone	
	Ziprasidone	
	Sertindole	
5-HT2/D2 partial agonist	Aripiprazole	
D2/D3 antagonist	Amisulpride	

Classification of Psychoactive Drugs. Table 2. Classification of antidepressants.

First generation		
Tricyclic antidepressants		
5-HT/NA reuptake inhibitors	Imipramine	Except lofepramine, all are cardiotoxic in overdose
	Amitriptyline	
5-HT<NA reuptake inhibitor	Clomipramine	Anticholinergic
NA<5-HT reuptake inhibitors	Desipramine	
	Nortriptyline	
	Lofepramine	"Atypical" first generation
Nonselective monoamine oxidase inhibitors (MAIO's)		
Block breakdown of NA and 5-HT	Phenelzine	Interact with dietary amines causing hypertension
	Tranylcypromine	
	Pargyline	
Second generation		
Selective serotonin reuptake inhibitors		
Fluoxetine Fluvoxamine Citalopram Escitalopram Paroxetine Sertraline		First line treatment of depression. Also used to treat anxiety disorders and OCD
Serotonin and Noradrenaline reuptake inhibitors (SNRI's)		
Dual action reuptake inhibitors	Venlafaxine	?More potent than SSRI's
5-HT>NA	Desvenlafaxine	
""	Duloxetine	
NA>5-HT	Milnacipran	
Noradrenaline reuptake inhibitors (NRI's)		
Reboxetine		
Reversible inhibitor of MAO		
Moclobemide		Less likely than first generation MAOI's to interact with diet
Noradrenaline and serotonin specific antidepressants		
Increase NA, 5-HT2 antagonist	Mianserin	
	Mirtazepine	Also anxiolytic and sedative
Atypicals	Trazodone	Weak antidepressant, sedative and axiolytic

7. ► Antidementia drugs comprise a series of compounds that show marginal benefit in slowing the mental decline, particularly in memory and some aspects of cognitive function, in patients with Alzheimer's disease and related dementias (Table 5).

In addition to these major groups of drugs that have specific therapeutic properties, there are many psychoactive drugs that affect brain function but whose therapeutic actions are not directed at the symptomatic relief of psychiatric disorders. Such drugs may be used to relieve pain (for example, the opiates) or to treat specific neurological disorders such as the epilepsies. In addition, there are a large number of recreational psychoactive drugs such as alcohol, the cannabinoids, the hallucinogens, cocaine and nicotine that have no or limited therapeutic use because of their dependence liability. Caffeine, a mild psychostimulant, is considered to be such a recreational drug by some psychopharmacologists! The recreational psychoactive drugs are predominantly ► drugs of abuse and their properties will not be further considered. Their basic properties are summarized in Table 6.

Classification of Psychoactive Drugs. Table 3. Classification of anxiolytics and hypnotics.

Benzodiazepines		
Enhance GABA inhibition by activation of benzodiazepine receptor		
Chlordiazepoxide Diazepam		Traditional anxiolytics, with long half lives
Flunitrazepam		Hypnotic, long $t_{½}$
Oxazepam Temazepam		Hypnotic, medium $t_{½}$ lives
Triazolam		Hypnotic, short $t_{½}$
Alprazolam		Potent anxiolytic; Also antipanic
Non benzoidiazepines with a benzodiazepine profile		
S-enantiomer of zopliclone	Eszopiclone	Hypnotic
Activate benzodiazepine receptor	Zopiclone	Hypnotic
	Zolpidem	
	Zaleplon	
5-HT1A partial agonist	Buspirone	Slow onset of action weak anxiolytic
Novel anxiolytics		
Calcium channel modulators?	Pregabalin	Also used in pain control
	GABApentin	

Classification of Psychoactive Drugs. Table 4. Classification of drugs to treat bipolar disorder.

Lithium salts		Mood stabilizer; long term action, Multi-system effects; slows repolarization
Anticovulsants, enhance GABA function		
Carbamazepine		
Oxcarbamazepine		
Sodium valproate		
Clonazepam		
Topiramate		
Lamotrigine		Effective in bipolar 2 depression
Gabapentin		
Atypical antipsychotic	Olanzapine	

Overview of the main classes of psychotropic drugs and their therapeutic uses.

The following account of the properties of psychoactive drugs and their main pharmacological properties is only intended as a brief overview. Readers are referred to standard texts for more complete account. (e.g., Iversen et al. 2009; Leonard 2003; Spiegel 2003).

Antipsychotics

These drugs are used for the symptomatic treatment of schizophrenia and psychotic disorders.

Schizophrenia is characterized by the following symptoms: delusions, hallucinations (visual and aural), disorganized speech, grossly disorganized or catatonic behavior. These symptoms are termed Positive symptoms. The Negative symptoms consist of affective flattening (referring to a reduction in the range and intensity of emotional expression), ► alogia (poverty of speech) and ► avolition (inability to initiate or persist in goal directed behavior). Patients with schizophrenia therefore fail to understand the external world and how to react appropriately to it and consequently lose touch with reality. This summary, and those relating to other major psychiatric disorders mentioned in this presentation, is based on the Statistical manual of mental disorders (2000).

The antipsychotic drugs can be divided into the "Typical" and "Atypical" types, sometimes referred to as the first and second generation antipsychotics respectively.

The typical antipsychotics are subdivided according to their chemical structures into the phenothiazines (such as chlorpromazine, fluphenazine, trifluperazine and thioridazine), the structurally related thioxanthines that have very similar pharmacological properties to the ► phenothiazine analogs (chlorprothixene, clopenthixol, and flupenthixol), the ► butyrophenones (haloperidol, benperidol, trifluperidol and pimozide) and the benzamides (sulpiride).

The atypical antipsychotics consist of a series of chemically unrelated drugs that differ from the typical antipsychotics by their reduced frequency of motor side effects. Thus whereas the use of the typical antipsychotics are often therapeutically limited because of their extrapyramidal side effects (Parkinsonism, akathisia, tardive dyskinesia etc.) due to their blockade of dopamine D2 receptors in the basal ganglia,the atypicals are less likely to have such side effects at normal therapeutic doses. This group consists of the multi-receptor antagonists that are chemically similar (clozapine, olanzapine and quetiapine), so called because they interact with multiple dopamine, serotonin, noradrenaline, acetylcholine and histamine receptors. The 5-HT_2/D2 receptor antagonists form the bulk of the atypical antipsychotics that consist of risperidone and its metabolite paliperone, ziprazidone, sertindole and zotepine. Other drugs in the atypical series include amisulpride (a D2/D3 antagonist that is related to the first generation benzamide, sulpiride) and the "atypical" antipsychotic aripiprazole.

The typical and atypical antipsychotics differ mainly in terms of the severity of their side effects. All antipsychotics in current use are D2 receptor antagonists, a property that is thought to be an essential component for the attenuation of the positive symptoms of schizophrenia. However, the atypicals, with the exception of amisulpride, are also 5-HT_2 receptor antagonists and action that is thought to block the tonic inhibitory effect of serotonin on the dopaminergic system in the prefrontal cortex thereby facilitating the inhibition by cortical dopamine on the overactive mesolimbic dopaminergic system that is thought to be responsible for the positive symptoms of schizophrenia. The atypical antipsychotics therefore specifically target the mesocortical dopaminergic system without having a major inhibitory effect on the striatal dopaminergic system (unlike the typical antipsychotics that lack this selectivity), thereby having a reduced frequency of motor side effects.

Because of their more acceptable side effects, combined with their efficacy in the treatment of positive, and secondary negative symptoms, the World Health Organization has recommended that the atypical antipsychotics be used as the first line treatment of schizophrenia (Sartorius et al. 2002).

Antidepressants

The DSM IV classification of major depressive disorder lists chronically depressed mood, anhedonia (diminished feeling of pleasure) insomnia or hypersomnia, psychomotor agitation or retardation, fatigue, anorexia (weight loss), feelings of worthlessness and inappropriate guilt, recurrent thoughts of death, suicide thoughts and attempted suicide as the characteristic features of the patient with major depression. Five or more of these symptoms must be present during the same 2-week period and must not be associated with drugs of abuse or other medications that can cause depression.

For the past 50 years, depression has been treated (with reasonable success) with different types of antidepressant drugs or with ECT therapy. All of the antidepressants in current use enhance noradrenergic and/or serotonergic function apart from buproprion that has a mild dopamimetic action. Thus antidepressants are thought to improve noradrenergic and/ or serotonergic function that is dysfunction in depression.

As with the antipsychotics, the antidepressants, may be divided into the first (tricyclic antidepressants TCAs, nonselective monoamine oxidase inhibitors MAOIs) and second generation (reversible inhibitors of monoamine oxidase RIMAs, selective serotonin reuptake inhibitors SSRIs, serotonin and noradrenaline reuptake inhibitors SNRI's, noradrenaline and serotonin selective antidepressants NaSSAs and noradrenaline reuptake inhibitors NRIs) drugs.

The main difference between the first- and second-generation antidepressants lies not in their therapeutic efficacy but in the safety in overdose and tolerability due to the reduction in the side effects of the second-generation drugs.

In terms of their therapeutic action, the second-generation antidepressants can be divided into those that are presumed to selectively increase serotonin function (the SSRIs such as fluoxetine, fluvoxamine, citalopram, escitalopram, sertraline and paroxetine), those that selectively increase noradrenergic function (the NRI reboxetine), the dual action antidepressants that enhance both serotonergic and noradrenergic function (venlafaxine, duloxetine and milnacipran) and buproprion that has a dopaminomemetic action. It should be noted that some of the first-generation TCAs also show some selectivity for the serotonergic system (clomipramine) or the noradrenergic system (desipramine, nortriptyline and maprotiline). The TCAs, SSRIs, SNRIs, NRIs are assumed to act by inhibiting the noradrenaline

Classification of Psychoactive Drugs. Table 5. Classification of psychostimulants and antidementia drugs.

Psychostimulants		
NA/DA releasers	D-amphetamine	Used in ADHA and narcolepsy
	Methylphenidate	""
NA reuptake inhibitor	Atemoxine	""
?Central histamine releaser	Modafinil	Used in daytime sleepiness
?Orexin modulator		
Anti-dementia drugs		
Acetylcholinesterase inhibitors	Donepezil	Used in mild-moderate dementia
	Rivastigmine	""
	Gallantamine	""
NMDA glutamate receptor partial antagonist		
Memantine		Used in moderate-severe dementia

Classification of Psychoactive Drugs. Table 6. Classification of recreational drugs and drugs of abuse.

Sedatives		
Enhance GABAergic function	Ethyl alcohol Barbiturates Gamma hydroxybutyrate	
Opiates		
Enhance mu receptor function	Heroin	Used in severe pain relief
	Morphine	
	Methadone	
Psychostimulants		
Enhance NA/DA release	D-amphetamine Methamphetamine Cocaine Nicotine	
Enhances 5-HT release>NA/DA	Methylenedioxymethamphetamine (MDMA)	
Cannabinoids		
Enhance CB1/CB2 receptors	delta-9 tetrahydrocannabinol	Tranquilizing action. Active component of hashish
Hallucinogens		
Activate 5-HT2C receptors	Lysergic acid diethylamide Dimethyltryptamine Mescaline	
Block NMDA glutamate receptors	Phencyclidine	

and or serotonin transporters on the neuronal membrane thereby prolonging the duration of action of the neurotransmitter in the synaptic cleft.

The tetracyclic antidepressant mirtazepine, and its precursor mianserin, enhance noradrenergic function by blocking the inhibitory presynaptic alpha-2 adrenoceptor on noradrenergic terminals. In addition, mirtazepine blocks post synaptic 5-HT_{2A} receptors and indirectly enhances 5-HT_{1A} receptor function.

Of the first-generation antidepressants, the MAOIs (such as phenelzine, pargyline, and tranylcypromine) increase the catecholamine by blocking their intraneuronal metabolism. These drugs have fallen into disuse as the inhibition of MAO in the gastrointestinal tract can lead to a hypertensive crisis should amine rich foods (cheese, beer, wine etc.) be taken concurrently. This has led to the development of RIMAs (such as moclobemide) that, being reversible inhibitors of MAO, are displaced from

the gastrointestinal MAO should high amine containing foods be consumed.

The use of the TCAs has been restricted in most industrialized countries due to their anticholinergic side effects and cardiotoxicity particularly in overdose. The exception is the TCA lofepramine that is less anticholinergic and cardiotoxic than the other members of this series.

Anxiolytics

Anxiety is an unpleasant state accompanied by apprehension, worry, fear, nervousness and heightened arousal. These psychological changes are usually associated with an increase in autonomic sympathetic activity (such as increased blood pressure and heart rate and gastrointestinal distress. While physiological anxiety is usually of short duration, often with rapid onset and abrupt cessation once the aversive event has terminated, pathological anxiety occurs when the response to an anxiety provoking event becomes excessive, prolonged, and affects the ability of the person to lead a normal life. This condition is referred to as Generalized anxiety disorder (GAD). The anxiolytics are drugs of choice for the treatment of GAD.

However, anxiety disorders comprise a number of conditions for which the conventional anxiolytics are of limited efficacy. Thus, panic disorder is effectively treated with SSRI antidepressants, as are the social phobias and obsessive compulsive disorder. This suggests that unlike GAD, in which the noradrenergic, serotonergic and GABAergic systems are thought to be dysfunctional, a malfunctioning serotonergic system plays a key role in the pathology of panic disorder, obsessive compulsive disorder and the phobic states.

For several decades, the treatment of anxiety has been dominated by the benzodiazepines, drugs that are rapidly effective (unlike most of the other psychotropic drugs), safe in overdose. For this reason, they replaced the barbiturates and meprobamate that had limited efficacy and were dependence producing. The benzodiazepines bid to a specific site on the multifunctional $GABA_A$ receptor (called the benzodiazepine binding site) and enhance the inhibitory action of GABA on the $GABA_A$ receptor. Shortly after the discovery of the first benzodiazepine anxiolytics (► chlordiazepoxide and ► diazepam) a wide range of benzodiazepines were developed for the treatment of anxiety, epilepsy, and as hypnotics, central muscle relaxants for spasticity and as anaesthetics. It is well established that most of these properties are present in diazepam and chlordiazepoxide. Thus low therapeutic doses of these drugs are anxiolytic but as the dose is increased sedation followed by an anticonvulsant effect becomes prominent. Such doses are also commonly associated with GABA dependent muscle relaxation. Dependence can occur in some patients who take high therapeutic doses of the benzodiazepines for long periods. This condition has led to the development of a series of novel non-benzodiazepine anxiolytics/hypnotics, such as ► zolpidem and ► zopiclone. However, these drugs also owe their therapeutic actions to the activation of the benzodiazepine site on the GABA receptor!

Buspirone, a partial 5-HT_{1A} receptor agonist that does not affect the GABA receptor was developed in the hope that, because of its unique action, it could replace the benzodiazepine type of drug. Despite its initial promise, buspirone has had a very limited clinical impact due to the delay in its onset of action, its minimal efficacy, and serotonin-linked side effects (nausea, headache). Nevertheless, the discovery of ► buspirone stimulated the use of the SSRI antidepressants and venlafaxine in the treatment of GAD and other anxiety disorders and, despite their delayed onset of action, the SSRIs are often considered as the first choice for treatment.

Mood Stabilizers

Bipolar disorder is characterized by episodes of mania or hypomania that alternates with periods of depression. The manic symptoms are characterized by an expansive, elated or irritable mood, pressured speech, flight of ideas, easy distractibility and a preoccupation with socially unacceptable, and potentially dangerous, activities. Such symptoms may persist for many days and may require hospitalization. The manic phase of bipolar disorder is usually followed by a euthymic phase or by depression. The depressive phase is often very severe leading to suicide in 10–25% of bipolar patients. The DSM IV classification divides bipolar disorder into bipolar1 disorder (a patient showing both mania and depression) and bipolar 2 (in which mania occurs in a less severe form, hypomania, that alternates with depression). In bipolar 2 disorder, the patient may show predominantly the manic or depressed state and only very occasionally switch to the opposite mental state. An uncommon type of bipolar disorder is the rapid cycling state in which the patient switches from one state to another in frequent succession.

Of the drugs available to treat bipolar disorder, ► lithium is still one of the most widely used. Like most of the psychotropic drugs used in the treatment of the major psychiatric disorders, lithium usually takes several weeks to produce its optimal therapeutic effect. Lithium is used prophylactically and lengthens the euthymic period between the phases of the illness. The pharmacology of lithium is very complex as its mode of action is based on the replacement of Na+ ions in the numerous transporters, ion channels and receptors throughout the body. This not only accounts for its therapeutic effects but also for its numerous side effects that often limit its clinical

use. This has resulted in lithium being replaced by more conventional drugs that are primarily used in other areas such as psychiatry and neurology. Of these, the anticonvulsants (such as ▶ carbamazepine, oxcarbamazepine, sodium ▶ valproate, ▶ topiramate, ▶ gabapentin, and ▶ lamotrigine) are the most widely used. The atypical antipsychotics clozapine and olanzapine have now been added to the list of effective antimanic agents. Conventional antidepressants such as the TCAs and SSRIs are limited efficacy in treated the depressed phase of bipolar disorder. This suggests that the etiology of depression in bipolar disorder differs from that of major depression.

Nootropics and Antidementia Drugs

Nootropic agents are defined as centrally acting drugs that improve higher integrative brain functions, such as memory and cognitive impairment, in the early stages of Alzheimer's disease and in dyslexia .These nonstimulant drugs that are available in some European countries include the central vasodilator co-ergocrine and the pyrrolidinone derivatives piracetam, amiracetam, aniracetam and levetiracetam. Despite the many years of research into the possible mechanisms of action of nootropic agents, their actions are unclear and their clinical efficacy is doubtful.

In contrast to the nootropic agents, the antidementia drugs have proven benefit when administered in the early stage of ▶ Alzheimer's disease. These drugs fall into one of two categories, namely the anticholinesterases and the glutamate *N*-methyl-D-aspartate (NMDA) receptor antagonists. The anticholinesterases (▶ donepezil, ▶ rivastigmine, ▶ galantamine), increase central cholinergic function, a mechanism that is assumed to be responsible for the drug induced reduction in the cognitive decline in the early stage of Alzheimer's disease. This view correlated with the pathological finding that there is severe damage to the nucleus basalis magnus-hippocampal cholinergic pathway in patients with Alzheimer's disease.

In contrast to the anticholinesterases, the partial NMDA receptor antagonist ▶ memantine is thought to protect central neurons from the neurodegenerative effect of excess glutmate that is released in the brain of the Alzheimer patient. Memantine has been shown to be effective in moderate to severe cases of Alzheimer's disease.

Psychostimulants

Psychomotor stimulants, such as D-amphetamine, methylphenidate, and atomoxetine, are most widely used to treat ADHD but are also known to counteract fatigue in normal adults. However, the effects on vigilance, verbal learning and memory are relatively small even though they may be sufficient to permit the individual to continue cognitively demanding tasks for long periods of time.

The ▶ psychostimulants enhance both noradrenergic and dopaminergic function particularly in the frontal cortex and thereby improve working memory. Such effects differ from the actions of the psychostimulants on the subcortical reward system where it is thought that the enhancement of the dopaminergic system results in dependence.

The most recent drug to be developed to improve cognitive function particularly in cases of fatigue is ▶ modafinil. This drug has been shown to improve cognitive function, verbal working memory, visual recognition and planning performance in those suffering from excessive daytime sleepiness often associated with narcolepsy and sleep apnea. Despite its proven therapeutic effects, the mode of action of modafinil is uncertain. It is nonstimulant, does not affect catecholamine function, but there is a suggestion that it modulates the orexinergic system that regulates the sleep-wake cycle.

Conclusion

Because the relationship between the chemical structure of psychotropic drugs and their pharmacological and therapeutic effects remains an enigma, the drugs have been classified according to their therapeutic uses. It is widely recognized that psychotropic drugs treat the symptoms or syndromes of specific psychiatric disorders and do not appreciably change the underlying psychopathology. As many of the symptoms of the different psychiatric disorders overlap, it is not surprising that their uses also overlap different disorders. Thus, anticonvulsants are not only used to treat the epilepsies but also bipolar disorder. The SSRI and SNRI antidepressants are widely used to treat a variety of anxiety disorders in addition to the affective disorders. Hopefully, with an ever increasing knowledge of psychogenetics and the underlying psychopathology of psychiatric disorders, a time will come when psychotropic drugs will target the underlying pathology and therefore revolutionize the psychiatric treatment.

Cross-References

▶ Acetylcholinesterase and Cognitive Enhancement
▶ Anticonvulsants
▶ Antidepressants
▶ Anti-Parkinson Drugs
▶ Antipsychotic Drugs
▶ Anxiolytics
▶ Atomoxetine
▶ Barbiturates
▶ Benzodiazepines
▶ Bipolar Disorder
▶ Caffeine
▶ Cannabinoids

- ▶ Cocaine
- ▶ Cognitive Enhancers
- ▶ Dementias: Animal Models
- ▶ Depression: Animal Models
- ▶ Generalized Anxiety Disorder
- ▶ Hallucinogens
- ▶ Hypnotics
- ▶ Lithium
- ▶ Methylenedioxymethamphetamine (MDMA)
- ▶ Methylphenidate and Related Compounds
- ▶ Modafinil
- ▶ Mood Stabilizers
- ▶ NARI Antidepressants
- ▶ Nicotine
- ▶ Nicotinic Agonists and Antagonists
- ▶ Nootropics
- ▶ Compulsive Disorders
- ▶ Opioids
- ▶ Psychostimulants
- ▶ Schizophrenia
- ▶ SNRI Antidepressants
- ▶ SSRI

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Clearance

Synonyms

CL; Excretion

Definition

Clearance is the fraction of a theoretical volume completely purified (i.e., no longer containing any of the drug concerned) per unit of time. Plasma clearance is the apparent volume of plasma purified per unit of time. Total clearance (CL t) is the fraction of the volume of distribution, V_D, which is completely purified per unit of time. The total clearance depends on the constant of elimination and thus on $t½$ and on V_D. Clearance is a constant in linear kinetics.

Cross-References

- ▶ Area Under the Curve
- ▶ Bioavailability
- ▶ Distribution Phase
- ▶ Elimination Half-Life
- ▶ First-Order Elimination
- ▶ Pharmacokinetics

Clinical Antipsychotic Trials of Intervention Effectiveness Study

Synonyms

CATIE

Definition

The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study was the largest, longest, and most comprehensive independent, three-phase, clinical trial ever conducted to examine existing pharmacotherapies for schizophrenia. The trial was funded by NIMH and intended to be "pragmatic," involving a representative sample of 1,493 schizophrenic patients from various real-life outpatient settings. The primary outcome measure was time to all-cause drug discontinuation that captured both efficacy and tolerability. Subjects in the CATIE trial were randomized in a double-blind fashion to treatment with olanzapine, quetiapine, risperidone, ziprasidone, or the mid-potency first-generation antipsychotic perphenazine for up to 18 months of treatment.

Cross-References

- ▶ First-Generation Antipsychotics
- ▶ Olanzapine
- ▶ Quetiapine
- ▶ Risperidone
- ▶ Schizophrenia
- ▶ Second and Third Generation Antipsychotics
- ▶ Ziprasidone

Clinical Depression

- ▶ Major and Minor and Mixed Anxiety-Depressive Disorders

Clinical Global Impression Scales

Synonyms
CGI

Definition
The clinical global impression (CGI) rating scales (Guy 1976) are commonly used clinician-rated measures of global symptom severity and treatment response for patients with mental disorders. Many researchers, while recognizing the validity of the scales, consider them to be subjective as they require the clinician to compare the subjects under examination to typical patients from their clinical experience.

The Clinical Global Impression – Severity scale (CGI-S) is a seven-point scale that requires the clinician to rate the severity of the patient's illness at the time of assessment, relative to the clinician's past experience with patients who have the same diagnosis. Considering total clinical experience, a patient is assessed on severity of mental illness at the time of rating.

1 = Normal, not at all ill
2 = Borderline mentally ill
3 = Mildly ill
4 = Moderately ill
5 = Markedly ill
6 = Severely ill
7 = Extremely ill

The Clinical Global Impression – Improvement scale (CGI-I) is a seven-point scale that requires the clinician to assess how much the patient's illness has improved or worsened relative to a baseline state at the beginning of the intervention.

1 = Very much improved
2 = Much improved
3 = Minimally improved
4 = No change
5 = Minimally worse
6 = Much worse
7 = Very much worse

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Guy W (ed) (1976) ECDEU assessment manual for psychopharmacology. US Department of Health, Education, and Welfare, Rockville, MD

Clinical Outcome

► Efficacy

Clobazam

Definition
Clobazam is a high-potency, medium-acting anxiolytic benzodiazepine medication used in the treatment of anxiety, panic, and phobic disorders. It has some useful anticonvulsant effects. It is not antidepressant. It is sometimes used in conjunction with antipsychotic medication in acute psychotic episodes. Unwanted effects include sedation, headaches, paradoxical excitement, confusion, cognitive and psychomotor impairment, and confusion in the elderly. Long-term use may induce dependence with withdrawal reactions. Recreational use and abuse can occur: alprazolam is a scheduled substance.

Cross-References
► Benzodiazepines

Clocapramine

Definition
Clocapramine is a first-generation (typical) antipsychotic drug that belongs to the iminodibenzyl class approved in Japan for the treatment of schizophrenia. It shows higher affinity for 5-HT_{2A}- than for D_2-receptors, but has more potent dopamine antagonist activity than carpipramine that belongs to the same class. Clocapramine can induce extrapyramidal motor side effects and insomnia, but it displays generally low toxicity.

Cross-References
► Carpipramine
► Extrapyramidal Motor Side Effects
► First-Generation Antipsychotics
► Schizophrenia

Clock-Speed Effect

Definition
Clock-speed effect refers to the immediate effect of a drug to speed up or slow down the subjective experience. In the PI procedure, a clock effect is observed by an immediate horizontal shift in the response function in peak trials following drug administration that is proportional to the estimated duration.

Cross-References
► Circadian Rhythms

Clomethiazole

Synonyms
Chlormethiazole

Definition
Clomethiazole is a sedative medication with a medium duration of action used in the symptomatic treatment of anxiety and insomnia, and in the management of alcohol withdrawal. Unwanted effects include excessive sedation, headaches, paradoxical excitement, confusion, cognitive and psychomotor impairment, and confusion in the elderly. Interaction with alcohol can be hazardous. It depresses respiration and is highly toxic in overdose. Long-term use induces dependence with severe withdrawal reactions, including fits. Recreational use and abuse can occur: it is a scheduled substance.

Cross-References
- ► Alcohol Abuse and Dependence
- ► Barbiturates
- ► Insomnias

Clomipramine

Definition
Clomipramine, the 3-chloro derivative of imipramine, is a tricyclic antidepressant with a tertiary amine chemical structure. It is a potent, but not selective, serotonin reuptake inhibitor; its primary active metabolite, desmethylclomipramine, inhibits reuptake of norepinephrine. Although originally introduced for the treatment of depression, clomipramine is now used more frequently for the treatment of obsessive–compulsive disorder. Even for this indication, it is usually employed only after nonresponse to a selective serotonin reuptake inhibitor (SSRI); while clomipramine may have slightly greater efficacy than the SSRIs, it also has a less-favorable side-effect profile. Side effects include marked sedation, cardiovascular effects, and anticholinergic effects (e.g., constipation, dry mouth, blurred vision, urinary retention). Clomipramine is dose dependently associated with a higher risk of seizures than other tricyclics; like other tricyclics, it has a high potential for lethality in overdose.

Cross-References
- ► Antidepressants
- ► Obsessive–Compulsive Disorder
- ► Selective Serotonin Reuptake Inhibitors
- ► Tricyclic Antidepressants

Clonazepam

Definition
Clonazepam is a benzodiazepine that has anxiolytic, sedative, and anticonvulsant properties; it has been used in the clinic as an anticonvulsant. It is a short-acting compound (i.e., elimination half-life 3 h) and does not have active (i.e., benzodiazepine) metabolites. Like most similar compounds, clonazepam is subject to tolerance, dependence, and abuse.

Cross-References
- ► Anticonvulsants
- ► Anxiolytics
- ► Benzodiazepines

Clorazepate

- ► Benzodiazepines

Clotiazepam

Definition
Clotiazepam is a benzodiazepine that has anxiolytic, sedative, and anticonvulsant properties. The clotiazepam molecule differs from most other benzodiazepines in that the benzene ring has been replaced by a thiophene ring. Relative to other benzodiazepines, clinical use of clotiazepam is relatively low.

Cross-References
- ► Anxiolytics
- ► Benzodiazepines

Cloxazolam

Definition
Cloxazolam is a benzodiazepine that has anxiolytic, sedative, and anticonvulsant properties. It is reported to have a long half-life (65 h) and its clinical use is low relative to other benzodiazepines.

Cross-References
- ► Anxiolytics
- ► Benzodiazepines

Clozapine

Definition

Clozapine was the first of the second generation of antipsychotic drugs. It has weak D_2 receptor antagonist activity and also blocks D_1 and D_4 receptors as well as α-adrenoceptors, 5-HT_2 receptors and muscarinic acetylcholine receptors. It is an effective anti-schizophrenia drug with little tendency to cause extrapyramidal motor disorders. Its main advantage is that it is effective in a substantial proportion of chronic schizophrenic patients who fail to respond to conventional antipsychotic medication. Its main disadvantage is its tendency to cause agranulocytosis in about 1% of patients and weekly monitoring of the white blood-cell count is mandatory. It has therefore become a third line antipsychotic.

Cross-References

► Antipsychotics
► Second generation antipsychotic
► Schizophrenia

CM

► Contingency Management
► Contingency Management in Drug Dependence

Coca Paste

► Cocaine

Cocaine

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Synonyms

Coca paste; Cocaine hydrochloride; Crack; Methyl (1R,2R,3S,5S)-3-(benzoyloxy)-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylate

Definition

Cocaine is a naturally occurring substance that is extracted from the leaves of the coca plant (*Erythroxylon coca*), which is traditionally found in South American countries such as Bolivia and Columbia. Its use by the native inhabitants was noted by the Spaniards who invaded South America, and the earliest descriptions of cocaine's effects were given by them. There was continued interest in the plant and its active substances, and cocaine was isolated from the plant in 1855 by the German chemist Fredrich Gaedcke. Its structure was elucidated and its synthesis achieved in 1898 by Richard Willstatter. Cocaine is a member of the ► psychostimulant class of drugs.

Pharmacological Properties

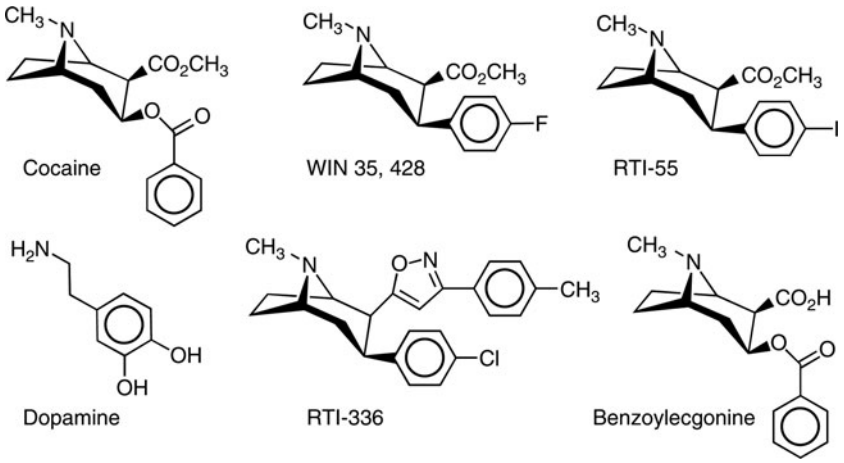
Briefly, the physiological effects of cocaine administration include increased heart rate and blood pressure, increased arousal, and a sense of well-being. Euphoria can occur with higher doses, and agitation and paranoia may occur with repeated doses. Cocaine is also a local anesthetic, and it was this property that intrigued and attracted many early investigators. Toxicities include cardiovascular problems and seizures. Users of cocaine often have a co-occurring psychiatric diagnosis such as ► depression or ► anxiety. ► Tolerance occurs with repeated use.

A serious result of chronic use of cocaine is addiction, and withdrawal from cocaine use in ► addicted individuals can result in craving, fatigue, dysphoria, depression, and sleepiness. Medications for treating cocaine abusers are in clinical trials; but till date, none has been approved for this use. Treatments are mainly behavioral, with management of various physiological symptoms as they occur.

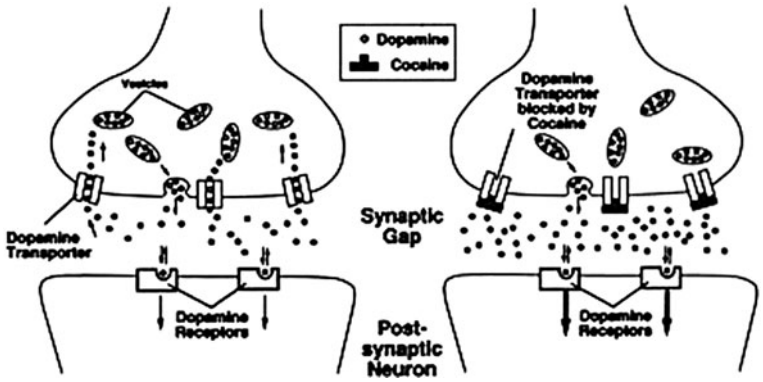
Cocaine has legitimate uses in current clinical medicine. It is used as a local anesthetic and as a powerful vasoconstrictor in the upper respiratory tract. It is swabbed onto the tissues in solutions whose concentrations vary from 1 to 10%. As shown in the chemical structure for cocaine (Fig. 1), there are two ester groups, which are susceptible to metabolism. Benzoylecgonine is produced by loss of the methyl group and is the major urinary metabolite of the drug. It is interesting and important that the ► half-life of benzoylecgonine is a few days (rather than approximately an hour for cocaine), and is therefore a more reliable indicator of recent cocaine use, and is, in fact, the target for urine test for cocaine use.

The Mechanism of Action of Cocaine in the Brain

The articles on ► neurotransmitters and ► transporters reveal that amine neurotransmitters (► dopamine, ► serotonin, and ► norepinephrine) are removed from the synapse by ► transport or reuptake into the synaptic terminal that released them (see Fig. 2). As noted in those articles, this uptake mechanism (the ► neurotransmitter transporter) is very important for turning off the signal created by the neurotransmitters interacting with



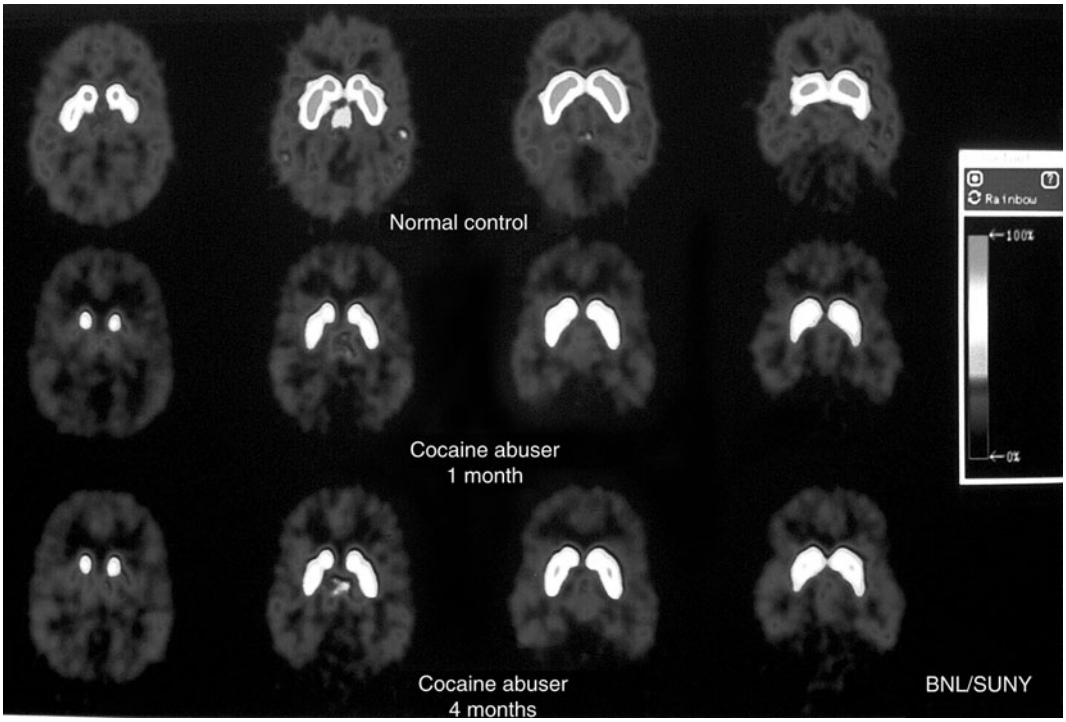
Cocaine. Fig. 1. Chemical structures of cocaine and related compounds. WIN 35,428, RTI-55, and RTI-336 are very similar to cocaine, but have somewhat different pharmacological properties. While cocaine is equipotent in inhibiting the uptake of norepinephrine, dopamine, and serotonin, WIN 35,428 and RTI 55 are more selective for the serotonin and DATs; and RTI-336 is more selective for DAT alone. Both WIN 35,428 and RTI-55, in their radiolabeled forms, are important tools for studying and imaging the DAT. RTI-336 is currently being tested as a medication for cocaine abusers. Benzoylecgonine, which lacks the methyl ester found in cocaine, is a longer half-life metabolite of cocaine and is the target of urine tests for cocaine ingestion. The figure was supplied by Dr Ivy Carroll with permission.



Cocaine. Fig. 2. The dopamine hypothesis of cocaine reinforcement. A variety of binding, behavioral, and neurochemical studies indicate that inhibition of DAT, rather than the norepinephrine or serotonin transporters, is responsible for the reinforcing (addicting) properties of cocaine. Thus, DAT is the initial molecular site of action of cocaine in regard to its addicting properties. (Reproduced from Kuhar et al. 1991.)

their receptors. Being able to turn off the signal is just as important as being able to turn it on; otherwise, there is no discrete signal, just a constant background. These transporters are the initial molecular sites of action of cocaine. The rewarding properties of the drug are due to cocaine's blockade of the ► dopamine transporter (DAT) (Kuhar et al. 1991), and not the serotonin or norepinephrine transporters.

The blockade of the transporters by cocaine results in a buildup of the neurotransmitter in the synaptic cleft and an increased signaling of the neurotransmitter at its receptors. This increased signaling is how cocaine imparts its actions. The brain has evolved hand in hand with neurotransmitters and has developed mechanisms to handle them. For example, dopamine is discretely released by action potentials at nerve terminals onto receptors, and then removed from receptors by reuptake. This occurs at a rapid time scale and, in a sense, in an orderly fashion. However, the brain is not equipped to "handle" cocaine in



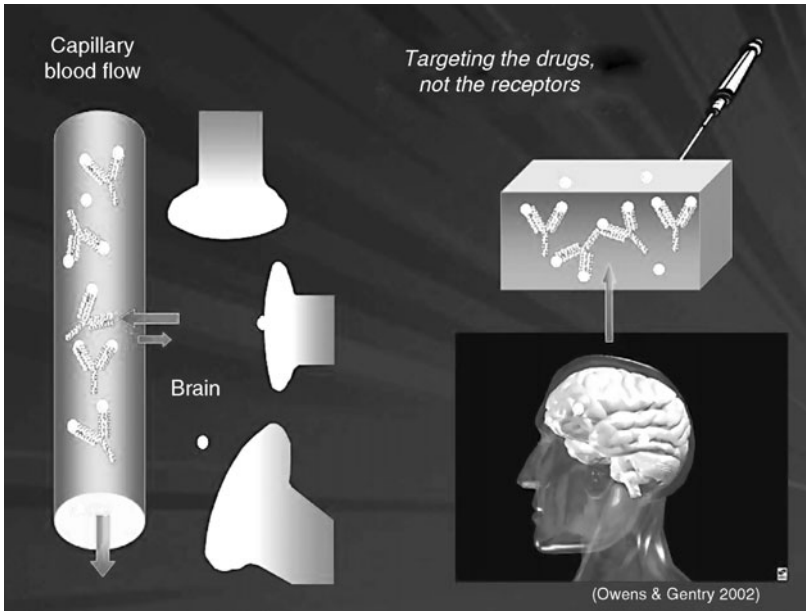
Cocaine. Fig. 3. Long-lasting changes in PET scans of dopamine receptors in cocaine-abstinent individuals. In each row, there are four "slices" of brain at different levels that show D_2 dopamine receptors in color-coded densities. The receptors are grouped together in the basal ganglia, which receives a very dense dopaminergic input. After 1 month of abstinence (middle figures), and after 4 months of abstinence (bottom figures), the receptors are increasing but are still not back to normal levels. Thus, changes in the brain are long-lasting, and likely have important implications for the duration of treatment. This figure shows changes only in D_2 receptors, but there are many additional documented changes of various types, and the challenge is to identify which of these changes are the most important. The changes in the levels of dopamine receptors imply a dysregulation of the reward/reinforcement system in chronic cocaine users. (Reproduced from Volkow et al. 1993.)

that there is no mechanism to control either its access to transporters or its removal from transporters. Thus cocaine's effects on signaling are controlled by external factors (dose, frequency of administration) and are not "normal or expected" by the brain. This must be one of the fundamental reasons why the effects of cocaine are so different and striking, and so powerful.

As noted above, cocaine also potentiates neurotransmission by serotonin and norepinephrine. Although inhibition of uptake of norepinephrine and serotonin are not mainly responsible for the rewarding properties of the drug, these actions do have effects. For example, inhibition of norepinephrine uptake contributes to the cardiovascular effects of cocaine. Inhibition of serotonin uptake has complicated effects; and serotonin, at some receptors, inhibits the rewarding effects of cocaine and dopamine. In any case, we are mainly concerned with the ▶ rewarding/reinforcing/addicting properties of cocaine which occurs by its action at the DAT.

Involvement of Specific Brain Regions

Cocaine can alter the metabolic activity (which reflects neuronal activity) of many brain regions (Everitt and Robbins 2005; Schmidt et al. 2005). When cocaine is taken the first few times, the ▶ nucleus accumbens and parts of the ▶ prefrontal cortex exhibit metabolic changes. But as more cocaine is taken repeatedly over a long time, more regions in the brain are affected as well (Porrino et al. 2007). These include the striatum, ▶ amygdala, ▶ hippocampus, and cortical areas. The progression from casual drug use to ▶ dependence is accompanied by and likely due to this enlargement of the pattern of activity in the brain. These changes in activity are accompanied by changes in proteins, and some of them are



Cocaine. Fig. 4. Antibodies can bind drugs before they enter the brain. The *right side* of the figure shows a brain capillary and brain drug receptors in close proximity. If the drug (shown by a small filled circle) cannot get out of the circulation because it is bound to an antibody ("Y" shaped structure), then the drug cannot have any effect in the brain. On the *left side* of the figure, injection of antibodies or antigens is shown schematically in a box. With permission of M Owens.

related to dopaminergic neurotransmission. This shift in activity and changes in protein levels likely have implications for treatment. Preventing or blunting the shifts, perhaps by using medications or behavioral treatments or both, could reduce or prevent dependence.

A striking finding is that the changes in brain found in cocaine addicts are long-lasting! It takes many months, perhaps more than a year, for the drug-related changes to revert to normality (Fig. 3). The persistence of these changes in brain over many months likely underlies one of the most striking features of addiction – that it is chronic and relapsing. The drive to take drugs persists over many months, and attempts to stop seeking and taking drugs often meet with failure because the duration and power of the brain changes are sometimes underestimated. This has very important implications for treatment. It seems reasonable to consider that treatments in some form should persist as long as the brain changes persist. This means that treatment in many cases will be a long-term process.

Attempts to Develop Medications for Cocaine Abusers: Small Molecules

A significant effort has been made toward developing medications for cocaine addicts (Vocci and Elkashef 2005). As of this writing (February 2009), no compound has been approved specifically for this purpose, although some existing compounds seem useful in this regard. There are different kinds of medications. When we talk of small molecule medications, we can divide them in roughly two classes – substitutes and blockers. "Substitute" medications tend to be similar to the drug itself but may also have some different or additional properties that make the medication especially helpful. Blockers simply block the action of the drug but cannot produce its effects.

Substitution therapy has worked reasonably well for opiate abuse (e.g., ▶ methadone) or ▶ nicotine abuse (nicotine patch). Hence, a major direction for medications for cocaine use is the development of substitutions. Because DAT is the target of cocaine as described above, many possible substitution medications also target this transporter. While no substitute has yet been approved, there are several possible compounds under consideration. One is RTI-336 (Fig. 1), which is more selective for DAT than cocaine. In other words, it has much less of an effect on serotonin and norepinephrine uptake than it does on dopamine uptake. It also likely enters the brain more slowly than cocaine and has a longer half-life than cocaine. If it passes clinical trials, it will be a new medication for cocaine abuse.

Other dopamine-related compounds under consideration include dopamine D_3 receptor partial agonists, and

► disulfuram, an inhibitor of dopamine beta hydroxylase. Aside from DAT inhibitors, which are basically cocaine-substitution medications, there are other neurotransmitter-targeted compounds that are very promising. Compounds that enhance ► GABA's actions, such as ► tiagabine, ► toperimate, and baclofen, have been tested and are being pursued. Compounds that have multiple actions such as dual dopamine and serotonin releasers are being studied as well. A stimulant, ► modafinil, may also be promising.

Antibodies as Therapeutic Agents

Antibody therapy for cocaine abusers is an interesting approach. Antibodies (already formed) against cocaine could be injected (passive immunization) to bind to cocaine and prevent it from entering the brain. Alternatively, specially prepared large molecules with many cocaine molecules attached to it could be used as a vaccine (active immunization). In the latter case, antibodies usually take some weeks to reach useful levels in the serum. In both cases, cocaine is bound by antibodies in the serum so that it cannot enter the brain (Fig. 4). An advantage of that approach is that we need not block the action of neurotransmitters such as dopamine in the brain. Many physiological functions depend on dopamine, and blocking dopamine as a drug abuse therapy would affect all of those physiological functions, and therefore have many side effects. But preventing cocaine from entering the brain with an antibody avoids those problems. This approach has been proven in animal studies where the behavioral effects of cocaine are reduced by the injection of antibodies (Orson et al. 2008).

The utilization of catalytic antibodies is possible in passive immunization procedures. Catalytic antibodies are those that can metabolize and break down cocaine rather than simply bind the cocaine molecule. This is obviously desirable and some progress has been made in this area as well.

This is an experimental approach and no vaccine or antibody preparation has been approved for use in humans yet. However, progress in clinical trials is being made by several companies. But there are still some issues that need to be addressed (Orson et al. 2008). A major issue is being able to induce higher more effective levels of antibodies more reliably.

Cross-References

► Addictive Disorder: Animal Models
► Cocaine Dependence
► Psychomotor Stimulants
► Psychostimulant Addiction
► Vaccines

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Cocaine Abuse

► Cocaine Dependence

Cocaine Addiction

► Cocaine Dependence

Cocaine Dependence

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Synonyms

Cocaine abuse; Cocaine addiction; Cocaine hydrochloride abuse; Cocaine hydrochloride addiction

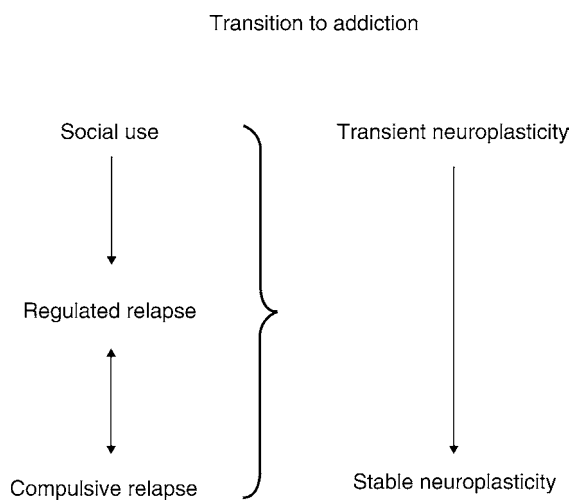
Definition

Cocaine dependence can be characterized as an increasingly difficult urge to resist cocaine whenever it is available. When problematic use is accompanied by tolerance, ► withdrawal, and an increase in the compulsion, or near-compulsion, to seek out and use cocaine, a diagnosis of cocaine dependence should be considered.

This is in contrast to cocaine abuse, where administration is less intense and frequent (American Psychiatric Association 2000).

Pharmacological Properties

According to the 2007 results from the National Survey on Drug Use and Health, 1.6 million Americans abused or were dependent on cocaine during the previous year, underscoring the need for treatment of cocaine dependence. The hallmark of cocaine dependence, and perhaps its most problematic aspect, is the propensity to ► relapse. Cocaine dependent individuals undergo treatment and abstinence from drug use and yet still face considerable desire to consume the drug (craving) and there are high rates of return to drug use (relapse). Clearly, the brains of such individuals have been altered by the repeated drug use such that the individuals have diminished control over their behavior. In addition, drug-seeking will take priority over the pursuit of natural rewards, i.e., reduced drive to obtain natural rewards. The transition from cocaine use to cocaine dependence takes place in different stages. The initial stage is characterized by repetitive, social use of the drug and changes in neural chemistry are largely due to the pharmacological action of the drug itself (Fig. 1). The second stage is defined by persistent changes in the brain circuits that regulate cognitive and emotional responses to environmental stimuli.



Cocaine Dependence. Fig. 1. The transition from cocaine use to cocaine dependence and the relationship with neuroplasticity. Social use can lead to regulated relapse, which can progress into compulsive relapse. This is typified by stable cocaine-induced neuroplasticity and the individual has "learned" to become addicted.

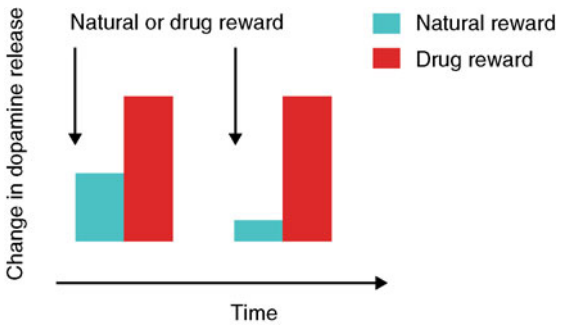
This is accompanied by regulated relapse where the individual consciously decides to relapse. It is therefore a declarative decision-making process to engage in cocaine-taking behavior. Eventually, regulated relapse can progress into compulsive relapse which is a procedural decision-making process and the individual relapses with relatively less consideration of environmental contingencies. Compulsive relapse can be triggered by environmental cues or stressors that were previously associated with drug use (Kalivas and O'Brien 2008). At this stage the cocaine-dependent brain exhibits stable cocaine-induced ► neuroplasticity and the individual has "learned" to become addicted. Accordingly, over the past two decades, a shift has occurred, in which drug addiction is now viewed as a disorder of learning and memory and motivation (Hyman 2005).

Cocaine can be insufflated (intranasal), inhaled (smoked, "freebased," "crack"), or injected. Smoked (freebase, crack) cocaine is derived from cocaine hydrochloride (HCl) using ammonia or sodium bicarbonate. This converts cocaine HCl into freebase cocaine, since most of the HCl form is destroyed by heat. Users report a greater "high" for smoked cocaine versus intranasal cocaine and a faster subjective "peak" versus intravenous and intranasal cocaine. Both the "high" and "feel of drug" peak faster for smoked (1–2 min) compared to intravenous (3–4 min) and intranasal cocaine (10–15 min). By contrast, intravenous cocaine provides the highest blood levels, but it has been suggested that smoked cocaine reaches sooner in the brain. The user initially experiences a euphoric state which is soon followed by cocaine-induced dysphoria. This dysphoric feeling contributes to the repeated use of cocaine, since the user wants to re-experience the initial euphoric rewarding state. Even though cocaine withdrawal lacks overt physical manifestations compared to some other drugs of abuse, the user is subjected to severe psychological withdrawal symptoms. Cocaine dependence often shares comorbidity with other psychiatric disorders (Vocci and Ling 2005). The self-medication hypothesis has been proposed as a possible explanation for cocaine dependence and depression comorbidity, but it does not explain the majority of cocaine dependence.

Different routes of administration are associated with specific side effects. For instance, intranasal cocaine administration could lead to septal necrosis and palatal perforation. Smoking freebase cocaine volatizes the drug and exposes the lungs directly to the smoked mixture, thereby increasing the risk of adverse pulmonary effects and complications. These include interstitial pneumonitis, fibrosis, pulmonary hypertension, alveolar hemorrhage, asthma exacerbation, barotrauma, thermal

airway injury, hilar lymphadenopathies, and bullous emphysema either directly due to the drug itself or associated cutting substances such as talc, silica, and lactose. Intravenous cocaine administration could lead to HIV, hepatitis, and systemic infections such as abscesses and bacteremia due to needle sharing and lack of sterile injection techniques.

After acute administration, there is an increase in dopaminergic neurotransmission in the mesolimbic ▶ dopamine pathway of the ventral tegmental area (VTA) and the ▶ nucleus accumbens (NAc), which is followed by the release of dopamine in the NAc, a reward-related brain structure. In addition, cocaine also inhibits the ▶ dopamine transporter (DAT), by blocking reuptake and thereby increasing extracellular dopamine. The VTA–NAc pathway also mediates the effects of natural rewards such as food and sex. Chronic cocaine use leads to an impaired dopamine system and the baseline levels of dopamine are reduced. Over time, repeated cocaine administration will lead to a sensitized dopaminergic response to the drug or to drug-associated cues from the VTA–NAc, while natural rewards will become less effective in increasing dopaminergic transmission (Koob and Le Moal 2008). In addition, the amplitude and duration of the dopamine release is greater after cocaine administration compared to natural rewards (Fig. 2). Furthermore, there is an increase in dopaminergic neurotransmission from the VTA to the ▶ prefrontal cortex (PFC) and basolateral ▶ amygdala (BLA). At a molecular level, D_1 and D_2 receptors exert opposite effects: D_2 receptors respond to numerous environmental stimuli while D_1 receptors only respond to the strongest stimuli. Chronic cocaine administration promotes a shift toward a D_1-like state. This is accomplished in part through an induction of AGS3 (activator of G protein signaling-3), a protein which is a negative regulator of Gi and therefore of D_2 signaling.



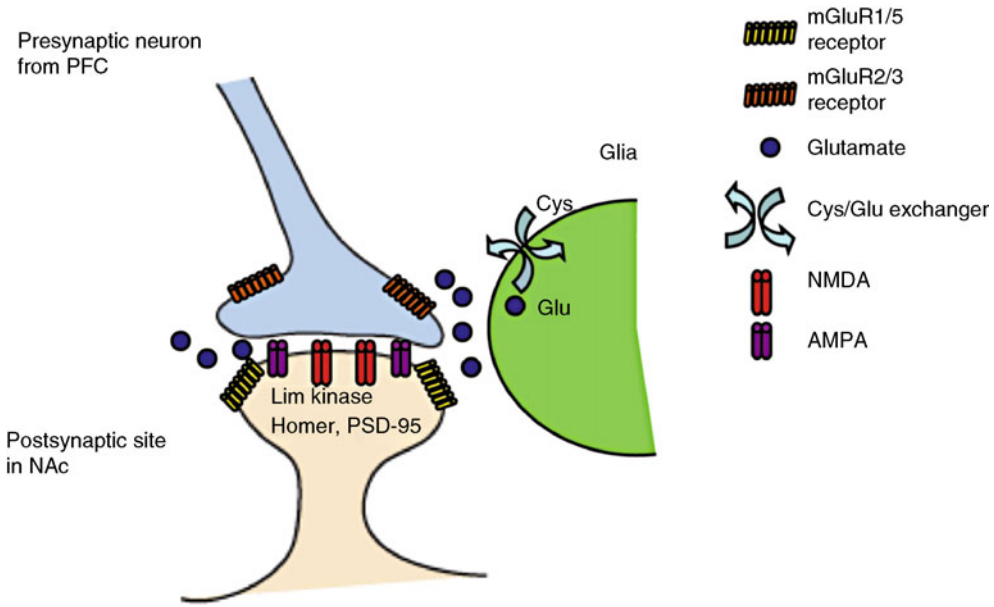
Cocaine Dependence. Fig. 2. Hypothetical histogram illustrating the changes in dopamine release to biological and cocaine reward. Repeated cocaine administration will lead to a sensitized dopaminergic response to the drug or to drug-associated cues, while natural rewards will become less effective in increasing dopaminergic transmission. Furthermore, the amplitude and duration of the dopamine release is greater after cocaine administration compared to natural rewards.

In addition to having effects on the dopaminergic system, chronic cocaine use also causes reduced basal activity in the glutamatergic pathway from several areas of the PFC to the NAc. These areas include the anterior cingulate and orbitofrontal cortices and contribute to executive functions, such as working memory, attention, and behavioral inhibition. The PFC–NAc pathway also mediates the impulsivity and compulsivity to engage in drug taking. Cortical neurons show a decrease in basal glutamatergic neurotransmission, while being hypersensitive to cocaine and cocaine-associated cues. The increase in glutamatergic neurotransmission from the PFC to the NAc corresponds to the increase in dopaminergic neurotransmission from the VTA to the PFC, BLA, and NAc. Human neuroimaging data have confirmed that there is a general reduction in cortical cellular metabolism and blood flow (Goldstein and Volkow 2002). Given the importance of the anterior cingulate cortex in regulating biologically motivated behaviors, and activation of the ventral orbital cortex, this hypofrontality has been characterized as a strong indicator of the reduced ability of addicts to regulate drug-seeking. Presentation of a cue previously associated with cocaine use activates the PFC, including the anterior cingulate and ventral orbital cortices. This activity is positively correlated with the intensity of the cue-induced desire for the drug and is larger than the activation of the PFC in control subjects after presentation of natural reward-related cues. By contrast, presentation of the same natural reward-related cues to cocaine addicts results in reduced PFC activity compared to controls. This is in accordance with the dogma that addicts show an impaired response to natural rewards.

On a cellular level, dysregulation of glutamatergic neurotransmission due to downregulation of the cystine–glutamate exchanger (system xc-) and presynaptic ▶ metabotropic glutamate receptors (mGluR's) has been established in preclinical models of cocaine dependence. Cells use cystine to synthesize the intracellular antioxidant glutathione by exchanging the uptake of one cystine for the release of one molecule of intracellular ▶ glutamate into the extracellular space. The nonsynaptic glutamate in the extracellular space stimulates inhibitory presynaptic

mGluR's and decreases synaptic glutamate release. Therefore, downregulation of xc- will lead to less extrasynaptic glutamate, a reduction in inhibitory tone and ultimately in enhanced synaptic glutamate release probability upon cocaine administration (Fig. 3). These presynaptic effects lead to long-term postsynaptic adaptations. Changes in dendritic spine density and morphology have been well established, which could be a result of an underlying increase in actin cycling. A reduction in Lim kinase which regulates F-actin depolymerization and spine maturation may contribute to the cocaine-induced increase in actin cycling. In addition, there is a decrease in Homer 1b/c and 2a/b scaffold proteins in the NA, which colocalizes with F-actin/Shank/PSD-95/GKAP/NMDA complexes. Additional postsynaptic effects include the membrane insertion of AMPA glutamate receptors and an inability to induce long-term depression (LTD). Controversy remains, since the inability to induce LTD is normally associated with a decrease in AMPA receptors.

As mentioned earlier the emerging view that cocaine dependence is a learning and memory disorder could lead to pharmacotherapy development related to reverting compulsive relapse to regulated relapse. These include normalizing glutamatergic neurotransmission either by altering glutamate levels in the PFC or glutamate receptor activity in the striatum. For example, ► N-acetylcysteine which is a cysteine pro-drug used in treating acetaminophen overdose, has been examined for its potential in affecting relapse, as it appears to increase cystine–glutamate exchange activity and thereby restore inhibitory tone on presynaptic metabotropic glutamate receptors. In fact, recent clinical trials have supported a role for *N*-acetylcysteine in the treatment of drug addiction. In 23 treatment-seeking cocaine-dependent patients, doses of 1,200, 2,400, or 3,600 mg/day were well tolerated. The majority of subjects either stopped using cocaine or significantly reduced their use of cocaine during treatment. Furthermore, in a crossover, double-blind, placebo-controlled inpatient trial, 15 cocaine-dependent participants received four doses of 600 mg *N*-acetylcysteine or placebo. After the final dose, participants completed a cue-reactivity procedure that involved presentations of four categories of slides (cocaine, neutral, pleasant, and unpleasant). Each participant rated how



Cocaine Dependence. Fig. 3. Molecular changes associated with glutamate synapses after chronic cocaine use. In a drug-naïve state, extrasynaptic glutamate provides inhibitory tone via the mGluR's on the presynaptic inputs from the PFC, thus preventing an increase in glutamate levels when cocaine is administered. Chronic cocaine use leads to the downregulation of system xc- and therefore less extrasynaptic glutamate. This decrease in glutamate results in a reduction in inhibitory tone (from the presynaptic mGluR's) and ultimately in enhanced synaptic glutamate release probability upon cocaine administration. In addition, there is a reduction in Lim kinase, Homer 1b/c and 2a/b scaffold proteins in the NA, which colocalizes with F-actin/Shank/PSD-95/GKAP/NMDA complexes and AMPA receptors are inserted into the membrane.

much craving, desire to use cocaine, and interest was evoked by each slide on a 21-point Likert scale. *N*-acetylcysteine significantly reduced the desire to use cocaine, interest in cocaine, and cue viewing time in these patients. Other potential new treatment strategies based on regulating glutamate transmission include the modulation of mGluR's. These include the mGluR2/3 agonist LY379268 ((−)-2-oxa-4-aminobicyclo[3.1.0]hexane-4,6-dicarboxylic acid), which is effective in inhibiting cocaine seeking in preclinical animal models and could decrease stress-induced relapse due to its anxiolytic effects. Similarly, the mGluR1/5 antagonists, 2-methyl-6-(phenylethynyl) pyridine (MPEP) and its analog 3-[(2-methyl-4-thiazolyl)ethynyl]pyridine (MTEP) have shown to be effective in preclinical models of cocaine addiction.

Cross-References

- ► Cocaine
- ► Contingency Management in Drug Dependence
- ► Excitatory Amino Acids and Their Antagonists
- ► Psychomotor Stimulant Abuse
- ► Reinstatement of Drug Self-Administration
- ► Self-Administration of Drugs
- ► Sensitization to Drugs
- ► Withdrawal Syndromes

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Cocaine Hydrochloride

► Cocaine

Cocaine Hydrochloride Abuse

► Cocaine Dependence

Cocaine Hydrochloride Addiction

► Cocaine Dependence

Codeine

Synonyms

Methylmorphine

Definition

Codeine is an opiate used for its analgesic, antitussive, and antidiarrheal properties. It is an alkaloid, derived from opium, an O-methylated derivative of morphine that is not directly active on the μ-opioid receptors. It is a prodrug that is metabolized to morphine and codeine-6-glucuronide when taken orally. Like most ► opioids, it is a drug of abuse and its continued use induces ► physical dependence and addiction. It is found in some cough syrups that are subject to abuse.

Cross-References

- ► Morphine

Coffee Nerves

► Caffeinism

Cognition

Definition

The mental ability to process information involving memory, learning, and attention.

Cognitive Behavioral Therapy

Synonyms

CBT; ERP; Exposure and response prevention

Definition

A therapeutic technique designed for the treatment of anxiety disorders, especially obsessive–compulsive disorder. The therapeutic effect is achieved when the patient

is able to confront his/her fear (e.g., the anxiety caused by the obsession) without performing the escape response (e.g., the compulsion). Therapists traditionally used well-thought out exposure situations in controlled environment to provoke the obsessions and engage in a contract with the patient not to perform the anxiety-relieving compulsion. The initial anxiety of the obsession typically attenuates with success exposures if the compulsion is not performed.

Cognitive Control

► Executive Functions

Cognitive Deficit

► Cognitive Impairment

Cognitive Enhancers: Neuroscience and Society

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Synonyms

Smart drugs

Definition

Pharmacological substances that induce improvement of various facets of cognition, such as attention and memory, are known as pharmacological cognitive enhancers (PCEs). Many pharmacological interventions are aimed at improving cognition in specific neuropsychiatric disorders where cognitive impairment is a prominent symptom, such as attention-deficit hyperactivity disorder (► ADHD), ► schizophrenia, mild cognitive impairment (MCI), and ► Alzheimer's disease (AD). Enhanced cognition would, in turn, lead to improved functional outcome and quality of life. Pharmacological enhancement of cognition is increasingly being considered in both the young and old healthy populations and seems set to become even more popular, extending from dietary supplements and caffeine to drugs specifically targeted at improving cognition.

Current Concepts and State of Knowledge

Cognitive enhancing drugs, also known as smart drugs, are needed to treat cognitive disabilities and improve the functional outcome, wellbeing, and quality of life for patients with neuropsychiatric disorders and brain injury (Sahakian and Morein-Zamir 2007). Cognitive enhancing drugs are used in treating cognitive impairment in disorders such as AD, schizophrenia, and ADHD. In neurodegenerative diseases, such as AD, cognitive enhancing drugs are used to slow down or compensate for the decline in cognitive and behavioral functioning that characterizes such disorders. There are currently 700,000 people with dementia in the United Kingdom, most of whom have AD. Each year, 39,400 new cases are diagnosed in England and Wales, translating to a new case every 14 min. Current costs of long-term care for dementia in the United Kingdom are estimated at £4.6 billion, and with an increasing aging population, this estimate is expected to rise to £10.9 billion by the year 2031. Likewise, the number of people placed in institutions is expected to rise from 224,000 in 1998 to 365,000 in 2031. Cognitive enhancing drugs are important in this context as it has been suggested that a treatment that would reduce severe cognitive impairment in older people by just 1% a year, would cancel out all estimated increases in the long-term-care costs due to the aging population in the United Kingdom.

Cognitive enhancers may be beneficial not only in neurodegenerative disorders but also in neuropsychiatric disorders for which they are not yet routinely prescribed. For instance, though it is common knowledge that people with schizophrenia typically suffer from hallucinations and delusions, it is the long-term cognitive impairments that often impede everyday function and quality of life for many patients. Twenty-four million people world wide suffer from schizophrenia. In the United States, direct and indirect costs were estimated at over $60 billion in the year 2000. It has been suggested that even small improvements in cognitive functions could help patients make the transition to independent living.

It is noteworthy that not only adults suffering from neuropsychiatric disorders can benefit from cognitive enhancing drugs. ADHD affects 3–7% of all children worldwide, and is the most prevalent neuropsychiatric disorder of childhood. ADHD is a highly heritable and disabling condition characterized by core cognitive and behavioral symptoms of impulsivity, hyperactivity, and/or

inattention. It has important implications for education provision, long-term social outcomes, and economic impact. For example, long-term studies indicate that it is associated with poorer long-term outcomes, including increased educational dropout, job dismissal, criminal activities, substance abuse, other mental illness, and increased accident rates. The annual excess cost of ADHD in the United States in 2000 was estimated to be $42.5 billion.

Importantly, in addition to pharmacological cognitive enhancers (PCEs), there are many other methods of enhancement such as education, physical exercise, and neurocognitive activation or cognitive training that are commonly being used (Beddington et al. 2008). However, with the popularization of the notion of cognitive enhancement, pharmacological interventions are being seen as a means not only to improve existing deficits, but also to prevent decline before its onset, and even to enhance normal functioning.

The effects of pharmacological substances on cognition are complex, as cognition is a multifaceted, construct-encompassing attention, executive function, and spatial and verbal learning and memory. Most cognitive enhancing drugs improve only specific aspects of cognition such as forms of executive functions or memory, which are mediated by different systems in the brain. The sizes of the effects to date range from small to moderate, but as pointed out by a recent report by the U.K. Academy of Medical Sciences, even small percentage increments in performance can lead to significant improvements. While the extension of enhancement from the controlled laboratory environment to daily life is controversial, several factors are contributing to the advent of increasingly effective approaches. These include the development of sophisticated neuropsychological tests and the routine inclusion of multiple, converging behavioral and brain-imaging measures. With the development of human pharmacogenetics, uncovering human genetic ► polymorphisms relating to cognition, cognitive enhancers may be matched to those that might benefit from them the most while reducing side effects. For example, the catecholamine-O-methyltrasferase (COMT) gene has been linked to the degree of effectiveness of COMT inhibitors and to the ► working-memory performance, such that the Val158Met polymorphism may also modify the effect of dopaminergic drugs (e.g., the COMT enzyme inhibitor ► tolcapone) in the prefrontal cortex.

Despite the fact that much research has been dedicated to the development and understanding of various cognitive enhancers, we still have limited knowledge of how specific cognitive functions are modulated by neurotransmitters. For example, while we know that ► methylphenidate improves symptoms of ADHD and also improves performance on objective behavioral tasks, such as spatial working memory and stop signal, we are yet to determine conclusively whether dopamine, noradrenaline, or both neurotransmitters are required for these effects on cognition. Some of the most notable PCEs being explored to assist individuals with neurological or neuropsychiatric disorders with executive function and attention difficulties include methylphenidate, ► atomoxetine and ► modafinil. Methylphenidate, also commonly known as Ritalin, increases the synaptic concentration of dopamine and noradrenaline by blocking their reuptake. Atomoxetine on the other hand, is a relatively selective noradrenaline reuptake inhibitor (SNRI). In the case of modafinil, despite considerable research, its precise mechanism of action is unclear, though it has been found to exhibit a multitude of effects including potentiation of noradrenaline and to a degree, dopamine neurotransmission; and elevation of extracellular glutamate, serotonin and histamine levels, and decreased extracellular GABA. Recent evidence suggests that some of its cognitive effects may be modulated primarily by noradrenaline transporter inhibition.

There are many additional considerations in examining the cognitive enhancing effects of various pharmacological agents. Neurotransmitter functions, at times, following an inverted U-shaped curve, with deviations from optimal level in either direction impairing performance. Moreover, different neurotransmitter levels can be found across brain regions, suggesting a complex interplay between baseline levels and drug administration. While some cognitive functions may improve following drug administration, others may worsen, as they depend on different optimum neurotransmitter levels. Drug-induced neurotransmitter increases may improve functioning in some groups but have no effect or even impair performance in others, already at optimum. Namely, the baseline abilities of the individual can limit the effectiveness of certain PCEs, and their effect will be more pronounced in those with an initial below-average level of performance.

An effective method of testing the effects of cognitive enhancers on cognition is by using double–blind placebo control studies where participants undergo a battery of objective cognitive tasks targeted at measuring various facets of cognition, including memory, attention, and executive functions. For instance, in the ► CANTAB Spatial Working Memory (SWM) task, a number of colored boxes are shown on the screen. The aim of this task is that, by touching the boxes and using a process of elimination, the subject should find one blue "token" in each of a

number of boxes. The number of boxes is gradually increased, until it is necessary to search a total of eight boxes. SWM is a test of the subject's ability to retain spatial information and to manipulate remembered items in working memory. It is a self-ordered task, which also assesses heuristic strategy. This test is sensitive to frontal lobe and "executive" dysfunction and is impaired in childhood and adulthood ADHD.

It has been demonstrated that methylphenidate improves SWM task performance in young volunteers and in children and adult patients with ADHD, whereby patients make less task-related errors when on methylphenidate. The neural substrates mediating SWM task performance have been examined using imaging techniques such as positron emission topography (► PET) and indicate that the dorsolateral- and mid-ventrolateral prefrontal cortex are particularly recruited. Studies using PET and contrasting [(11)C] raclopride binding on methylphenidate versus placebo have further indicated that methylphenidate influences dopaminergic function, particularly in the striatum. Methylphenidate has been found to improve both performance and efficiency in the spatial working memory neural network involving the dorsolateral prefrontal cortex and posterior parietal cortex in healthy volunteers. Similar studies using the double-blind, randomized, placebo-controlled methodology have reported that additional drugs such as modafinil and atomoxetine can improve performance in some tasks of executive functioning. Thus, modafinil has been found to improve spatial planning and response inhibition in ADHD patients, as measured by a variant of the Tower of London task and the stop-signal task, respectively. It has been further demonstrated that modafinil produces improvements in performance in a group of healthy volunteers on tests of spatial planning, response inhibition, visual recognition, and short-term memory. Likewise, administration of an acute dose of atomoxetine has been found not only to improve response inhibition in ADHD patients, but also in healthy adults. Using functional magnetic resonance imaging (► fMRI), the brain mechanisms by which atomoxetine exerts its effects in healthy volunteers has been examined in a double-blind placebo-controlled study. Atomoxetine led to increased activation in the right inferior frontal gyrus when participants attempted to inhibit their responses in the stop-signal task. Inhibitory motor control has been shown previously to depend, at least in part, on the function of this brain region.

There is a clear trend in many Western countries toward increasing prescriptions of methylphenidate. With the advent of psychiatric medications with greater tolerability and fewer side effects, these trends are set to continue. However, it is not only those who suffer from neuropsychiatric disorders and brain injury who are appearing to use pharmacological cognitive enhancers (Sahakian and Morein-Zamir in press); but the use of stimulants, including methylphenidate and ► amphetamines by students has been rising as well. Trends suggest that between 1993 and 2001 there was a clear increase in the life-time and 12-month prevalence rates of nonmedical use of prescription drugs in college students. In the United States, studies indicate that up to 16% of students on some college campuses use stimulants, while 8% of university undergraduates report having illegally used prescription stimulants. Surveys on students indicate that most illicit use of prescription stimulants reported in the past year involve amphetamine–dextroamphetamine combination agent, with higher use among Caucasians and Hispanics when compared with African-Americans and Asians and considerable variations between colleges. The most commonly reported motives for use were to aid concentration, help study, and increase alertness. There is also a trend for increasingly younger students to use such drugs with one report indicating 2.5% of eighth grades (13–14 years), abused methylphenidate; as did 3.4% tenth graders and 5.1% twelfth graders. The trends are also not reserved for North America alone, as prescriptions rates in England of stimulants have been rising steadily from 220,000 in 1998 to 418,300 in 2004. Although drugs such as modafinil are prescribed off-label in North America, they can be freely obtained without a prescription via the internet from multiple websites in various countries. In fact, a recent survey identified 159 sites offering drugs for sale, of which only 2 were regulated and 85% not requiring a physician's prescription from the patient. Another cognitive domain of great interest is memory.

These trends of growing use are likely set to increase as presently there are also novel cognitive enhancers under development, many of which are aimed at improving memory and learning. Given the aging population in the United Kingdom and elsewhere, and the fact that the lifespan of individuals is being extended, it is highly likely that cognitive enhancing drugs that can improve memory in healthy elderly will prove to be in demand.

For example, ► Ampakines, which work by enhancing the AMPA receptor's response to glutamate, improve cognition in healthy aged volunteers. Novel compounds such as nicotinic alpha-7 receptor agonists are now in Phase 2 of clinical trials in AD and schizophrenia (e.g., MEM 3454, Memory Pharmaceuticals/Roche).

The popular media has reported extensively both on studies finding improved performance in healthy individuals and on the rising use of PCEs in healthy individuals

(see also Maher 2008). For example, the results from the authors' laboratory on modafinil were reported in the media, including newspapers, magazines, and radio. Publications ranging from *The Guardian newspaper* (London) to *The New Yorker* and *Nature*, as well as the BBC, have discussed their potential for wide-spread use. Maintaining an optimum level of alertness, arousal, and attention might be expected to prove valuable in a range of work and leisure activities. Indeed, the use of PCEs is not restricted to academic use, and American sprinter Kelli White received a two-year ban in 2004 for using modafinil when competing in the world championships and other US national events.

The study of cognitive enhancing drugs, and their influence both on patients with neuropsychiatric and neurological disorders and healthy adults, raises numerous neuroethical issues. In the area of ▶ neuroethics, there are several important considerations in regard to the use of cognitive enhancing drugs, particularly in children and adolescents where the brain is still in development (Marcus 2002). For example, certain drugs such as the stimulants have abuse potential and we do not even know what side effects may emerge with long-term use in healthy people. There are also many other issues, including possible direct and indirect coercion and greater societal disparity, which will impact on the individual and on society.

As pharmacological cognitive enhancement appears set to become increasingly widespread, the profile of cognitive effects of each drug on specific populations should be mapped, along with its potential for harms. This will facilitate ethical and regulatory discussion about each pharmacological substance. At present, regulatory bodies (e.g., FDA, MHRA, EMEA) are concerned with treatments for disorders or diseases, but this may change in future with the increasing use of cognitive enhancing drugs by healthy people (Greely et al. 2008). The development of tailored, cognitive enhancing treatments for a wide range of neuropsychiatric disorders, as well as for normal function, holds much future promise. As ▶ pharmacogenomics and individualized medicine continues to develop, cognitive enhancing drugs may prove of great benefit to society in terms of improving wellbeing and quality of life for people with neuropsychiatric disorders, brain injury, and age-related memory impairment.

Cross-References

▶ ADHD
▶ Alzheimer's Disease
▶ Atomoxetine
▶ Methylphenidate
▶ Modafinil
▶ MRI
▶ Neuroethics
▶ PET
▶ Pharmacogenomics
▶ Schizophrenia
▶ Working Memory

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Cognitive Enhancers: Role of the Glutamate System

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Synonyms

Nootropics

Definition

Cognitive enhancers are drugs that are used to treat problems of memory, attention and inhibitory control.

Pharmacological Properties

Cognitive problems exist in a variety of psychiatric and neurological disorders. Current nootropics, the ▶ acetylcholinesterase inhibitors, are used primarily to treat

► Alzheimer's disease. These drugs have limited efficacy and cannot be used ubiquitously across all disorders where cognitive enhancement might be beneficial (for example, they are inappropriate for the use in patients with ► Parkinson's disease as they can aggravate the motor disability). Therefore, the future development of a range of drugs with different mechanisms of action is likely to occur.

Ionotrophic Glutamate Receptors

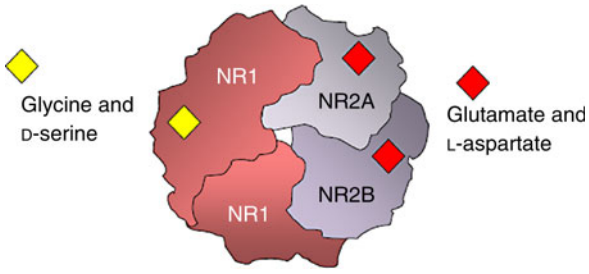
Ionotrophic ► glutamate receptors as a target for cognition enhancement have been of interest since the 1980s following the discovery of their involvement in ► Long-term potentiation (LTP; a persistent strengthening of synapses). This form of synaptic plasticity requires the activation of *N*-methyl-D-aspartate (NMDA)-receptors for its induction. Alpha-amino-3-hydroxy-5-methyl-4-isoxazoleproprionate (AMPA)-receptors can also promote the induction of LTP, and they play an important role in the expression of the potentiated response (Cooke and Bliss 2005). It has been presumed that LTP underlies some forms of learning and memory for two reasons. First, because the induction of LTP at any particular synapse requires coincident activity, it fulfils the criterion for a Hebb Synapse, predicted in 1949 to be necessary for the formation of associations. Second, compounds that act as antagonists at NMDA-receptors both impair the induction of LTP and produce clear cognitive deficits in animals and humans (see Robbins and Murphy 2006). Not surprisingly then, the enhancement of cognition with ligands that positively modulate NMDA- and AMPA-receptors has been a goal for some time. While it is not possible to use agonists that act by stimulating these receptors via the glutamate binding site, due to the risk of causing neurodegeneration or inducing seizures, in recent years, ligands that act through other binding sites to modulate receptor activity and which have pro-cognitive effects have emerged.

Drugs Acting at NMDA Receptors

► NMDA-receptors are comprised of four protein subunits clustered around an ion channel. The channel is normally occupied by magnesium, but when the neuronal membrane is sufficiently depolarised, magnesium dissociates and calcium influx into the cell is permitted. Each heteromeric NMDA-receptor is believed to consist of two protein NR1 subunits plus two NR2 subunits. There are four variants of the NR2 subunit, denoted A,B,C, and D. While glutamate itself binds to sites on the NR2 subunits, there are a number of other binding sites located at different parts of the receptor, including those for the endogenous "co-agonists," glycine and D-serine which bind to the NR1 subunits, at $Glycine_B$ sites (see Fig. 1). Although glutamate and $Glycine_B$ sites are located on different subunits of the NMDA-receptor, both glycine and D-serine can enhance the action of glutamate. In turn, the effectiveness of glycine and D-serine at $Glycine_B$ sites is determined by the variant of NR2 subunit(s) present in the receptor (Millan 2005). In terms of putative nootropics acting at NMDA-receptors, compounds acting on receptors containing NR1 plus NR2A/NR2B subunits are of interest, as these subunits are distributed in brain areas such as the ► hippocampus and the frontal cortex. Ideas about enhancement of cognition via these particular NMDA-receptors have also been encouraged by the seminal publication of Tang et al. (1999), indicating that mice that are genetically engineered to over express receptors containing NR2B subunits showed superior performance in several tests of learning and memory. Although the $Glycine_B$ site was once thought to be saturated by its endogenous ligands, it is now recognized that it is, which opens up the possibility that this site might be targeted by drugs to produce procognitive actions via the NMDA-receptor.

Agonists at the $Glycine_B$ Site

Agonists acting directly at the $Glycine_B$ site of the NMDA-receptor include the amino acids glycine, D-serine, and the synthetic ► partial agonist D-cycloserine. In preclinical studies, the full agonists such as glycine and D-serine have been investigated as cognition enhancers. Large doses are required for efficacy, but they do reverse deficits in ► novel object recognition tests and the impairment seen in a developmental model of sensorimotor gating deficits. Human studies have also investigated the effects of full agonists such as glycine, D-serine, and D-alanine. In healthy humans, many studies report that glycine is ineffective in a variety of tests and that high doses may



Cognitive Enhancers: Role of the Glutamate System.
Fig. 1. Schematic diagram of subunits of the NMDA-receptor showing binding sites for glutamate and the co-agonists glycine and D-serine.

even impair some aspects of cognition. One study employing a very low dose, however, has reported retrieval improvements in a test of word recall. The effects of the full agonists have also been investigated in ► schizophrenia where they appear to produce some improvement in negative symptoms. Their cognitive benefits appear less clear though.

The effects of the partial agonist D-cycloserine have been more studied than those of the full agonists. Preclinical experiments in rats have shown that it can enhance ► spatial memory, such as that measured in radial and water mazes, in addition to visuospatial memory and visual recognition in primates. Reversal of decrements in cognition can also be seen in ageing animals. In rats, some elegant studies by Davies and colleagues have demonstrated the ability of D-cycloserine to facilitate fear extinction. Fear extinction refers to the process of reducing a response to a cue previously paired with a fear-evoking event, by exposure to the cue in the absence of the associated event. This is the basis of exposure therapy, where a patient is repeatedly exposed to a feared object or situation, with support and without any adverse consequences. Importantly, extinction of the fear response occurs through new learning which inhibits the original fear, rather than by simple forgetting. As with some other forms of learning, extinction is a process that can be prevented by antagonists acting at NMDA-receptors. Davis and colleagues therefore predicted that ligands that positively modulate the NMDA-receptor should facilitate fear extinction and in preclinical studies they went on to show that D-cycloserine could do exactly that. These and later studies led to clinical trials of D-cycloserine in humans as an adjunct to improve exposure therapy for acrophobia (fear of heights). During these trials that were carried out in a virtual reality environment, patients were given D-cycloserine (or placebo) before two therapy sessions and retested 1 week and 3 months later. At the retests, patients who had received D-cycloserine during therapy sessions, showed enhanced fear reduction in the virtual reality environment (Davis et al. 2006). Therefore, by potentiating the action of glutamate through the $Glycine_B$-site, extinction learning can be accelerated in both animals and humans.

In other studies, D-cycloserine has been found to improve different aspects of learning, memory and also performance in tests of cognitive flexibility in both healthy humans and in patients with schizophrenia or Alzheimer's disease. As in the fear extinction studies, these procognitive actions of D-cycloserine have invariably been seen at small doses only, perhaps because its efficacy as an agonist may be lost at larger doses (Priestley et al. 1995).

Glycine Reuptake Inhibitors

Another way to enhance the activity of NMDA-receptors via the $Glycine_B$-site is to elevate the synaptic levels of endogenous glycine itself. Normally, the action of glycine would be terminated by its removal from the synapse by specialized transporters located on neuronal membranes and on the surrounding glial cell membranes. Although there are multiple subtypes of transporter, glycine-1 transporters (GLYT-1) located on the glial cells play a major role in the removal of glycine from the synapse and it is the activity of these transporters that is thought to be the reason why $Glycine_B$-sites are not saturated in vivo. Drugs that prevent the activity of GLYT-1, glycine reuptake inhibitors (GRIs) should therefore increase glutamate action at NMDA-receptors.

The first generation of GRIs were based on sarcosine (*N*-methyl-glycine), a selective inhibitor of glycine uptake at GLYT-1 and include NFPS (*N*-[3-(4′-Fluorophenyl)-3-(4′-phenylphenoxy)propyl]sarcosine) and Org24461/24598. Second generation GRIs are non-aminoacid-based compounds, such as SSR504734. Accompanying the rise of the glutamatergic hypothesis of schizophrenia, our knowledge of the procognitive actions of GRIs comes mostly from preclinical studies aimed at modeling aspects of cognition that are impaired in the disorder. Pre-pulse inhibition, or PPI, describes the ability of a small pre-stimulus to inhibit the startle response to a larger stimulus. In animal models, deficits in PPI arise spontaneously in the DBA/2 strain of mouse or can be seen to develop in adult rats, following neonatal treatment with phencyclidine. These are thought to model a schizophrenic abnormality in filtering information and studies in animals have consequently shown that GRIs can reverse these deficits. Other studies have shown their effectiveness at improving object recognition or reference memory, in tests where deficits have been pharmacologically induced with NMDA-receptor antagonists. In human schizophrenia patients, sarcosine and other GRIs can improve "cognitive symptoms" but the nature of these improvements is not yet well described.

Overall, drugs targeting the $Glycine_B$-site of the NMDA-receptor do appear to have procognitive effects on several aspects of learning and memory. There is little evidence for improvements in attention and their effectiveness for enhancing other cognitive domains remains to be fully investigated.

Drugs Acting at AMPA-Receptors

Most of the fast glutamatergic neurotransmission in the brain is mediated by ► AMPA-receptors. In addition, changes in synaptic plasticity are associated with

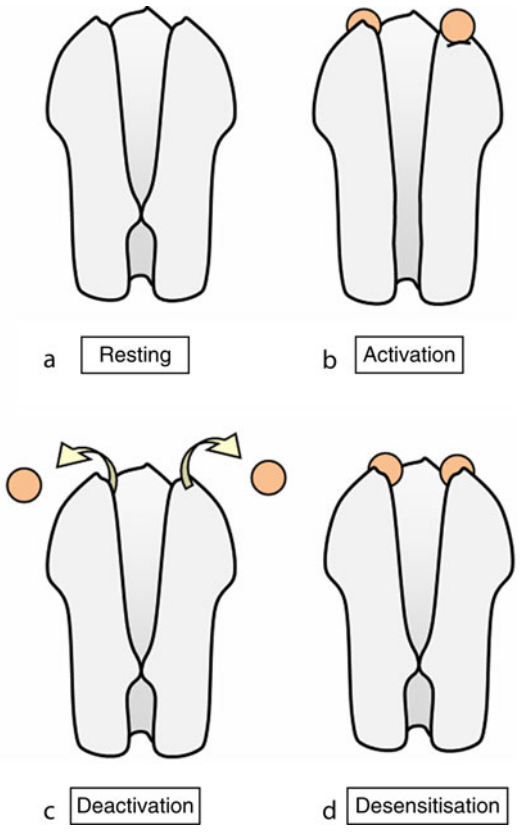
AMPA-receptor insertion and removal from the neuronal membrane (receptor trafficking). They are composed of four protein subunits (tetramers) clustered around an ion channel and which are denoted by GluR1-4. These subunits can also exist as "flip" and "flop" variants. There is therefore AMPA-receptor subtype diversity throughout the brain. The calcium permeability of the receptors depends on the subunit composition – those containing GluR2 subunits are impermeable. The ►hippocampus and the ►amygdala are areas of the brain containing receptors that lack the GluR2 subunit and as a consequence, they have high calcium permeability.

There are two ways in which glutamate neurotransmission at AMPA-receptors is terminated. In the first case, deactivation, glutamate dissociates from the binding site and the ion channel closes. In the second, desensitization, glutamate remains bound, but a conformational change in the receptor causes a closing of the ion channel with the ligand trapped (see Fig. 2). The subunit constitution of the receptor can alter the rate at which it desensitizes. In principle then, any compound that prevents the deactivation or the desensitization of the receptor should prolong the receptor response to glutamate. Such drugs are termed AMPAkines or AMPA-receptor potentiators and most act by preventing desensitization.

Four main classes of AMPA-receptor potentiators have been developed to date (see Table 1).

The exact pharmacology of each compound varies due to receptor diversity, but all can enhance glutamatergic neurotransmission at AMPA-receptors and this has a number of consequences. First, because AMPA-receptors play a key role in LTP, potentiation of their activity can remove the magnesium block on NMDA-receptors resulting in the enhancement of synaptic plasticity. Second, their activation can also increase the expression of the neurotrophin ►brain derived neurotrophic factor (BDNF); the result of this is to increase neurogenesis. It is therefore not surprising that AMPA-receptor potentiators should be of interest in regard to cognition enhancement.

The preclinical profile of the AMPA-receptor potentiators, with respect to therapeutic potential, including as cognition enhancers was reviewed by Black (2005). Several studies have shown that they can have beneficial effects on new learning. These procognitive actions have been reported in rodent maze tasks tapping spatial memory and in conditioning tests, such as passive avoidance or conditioned fear. In primate studies, they can also reverse pharmacologically-induced deficits in new learning. Also, there is evidence for positive benefits on ►working memory in both rodents (using models such as ►delayed matching to sample tests) and primates (►delayed non-matching to sample) and for improved performance in object recognition tests. Enhanced impulse control has been reported in rat studies. This latter finding, however, rests solely on the effect of aniracetam, and it is not yet



Cognitive Enhancers: Role of the Glutamate System.
Fig. 2. Schematic diagram of different states of the AMPA receptor. (**a**) and (**b**) show resting and activation by glutamate respectively. Deactivation (**c**) and desensitisation (**d**) represent two different mechanisms by which glutamatergic neurotransmission at AMPA-receptors is terminated.

Cognitive Enhancers: Role of the Glutamate System.
Table 1. The main classes of AMPA-receptor potentiators. (From O'Neill and Dix 2007.)

Chemical class	Examples
Pyrrolidones	Aniracetam, piracetam
Piperidines	1-BCP, CX-516
Benzothiazides	Diazoxide, cyclothiazide, IDRA-21
Biarrlpropylsulphonamides	LY-392098, LY-404187

clear whether this is a class effect of the AMPA-receptor potentiators.

Preclinically then, the cognitive effects of the AMPA-receptor potentiators are in many ways similar to those of drugs aimed at positively modulating the NMDA-receptor, perhaps because of their ability to enhance LTP, although this picture is likely to be biased by the use of animal models designed to detect specific pharmacological effects believed to be therapeutically useful in particular disorders.

Very few studies on the effects of AMPA-receptor potentiators have been carried out in humans. An early study found some evidence for improved free recall of nonsense syllables in elderly volunteers and a small clinical trial in younger adults was also able to detect enhanced performance in four different memory tasks (Lynch 2004). There is also some evidence for alerting effects in sleep deprived volunteers. In schizophrenic patients, equivocal results have been obtained, with CX516 as an add-on treatment to current antipsychotic medication. Results have also been disappointing with LY451395 in a trial in patients with Alzheimer's disease, where the measure of cognitive assessment was the cognitive subscale of the Alzheimer's disease assessment scale. Lastly, no improvement was seen in a variety of cognitive measures in a trial of CX516 in patients with ▶ Fragile X Syndrome. Fragile X Syndrome is an inherited disorder characterized by intellectual and emotional disabilities and where there may be abnormalities of AMPA-receptor trafficking. The reason for the negative results in patients is unclear, although some of the AMPA-receptor potentiators are not particularly potent drugs and the difficulty of achieving adequate concentrations has been debated.

Overall, the preclinical studies indicate that AMPA-receptor potentiators can promote learning and memory. However, there is room for investigation of their effects across more cognitive domains. There is a paucity of clinical studies, although those carried out in healthy volunteers are suggestive of some of the preclinical findings being translatable to humans.

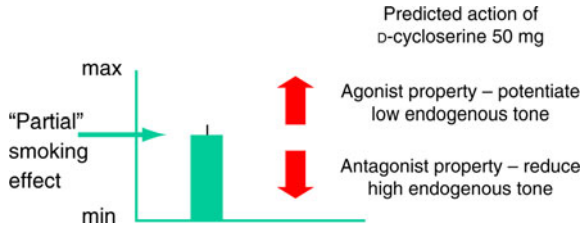
Cognition Enhancers as Investigational Tools

For the most part, drugs such as the GRIs and the AMPA-receptor potentiators have been developed in attempts to provide new medicines for specific psychiatric disorders, most notably for schizophrenia. While this hopefully proves fruitful, many of the positive modulators of ionotrophic-receptor activity can also be used effectively as tools to investigate the role of ▶ glutamate in a broader range of cognitive functions and aspects of other mental health disorders. One obvious area for their use as tools is in addiction studies. This is partly because a role for glutamate-mediated neuroadaptations in addiction has been known for some time (see Kauer and Malenka 2007) partly as many drugs of abuse induce glutamate release in reward-related areas of the brain and also because the cognitive aspects of addictions, such as inhibitory control over drug-seeking behavior, are increasingly being recognized.

With the possible exception of the compounds that may require large doses, many of the drugs mentioned above could be used as tools in addiction research, in both animal and human studies. In using them as tools, one important factor needs to be taken into account. A common property of the $Glycine_B$-site agonists, GRIs and the AMPA-receptor potentiators is that they do not directly activate receptors themselves. Instead, as they modulate the action of glutamate, it may be presumed that some level of endogenous activity would be required for their effects to emerge. In the case of the $Glycine_B$-site agonists and the GRIs, the endogenous levels of glycine and D-serine are also likely to be a factor. It might be possible to predict however, certain situations where a level of endogenous activity is to be expected. First, where new learning occurs during the extinction of drug-taking behavior, thus in an analogy with the studies on fear extinction, these drugs would be expected to facilitate the process. Second, in line with much evidence from studies using NMDA-antagonists which indicates a role for glutamate in inhibitory control, it could be predicted that the $Glycine_B$-site agonists and GRIs would aid active inhibition of impulsive behavior.

D-cycloserine, the partial agonist at the $Glycine_B$-site, is well tolerated in humans and therefore being used increasingly as an investigative tool. As D-cycloserine is a partial agonist, it has the ability not only to potentiate glutamate-receptor function, but for a given dose, it can also block the action of glycine through its antagonist property. Like any partial agonist then, the "direction" of its behavioural effect depends on levels of endogenous activity. As a pure cognitive enhancer the effects of D-cycloserine therefore, may only be useful under particular conditions, but for the purposes of investigating the role of glutamate in cognition and behavior it may be a uniquely useful tool. A recent study by Jackson and colleagues illustrates how it can be used.

As there is a considerable amount of preclinical evidence implicating a role for glutamate in the effects of nicotine, D-cycloserine was used to investigate the role of glutamate in the cognitive and subjective effects of smoking in humans. Figure 3 illustrates the theoretical approach that was used for the study. Volunteers were asked



Cognitive Enhancers: Role of the Glutamate System.
Fig. 3. Theoretical approach to the use of the partial agonist D-cycloserine in investigating the role of glutamate in the effects of smoking.

to "partially smoke" a cigarette after taking 50 mg of D-cycloserine (or placebo). They then completed a series of cognitive and subjective tests. Volunteers who had received D-cycloserine reported less subjective effects after smoking, compared with those given placebo. In contrast, the same dose of D-cycloserine *enhanced* inhibitory control after smoking compared with those given placebo. Thus by using the bidirectional pharmacological property of D-cycloserine, a role for glutamate in some of the cognitive and subjective effects of smoking was confirmed in humans.

Ultimately, it is not possible to know what the level of endogenous glutamate activity was during the smoking study. Although the results with D-cycloserine indicated a role for glutamate in the effects of smoking, the interpretation of that role is made in the light of numerous other studies that have employed the use of NMDA-antagonists. Similarly, if the AMPA-receptor potentiators are to be used as effective tools, it might first be important to understand the consequences of reduced AMPA-receptor function, as a null result with these drugs might simply be a reflection of preexisting conditions of high endogenous activity. However, provided that their pharmacological mode of action as modulators of glutamate activity (as opposed to direct activators of receptors) is taken into account during the design of studies and in the interpretation of results, their use as investigational tools is possible and should provide valuable further information about the processes involved in cognition.

Cross-References

- ▶ Acetylcholinesterase Inhibitors
- ▶ Long-Term Potentiation
- ▶ Novel Object Recognition
- ▶ Partial Agonist
- ▶ Spatial Memory
- ▶ Working Memory

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Cognitive Flexibility

▶ Behavioral Flexibility: Attentional Shifting, Rule Switching and Response Reversal

Cognitive Impairment

Synonyms

Cognitive deficit; Neurocognitive dysfunction

Definition

Cognitive impairment is considered a core feature of *schizophrenia* that is related to the daily functioning of patients. On average, *cognitive impairment* in schizophrenia is severe to moderately severe compared with healthy controls. *Cognitive impairment* is not state-related and is not specific to subtypes of the illness. It includes problems in speed of processing, attention/vigilance, working memory, verbal learning, visual learning, reasoning and problem solving, and social cognition. These deficits can also serve as an endophenotype for the illness and are

considered a reasonable treatment target in individuals with schizophrenia.

Cross-References
► Endophenotype
► Schizophrenia

Cognitive Neuroscience

Definition
The field of cognitive neuroscience is concerned with the study of the brain basis of mental processes in humans – or how the brain enables the mind. It seeks to understand how specific mental abilities and their behavioral correlates are supported by brain systems (regions, networks) both in healthy and disordered populations. Cognitive neuroscience integrates the theoretical background and experimental practices of cognitive science, cognitive psychology, neuroscience, and psychophysiology. The advent of functional neuroimaging techniques, in particular fMRI, has had a major influence on the growth of this field.

Cross-References
► Magnetic Resonance Imaging (Functional)

Cognitive Processing

Definition
Thinking and use of thoughts to organize perceptual information and to plan, decide, and coordinate motor reactions.

Cognitive Subtraction

Synonyms
Pure insertion; Subtraction method

Definition
In functional neuroimaging studies, cognitive subtraction refers to an aspect of experimental design involving the comparison of two conditions or brain states that are presumed to differ in only one discrete feature (the independent variable). Cognitive subtraction designs rely on the assumption of "pure insertion" – the notion that a single cognitive process can be inserted into a task without affecting the remaining processes, or that there are no interactions among the cognitive components of a task.

Cross-References
► Magnetic Resonance Imaging (Functional)

Comorbid

Definition
Comorbid describes when two or more diseases (diagnoses) occur at the same time in the same person.

Cross-References
► Agoraphobia

Comorbid Insomnia

Definition
Comorbid or secondary insomnia can be precipitated or aggravated by another sleep disorder, a disturbance of circadian rhythm, a neurological or psychiatric disease, a general medical condition, or the direct effects of a medication or a substance of abuse.

Cross-References
► Insomnias

Companion

► Complements

Complements

Synonyms
Companion

Definition
Complements have a parallel relationship between a complement and the alternative – as the price of the complement increases the demand for both the alternative and the complement decreases.

Cross-References
► Behavioral Economics

Comprehensive Behavioral Intervention for Tics or Trichotillomania

► Habit Reversal Therapy

Comprehensive Drug Abuse Prevention and Control Act of 1970

Definition

Enacted into law by the U.S. Congress, the Comprehensive Drug Abuse Prevention and Control Act of 1970, also known as the Controlled Substances Act, outlines the policies for the manufacture, importation, possession, use, and distribution of certain chemical substances. The Controlled Substances Act divides these substances into five schedules (classifications) and the decisions for classification are based upon the potential for abuse and current medical uses by the Drug Enforcement Administration and the Food and Drug Administration.

Compulsions

Synonyms

Compulsive acts; Compulsive rituals

Definition

Compulsions are repetitive behaviors (e.g., hand washing, ordering, checking) or mental acts (e.g., praying, counting, repeating words silently) the goal of which is to prevent or reduce anxiety or distress, not to provide pleasure or gratification. The person feels driven to perform in response to an obsession, or according to rules that must be applied rigidly. The behaviors or mental acts are aimed at preventing or reducing distress or preventing some dreaded event or situation. However, these behaviors or mental acts either are not connected in a realistic way with what they are designed to neutralize or prevent or are clearly excessive. At some point during the course of the disorder, the person recognizes that the obsessions or compulsions are excessive or unreasonable. The compulsions cause marked distress, are time consuming (>1 h/day), or significantly interfere with the person's normal routine, occupational or academic functioning, or usual social activities or relationships.

Cross-References

► Obsession

Compulsive Acts

► Compulsions

Compulsive Disorders

Definition

Psychiatric disorders that are characterized by the drive to repeatedly or habitually perform excessive, time-consuming, or irrational behaviors, typically in an effort to reduce anxiety.

Compulsive Gambling

► Pathological Gambling

Compulsive Rituals

► Compulsions

Compulsory Ambulatory Treatment

Definition

Prescription against the will of the patient authorized by the court.

COMT Inhibitor

Definition

A drug that blocks the action of catechol-o-methyl transferase.

Concept Formation Test

► Wisconsin Card Sorting Test

Concretism

Definition

Concrete interpretation of abstract definitions and metaphors.

Conditional Dependence Rate

Definition
The percentage of persons who have ever used a specific drug that go on to develop dependence to that drug.

Cross-References
► Alcohol Abuse and Dependence
► Cocaine Dependence
► Hallucinogen Abuse and Dependence
► Nicotine Dependence and Its Treatment
► Opioid Dependence and Its Treatment
► Sedative, Hypnotic and Anxiolytic Dependence

Conditional Knockout

Synonyms
Cell type-specific knockout; Site-specific knockout; Region-specific knockout

Definition
The removal or complete disruption of a specific gene in a manner that controls the cell types and brain region or site where the disruption occurs. The Cre/loxP system is frequently used to produce conditional knockouts and in this system, the promoter expressing Cre recombinase will give rise to the specificity of the excised gene.

Cross-References
► Ethopharmacology
► Genetically Modified Animals
► Phenotyping of Behavioral Characteristics

Conditioned Activity

Synonyms
Conditioned locomotion; Conditioned locomotor activity

Definition
Conditioned activity occurs when a history of pairing the administration of a psychomotor stimulant drug, such as cocaine or amphetamine, with a particular environment results in acquisition by that environment of the ability to elicit locomotor activity in the absence of the previously administered substance.

Conditioned Avoidance Response

► Active Avoidance

Conditioned Catalepsy

► Context-Dependent Catalepsy

Conditioned Drug Effects

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Synonyms
Context-specific drug effects

Definition
The following essay will examine the historical and more recent scientific contributions in the field of conditioned drug effects. The focus will remain on drugs as the unconditioned stimuli. The aim is to provide an outline of the present state of knowledge and also present a framework on how to examine the direct and indirect influence of many experimental and clinically used psychoactive compounds and their conditioned effects.

Impact of Psychoactive Drugs
Drugs can produce physiological changes (e.g., salivation, hypothermia) or behavioral changes (e.g., locomotor stimulation). Cues that are repeatedly associated with drug administration can acquire the ability to elicit similar physiological changes or in some cases, opposite responses to those elicited by the drug itself. Collectively, responses elicited by cues associated with drugs are termed conditioned responses (CRs) or conditioned drug effects. The following chapter is organized into two parts: Part 1 is concerned with conditioned physiological responses to drugs and Part 2 is concerned with conditioned behavioral responses to drugs.

Part 1: Conditioned Physiological Responses to Drugs
The Nobel Prize-winning Russian physiologist IP Pavlov showed that the responses produced by a drug can be

evoked by cues associated with drug administration even in the absence of the drug. Pavlov described this phenomenon as ▶ classical conditioning. The drug serves as the unconditioned stimulus (US) and produces an unconditioned response (UR). Pairing of an initially neutral stimulus with the drug leads to acquisition by that stimulus (the conditioned stimulus or CS) of the ability to produce a response like the US, termed the conditioned response (CR).

The earliest studies examining physiological responses to drugs tested morphine effects on salivation. Pavlov showed that injection of ▶ morphine (the US) evoked salivation (the UR) in dogs; after a number of morphine injections, the cues associated with drug administration (the CS) were able to elicit the response (the CR) produced by morphine. Pavlov showed further that injection of atropine inhibited salivation; perhaps surprisingly, after a number of atropine injections, cues associated with its administration elicited salivation, a CR opposite to the UR.

In Pavlovian conditioning, it is essential to identify the US and the UR when drugs are used to induce physiological changes. Eikelboom and Stewart (1982) argued that the unconditional stimulus is a "...physical event that results in neuronal consequences...what is crucial in this definition is that the (unconditioned) response is an outcome of neural activity" (p. 509). Learning and conditioning are activities of the central nervous system (CNS); hence, stimuli need to be viewed as inputs to and responses as outputs from the CNS. Only when a drug acts on the input side of the CNS should its action be considered an US and only those observed drug effects that are CNS-mediated physiological reactions to unconditioned stimuli should qualify as a UR. Drug-manipulated thermoregulation provides an example. Two widely studied drugs are morphine that causes hyperthermia and ethanol that causes hypothermia. Morphine has been shown to act directly through the CNS to produce effects on the thermoregulatory system. The CR to morphine mimics the drug effect, hyperthermia. On the other hand, ethanol acts peripherally to produce increased cutaneous blood flow leading to heat loss and a decrease in body temperature that is detected by the CNS that then mounts a compensatory hyperthermic response. When the drug-associated cues (the CS) are subsequently presented alone, only the (CNS-mediated) hyperthermic response (the CR) is observed. The CR in this case is opposite to the drug effect (the UR).

The classic study by Zubkov and Zilov (see Bespalov et al. 2001) reveals some further complexities for identifying the true UR. They examined the CR to epinephrine-associated cues on heart rate in dogs. Epinephrine produced heart rate acceleration upon initial injection. However, the effect was substantially attenuated after several injections and complete ▶ tolerance was reported by the sixth injection. When the dogs with a history of epinephrine administration were injected with saline the heart rate was significantly decelerated. This phenomenon was termed associative tolerance: CRs elicited by environmental stimuli paired with epinephrine injection were opposite in direction to the initial UR produced by the drug.

The aforementioned observations conflict with Pavlovian conditioning where the CR is the same as the UR evoked by the US. In defense to their findings, Zubkov and Zilov argued that the CR need not mimic the UR and under certain circumstances, it may actually counteract the effects of the US. However, a related study by Androsova (see Bespalov et al. 2001) did not support this compensatory CR explanation of associative tolerance – instead, it was shown that epinephrine has dual actions on heart rate. The direct effect is seen as tachycardia and the indirect effect is a result of increased blood pressure via the baroreflex mechanism. Thus, during acute treatment with epinephrine, the cardiac increase effects overshadow the indirect vagal stimulation. It was argued that the indirect vagal reflex effect that was evident during the drug-free test was the true UR that became conditioned to stimuli that accompanied repeated epinephrine injection (Bespalov et al. 2001).

Morphine has been known to produce dose-dependent, biphasic, physiological and behavioral responses. When a naïve rat is injected with a large dose of morphine, it initially shows hypothermia, followed by hyperthermia. Similarly in behavior analysis, a dose of morphine will evoke initial hypokinesia followed by later-onset hyperkinesias. Therefore, it is essential to identify each UR that occurs throughout the action period of the drug. These opposite effects may acquire associations with different conditioned stimuli that elicit a number of CRs across time.

There is some debate concerning associative tolerance of morphine analgesia. Siegel (1975) first demonstrated that the tolerance observed to the analgesic effect of morphine is context- or environment-specific. Rats previously injected with morphine and then tested with saline (in the environment previously associated with morphine) showed increased sensitivity to pain; this effect was not observed when the rats were tested in a novel environment. Siegel subsequently proposed a conditioning model of tolerance to explain his findings, suggesting that conditioned hyperalgesic responses to morphine develop as an adaptive homeostatic mechanism in response to

predictable changes caused by the drug. Therefore, this conditioned opponent response that counteracts the analgesic action of morphine is elicited by the environment in which morphine was administered.

In associative tolerance, the CR elicited by environmental stimuli paired with morphine injection is reported to be opposite in direction to the UR produced by the drug. This observation conflicts with Pavlovian associative learning, yet it follows the same rules of conditioning. Firstly, like Pavlovian CRs, associative tolerance to morphine can be extinguished with repeated presentation of environmental cues that were previously associated with morphine but without morphine injection. Secondly, like Pavlovian CRs, associative tolerance to morphine is subject to latent inhibition. Exposure to conditioning stimuli prior to pairing with the drug inhibits the acquisition of tolerance. Lastly, like Pavlovian CRs, tolerance is not seen when the drug cues are absent. Based on this evidence the question remains: Why is the CR opposite to the observed drug effect? A parsimonious explanation would argue that it is possible that morphine may have a dual effect on pain sensitivity. Siegel (1975) reported that rats had shorter paw-lick latencies on the hot plate on the last six out of eight test trials following administration of morphine, when compared with saline controls. Therefore, following morphine administration rats appeared hyperalgesic. Perhaps, hyperalgesia is an observed drug effect, i.e., an UR that can become conditioned and is evoked as a CR.

In accordance with this idea, Celerier et al. (2001) reported that acute administration of heroin induces delayed hyperalgesia in rats and that this increased sensitivity to pain may serve as the UR during the CS–US pairings. Furthermore, this effect was seen initially for 4–5 h following each treatment, and sensitized upon repeated heroin treatments shifting the curve to the left; hence, increasingly counteracting the opioid-induced analgesia. Therefore, hyperalgesia following morphine treatment may be masked by morphine's initial analgesic activity.

Both analgesia and hyperalgesia are direct effects of morphine on the CNS, but they appear at different times after injection. However, only hyperalgesia is expressed as a CR when rats are exposed to the test environment. The reason for this may be that different drug effects can be paired with different cues and the strength of conditioning to a particular cue is affected by that cue's salience. The environment previously paired with morphine injections consists of many cues of variable relevance, where each is competing to gain the most associative weight. It was reported that from a number of stimuli conditioned to morphine, only the morphine-associated gustatory stimulus showed an analgesic CR. Thus, different drug effects may be conditioned at different times to a variety of stimuli within different modalities. This was addressed by Eikelboom and Stewart (1982), where temporal and environmental cues were found to play a different role during conditioned hypothermia and hyperthermia based on morphine.

Morphine acts directly through the CNS on the thermoregulatory system and acts as an US to produce hyperthermia. In studies where saline was injected in a distinctive conditioning environment that was paired previously with morphine, robust-conditioned hyperthermia was observed. Subsequently, a second-conditioning component of the experiment was reported. It was observed that rats consistently showed hypothermia 1 h before each expected morphine injection (given at 24 h intervals), although their body temperatures were normal 2 h prior to the injection. It was hypothesized that the temporal cues became predictive of the next morphine injection and elicited conditioned hypothermia. However, if rats were given injections at irregular temporal intervals and temperatures were taken throughout the 24 h period, the rats exhibited hypothermia at all hours of the day relative to controls. Therefore, only when injections were given at the same time each day, making temporal cues predictive of the next morphine injection, did the hypothermia become locked into the time of day (i.e., a true conditioned compensatory response). Thus, two conditioned temperature responses were evoked by two different CSs: conditioned hyperthermia by contextual environmental cues and conditioned hypothermia by temporal cues. If both CRs had been elicited by the same cues, only the net effect would be evident. When animals were tested in the presence of both types of conditioned stimuli (temporal and environmental), no temperature changes were evident.

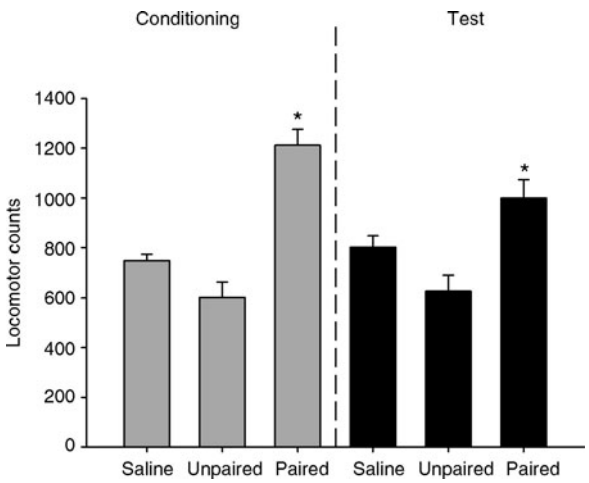
In summary, physiological effects of drugs such as changes in body temperature or changes in pain sensitivity can become associated with cues that signal the administration of these drugs. In some cases, the physiological responses produced by conditioned stimuli mimic the URs produced by the drug. In other cases, the physiological responses produced by conditioned stimuli are opposite in direction to those produced by the drug. A consideration of the locus of action of the drug and the point where the drug itself or its somatic effects influence the CNS provides a framework for predicting the direction of CRs. Consideration also needs to be given to the acute versus chronic unconditional effects of drugs and which of these are being associated with conditioned stimuli. When these elements have been identified and

understood, most conditioned physiological responses to drugs can be seen to conform to the conditioning paradigm developed by Pavlov.

Part 2: Conditioned Behaviors

A useful paradigm for the behavioral evaluation of conditioned drug effects is ▶ conditioned activity. Pickens and Crowder (1967) were among the first to report that environmental stimuli paired with the psychomotor-stimulant drug ▶ amphetamine produced conditioned locomotor activity in rats. In this paradigm, the CR is not a specific operant but rather a general increase in locomotion, rearing, and other related behaviors in the drug-associated environment.

The procedure involves injecting animals with a drug and then placing them into a distinct environment for a period of time (e.g., 1 h). After several drug-environment pairings, experimental animals are injected with saline and again placed into the test environment. The animals that received drug-environment pairings are observed to be more active than control animals with a similar history of placement in the environment and a similar history of drug injections but without having received the drug in the test environment (Fig. 1). Therefore, the effect of increased activity in rats having received environment–drug pairings can be attributed to the association of environmental stimuli with the effects of the drug rather than a previous history of drug treatment. Conditioned activity has been demonstrated with a number of drugs including amphetamine, ▶ cocaine, ▶ nomifensine, (+)-4-propyl-9-hydroxynaphthoxazine (PHNO), quinpirole, ▶ apomorphine, morphine, and etorphine.



Conditioned Drug Effects. Fig. 1. Locomotor activity (count per 60 min) typically observed during conditioning based on cocaine (10 mg/kg; *left side*) and test of conditioned activity (*right side*). Three groups ($n = 18$ per group): *saline controlled, unpaired* (saline in conditioning environment; cocaine in homecage), *paired* (cocaine in conditioning environment; saline in homecage). *Significantly greater than unpaired and saline groups by analysis of variance followed by pairwise comparisons, $p < 0.05$.

The conditioning procedure used in this paradigm is often referred to as Pavlovian, where the drug is the US, the distinctive environment is the CS, and the increased activity in response to the drug is the UR. Increased activity during the CS alone is the CR. In spite of this apparent similarity, some research has shown that the CR does not strongly resemble the UR as is usually assumed in Pavlovian conditioning. In particular, behaviors not manifested during the drug-conditioning phase have been reported on the drug-free test day. For example, rats that received the dopamine reuptake inhibitor nomifensine on conditioning days were observed to gnaw on the drug-free test day, but gnawing was never produced by the nomifensine. In another study, the pattern of cocaine-induced turning during the drug-free test day did not resemble the pattern of turning observed on conditioning days. Based on these reports, Martin-Iverson and Fawcett (1996) examined whether behaviors of rats placed in an environment previously paired with amphetamine or the direct dopamine D_2-like receptor agonist PHNO, looked like the drug-induced behaviors. The authors found that out of the 11 behavioral measures increased by amphetamine on conditioning days, only four were increased on the drug-free test day. The total duration of sniff, head movement, snout contact, and stand were significantly greater than that of control animals. Furthermore, rearing behavior was increased on the drug-free test day but this was not so during conditioning. The authors argued that some of the behaviors observed during the test session represented an increase in scanning of the test environment as a result of a change in that environment due to the absence of the drug cue. The drug-free day may alter the affective state of the animal by removing an anticipated rewarding stimulus; this in turn, might lead to a frustrative affective state that is behaviorally activating. Similar differences in behaviors observed during conditioning and test sessions were seen when PHNO was the drug used for conditioning. Out of 19 behaviors increased by PHNO during conditioning only three were significantly increased when compared with control rats in the test. Thus, behaviors evoked by an environment previously paired with either amphetamine or PHNO are not always the same as those produced by the drugs used for conditioning.

Ahmed et al. (1998) tested whether three variables known to affect the acquisition of Pavlovian conditioning would interfere with conditioned activity using amphetamine. The authors examined sensitivity to CS–US temporal order, to unsignaled occurrences of the drug US between CS–US pairing trials and CS-alone test, and to the US preexposure effect. With respect to the first, the acquisition of a Pavlovian CR is abolished if the US is presented simultaneously or before the CS. In the case of conditioned activity however, a 25 or 50 min drug US–CS delay during the six pairing sessions had no significant effect. Second, in Pavlovian conditioning, unpaired presentations of a US alone between CS–US pairings lead to a diminished CR in the test. Conditioned activity was not influenced by the number of unsignaled amphetamine injections given between the pairings of the CS and the drug US. Third, according to Pavlovian conditioning, preexposing the animal to the US alone usually has a detrimental effect on the acquisition of a CR. However, the acquisition of conditioned activity was not influenced by 10 days of preexposure to amphetamine prior to CS–US conditioning. Therefore, research argues that conditioned activity based on drug stimuli is not controlled by the same variables that control Pavlovian conditioning.

It has been suggested that conditioned activity can be understood as involving ▶ reward-related incentive learning (Beninger 1983; Beninger and Olmstead 2000). In this view, the environment paired with the rewarding properties of the drug acquires an increased ability to elicit approach and other responses during conditioning that manifests as a conditioned activity during testing. All drugs that elicit conditioned activity share a common feature: they all exhibit facilitative effect on the ▶ mesotelencephalic dopamine reward system especially in the striatal regions of the mammalian brain. Further, it has been shown consistently that conditioned activity does not develop if dopamine function is blocked during conditioning. Drugs that block dopamine transmission at D_1- and/or D_2-like receptors block the acquisition of conditioned activity. Classical Pavlovian learning has been shown to be relatively independent of dopamine; e.g., animals are able to learn CS–US associations under the influence of dopamine receptor blocking drugs. When the dopamine receptor blocker ▶ pimozide was administered during tone–food pairings, learning of the stimulus–stimulus associations was not blocked but the tone failed to acquire incentive motivational properties and consequently, could not be used as a conditioned reinforcer to control instrumental responding.

Another conditioned behavioral phenomenon that involves reward-related incentive learning, although in the opposite direction, is ▶ context-dependent catalepsy. Unlike conditioned activity that depends on enhanced dopamine transmission in the striatum, conditioned catalepsy depends on the lack of dopamine transmission in striatal regions. In one version of this paradigm rats were treated with a low dose of ▶ haloperidol, a dopamine D_2-like receptor blocker, for 8 days. Paired rats were injected with haloperidol 1 h before being tested for catalepsy and were injected with saline 30 min after the test. Unpaired rats were injected with saline 1 h before the catalepsy test and then with haloperidol 30 min post test. Control rats received saline 1 h before and 30 min after the test. The dose of haloperidol did not produce catalepsy on the first session; however, a day-to-day increase in catalepsy was observed from day 1 to day 8. On day 9, paired rats were administered saline only and showed context-induced catalepsy in the environment previously paired with haloperidol. The unpaired group did not differ from saline control rats, thus history of haloperidol injections alone could not account for this effect. Conditioned catalepsy shares a number of characteristics with conditioned activity; however, the net effect is not an enhanced activity in the conditioned environment but a decrease in the locomotor output (Schmidt and Beninger 2006).

In the conditioned catalepsy studies, a day-to-day ▶ sensitization to haloperidol was also seen. This is similar but opposite in direction to the augmentation of behavior observed with repeated administration of psychostimulant or opiate drugs. The context in which the drug is expected facilitates the expression of sensitization to the effects of both haloperidol and stimulant drugs. Normally, this context-dependency is extinguishable by repeated exposure to the test environment without the drug. However, retesting animals with haloperidol following extinction resulted in a slight but significant cataleptic response in the paired group and not in the unpaired group. This suggested that haloperidol itself may act as an interoceptive cue that was conditioned along with the environment. Thus, sensitization might involve two separate learning components: first, a context-conditioned component that is not expressed following extinction and second, an interoceptive cue-related component that had become associated with the conditioning environment and was not weakened by exposures to that environment while in a drug-free state.

The development of sensitization has been shown to depend on the dopamine activity in the ▶ ventral tegmental area (VTA) and ▶ nucleus accumbens. This enhancement is also glutamate dependent. Studies using the glutamate *N*-methyl-D-aspartate receptor antagonist MK-801 have shown that glutamatergic input to the

dopamine system is vital for context-induced sensitization. Environment-dependent sensitization may also be considered to result from dopamine-mediated incentive learning. In the case of psychostimulants or opiate drugs, dopamine released in the striatum may lead to enhanced motor responses to stimuli associated with that drug. This is observed as enhanced behavioral responses to these drugs over repeated conditioning days. In the case of dopamine deficiency produced by haloperidol an antireward signal may lead to attenuated future responding in the presence of stimuli associated with that drug. This would produce a decline in motor responses to the drug with repeated testing. Dopamine can be viewed as a modulator where too much dopamine produces a test-to-test increase in behavior and too little dopamine produces a test-to-test decrease in behavior.

In summary, some drugs produce reliable increases or decreases in general locomotor activity. and research has shown that the stimuli associated with the drug state acquire the ability themselves to elicit increases or decreases in general locomotor activity similar to those elicited by the drugs. This phenomenon of conditioned activity or conditioned catalepsy has the appearance of Pavlovian conditioning, the drug being the US, the change in locomotor activity the UR, the environment associated with the drug the CS, and the motor response in that environment in the absence of the drug the CR. However, Pavlovian conditioning originally involved physiological reflexes that were shown to be affected in predictable ways by parametric manipulations. Studies have shown that when instrumental-type responses are conditioned they are not similarly affected by these manipulations. In addition, conditional responses to drug-related stimuli were shown to differ from the URs produced by those stimuli. The ability of many drugs to produce conditioned behaviors depends on mesotelencephalic dopamine reward systems, and likewise, conditioned activity can be understood as an example of reward-related incentive learning. Thus, stimuli associated with activation of dopamine neurons acquire the ability to elicit approach and other responses manifested as a conditioned activity.

General Conclusion

- Drugs can produce physiological or behavioral effects. Physiological effects can result from a direct action of the drugs on the CNS or from direct actions of the drug on a peripheral effector. In the latter case, the response of the effector may influence the CNS. The effects of drugs on the CNS can become conditioned to stimuli associated with the drug state so that those stimuli can elicit the drug-like effect in the absence of the drug stimulus. In the case of drugs that act directly on the CNS, the CR will mimic the unconditioned effect of the drug; in the case of drugs that act indirectly on the CNS, the CR may be opposite in direction to the UR. Conditioned physiological effects or reflexes conform to the Pavlovian conditioning paradigm.
- Drugs can also produce changes in instrumental-type behaviors such as locomotor activity. Stimuli associated with the drug state acquire the ability to elicit behaviors like those produced by the drug. Although the phenomena resembles Pavlovian conditioning, studies have shown that conditioned activity changes do not conform to a number of parametric manipulations that reliably affect conditioned physiological effects or reflexes. Conditioned activity may be better understood as an example of reward-related incentive learning.
- Drug placebo effects may provide a common example of conditioned drug effects. For example, in ► Parkinson's disease placebo effects are well documented. When a patient believes she is receiving medication even though she is not, there is a notable benefit. This can be understood as a conditioned drug effect where the stimuli associated with anti-Parkinson's medication acquire the ability to produce a response like that produced by the drug itself. From observation like these it has been suggested that nondrug placebo administration may be used periodically to good effect in some treatment regiments.
- The study of conditioned drug effects remains an active area of research in behavioral neuroscience. As the mechanisms of ► neuronal plasticity underlying learning and memory continue to be unveiled, they will be recruited to the further understanding of the mechanisms underlying conditioned drug effects. This knowledge will enhance our ability to maximize the therapeutic use of drugs with a more complete understanding of their combined unconditioned and conditioned effects.

Cross-References

► Behavioral Tolerance
► Classical (Pavlovian) Conditioning
► Delayed Onset of Drug Effects
► Motor Activity and Stereotypy
► Opioid Drug
► Placebo Effect
► Psychomotor Stimulant Drug
► Sensitization to Drugs

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Conditioned Emotional Response

► Pavlovian Fear Conditioning
► Punishment Procedures

Conditioned Fear

Synonyms

Fear conditioning

Definition

Conditioned fear is a state of fear (or anxiety) that occurs in animals after a few pairings of a threatening stimulus with a formally neutral stimulus using a classical (Pavlovian) conditioning procedure. For example, in experimental animals, when a tone (i.e., the conditioned stimulus) is paired with the occurrence of a mild footshock (i.e., the unconditioned stimulus), after a few pairing, the presentation of the tone alone is sufficient to elicit a state of fear (i.e., the conditioned response). Sometimes, the fear response is conditioned to specific features of the setting or the context in which the stimulus was presented (i.e., the contextual stimuli). Conditioned fear provides a critical survival function, which activates a range of defensive behaviors that protect the animal against potentially dangerous environmental threats.

Cross-References

► Classical (Pavlovian) Conditioning

Conditioned Flavor Preferences

► Conditioned Taste Preferences

Conditioned Freezing

► Pavlovian Fear Conditioning

Conditioned Inhibition

► Conditioned Inhibitor

Conditioned Inhibitor

Synonyms

Conditioned inhibition

Definition

The classic example of Pavlovian (classical) conditioning is that of one stimulus such as a buzzer signaling the occurrence of some other stimulus like meat powder (i.e., unconditioned stimulus or US). With repeated parings, the buzzer or conditioned stimulus (CS) in this situation acquires the ability to excite a response (e.g., salivation) and, hence, is sometimes referred to as a conditioned excitor. In contrast, a CS can also signal the absence or nonoccurrence of the US. In this case, the CS may be called a conditioned inhibitor. Conditioned inhibition is often conceptualized as a directly opposing process to conditioned excitation. In fact, the two primary

tests for conditioned inhibition, summation and retardation of acquisition tests, are based on this assumption.

Cross-References

- ► Blocking, Overshadowing, and Related Concepts
- ► Classical (Pavlovian) Conditioning
- ► Occasion Setting With Drugs
- ► Pavlovian fear conditioning

Conditioned Locomotion

► Conditioned Activity

Conditioned Locomotor Activity

► Conditioned Activity

Conditioned Place Preference and Aversion

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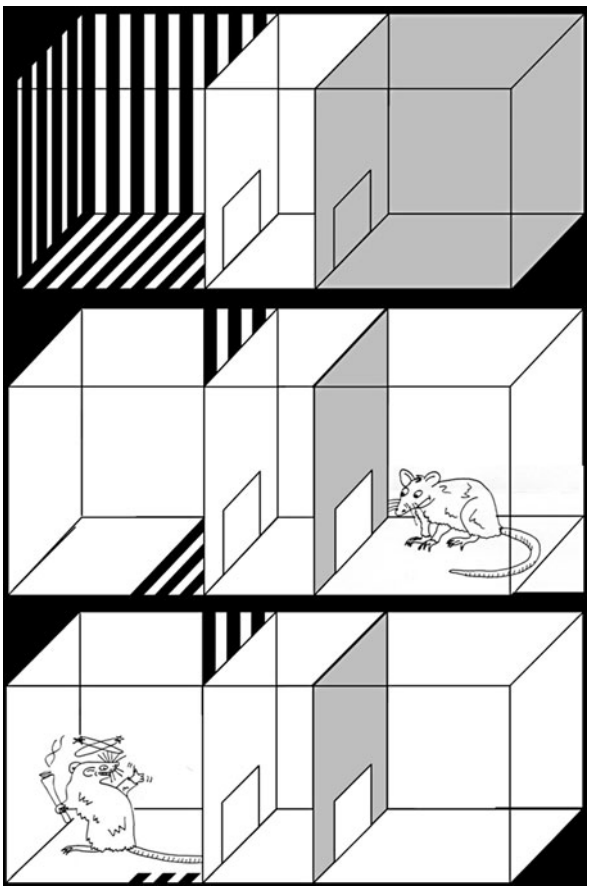
Synonyms

Place conditioning

Definition

Conditioned place preference (CPP)/conditioned place aversion (CPA) is a behavioral paradigm largely based on principles of ► classical (Pavlovian) conditioning. For conditioning, a distinct set of environmental cues is explicitly paired with a particular drug or nondrug treatment, and a distinctly different set of environmental cues is paired with a control treatment. Most commonly, treatment and control pairings are repeated several times, usually once per day. Over the course of conditioning, the rewarding or aversive treatment effects will become associated with the particular set of cues paired with the treatment, such that in a post-conditioning test trial, these cues will elicit approach (when the treatment had rewarding effects) or avoidance (when the treatment had aversive effects), resulting in a conditioned preference or aversion for the treatment-paired environment (or "place") (Fig. 1).



Conditioned Place Preference and Aversion. Fig. 1. Common design of a conditioning apparatus (top panel) and illustration of the conditioning principle: one compartment is paired with vehicle administration (middle panel), and one compartment is paired with drug administration (bottom panel). Rat cartoon by Axel Strobl.

Principles and Role in Psychopharmacology

CPP/CPA is among the most widely used behavioral pharmacological models to assess the rewarding or aversive effects of drugs or nondrug treatments (Tzschentke 1998, 2007). The consideration of drug effects is closely related to the issue of validity of the model, in particular, ► predictive validity, which describes to what extent the effects of a drug seen in an animal model can predict the effect of the drug in healthy humans or in a human disease condition. Under this perspective, the CPP/CPA model is very frequently used in the context of ► abuse liability evaluation of known and novel drugs (Buccafusco

2001; Willner 1991). Over the past decade, place conditioning has also become one of the standard procedures for the behavioral phenotyping of ► genetically modified animals (Tzschentke 2007).

Virtually all classes of psychoactive drugs and drugs acting on the central nervous system have been evaluated in the CPP/CPA paradigm. Overall, the predictive validity of the model has been found to be very good, with some exceptions, as a few false-positive effects (i.e., CPP despite demonstrated lack of abuse potential), as well as false-negative effects (i.e., lack of CPP despite abuse in humans) were found. While these discrepancies may be related to genuine species differences, procedural aspects may also play an important role.

Advantages and Disadvantages of the Model

There are a number of features that make place conditioning a very useful and very versatile model. One of the major advantages, in particular, as compared to ► operant conditioning paradigms, is that drug-induced side effects cannot interfere with the expression of behavior during the test session, since the test session is conducted in the drug-free state. In other words, the effects of a drug (during conditioning) are assessed in the absence of the drug, i.e., sedative, ataxic, stimulatory, or other side effects do not affect the outcome of the test session.

A further advantage, in particular, as compared to operant intravenous self-administration paradigms, is that the outcome is bidirectional, i.e., rewarding as well as aversive effects can be measured within one single experiment, resulting in CPP or CPA, respectively. This feature is particularly useful when new drugs with unknown motivational effects are tested, or when a large dose range of a drug is evaluated (often, low-to-moderate doses can produce rewarding effects, whereas high doses result in aversive effects due to side effects). Another distinguishing advantageous feature of place conditioning is that nondrug rewards or punishers can be studied, such as foods and liquids, social or sexual interaction, electric footshocks, states of pain, states of ► withdrawal, etc.

Finally, the technical requirements to do CPP/CPA studies can be reduced to a minimum. Although most commonly, location and locomotor activity are monitored by computer-controlled infrared light beams or a video-tracking system, a simple wooden or plastic box and a patient observer is all that is needed to run experiments and to generate valid data.

Despite these advantages, there are also a number of disadvantages to the model that can limit its usefulness, or that at least prevents an unreflected use of the model and/or interpretation of data.

More often than not, no clear dose–response relations are observed in place conditioning. Often, an all-or-nothing effect is observed, with a threshold dose above which CPP/CPA is observed, albeit not with a dose-dependent increase in effect magnitude. This also means that effect size is not a good measure of the efficacy of a drug to produce rewarding or aversive effects. In the absence of dose-dependent effects, the potency of a drug can be best determined from the threshold dose for CPP/CPA, and this can be used to compare different drugs. Nevertheless, overall, place conditioning is not a very quantitative model and is not well suited to compare the potency, and, in particular, the efficacy of drugs to produce rewarding or aversive effects. The data generated with this model have a more qualitative than quantitative character.

Furthermore, care has to be taken that the experimental parameters are adjusted to match the particular properties of the drug under investigation. Otherwise, the model is prone to false-negative results. In particular, since conditioning depends on the close temporal pairing of rewarding/aversive drug effects with the environmental cues, it is important that the temporal contingencies of drug-cue pairing are appropriate for the pharmacokinetic properties of the drug under investigation.

Finally, the field of place conditioning is suffering from the fact that there is a very small degree of standardization of experimental parameters across laboratories. The use of biased or unbiased designs (referring to the use of conditioning apparatuses, in which animals do or do not show, respectively, an unconditioned preference for one of the compartments), different numbers and designs of conditioning compartments, number and duration of conditioning sessions, duration of test sessions, number of preconditioning (habituation) sessions, delay between drug administration and conditioning session, and different statistical methods to analyze the data (comparison vs. vehicle compartment or vs. pretest; pairwise *t*-tests vs. analysis of variance (ANOVA) across all groups; raw data vs. transformed data scores), all make comparisons of data across laboratories almost impossible, since at least one of these important parameters is always different between individual studies from different labs.

See Carr et al. (1989) and Bardo et al. (1995) for review of the issues mentioned in this section.

Procedural/Methodological Aspects to Consider

State-dependency: ► State-dependent learning or state-dependent retrieval, refers to the fact that information or a behavioral response that has been learned or acquired while the subject was in a certain (drug-induced) state can only (or at least better) be retrieved or reproduced when

the subject is in that same state, but not when in a different state (e.g., in an undrugged state). The potential influence of state-dependency effects on the outcome of place conditioning experiments is obvious, as animals are conditioned in a certain (drugged) state, but are usually tested for CPP or CPA in an undrugged state. To control this potential caveat, one can include an additional test session in the experimental protocol, during which the animals are tested after administration of the conditioning drug.

Choice of comparator: In by far the most place conditioning studies, the treatment under investigation is compared with an appropriate vehicle treatment (i.e., drug is paired with one compartment, and vehicle is paired with the other compartment), yielding information about a treatment's "absolute" rewarding or aversive effects. However, place conditioning can be more versatile than this. The effects of one drug can be directly compared with those of another drug (by pairing one drug with one compartment and the other drug with the other compartment); likewise, two doses of the same drug can be compared with each other. This approach, which is very rarely used, yields information about the "relative" rewarding or aversive effects of two treatments.

Latent inhibition and within-session extinction: ► Latent inhibition refers to the phenomenon that if a subject is exposed to a to-be-conditioned stimulus in the absence of the unconditioned stimulus, the subsequent formation of an association between unconditioned and conditioned stimulus is impaired. Applied to the CPP/CPA paradigm, this means that exposure of the animal to the conditioning environment without drug administration will impair subsequent formation of CPP/CPA. This issue is of relevance, since a place conditioning experiment almost always involves preconditioning ► habituation exposures of the animals to the conditioning apparatus. The number and duration of these preexposures needs to balance maximal habituation (i.e., long preexposure) and minimal latent inhibition (i.e., short preexposure). Establishing the optimum amount of preexposure should be part of the model establishment and validation procedures.

Classical conditioning depends on the temporal association between the unconditioned and the conditioned stimulus. Applied to the CPP/CPA paradigm, this means that exposure of the animal to the conditioning environment has to coincide with the experience of the drug effect. Thus, the timing and duration of conditioning must be appropriate for the ► pharmacokinetics of the drug under investigation. If a drug has very rapid kinetics (fast onset and short duration of action), the conditioning sessions need to commence directly after drug administration and be of short duration. Otherwise, the animal could experience the conditioning environment in the absence of any drug effect late in the conditioning session, resulting in within-session extinction. On the other hand, if a drug has very slow kinetics (in particular, late onset of action), there needs to be an appropriate delay between drug administration and commencement of conditioning session. Otherwise, the animal would experience the conditioning environment in the absence of any drug effect early in the conditioning session, resulting in a latent inhibition effect, or the experience of drug effect may be missed altogether during the conditioning session.

See Tzschentke (1998) for review of the issues mentioned in this section.

Recent Developments

Place conditioning is most commonly used, past and present, to study the rewarding/aversive effects of a drug (applied systemically or intracranially), or of drug combinations. More recently, the paradigm has become a standard procedure in the characterization of knockout and otherwise genetically modified mice.

However, beside these straightforward uses, the paradigm is also increasingly used to study more complex phenomena. For example, place conditioning can be used to study the development of ► sensitization or tolerance to rewarding effects of drugs upon repeated administration. Besides being an interesting scientific issue in its own right, it bears particular relevance to the question of to what extent early drug exposure (e.g., in childhood or adolescence) would affect the response to drugs later in life. To this end, animals can be treated acutely or repeatedly at one point and subjected to a place conditioning experiment at a later point in their life. This approach has been used, for example, to study the impact of treatment of juvenile or adolescent rats with ► methylphenidate (a psychostimulant drug, used to treat children with ► attention-deficit hyperactivity disorder) on the response to drugs later in life (as there is a continuing concern that methylphenidate treatment in childhood could predispose the individuals to increased risk of addictive behaviors later in life).

Another approach that has been developed and used with increasing frequency in the context of place conditioning is the study of extinction and ► reinstatement phenomena. This has most commonly been studied in operant intravenous self-administration paradigms (Epstein et al. 2006), and only the last decade has seen a strong increase in the number of studies addressing these issues by means of place conditioning. Although the operant behavior may be more robust and more easily

quantifiable, the place conditioning approach also has certain advantages. It is technically much easier – experiments often involve protracted extinction and withdrawal periods prior to the reinstatement sessions, and it can be challenging to keep intravenous catheters patent for such long periods. Furthermore, the classical conditioning approach may have better face validity for human addiction than the operant conditioning approach, since withdrawal, abstinence, and confrontation with drug-predictive cues (that can lead to relapse in abstinent addicts) are normally not contingent upon the addict's behavior, and are more closely matched by classically conditioned cues.

Apart from the issue of reinstatement, extinction, and, in particular, the time to or resistance to extinction may be an additional useful readout in place conditioning studies. As mentioned previously, place conditioning usually is not a very quantitative method, and it is difficult to directly compare the rewarding/aversive efficacy of two or more treatments (either different doses of the same drug or given doses of different drugs). Analyzing the number of test sessions needed until the conditioned effect has undergone extinction may offer an additional, more quantitative readout, in that, within limits, the resistance to extinction is related to the "strength" of conditioning, which, in turn, is related to the magnitude of the unconditioned stimulus, i.e., the drug dose.

Finally, the place conditioning approach is increasingly used to study the emotional component of pain. Pain research is, in large part, focused on the study of evoked pain reactions. While this may be appropriate for certain kinds of pain in humans, spontaneous or continuous pain (i.e., not evoked by a particular external stimulus) cannot be studied by the traditional methods. Likewise, the traditional methods cover only the sensory aspects of pain, but cannot access the adverse emotional dimension of pain, which, for pain patients is often more troublesome than the sensory pain experience. Several interesting findings have been reported, combining pain models with place conditioning. For example, in animals that are in a state of pain (acute or chronic), the dose–response curve of morphine to produce CPP is shifted to the right, i.e., larger doses are needed to produce a rewarding effect. In other words, pain reduces the rewarding effects of an opioid. This finding corresponds well with the clinical observation that abuse of, and addiction to ▶ opioids in patients receiving them for pain relief is only rarely observed.

Like other unpleasant stimuli, acute and chronic pain can produce a conditioned aversion for a pain-associated context, i.e., a CPA. This CPA is likely due to the negative emotional component of pain. Interestingly, opioids are highly potent in abolishing this pain-induced CPA, and they do so at doses that are neither rewarding by themselves nor have an analgesic effect in a standard pain model. This means that the abolition of CPA is not simply due to a summation of an aversive pain effect and a rewarding drug effect, or to a blockade of the sensory pain experience, but is likely due to a selective inhibition of the aversive component of pain. This again corresponds with clinical observations that when pain patients are treated with low doses of an opioid, they may still have the sensory experience of pain, but this experience is no longer aversive, i.e., they feel the pain but they do not care about it anymore.

See Tzschentke (2007) for review of the issues mentioned in this section.

Outlook

Place conditioning is a long and well established model. In most laboratories, it is used in its "basic" form to test for rewarding or aversive effects of drugs or drug combinations. Nevertheless, new and innovative applications of the model, as described in this essay, continue to be explored, and it can be expected that new ideas and applications continue to be developed in the future. Likewise, the more procedural and theoretical aspects of the model are also still being explored (see e.g., Groblewski et al. 2008). This will lead to a better knowledge about the model and its implications and will likely further enhance the usefulness and validity of the model.

Cross-References

- ▶ Abuse Liability Evaluation
- ▶ Attention Deficit and Disruptive Behavior Disorders
- ▶ Classical (Pavlovian) Conditioning
- ▶ Genetically Modified Animals
- ▶ Habituation
- ▶ Latent Inhibition
- ▶ Methylphenidate and Related Compounds
- ▶ Operant Behavior in Animals; Instrumental Conditioning
- ▶ Opioids
- ▶ Pharmacokinetics
- ▶ Reinstatement of Drug Self-Administration
- ▶ Self-Administration of Drugs
- ▶ Sensitization to Drugs
- ▶ State-Dependent Learning
- ▶ Withdrawal Syndromes

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Conditioned Reinforcement

► Appetitive Responses

Conditioned Reinforcers

Synonyms
Secondary reinforcer

Definition
Conditioning is a learning process by which the function of a stimulus event is altered through repeated pairing with other stimuli. A conditioned reinforcer is a previously neutral stimulus that functions as a reinforcer after repeated pairings with a primary reinforcer.

Cross-References
► Conditioned Drug Effects

Conditioned Response

Synonyms
CR

Definition
A defensive response related, the UR, because of pairing of the CS and US.

Conditioned Stimulus

Synonyms
CS

Definition
An initially neutral cue that comes to elicit a response (the conditioned response) because of its pairing with an unconditioned stimulus that has the ability to produce the response.

Conditioned Taste Aversions

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Synonyms
Conditioned taste avoidance; Taste aversion learning

Definition
Conditioned taste aversion (CTA) refers to a learning phenomenon in which the pairing of a taste with the effects of a drug results in the subsequent avoidance of that taste. The robust nature of CTA, induced by a variety of drugs belonging to a wide range of pharmacological classes, has made aversion learning a sensitive and widely used index of a drug's aversive effects.

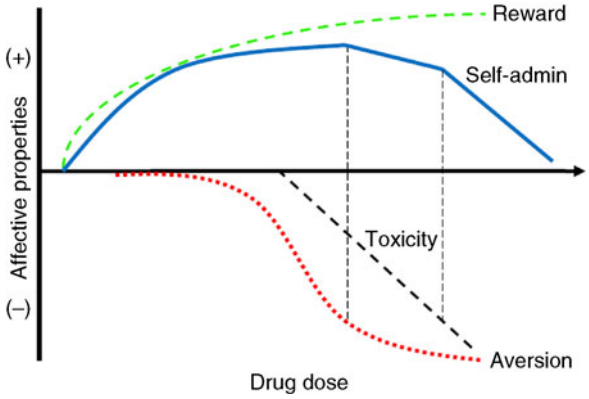
Impact of Psychoactive Drugs
The phenomenon of CTA learning emerged from studies on radiation toxicity when Garcia et al. (1955) presented rats with access to a distinct saccharin solution that was then paired with exposure to radiation (for a historical perspective, see Freeman and Riley 2008). Although the initial preference for saccharin-flavored water was much greater than unflavored water (86% preference for saccharin), pairing the taste with radiation produced a dramatic decrease in saccharin preference relative to the initial baseline and to sham-irradiated controls (or subjects irradiated, but that had not received access to saccharin). This decrease was sufficiently robust enough to persist for almost 30 days post irradiation despite continuous and free access to the radiation-associated solution. Garcia

et al. (1955) went on to suggest that it was the nausea-inducing effects of the radiation that were responsible for the decrease in saccharin consumption. That is, the gastrointestinal disturbance brought on by the radiation had become associated with the taste of the saccharin solution, resulting in the animal's avoidance of the solution on its subsequent presentation (i.e., a ▶ classical conditioned taste aversion). In addition to being robust (and as revealed in follow-up research with radiation and classical emetics), CTA learning is acquired rapidly (usually taking very few pairings, and in some instances, only a single pairing), occurs with ▶ long delays between consumption and the onset of illness, and is established selectively to gustatory stimuli, i.e., non-gustatory cues are only weakly associated with illness. This avoidance has been suggested to be an evolutionarily significant response to ingestion of foods that could be potentially toxic to the animal. Thus, the ability of an animal to quickly (and selectively) ▶ associate ingestion of specific foods or tastes (likely sources of natural toxins) with disruption to its internal milieu could be thought of as a protective factor against accumulating dangerous or fatal amounts of a toxin due to overconsumption. Later studies showed that a wide number of compounds, many of which were considered to be toxins, produced a CTA, and often at doses lower than those shown effective in other measures of ▶ drug toxicity, suggesting that the CTA design may provide a sensitive measure to assess drug toxicity.

Although based on toxicology, CTA learning was not limited to classical emetics (see bibliographic database www.ctalearning.com). In fact, drugs such as ▶ alcohol, ▶ morphine, and ▶ cocaine that are abused by humans are also effective at inducing CTAs, leading some to classify this phenomenon as "▶ paradoxical" in that drugs of abuse are typically considered to be reinforcing stimuli (Hunt and Amit 1987). In this context, the issue becomes how drugs that produce an approach response in maintaining ▶ self-administration also produce the avoidance seen in CTA. Drugs that are abused by humans have been shown to produce multiple stimulus effects in the user. Rather than being reported as only rewarding or aversive, drugs of abuse typically produce an array of effects that combine to produce an overall drug experience. Preclinical, as well as some clinical, evidence provides support for these multiple stimulus effects. For example, animals will bar-press for an injection of a drug, but they will avoid a saccharin solution that is paired with the same self-injection. In a runway model of self-administration, animals will increase the speed with which they run to a goal box for an injection of a drug, but then hesitate prior to entering the goal box, suggesting concurrent rewarding (increased running speed) and aversive (hesitation) drug effects. Finally, individual animals display both an approach and avoidance response to stimuli paired with a drug injection such that they spend more time in an environment that is paired with drug effects, but at the same time avoid a sweet solution paired with that same drug. Interestingly, in humans, both rewarding and aversive effects have been reported for opiates, as first time users report the subjective effect of heroin as a "good sick," while cocaine users indicate a "rush" produced by the anxiogenic effects of the drug. Subjective ratings for specific drugs such as alcohol include not only positive ratings such as euphoria and relaxation, but also include negative ratings such as drowsiness, loss of motor coordination, ▶ withdrawal (or hangover), etc.

Although there is ample evidence that a complex array of effects are produced by drugs of abuse, it is important to view the "aversive" and "rewarding" properties of these drugs, not as a simple dichotomy (Hunt and Amit 1987) of drug effects, but rather as dynamic and interacting sets of effects that determine the abuse liability of a particular drug as well as the abuse potential for any individual. The likelihood of a drug becoming abused by an individual (or ▶ abuse liability) then would be the result of the balance between the rewarding and aversive effects of the drug (see Fig. 1; see also Stolerman and D'Mello 1981). There are many environmental, genetic, individual, and pharmacological factors that can influence this vulnerability to addiction. The individual experience of a given drug will not be the same for all users, which would help to explain why only a small subset of the population which tries a drug continues its use, escalates its pattern of intake, or becomes addicted.

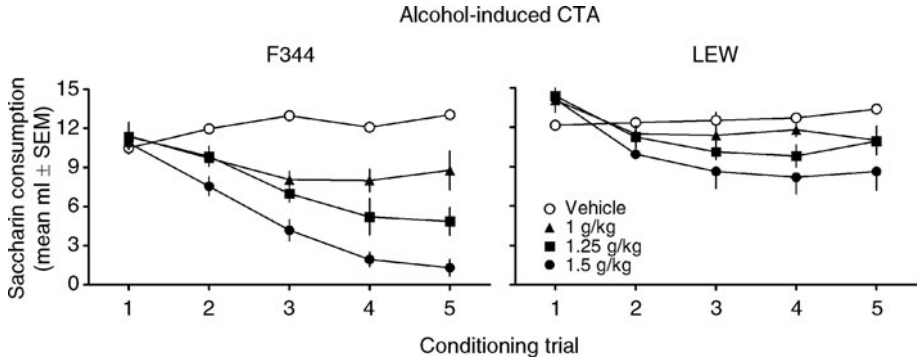
Understanding which factors influence some individuals (but not others) to become addicted has been a central issue in drug addiction research. One factor that seems to be crucial for continued drug-taking is the user's initial response to the drug. In a population of drug addicts, Haertzen et al. (1983) found that the reinforcing quality of an individual's first drug experience was related to its likelihood of subsequent use. This was true for a number of abused drugs, including alcohol, the opiates, and cocaine. Thus, users that reported having a greater euphoric or pleasant experience when taking the drug for the first time were more likely to continue taking that drug, making them more vulnerable to addiction. Conversely, individuals who experienced negative or aversive effects of the drug on this initial exposure were less likely to try the drug again. This work suggests that some individuals may be more sensitive to the aversive effects produced by a drug, which apparently acts as a limiting or



Conditioned Taste Aversions. Fig. 1. The balance between the rewarding and aversive affective properties of a drug influences total drug intake. When a drug of abuse is administered at low doses, the subjective effects are primarily rewarding (green-dashed line), leading to dose-dependent increases in drug intake or self-administration (blue-solid line). However, as the dose of the drug increases, aversive drug effects (red-dotted line) begin to influence the amount of drug self-administered (in their balance with the drug's rewarding effects), leading to lower levels of overall intake. The intensity of the aversive effects experienced during initial drug use impacts the probability of future drug taking. Changes in the aversive effects (resulting from experience with the drug or specific characteristics of the individual) impact a user's likelihood of subsequent use or abuse of the drug. This is based on a conceptualization by Greg Busse (2004).

protecting factor for continued use (Fig. 1). If this is the case, studying the various factors that can influence such aversive effects becomes just as important as studying the factors that can alter drug reward. CTA learning offers such a model in which the drug's aversive effects become paired with a distinctive flavor. In this case, changes in consumption (reductions) index the drug's aversive effects. The procedure also allows one to see how such effects vary with experimental manipulations and subject characteristics.

As noted, a variety of factors affect the likelihood of drug use and abuse. Some are specific manipulations such as dose of the drug and frequency of its use, while other factors are more characteristic of the user. A subject characteristic that is widely considered to be important in drug addiction is genetic predisposition or ► pharmacogenetics. One way that the genetic influence on drug abuse has been studied in the laboratory is through the use of selected or ► inbred rat strains, or mouse lines as ► animal models of particular aspects of the disease. An animal model that has received considerable attention in drug abuse research in recent years is that of the ► Fischer (F344)/Lewis (► LEW) ► inbred rat strains which show diverse drug intake and responsivity patterns across a number of drug classes (a review of genetic effects on CTA in rodents can be found in Riley et al. 2009). One among the drugs for which these strains show marked differences is alcohol. During oral self-administration studies, the LEW strain consumes greater amounts of alcohol than the F344 strain. However, it does not appear to be the case that the alcohol is more rewarding in LEW compared to F344, because both strains show comparable alcohol-induced ► conditioned place preferences, a model of ► conditioned drug effects sensitive to drug reward. Instead, the differences in alcohol consumption appear to be rooted in a differential sensitivity to the aversive effects of the drug. Specifically, F344 rats show greater suppression of saccharin drinking (i.e., a stronger CTA) when saccharin is paired with a dose of alcohol than the LEW strain (see Fig. 2). That alcohol is reinforcing in F344 rats is evidenced by acquisition of alcohol self-administration, yet their failure to exhibit the levels of intake seen in the LEW strain may be due to the aversive effects of the drug serving as a limiting factor in overall intake. The relation of CTA to drug self-administration is also exemplified in correlational analyses of these behaviors in various mouse strains with similar results. Using a number of genetically distinct mouse lines, it has been shown that the degree of alcohol-induced CTA is related to overall levels of alcohol intake such that the mouse lines that consume high levels of alcohol display little or no CTAs when an alcohol injection is paired with saccharin intake. Those mouse lines that drink very little alcohol are the ones that show the greatest levels of alcohol-induced taste aversion conditioning. Interestingly, mice that show the greatest levels of CTA also show greater severity of alcohol withdrawal, suggesting an overall increased sensitivity to the aversive effects produced by alcohol. The oral self-administration of alcohol appears unrelated to the acquisition of alcohol-induced place preferences in these strains, suggesting that the differences in alcohol self-administration are mediated more by differences in alcohol aversion than alcohol reward. While we have chosen to focus on alcohol, parallel effects with the F344/LEW model, in particular, are evident with a diverse range of drug classes and include compounds such as morphine, ► nicotine, and cocaine. Further, a variety of parameters other than strains, for example drug history, dose of the drug, route of administration, age, and sex have been shown to impact taste aversion learning (see Riley and Freeman 2004) as well as drug self-administration (see Schuster and Thompson 1969) in related ways, suggesting



Conditioned Taste Aversions. Fig. 2. Dose effect of alcohol-induced conditioned taste aversions (CTA) in the Fischer (F344) and Lewis (LEW) rat strains. Both strains show dose-dependent reductions (from vehicle-treated rats) in saccharin consumption when alcohol (injected intraperitoneally) followed saccharin. However, the F344 strain displays a greater sensitivity to the aversive effects compared to the LEW strain. Interestingly, LEW rats consume greater amounts of an available alcohol solution (per body weight) than F344 rats, suggesting that the greater sensitivity to the aversive effects limits alcohol intake in the F344 strain. Conversely, the LEW strain, which shows weak CTAs, may be more vulnerable to greater alcohol consumption because of their apparent insensitivity to its aversive effects. (Figure redrawn from Roma et al. 2006.)

that the drug's aversive effects limit drug intake in self-administration studies. More work is needed to further characterize how the avoidance response seen during CTA ultimately impacts drug self-administration.

Although these animal models of genetic predisposition to drug abuse are important in demonstrating the relationship between the aversive effects of drugs and drug intake and how various factors may influence these aversive effects, analogous findings in humans is essential for validation as a true model of the human condition. The clearest example of this comes from high prevalence rates of ► alcohol abuse and dependence in sons of alcoholic fathers. Through a genetic variation in enzymes important for alcohol metabolism, these individuals are thought to be less sensitive (i.e., a biological predisposition for tolerance) to the aversive (or punishing) effects of alcohol (for a review of human CTAs to alcohol, see Baker and Cannon 1982). The decreased sensitivity to the behavioral (ataxia) and physiological (cortisol release, disruption to EEG patterns) responses to alcohol may be among the factors that limit intake in the normal population. Without the experience of the aversive alcohol effects, sons of alcoholics are more likely to exhibit patterns of heavy drinking. In a second example, a genetic enzymatic variation seen in the Asian population, which has a very low incidence of alcoholism, exacerbates the aversive effects of alcohol (via a failure to metabolize ► acetaldehyde), producing greater facial flushing and more reported subjective complaints. Such effects are seldom seen in Caucasians (who have a low frequency of this specific allele and a higher frequency of alcohol abuse).

This relationship between the aversive effects of drugs and a risk for drug use and abuse seems to be important for the human user as it is in our animal models. CTA offers a procedure by which we can assess the aversive effects of a drug and how they might impact overall drug acceptability for an individual or group. Understanding the contribution of a drug's aversive effects to drug intake and addiction vulnerability (as well as how these effects are impacted by the numerous factors known to affect drug self-administration) may give insight into the etiology of drug use and abuse and its potential treatment.

Cross-References

► Abuse Liability Evaluation
► Addictive Disorder: Animal Models
► Alcohol
► Alcohol Abuse and Dependence
► Classical (Pavlovian) Conditioning
► Cocaine
► Conditioned Drug Effects
► Conditioned Place Preference and Aversion
► Nicotine
► Opioids
► Pharmacogenetics
► Self-Administration of Drugs
► Sex Differences
► Withdrawal Syndromes

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Conditioned Taste Avoidance

► Conditioned Taste Aversions

Conditioned Taste Preferences

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Synonyms

Conditioned flavor preferences

Definition

Conditioned taste preferences refer to ► appetitive responses evoked by tastes associated with the effects of a drug manipulation. Taste preferences are best seen when a drug-paired taste is presented on a drinking test concurrently with a control taste not paired with the same drug manipulation; the conditioned taste preference is evidenced by a relative increase in the consumption of the paired taste. There are conditioned preferences for tastes paired with most self-administered drugs due to the conditioning that takes place during the training for self-administration. Taste preferences can also be produced in experimentally naive rats without extensive training by pairing tastes with an injection of low doses of ► opioid analgesics or with the offset of drugs having acute aversive effects. Conditioned taste preferences help understand the interplay between initially aversive effects of drugs and incentive effects that characterize motivation for drugs in the dependent organism. They also provide an interdisciplinary model of ► drug cues. Taste stimuli and related oral stimulation are important for the intake, enjoyment, and quality of self-administered drugs that are drunk, chewed, or smoked.

Current Concepts and State of Knowledge

Conditioned taste preferences are formed by the pairing of a distinct taste with the motivational effect of a drug with ► abuse liability. This effect is variously referred to as incentive, reinforcer, or reward. It is generally believed that the preferences are due to the activity of the drugs in the reinforcement system in the brain (see ► Reinforcement Disorders) and that they underlie the ► self-Administration of drugs. It is further understood that these effects can also be transferred through the pairing to the paired stimulus such that the stimulus comes to elicit some of the effects of the reinforcers.

The protocols used for studying conditioned taste preferences fall within the general literature on ► conditioned drug effects. They constitute simple conditioning paradigms, which model features of the motivational processes underlying the addictive properties of drugs (see ► Addictive Disorders: Animal Models). They are similar to the procedures of ► conditioned place preference and aversion and the same as those used to study ► conditioned taste aversions. Moreover, the latter two procedures define the ► paradoxical effects of drugs; the conditioned taste preference phenomenon bridges the outcomes that give rise to this paradox.

Unfortunately, drug-produced conditioned taste preferences do not have a concentrated systematic body of data. The relevant findings are found over a wide range of parametric aspects of the phenomenon (protocols used, degrees of training, methods of applying the taste, nature, and forms of application of drugs used to train, species, age and developmental stage of subjects, purpose of the

studies). Studies on paradigms other than those for taste preference conditioning are also relevant. Taste preferences have often been missed only because the designs and the methods were intended to detect the exact opposite effect. These are relevant for epistemological reasons and serve to indicate the voids and points of emphasis in the literature. Moreover, conditioned taste preferences likely occur for different reasons. Listed below are a few of the issues, which largely serve only to define the phenomenon.

Conceptual Issues of a Taste Conditioning Produced by Drugs

Conditioned taste preferences have been validated in different ways using nondrug reinforcers. They are seen to previously neutral tastes paired on a small number of occasions with electrical brain-stimulation reward, with pleasant foods or with pleasant flavors. More commonly, conditioned preferences are found for flavors of a food and this can be enhanced by the deprivation of the nutrient.

In the area of alcohol and drug dependence, the oral route is a historically old and simple method of drug application, and with few exceptions, oral drug application embodies taste stimuli that will undergo conditioning. Even for smoking, the sensation in the mouth and throat is reported as important for the pleasure derived. The conditioning does not have to be strong, if it is considered that smoke intake occurs at least 10 times per cigarette. A middle-aged smoker on a pack a day for three decades would have in the order of 2 million pairings of oral stimulation and the effects of smoking.

The self-administration procedure often requires extensive and complex training (Meisch 2001; Stolerman and D'Mello 1981) and it is important that cues be available to the organism. Tastes play an important role in the oral self-administration, since the swallowing of drugs is not pharmacologically efficient. The onset of the pharmacological effect after oral drug application is generally slow and variable. Only little drug may reach the brain due to problems of absorption from the gut wall and high metabolism as the blood passes through the liver before being sent to the brain. Therefore, tastes of the drug are particularly important for signaling the reinforcing effects of the drug (Meisch 2001; Stolerman and D'Mello 1981). The paired taste would simply increase the probability that the fluid carrying the taste would be consumed. For example, the taste of a fluid can act as discriminative stimuli for further drinking. It ensures that drinking occurs and that it is the fluid containing the drug and not another fluid that is chosen and swallowed. The paired taste can also act as conditioned stimuli due to the pairing with the drug effects. After the taste is sampled, one could say that the paired taste keeps the organism in its vicinity or "pulls" it back if it does leave. This is the generally the way drug cues are thought to maintain drug intake in drug consumers and to re-initiate high intake in abstinent individuals.

However, it was originally found that the formation of taste preferences after pairing with psychotropic drugs would not occur without long-term exposure to the drug and to the taste. Solutions of drugs needed to produce pharmacological effects usually have disturbing tastes. For example, both alcohol and morphine taste badly, by leaving a burning sensation on the tongue and by being bitter like the rind of a grapefruit, respectively. In addition, the rat is the preferred experimental animal for studying motivational processes and it is an omnivorous eater that does not consume any new foods or fluids without confirming that they are not toxic. Rats will avoid the taste of any newly ingested material associated with perceived changes in internal state, as it could be an indicator that the ingested substance has toxic effects (see ► conditioned taste aversions). As this might suggest, conditioned taste aversion is a very common effect seen on the initial dosing of most psychotropic drugs. Consequently, the conditioning of taste preferences has traditionally received little attention in the drug-naive organism.

The Traditional One-Choice Method for Studying Taste Conditioning

The systematic study of conditioned taste preference in laboratory animals is closely related to the application of special conditioning protocols. In taste conditioning procedures where conditioned aversion is the target of interest, the drug manipulation is usually paired with a single very palatable experimental solution. A high baseline of taste consumption under control conditions makes a condition taste preference difficult to observe and only a few significant effects have been reported (Gaiardi et al. 1991; Mucha 1992). Appropriate would be the application of experimental tastes that do not show maximal consumption, thereby making it easier to demonstrate an increase in its consumption after pairing with a drug-related effect. Aside from some exceptions (e.g., Green and Garcia 1971) this has not been routinely used. Indirect evidence for the existence of a preference effect has also been suggested in the data of the one-taste conditioning model by comparing the pattern of dose-response curves for taste conditioning produced by different drugs and to those of toxins. Thus, Hunt and Amit (1987) compared taste aversions to other acute responses

produced by drugs and concluded that a simple process of conditioned aversion could not account for all of the findings.

A variation of a one-taste model where preferences do emerge involves ► drug taste preference conditioning (see ► Alcohol Preference Tests). In the case of morphine taste preference conditioning, the development of a preference for the solution containing morphine can be made apparent against a baseline comprising a normal rejection of the aversive solution of morphine in subjects that do not have the pairing. However, the gradual consumption of a solution that is unpalatable does not necessarily evidence the development of a preference for several reasons. For example, repeated exposure to tastes lead to habituation, sensitization, contrast effects, changes in food intake, and so on. Thirst develops under conditions of forced drinking of an aversive solution and this would counteract the aversion. These processes and the drinking will also interact with the acute drug effects. The actual treatment drug may produce, for example, general malaise and hyperactivity. Drug effects would also affect taste sensitivity, alter general motivational states, and produce sensory impairment, overshadowing stimuli, etc. In such a one-taste paradigm like these, confounds can only be dealt with by applying additional groups and control conditions (Mucha 1992; Stolerman and D'Mello 1981).

An efficient solution to some of these problems is to offer the same test subject an alternate taste in a choice test. Much work on both conditioned aversion and conditioned preferences involve simply offering the test subjects a choice with water. For example, one can conclude that a preference is present when taste that was previously strongly avoided is now preferred relative to the water (see ► alcohol preference tests). The overall levels of fluid consumption would control for nonspecific effects of the training drug on fluid regulation. Care is nevertheless needed to avoid biases due to the left or right position of the experimental test on choice tests (Stolerman and D'Mello 1981). The use of choice tests with a water choice is still not fully adequate. In the case of drug taste preference conditioning using morphine-containing fluids, the preference produced by morphine could only be interpreted when the morphine solution was substituted for a taste similar to the bitter taste of morphine (Stolerman and D'Mello 1981).

The Two-Taste Test Paradigm and the Study of Experimentally Naive Rats

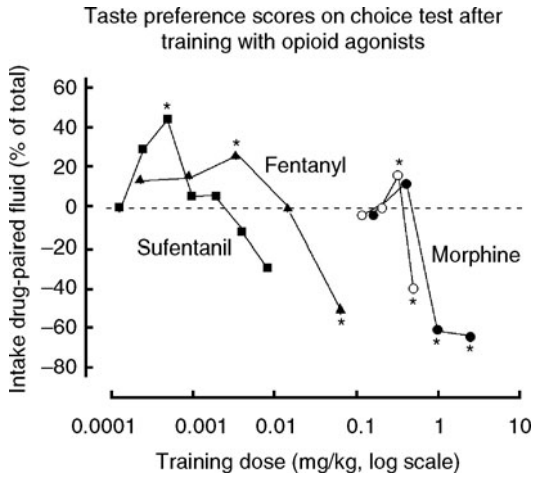
The two-taste method is a differential two-stimulus classical conditioning procedure. In this procedure, one taste is paired with the drug manipulation and a second taste is paired with a control manipulation. It provides robust within-subject control conditions and can be used to show subtle conditioned changes after only a few drug exposures (Mucha 1992). This method was first used to show a preference for a taste paired with a drug-related effect by Green and Garcia (1971). They paired a taste with the offset of the effect of a high dose of the ► dopamine agonist, ► apomorphine. The direct effect of the dosing induced illness: the same rats showed a taste aversion to a different taste presented just before the same injection. The conditioned preference was referred to as a "medicinal" effect of the offset of the emetic. Such a medicinal effect was also noted when the effects of nicotine infusions were blocked with a nicotine antagonist.

The use of two taste cues for discriminated conditioning procedures was largely developed over the course of work on the aversive effects of psychoactive substances (e.g., ► morphine, ► psychostimulants, and opioid agonists) during neuropharmacological studies at the University of Birmingham (UK) by David Booth, Charles Pilcher, Ian Stolerman, and others. However, the appetitive responses of tastes paired acutely with drugs only became apparent later when the procedure was applied to study low doses of sufentanil and fentanyl, two highly potent opioids (reviewed by Stolerman 1985).

In Fig. 1, there are taste preferences seen with adult rats in a two-taste conditioned preference procedure. There is a biphasic effect of dose with a preference effect seen at lower doses and aversion at higher doses. Thus, after a phase of adaptation to a water-deprivation schedule, rats were allowed to consume a target taste. This taste was paired shortly after using a subcutaneous injection of one of a range of doses of a test drug. The drug comprised one of three opioid analgesics (see Fig. 1). On another occasion, the same rats also received a second taste paired with a control manipulation (saline injection). The experimental and control pairings were repeated each day over 3 days. On a subsequent day each rat was then tested by offering the two tastes simultaneously for 24 h. Morphine shows the biphasic dose effect only with extended pairings (Fig. 1, *open symbols*).

Mechanisms of Conditioned Taste Preferences

Like conditioned place preferences (see ► conditioned place preference and aversion), taste preferences index simple approach or appetitive responses produced by a previously neutral stimulus paired with a drug reinforcer. They extend to gustatory and flavor stimuli experimental work based on environmental or place cues. However, until the 1980s, considerable attention was given to the idea that the initial application of self-administered



Conditioned Taste Preferences. Fig. 1. Taste preference scores of rats trained with different doses of three mu-opioid receptor agonists; the data for each point were collected using independent groups of subjects. *Abscissa*: the doses of the pairing drug. *Ordinate*: mean of the difference between the volume of consumption of the drug- and the vehicle-paired tastes expressed as a percent of total fluid consumed. The *open circles* indicate data from rats trained with morphine using six pairings instead of three pairings. The *asterisks* indicate significant effects. (redrawn from Mucha and Herz (1985) Psychopharmacology 86:274–280.)

substances only produced taste aversions and that taste preferences were not produced in these situations. The fact that low doses of opioids in drug-naive animals also show conditioned taste preferences refute this notion. Some of the paradoxical effects of self-administered drugs are indeed due to the toxicity of high dosing typically used in the study of conditioned taste aversions. However, there are important differences between classes of addictive drugs, such as between opioids and psychostimulants. Indirect dopamine agonists such as ► amphetamine, for example, do not appear to evoke conditioned taste preferences, despite the fact that they act in the same general area of the brain as the opioids (Stolerman 1985). Therefore, conclusions about the opioids in the drug-naive animal probably do not generalize to drugs from other pharmacological classes.

The pattern of conditioned taste preferences in Fig. 1 likely reflects the activity of these training drugs on the mu-opioid receptors, as ► kappa-opioid agonists produced only aversions. The peak increases in intake of the drug-paired taste in the figure also correspond to the known relative activities of the test substances on the mu-opioid receptor. The conditioned taste preference also only occurs with ► stereoisomers active on the mu receptor, suggesting that, indeed, opioid receptors are involved. However, it is still not known whether opioid antagonists block the formation of these preferences (Stolerman 1985). Opioid antagonists used as training drugs also produce conditioned taste aversion in morphine-naive rats and this response is potentiated in animals treated chronically with opioids, (Mucha 1992). The taste aversions produced by opioid antagonists in drug-naive rodents are also limited to the stereoisomer active on the opioid receptors. Therefore, taste preference and taste aversions conditioning appear to be modulated by increases and decreases in activity on the opioid receptors, respectively (Stolerman 1985).

The conditioned taste preferences have not been studied using local brain injections, which would be necessary to show that they occur in the reinforcement system in the brain. The pattern of effects seen for the opioids in Fig. 1 parallel conditioned place preferences produced by these substances, which are known to be centrally mediated. Consistent with this, the potent opioid analgesics, sufentanil and ► fentanyl, which have the strongest effects in Fig. 1, have physicochemical properties allowing them to penetrate into the brain much more readily than morphine. However, there are a number of open questions, particularly regarding other substances active on the reinforcement system that fail to produce conditioned taste preferences under acute treatment conditions (e.g., amphetamine).

An important issue is that opioids give rise to physical dependence and their removal results in ► withdrawal syndromes. These states are highly aversive and can be alleviated by the reapplication of opioids (Mucha 1992). This was a major explanation of the motivation for the oral intake of drugs in the early studies of oral self-administration of drug. Clear evidence for the hypothesis is actually rare partly because incentive effects of a training drug confound tests for conditioned taste preferences produced by withdrawal. The effects in Fig. 1 are also seen at doses that are too low and infrequent to produce dependence. There are data from one-taste conditioning work and on morphine taste preference conditioning where animals were given supplementary injections of morphine independent of the taste preference conditioning. There was a suggestion for a facilitation of the preference conditioning in injected animals; however, the conclusions were still not fully in line with a withdrawal alleviation hypothesis. It was possible that the injections sensitized the incentive effects of the morphine or produced a habituation of the initial aversive effects (Gaiardi et al. 1991; Stolerman and D'Mello 1981). However, this

does not preclude a role for withdrawal alleviation with regard to other drugs, such as in ► alcohol preference tests.

Consumption of food can condition taste preferences and a conditioned taste preference may arise from a drug's nutritional effect. This can be the case for conditioned taste preferences reported for ethanol. This drug provides an organism with calories as well as pharmacological consequences and both of these effects seem to be important in accounting for its conditioned taste preferences (Cunningham and Niehus 1997). However, this cannot be the case for many other drugs that do not have nutritional effects, including the opioid analgesics in the figure.

Regarding other mechanisms, there are special issues of conditioned taste preferences formed in the human during a career of oral drug intake. Because of a paucity of data in the drug area, one needs again to address as models factors important for the development of preferences for and the eventually liking of the taste of foods. For example, Paul Rozin and colleagues have studied the development of preferences for flavors that were initially aversive, such as those that are spicy or bitter (see article by Debra Zellner in Bolles 1991). Peer group pressures or modeling (seeing another individual enjoy a spicy or bitter substance) promotes the liking for an initially aversive substance. Flavors can also be paired with reinforcing effects that do not come from the biological consequence of the ingestion, such as due to a pleasant environment or social interaction. In addition, expectations that a flavor is aversive may actually be seen as a goal for some individuals seeking adventure or thrills; indeed, such individual have a risk for developing alcohol and drug dependence (► risk taking, ► Attention Deficit and Disruptive Behavior Disorders). General anticipatory information about drug effects can also have a role in the formation of taste preferences, as predicted by other ► expectancies and their influence on drug effects. When the consumption of a flavor is found to have fewer negative consequences than originally anticipated, the flavor can thereafter be viewed as more pleasant. Also, experience with predictable negative events may give rise to anticipatory opponent processes that are hedonically positive.

Conditioned Taste Preferences as an Interdisciplinary Probe for Appetitive Effects of Drugs

Taste conditioning is easy to apply. The taste stimuli can be applied as liquids consumed for fluid balance and for nutrition or as fluids applied on to the tongue of experimental subjects. Therefore, unconditioned and conditioned tastes can be examined in many interdisciplinary situations. There is some experimental work on taste preference conditioning produced by drugs in the human. For example, a body of data in healthy coffee drinkers show that previously neutral tastes will evoke taste preferences when paired with ► caffeine intake (Yeomans et al. 2005). It may be important that this effect is not found in persons who are not high caffeine consumers. The methods for producing the taste conditioning are remarkably similar to those in animals and two taste, differential conditioning procedures have also been used. However, most of the preference effects produced by caffeine are based on subjective reports on the test flavors, rather than on actual consumption as used in animals.

Conditioning using tastes and related stimuli can also be seen in the perinatal organism. There are examples of conditioning to tastes delivered *in utero*; effects of drugs of abuse have not been paired with these, however. Gary Beauchamp and colleagues did confirm in the human that tastes taken in by breast-feeding women can be detected in the milk expressed from the mother; the taste of ethanol is one of these. Work with other aversive flavors such as garlic as models has also shown that the experience of such flavors by the young breast-feeding infant can promote a subsequent acceptance of those flavors by the infant itself.

Only neonatal rodents have been routinely used to study conditioned preferences produced by drugs. In 5-day old rat pups, Priscilla Kehoe and Elliot Blass showed with morphine a biphasic dose pattern of taste preference conditioning. A variation of the one-taste method was used. Rats received a single pairing of saccharin prior to a morphine injection. Five days later, the saccharin solution was infused over the tongue for testing. As compared to control animals, those injected with 0.5 mg/kg swallowed more of the solution; animals injected with 2.0 mg/kg swallowed less. The perfusion was carried out with a catheter implanted directly into the tongue of the animal, which may be traumatic and interact with the opioid effects. Therefore, it is important that the same pattern of effects was observed using an odor-conditioning paradigm. Taste is closely associated with olfactory processes; in fact, the flavors of most fluids are comprised of smells as well as tastes. Randall et al. (1992) used a single pairing with morphine in a two-odor conditioning paradigm and confirmed the low-dose preference and a high-dose aversion, as seen in Fig. 1 for the adult rat.

For a focused perspective on reinforcement processes, conditioned taste preferences and aversion are the phenomena of choice. Most investigators remain only interested in appetitive-conditioned effects and avoid any confusion seen with the competing conditioned taste

aversion effects. The conditioned taste preference procedures are often used in the literature to examine the interplay between aversive and incentive effects. For example, the taste conditioning methods are used together with other paradigms (e.g., place preference conditioning) to show different conditioned responses in the same study (e.g., Gaiardi et al. 1991). However, there is growing interest in assessing taste stimuli using the ► taste reactivity test. As systematically explored by Linda Parker and colleagues, this test is similar to the tests of a two-taste preference conditioning paradigm, since it can also evidence motivational responses of both positive and negative valence to a taste. However, this test has the additional feature that it can differentiate between different forms of conditioned aversive effects, such as the aversion produced by a self-administered drug such as morphine and one produced by a toxin. Data from a taste reactivity test were originally used to evidence ► liking and wanting produced by reinforcers.

Cross-References

► Alcohol Preference Tests
► Caffeine
► Classical (Pavlovian) Conditioning
► Conditioned Place Preference and Aversion
► Conditioned Reinforcers
► Conditioned Taste Aversions
► Drug Cues
► Drug Discrimination
► Drug Self-Administration
► Mu-Opioid Agonists
► Nicotine
► Opioid Analgesics
► Paradoxical Effects
► Relapse
► Withdrawal

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Conditioned Tolerance

Synonyms

Behavioral tolerance; Learned tolerance

Definition

Conditioned tolerance refers to those instances of tolerance where it is a consequence not only of neuronal adaptations to the effects of a drug, but also involves either (1) associative learning in a classical (Pavlovian) conditioning situation or (2) differential tolerance arising from the impact of contingencies of reinforcement in operant conditioning procedures. Tolerance within a classical conditioning paradigm may be seen as a ► conditioned drug effect and is sometimes called situationally specific tolerance; when results are interpreted according to the concepts of operant conditioning it is called ► behavioral tolerance.

Confusion Assessment Method

Synonyms

CAM

Definition

The CAM is a nine-item delirium diagnostic scale based on the DSM-III-R criteria for delirium. A unique and helpful feature of the CAM is that it has been simplified into a diagnostic algorithm that includes only four items

of the CAM designed for rapid identification of delirium by nonpsychiatrists. The four-item algorithm requires the presence of: (a) acute onset and fluctuating course, (b) inattention, and either (c) disorganized thinking, or (d) altered level of consciousness. CAM has also been validated in palliative care settings with a sensitivity of 88% and a specificity of 100% when administered by well-trained clinicians.

Confusional Arousals

► Parasomnias

Congestive Heart Failure

Definition

Heart failure is a global term for the physiological state in which cardiac output is insufficient for the needs of the body. In case the low cardiac output itself is the underlying cause, this is often termed congestive heart failure. Common causes of heart failure include myocardial infarction, hypertension, valvular heart disease, and cardiomyopathy. The PDE3 inhibitor milrinone is used for the treatment of congenital heart failure. However, one of its side effects is ventricular arrhythmias which might be fatal and therefore it is only prescribed when conventional treatment with vasodilators and diuretics has proven to be insufficient.

Cross-References

► PDE3 Inhibitors

Consciously Accessible and Nonconsciously Accessible Memory

► Declarative and Non-Declarative Memory

Consolidation

Definition

The process by which recently acquired information (i.e., labile, short-term memory) is progressively stabilized into a persistent form known as long-term memory.

Consolidation and Reconsolidation

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Synonyms

Memory restabilization; Memory stabilization

Definition

Consolidation and reconsolidation refer to transient memory stabilization processes: While consolidation processes stabilize newly acquired memories, reconsolidation processes re-stabilize reactivated, i.e., retrieved, established memories. Although synaptic consolidation and reconsolidation are universal properties of neurons, certain experimental conditions can reduce the probability of reconsolidation. For example, very strong memories are less likely to reconsolidate than weaker ones.

Impact of Psychoactive Drugs

Synaptic consolidation posits that new memories initially exist in an unstable state and are susceptible to amnesic treatments. Once they are resistant to these treatments they are referred to as ► long-term memories (McGaugh 1966). The predominant view of synaptic consolidation posits that new RNA and proteins must be synthesized by neurons to stabilize new memories (Kandel 2001). In addition, at the physiological level changes in the efficacy of synaptic connections (i.e., long-term potentiation; see ► long-term potentiation) are thought to reflect the biological substrate of memory (Martin et al. 2000).

The empirical evidence for the existence of a consolidation period is that new learning induces a time window during which subsequent memory performance can be (1) diminished by impairing neuronal function (e.g., inhibiting protein synthesis), (2) impaired by new learning, and (3) increased by manipulations that improve neuronal function (e.g., ► psychostimulants such as ► amphetamine) (McGaugh 2000).

► Synaptic reconsolidation posits that retrieval can transfer a consolidated memory from an unstable to a stable state. The currently available evidence suggests that new RNA and protein synthesis can be required for restabilization. In addition, there is preliminary evidence that changes in synaptic efficacy, thought to represent the biological substrate of memory, are subject to restabilization processes, i.e., reconsolidation (Nader and Hardt 2009) (see ► Learning & Memory: Molecular Mechanisms).

The existence of a reconsolidation period is deduced from evidence showing that reactivation of a consolidated memory induces a period of time during which subsequent memory performance can be (1) impaired by challenging neuronal function, (2) impaired by new learning, and (3) enhanced by manipulations that facilitate neuronal function (including ▶ psychostimulants (Nader and Hardt 2009)).

Synaptic consolidation and reconsolidation are different from Systems Consolidation. Systems consolidation and reconsolidation refer to the idea that the ▶ hippocampus plays a time-limited role in supporting memory. When found, the time course of systems consolidation in humans ranges from months to years, and in rodent models from weeks to months.

Constraints on Reconsolidation

Memory reconsolidation has been found in many paradigms and for many amnesic agents, but reconsolidation is not ubiquitous. Some memories, such as memories of unreinforced contexts (i.e., pure space), do not seem to undergo reconsolidation. Other memories can undergo reconsolidation when certain paramters or conditions are met. Several parameters that have been found to inhibit memories from undergoing reconsolidation include ▶ extinction consolidation, memory age, predictability of the reactivation stimulus, and training intensity.

Therefore, studies that test for the neuropsychopharmacology of reconsolidation must ensure that the training-parameters allow a memory to undergo reconsolidation. Otherwise, reconsolidaiton may not occur, and a negative effect of a neuropsychopharmacology challenge will be obtained, which might not reflect the inability of the pharmacological treatment to principally affect reconsolidation.

Comparing Reconsolidation and Consolidation

Care must be taken when directly comparing the results obtained from studies testing consolidation and reconsolidation, as often different protocols are used to study the two memory processes. For example, in a Pavlovian paradigm consolidation is studied by presenting both a conditioned (CS) and an unconditioned stimulus (US), whereas reconsolidation is usually induced by presenting the CS alone. Such small changes in protocols can lead to surprising changes in the molecular mechanisms mediating consolidation. For example, the mitogen-activated protein kinase (MAPK) pathway is engaged in the gustatory cortex when a novel, but not a familiar, taste is used in a ▶ conditioned taste aversion paradigm. Consolidation of contextual fear conditioning requires either one or two phases of protein synthesis and protein kinase A (PKA), depending on whether animals received one or two foot shocks. Therefore, reported differences in the neuropsychopharmacoloygy of consolidation and reconsolidation may reflect that a difference in mechanisms mediating the two memory processes exists, or simply that the induction protocols were different.

The neuropsychopharmacology of consolidation has been well described (McGaugh 2000). Although the neuropsychopharmacology of reconsolidation, has been a relatively new field, already many neurotransmitter systems and signaling molecules have been implicated in the mechanisms that underly memory reconsolidation (Diergaarde et al. 2008; Tronson and Taylor 2007). A number of studies have investigated the memory enhancing or disrupting effects of various pharmacological agents, which act on different neurotransmitter systems during the reconsolidation process. In these studies, the pharmacological agents were administered (rodents or humans) just before or after the reactivation of an established memory. Various paradigms have been used, including aversive memory tasks such as ▶ pavlovian fear conditioning and ▶ conditioned taste aversions; appetitive learning paradigms such as conditioned place preference (CPP); and ▶ passive avoidance tasks.

Glutamatergic System

The activation of ▶ NMDA receptors seems to be crucial for memory reconsolidation. The administration of drugs that affect these receptors pre or post retrieval has been shown to interfere with the reconsolidation process in a manner consistent with consolidation (Kandel 2001; Martin et al. 2000).

Several studies have tested the effect of NMDA antagonists on reconsolidation in rodents. When administered systemically, the non-competitive antagonist MK801 impairs the reconsolidation of fear memory, of appetitive memory for food-rewarded spatial discrimination task, of appetitive pavlovian task, and long-term cocaine or amphetamine-associated memories as measured by a conditioned place preference paradigm. With regard to NMDA agonists, there is evidence that d-cycloserine adminstered systemically or into the ▶ amygdala facilitates fear memory reconsolidation in rats.

Adrenergic System

As is the case for conslidation, memory reconsolidation can also be disrupted by ▶ beta-adrenergic antagonists. The antagonist ▶ propanolol impairs reconsolidation of aversive memory and reward-related memories when injected systemically in rodents. Propanolol can also

impair reconsolidation of addictive-drug associative memories such as cocaine and morphine-CPP.

In humans, oral administration of propanolol disrupts the reconsolidation of fear memories, resulting in a loss of the behavioral expression of fear in ► pavlovian fear-conditioned subjects (Kindt et al. 2009); and in patients with post-traumatic stress disorder, propanolol given after memory retrieval reduced the physiological response to the traumatic event.

GABAergic System

Memory reconsolidation can also be disrupted by administration of drugs that act on the GABAergic system. Systemic injection of the ► $GABA_A$ receptor agonist after memory reactivation reduced contextual fear. However, GABA antagonists seem to not have an effect on reconsolidation, as a study suggests in which the ► GABA antagonist bicuculline did not affect the reconsolidation of contextual fear memories.

Glucocorticoids

The ► glucocorticoid receptors, which are important for modulation of consolidation, have also been shown to be a target for the modulation of reconsolidation of aversive memories. Several studies have demonstrated that infusion of the glucocorticoid receptor antagonist RU38486 into the basolateral amygdala (BLA) after reactivation impairs long-term fear memories in rats.

Endocannabinoid System

There is clear evidence from experiments in rats that the ► endocanabinoid system plays an important role in the modulation of the reconsolidation process in various types of memories involving different brain areas. Post-retrieval infusion of the cannabinoid agonist WIN55,212-2 into the insular cortex blocked the expression of conditioned taste aversion memory. Bilateral infusion of WIN55,212-2 or HU210, another canabinoid agonist, into the ► amygdala after memory retrieval disrupted the reconsolidation of fear memory.

Infusions of the canabinoid agonist ► anandamide into the CA1 region of the dorsal hippocampus after memory reactivation impaired the reconsolidation of contextual fear memory whereas the infusion of a canabinoid antagonist AM251 facilitated it (de Oliveira Alvares et al. 2008).

Cannabinoids also play a major role in the reconsolidation of drug-reward-related memory as the antagonist ► rimonabant disrupted the reconsolidation of metamphetamine-conditioned place preference in mice (Yu et al. 2009).

Dopaminergic System

► Dopamine signaling via the D1 receptor is thought to be especially important for consolidation. This receptor is coupled to the cyclic AMP signaling pathways that are thought to be engaged during learning. Drugs that affect the dopaminergic system have shown to interfere with the reconsolidation process in some types of memories. In chicks, the D1 receptor antagonist SCH23390, when administered before retrieval, impaired passive avoidance memory. Drugs that affect dopamine reuptake also influence memory reconsolidation. Cocaine treatments after memory reactivation enhanced active avoidance memory in rats, but amphetamine did not affect reconsolidation of a morphine-related memory in a CPP task.

Cholinergic System

The effects of cholinergic drugs on memory reconsolidation are not as clear as for other neurotransmitter systems. Evidence in favor for ► acetylcholine neurotransmission in reconsolidation stems from studies in which the choline-uptake inhibitor hemicholinium was administered intracerebrally, and blocked consolidation and reconsolidation of an inhibitory avoidance in mice. In addition, there is some evidence that systemic injections of the acetylcholine receptor antagonist ► scopolamine impair reconsolidation of morphine-conditioned place preference in rats. However, administration of scopolamine into the ► amygdala had no effect on the reconsolidation of contextual fear memory.

Protein Kinases

In addition to the pharmacological agents that act directly on neurotransmitter systems, drugs that interfere with activation of some protein kinases (see ► kinase inhibitors) have been shown to affect memory consolidaton and reconsolidation (Tronson and Taylor 2007). For example, in rats, inhibition of PKA in the BLA by administration of Rp-cAMPS after memory retrieval disrupted conditioned fear memories and conditioned taste aversion. Activation of PKA by 6-BNZ-cAMP in the BLA enhanced fear-conditioned memories. However, in *lymnea* the PKA inhibitor KT5720 impairs long-term associative memory only when injected 6 h after, but not shortly after, memory retrieval.

Administration of the mitogen-activated protein kinase (MAPK) inhibitors UO126 impairs reactivated fear memories when inejected into the amygdala, and the reconsolidation of recognition memory when injected intracerebroventricularly. Reconsolidation of cocaine-CPP was also disrupted by infusing UO126 into the core of nucleus accumbens, and by systemic administration of the MAPK inhibitor SL327.

Cross-References

- ▶ Amphetamine
- ▶ Amygdala
- ▶ Conditioned Place Preference
- ▶ Conditioned Taste Aversions
- ▶ Dopamine
- ▶ Extinction
- ▶ GABA
- ▶ $GABA_A$
- ▶ Glucocorticoids Receptors
- ▶ Hippocampus
- ▶ Kinase Inhibitors
- ▶ Learning & Memory: Molecular Mechanisms
- ▶ Long-Term Potentiation
- ▶ NMDA Receptor
- ▶ Passive Avoidance
- ▶ Pavlovian Fear Conditioning
- ▶ Psychostimulants
- ▶ Synaptic Plasticity

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Constitutional

- ▶ Legal Aspects of Psychopharmacology

Constitutive Activity

Definition

The spontaneous isomerization of a receptor into an active (signaling) state in the absence of ligand, resulting in an increase in the basal tone of the system.

Constitutive Knockout

- ▶ Knockout/Knockin

Construct Validity

Definition

The extent to which an animal model of a psychiatric state has a sound theoretical rationale: in particular the extent to which the model and the disorder are homologous (see also: predictive validity, face validity).

Cross-References

- ▶ Animal Models of Psychiatric States

Content-Disordered Thought Processes

Definition

Abnormal, apparently unreasonable interpretations of one's own experiences and perceptions to which the person concerned adheres despite refutation by others.

Context and Cued Conditioning

- ▶ Pavlovian Fear Conditioning

Context-Dependent Catalepsy

Synonyms

Conditioned catalepsy

Definition

Context-dependent catalepsy occurs when a history of pairing the injection of a catalepsy-inducing drug, such as haloperidol, with the testing of catalepsy in a particular

environment results in acquisition by that environment of the ability to elicit catalepsy in the absence of the previously administered drug.

Context-Induced Reinstatement

Definition

In this procedure, laboratory animals are first trained to self-administer a drug or nondrug reinforcer in an environment (typically termed context A) associated with a specific set of "background" stimuli (e.g., operant chamber fan, time of day). During training, these stimuli become associated with the availability and effects of the reinforcer. Lever pressing is then extinguished in a different environment (typically termed context B) with a different set of "background" stimuli. During reinstatement testing under extinction conditions, exposure to the context previously paired with the reinforcer (context A) reliably reinstates operant responding.

Cross-References

► Reinstatement of Drug Self-Administration
► Self-Administration of Drugs

Context-Specific Drug Effects

► Conditioned Drug Effects

Contextual Fear

Definition

Fear of the environmental context associated with the administration of the unconditioned stimulus.

Contingency Management

Synonyms

CM

Definition

An intervention wherein behavior change is promoted by systematically providing reinforcement when treatment goals are achieved and withholding reinforcement or providing punitive consequences when treatment goals are not met.

Contingency Management in Drug Dependence

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Synonyms

CM; Financial incentives; Voucher-based reinforcement therapy

Definition

► Contingency management (► CM) is an intervention to change behavior by systematically reinforcing meeting treatment goals and withholding reinforcement or providing punitive consequences for unmet goals. This treatment approach is based on principles of ► operant conditioning, an area of psychology concerning the effects of reinforcement and punishment on the probability of future behavior. ► Reinforcement refers to the behavioral process whereby an environmental consequence increases the probability of a response, and ► punishment refers to a behavioral process where the probability of a response is decreased because of its consequence.

Current Concepts and State of Knowledge

Clinical and Scientific Rationale: CM is designed to increase motivation for behavior change in patients whose motivation to change varies over time. While drugs themselves can serve as positive reinforcers, CM is designed to replace these reinforcers with other healthier positive reinforcers for abstaining from substance use, attending therapy sessions, and taking prescribed medications (Higgins et al. 2008).

Important Features of CM Interventions: CM interventions promote behavior change using positive and negative reinforcement. Positive reinforcement involves the delivery of a reinforcing consequence such as a voucher to purchase retail items contingent on meeting a therapeutic goal such as abstaining from recent drug use. ► Negative reinforcement involves the removal, or a reduction in the intensity of an aversive event such as job suspension contingent on meeting a therapeutic goal such as successful completion of treatment. Positive punishment involves the delivery of an aversive event such as a social

reprimand contingent on a therapeutically undesirable response such as failure to attend therapy sessions. Finally, negative punishment, involves the removal of a positive condition such as forfeiture of clinic privileges contingent on the occurrence of an undesirable response such as resumption of substance use.

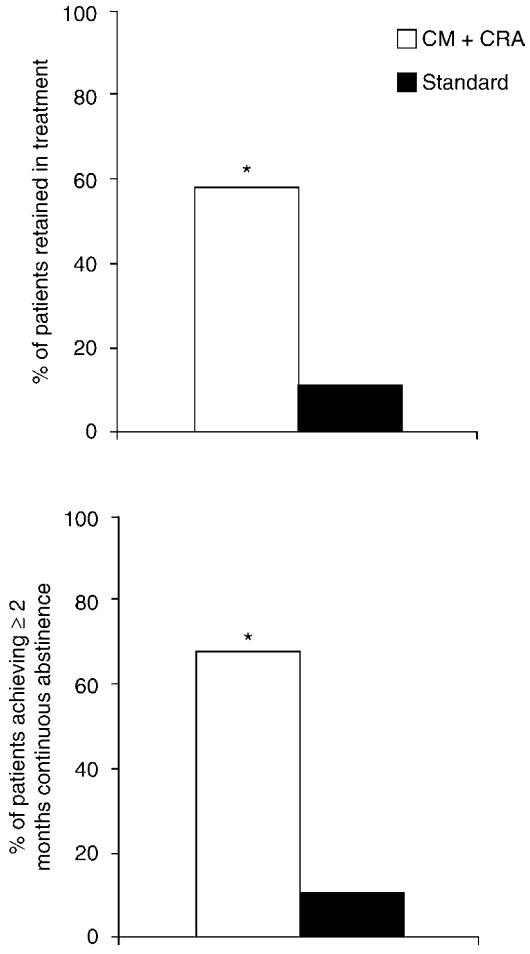
While reinforcement and punishment contingencies are effective, punishment is typically disliked by patients and staff, and can inadvertently increase treatment dropout. Nevertheless, judicious use of negative punishment can help to retain patients in treatment, reduce substance use, and improve other therapeutic targets.

Several practical considerations improve outcomes with CM interventions: (1) the details of the intervention should be explained carefully to patients prior to treatment, accompanied by written contracts; (2) the response being targeted by the CM intervention (e.g., drug abstinence) should be defined objectively (e.g., drug-negative urine toxicology results); (3) the methods to be used for verifying that the target response has occurred (e.g., urine toxicology testing) should be identified in advance; (4) the schedule for monitoring progress (e.g., Monday, Wednesday and Friday) should be outlined clearly; (5) progress should be monitored frequently to provide opportunities for patients to experience the programmed consequences; (6) the duration of the intervention should be clearly stipulated in advance; (7) the treatment should focus on a single target (e.g., abstinence from a single substance) rather than targeting multiple behaviors (e.g., abstinence from multiple substances); (8) the consequences of success and failure should be clear; (9) the delay to delivering consequences should be as short as possible. For example, delivering the consequence on the same day that the target response is verified produces larger treatment effects than delivering the consequence at a later time; (10) larger value incentives produce larger treatment effects.

Applications of Contingency Management: CM was first used with substance use disorders (SUDs) in a programmatic manner in the 1980s to reduce unauthorized drug use among patients enrolled in methadone treatment for opioid dependence (Stitzer et al. 1982). These studies showed that illicit drug use, even among severely dependent individuals, could be reduced using reinforcement contingencies, and they showed that medication take-home privileges for patients who otherwise had to report to the clinic daily were an effective incentive for increasing abstinence from unauthorized drug use (Stitzer et al. 1992).

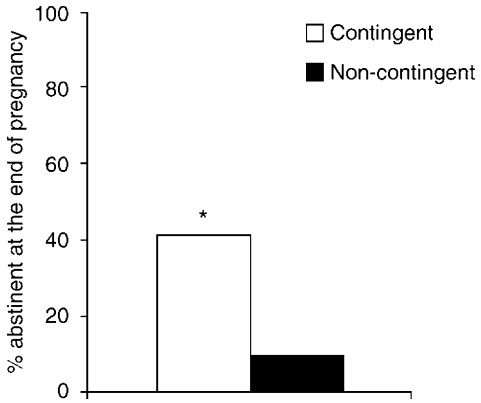
Later in a seminal study, ▶ cocaine dependent outpatients were randomly assigned to 24 weeks of behavior therapy including CM or to standard drug abuse counseling (Higgins et al. 1993). The CM intervention was 12 weeks in duration and explicitly integrated with routine urine toxicology testing. Participants earned points for drug-free urines that were recorded on vouchers. The first negative test results earned 10 points or $2.50 in purchasing power, the number of points earned increased by 5 with each consecutive cocaine-negative test result. Cocaine-positive test or failure to provide a specimen reset the value of the vouchers back to the initial low level. Five consecutive test results following a reset restored voucher value back to where it was prior to the reset. Money was never given to patients. Instead, patients were given vouchers to purchase retail items in the community such as gym memberships, fishing licenses, or gift certificates to local restaurants. Staff counseled patients to use vouchers to support involvement in healthy activities that could serve as attractive alternatives to cocaine use. If a patient earned all the points available across 12 weeks, he/she could earn a total of $997.50 in purchasing power. The CM treatment was combined with an intensive behavioral counseling intervention known as the community reinforcement approach (CRA) that focused on promoting healthy lifestyle changes. In that study, the majority (58%) of patients in the CM+CRA condition remained in treatment for the recommended 24 weeks of treatment compared to only 11% in the comparison treatment using standard drug abuse counseling (Fig. 1, top panel). Regarding cocaine abstinence, 68% of those treated with CM+CRA, achieved two or more months of continuous cocaine abstinence during the recommended treatment period that was verified by urine toxicology testing. By contrast, among those assigned to standard treatment, the majority either dropped out of treatment or resumed cocaine use, with only 11% achieving two or more months of objectively verified abstinence from cocaine use (Fig. 1, bottom panel). Subsequent studies on the treatment of cocaine dependence, replicated the findings described above, showed that voucher-based CM was an active contributor to the positive outcomes achieved with the CM+CRA approach, and also demonstrated continuing benefits for approximately 2 years after the CM program was discontinued.

CM has been applied to different types of SUDs in several different populations. A meta-analysis of controlled studies using voucher-based or related monetary-based CM to treat SUDs from January 1991 and March 2004 (Lussier et al. 2006), identified 63 reports of studies that targeted abstinence from substance use, clinic attendance, or medication compliance. The review supported the efficacy of CM.



Contingency Management in Drug Dependence. Fig. 1. Percent of patients retained for the recommended 24 weeks of treatment (top panel) and percent of patients achieving two or months of continuous cocaine abstinence during treatment (bottom panel). * indicates a significant difference between conditions ($p < 0.05$). (Adapted from Higgins et al. 1993.)

CM has been used with subpopulation, special subpopulation such as pregnant cigarette smokers (Heil et al. 2008). Eighty-two women who were still smoking upon entering prenatal care were randomly assigned to a condition where they received vouchers contingent on abstinence from recent smoking through 12 weeks following delivery of the baby or to a control condition where they received vouchers independent of smoking status (even if they kept smoking). Significantly more women in the condition where vouchers were earned contingent on recent smoking abstinence successfully abstained from smoking during pregnancy (41% vs. 10%; Fig. 2).



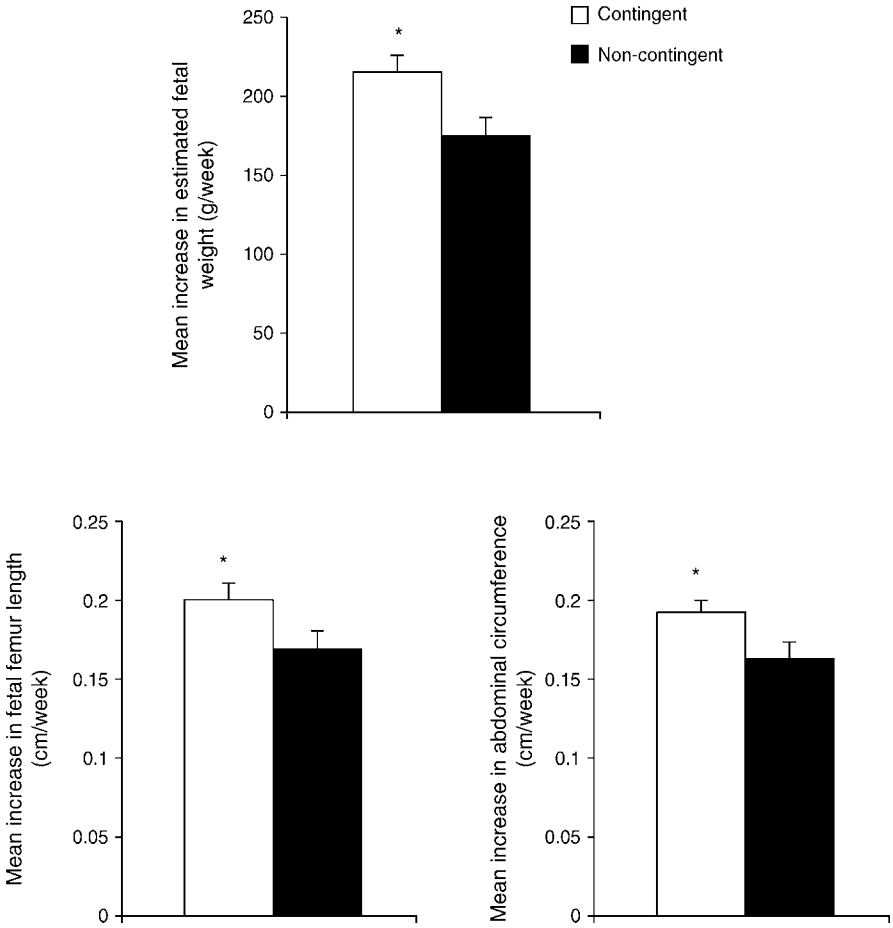
Contingency Management in Drug Dependence. Fig. 2. Point-prevalence smoking abstinence at the end of pregnancy. * indicates a significant difference between conditions ($p < 0.05$). (Adapted from Heil et al. 2008.)

Additionally, fetal growth was significantly greater in the condition where vouchers were earned contingent on smoking abstinence compared to the control condition (Fig. 3). Those outcomes were achieved with average payouts of $\$461 \pm 461$ in vouchers across, approximately 9 months of treatment.

CM has been successful in other applications with pregnant women. For example, it has been used effectively to increase abstinence from cocaine and heroin use among pregnant women (Silverman et al. 2002). CM is also effective at improving the likelihood of taking medication among those with infectious diseases. Improving compliance with antiretroviral medications for HIV/AIDS patients with SUDs is one example in that area (Rounsaville et al. 2008). Another special population with whom there is growing evidence of CM's efficacy is the seriously mentally ill who also have SUDs (Sigmon and Higgins 2006). CM is effective at reducing substance use in that population and reducing other complicating factors such as re-hospitalization rates that often go along with drug abuse among the mentally ill. CM is effective with adolescents with SUDs, with the evidence mostly centering on cigarette smoking and marijuana use. Finally, CM is an essential component in multi-element treatments for homeless crack and other drug abusers (Milby and Schumacher 2008).

Conclusion

CM treatments represent an important part of evidence-based interventions for SUDs. They are effective and sufficiently versatile to be used in different settings and with different population in need of treatment for SUDs.



Contingency Management in Drug Dependence. Fig. 3. Mean (±SEM) rates of growth in estimated fetal weight (top panel), fetal femur length (bottom left panel), and fetal abdominal circumference (bottom right panel) between ultrasound assessments conducted during the third trimester. * Indicates a significant difference between conditions ($p < 0.05$). (Adapted from Heil et al. 2008.)

While very effective, they do not represent a silver bullet. For example, improvements are needed to help the interventions succeed with a larger proportion of the patients treated, to develop methods that will ensure longer-term maintenance of beneficial effects over time, and to continue to develop and refine practical applications that will be used widely in society. The broad success to date should give great confidence in the continuing development and improvement of this approach to help address the adverse individual and societal consequences of SUDs. Moreover, CM interventions are being successfully extended to a wider range of public health problems, including, for example, increasing physical activity levels among the elderly and increasing weight reduction among obese adults. Taken together, CM interventions offer much promise for making important improvements in the public health.

Acknowledgments

Preparation of this chapter was supported by research grants DA009378 and DA008076 from the National Institute on Drug Abuse.

Cross-References

► Alcohol Abuse and Dependence
► Behavioral Economics
► Cocaine Dependence
► Nicotine Dependence and Its Treatment
► Opioid Dependence and Its Treatment
► Reinforcement Disorders

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Contingency of Reinforcement

Definition

A particular arrangement of consequences for an operant. The arrangements can differ in a variety of ways including differences in schedule of reinforcement and limits on the forms of behavior that are reinforced.

Contingent Tolerance

► Behavioral Tolerance

Continuous Reinforcement

► Fixed Ratio

Continuous Reinforcement Schedule

Definition

A schedule of responding used in operant conditioning. Emitting one response, such as a lever press or nose poke, results in the presentation of the reinforcer. This is also referred to as a fixed ratio 1 (FR1) schedule.

Controlled Clinical Trial

► Phase II Clinical Trial
► Phase III Clinical Trial

Controlled Clinical Trials

► Randomized Controlled Trials

Controlled Substances Act

Synonyms

CSA

Definition

The Controlled Substances Act (CSA) is the commonly used name for the Title II of the Comprehensive Drug Abuse Prevention and Control Act of 1970 passed by the U.S. Congress. It provides the basis for the current regulation of drugs of abuse in the USA (http://www.usdoj.gov/dea/pubs/csa.html). Drugs controlled under the CSA are assigned to one of five Schedules (I to V) based on their abuse liability. Restrictions on possession, sale, and distribution of drugs differ among the Schedules, with the most severe penalties given for violations involving drugs in Schedule I.

Cross-References

► Abuse Liability Evaluation

Conventional Antipsychotics

► First-Generation Antipsychotics
► Typical Antipsychotics

Conventional Neuroleptics

► First-Generation Antipsychotics

Convulex

► Valproic Acid

Cortical or Brain Waves

► Electroencephalography

Corticosteroid Receptors

Definition

Intracellular receptors for corticosteroid hormones. On hormone binding, they function as transcription factors in the nucleus of the cell to change mRNA expression and protein synthesis of target genes. There are two types: mineralocorticoid receptors (MR) and glucocorticoid receptors (GR).

Corticotropin-Releasing Factor

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Synonyms

Corticotropin-releasing hormone; CRF; CRH

Definition

The major neuropeptide transmitter responsible for orchestrating the endocrine, autonomic, immune, and behavioral responses to stress.

Pharmacological Properties

Introduction

Corticotropin-releasing factor (CRF), also known as corticotropin-releasing hormone (CRH), orchestrates the stress response in the endocrine, autonomic, immune, and behavioral systems through the activation of the hypothalamic–pituitary–adrenal (HPA) axis and extrahypothalamic pathways. The peptide itself is highly conserved between species, and its evolutionary role is to mobilize energy stores and appropriate behavior(s) in response to a stressor. It has since evolved to regulate a variety of responses to stress. CRF was first isolated and characterized by Vale and colleagues in 1981. Due to the similarity in sizes of ACTH and CRF and limits on detection techniques, purification was performed on approximately 490,000 sheep (ovine) hypothalami in order to generate enough samples for isolation. This was part of an ongoing study elucidating a variety of hypothalamic peptides. In the majority of studies, the CRF system has consistently been shown to be dysregulated in many patients suffering from a variety of psychiatric illness including post-traumatic stress disorder (PTSD), early life trauma, and major depressive disorder (MDD) (Nemeroff et al. 1984). In a few studies, the dysregulation of CRF activity has also been implicated in anorexia nervosa and Alzheimer's disease. During pregnancy, CRF plasma levels spike during the third trimester and have been implicated in parturition. The variety of molecular and behavioral responses orchestrated by this single peptide defines it as the central focus of stress research today.

Pharmacological Properties

CRF belongs to a family of ► neuropeptides including sauvagine (a peptide secreted from the skin of a South American frog *Pyllomedusa sauvagei*), the urocortins (endogenous neuropeptides with effects similar to those of CRF), and urotensin (a peptide secreted by the Goby fish). The CRF gene was cloned by Furutani and colleagues 2 years after the isolation and characterization of CRF itself and is expressed in diverse animal species, from zebrafish to all higher mammals. Human CRF is localized to the long arm of chromosome 8 at position q13.

The CRF gene is first activated by transcription factors to produce a 196 amino acid polypeptide. The polypeptide is posttranslationally cleaved at the N-terminus at position 147. The C-terminus is cleaved at amino acids 195–196 and undergoes posttranslational ► amidation. The importance of amidation is not clearly understood; however, sauvagine and urocortin, which also bind and activate CRF receptors, are amidated (Petrusz and Merchenthaler 1992). In vitro receptor binding experiments studying CRF receptors have shown that deamidated CRF has reduced binding affinity for the CRF receptor, clearly demonstrating an important albeit elusive role for amidation. The mature product is a 41 amino acid neuropeptide with a molecular weight of 4,758.4 Da

and an isoelectric point of 5.09. Human, rat, and mouse CRF are identical to each other and display significant sequence homology to ovine CRF (Table 1).

The CRF mature peptide structure was characterized by Lau in 1983 and forms a random coil monomer under physiological conditions. However, in an ► amphiphilic environment such as the cell surface, CRF forms an α-helix and displays an amphiphilic pattern of hydrophobic and hydrophilic surfaces segregated on opposite sides of the α-helix. Upon binding to the CRF receptor at the extracellular domain, the CRF peptide undergoes a conformational change to produce the α-helical secondary structure.

Peripherally administered CRF does not cross the ► blood–brain barrier but exerts effects via peripheral CRF receptors in the gut, on immune cells, or its major endocrine action on corticotropes of the anterior pituitary. Direct central administration of CRF in the ► hypothalamus and/or ► amygdala, as well as the cerebroventricular system, results in a pronounced endocrine and behavioral stress response.

CRF neurons are highly distributed but selectively clustered in the CNS. The densest region of CRF neurons is the parvocellular region of the paraventricular nucleus of the hypothalamus. These neurons project to the median eminence where CRF is released into the portal vessel system supplying the anterior pituitary to initiate the pituitary–adrenal axis endocrine response to stress. A significant number of CRF cell bodies are also localized in the central nucleus of the amygdala, the bed nucleus of the stria terminalis (BNST), and the locus coeruleus where CRF mediates appropriate behavioral and autonomic responses (Owens and Nemeroff 1991). The expression of CRF neurons in these areas, as well as others, infers a role of CRF in modulating monoaminergic systems. CRF neurons innervate noradrenergic cells of the locus coeruleus, the major noradrenergic cell body nucleus. Within the hypothalamus, CRF neurons are innervated by serotonergic, GABAergic, cholinergic and dopaminergic neurons as well as additional CRF neurons. This provides a feedback loop and turns off CRF expression (Petrusz and Merchenthaler 1992). Specific innervation patterns of extrahypothalamic CRF are not known but similar interactions with various transmitter systems are expected.

CRF immunoreactivity has also been localized in diverse areas outside of the brain. CRF is present in the adrenal medulla, pancreas, small intestine, stomach, and testis but a function in these organs is still unclear. It is believed that CRF and CRF receptor expression in lymphocytes and the organs of the GI tract may be involved in inflammation mechanisms in a variety of GI disorders. CRF is also present in the blood plasma to a small extent, although its use as a biomarker for stress has not been supported. During pregnancy, CRF plasma levels spike 6–40-fold during the third trimester of pregnancy but circulating ACTH and cortisol remain level during the entire course of pregnancy due to multiple mechanisms to keep free cortisol in check. Therefore, there is some other non-endocrine function of placental CRF, probably in the process of parturition.

The Hypothalamic–Pituitary–Adrenal Axis

"*My mind sent a message to my hypothalamus, told it to release the hormone CRF into the short vessels connecting my hypothalamus and my pituitary gland... It would help me fight like a wildcat or run like a deer.*"

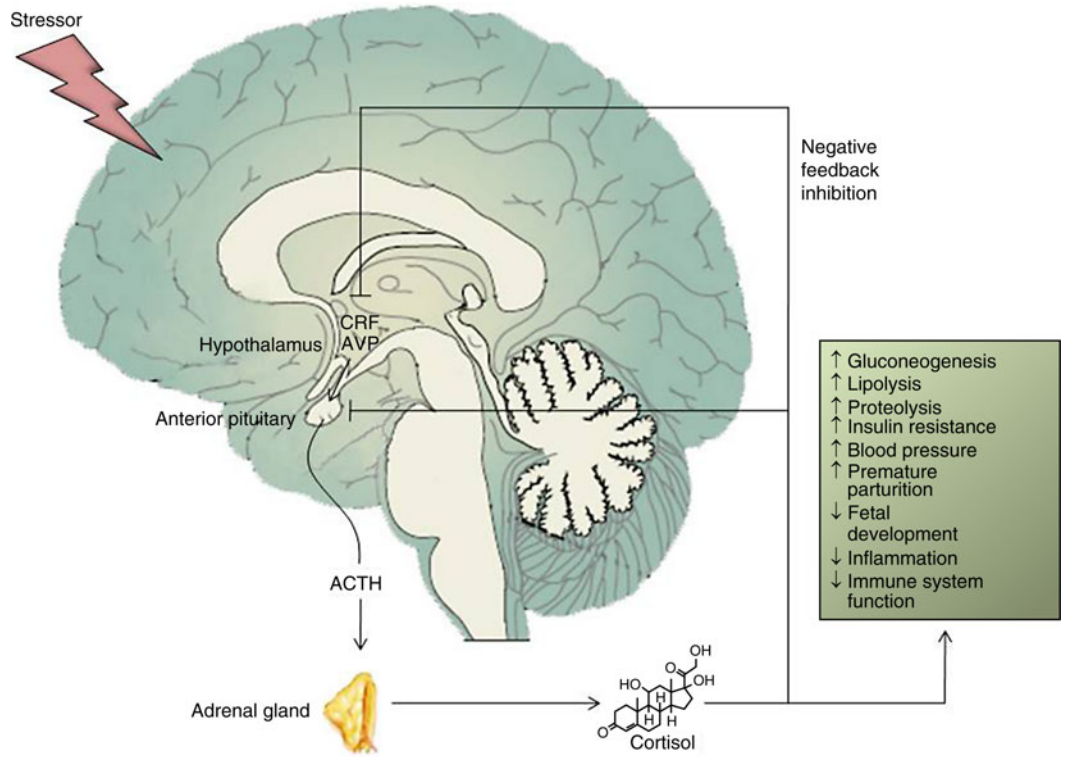
-Kurt Vonnegut, *Breakfast of Champions*

Corticotropin-Releasing Factor. Table 1. Pharmacological properties of CRF family peptides and antagonists. Homologous amino acid sequences to human CRF are highlighted (Adapted by permission from Grigoriadis 2003).

Peditpe	Amino acid sequence	CRF_1 K_i (nM)	CRF_{2A} K_i (nM)	CRFBP K_i (nM)
Human/Rat/Mouse CRF	SEEPPISLDLTFHLLREVLEMARAEQLAQQAHSNRKLMEII-NH2	1.5	42	0.19
Ovine/Caprine CRF	SQEPPISLDLTFHLLREVLEMTKADQLAQQAHSNRKLLDIA-NH2	1.1	230	310
Frog Sauvagine	PYR-GPPISIDLSLELLRKMIEIEKQEKEKQQAANNRLLLDTI-NH2	1.6	5.2	13
Zebrafish Urotensin I	NDDPPISIDLTFHLLRNMIEMARIENQREQAELNRKYLDEV-NH2	0.4	1.8	0.17
Human Urocortin 1	RDNPSLSIDLTFHLLRTLLELARTQSQRERAEQNRIIFDSV-NH2	0.4	0.3	0.23
Human Urocortin 2	GSRIVLSLDVPIGLLQILLEQARARAAREQATTNARILARV-NH2	>100	1.7	
Human Urocortin 3	RTKFTLSLDVPTNIMNLLFNIAKAKNLRAQAAANAHLMAQI-NH2	>100	22	
Rat/Mouse Urocortin 1	RDDPPLSIDLTFHLLRTLLELARTQSQRERAEQNRIIFDSV-NH2	0.3	0.6	
Rat Urocortin 2	DTRVILSLDVPIGLLRILLEQARNKAARNQAATNAQILARV-NH2	>100	0.7	
α-Helical CRF (9-41)	DLTFHLLREMLEMAKAEQEAEQAALNRLLLEEA-NH2	19	1.1	0.26
dPhe ^{12}Nle^{21,38}rCRF(12-41)	FHLLREVLEXARAEQLAQQAHSNRKLXEII-NH2	19	4.4	None
Antisauvagine-30	FHLLRKMIEIEKQEKEKQQAANNRLLLDTI-NH2	400	1.1	190
Astressin	FHLLREVLEXARAEQLAQEAHKNRKLXEII-NH2	0.7	0.6	
Astressin$_2$B	DLSFHLLRKXIEIEKQEKEKQQAENNKLLLDLI-NH2	>500	1.3	

The endocrine response to stress is mediated by the hypothalamic–pituitary–adrenal axis. The HPA axis is activated by a combination of neurons projecting from the amygdala and hippocampus along with the serotonergic and cholinergic (and possibly opioid) neuronal stimulation of CRF neurons in the paraventricular nucleus of the hypothalamus. This stimulates the release of CRF and increases the gene expression of CRF and vasopressin (Fig. 1). The peptide(s) are secreted from nerve terminals in the median eminence through the blood to the anterior pituitary gland via the portal plexus system. On the surface of corticotroph cells in the pituitary, CRF binds to the CRF receptors producing a G protein-coupled receptor (GPCR) signal transduction cascade activating G_s or G_i. The stimulatory G protein (G_s) activates adenylate cyclase, converting ATP into cAMP, which causes PKA activation. PKA activates CREB, a transcription factor, which increases the gene expression of proopiomelanocortin (POMC). As it undergoes intracellular trafficking, proteolytic cleavage processes POMC to produce the mature adrenocorticotropin hormone (ACTH) which is secreted into the peripheral blood circulation. There is a readily releasable pool of ACTH immediately available for release into the bloodstream as well. ACTH travels through the peripheral blood stream until it binds ACTH receptors/melanocortin type-2 receptors located on the zona fasciculata of the adrenal gland. The binding of ACTH causes a similar GPCR signal cascade resulting in PKA activation, which causes cholesterol sequestering and transfer to the mitochondria within steroidogenic cells. There, P450 side-chain cleavage enzyme binds cholesterol and converts it into pregnenolone, which undergoes further enzymatic reactions to form the glucocorticoid cortisol (Minneman and Wecker 2005). Cortisol is important in energy production, inflammation, fetal growth, development, and protein and lipid catabolisms.

The HPA axis is modulated by a negative feedback loop encompassing the hippocampus, hypothalamus, and anterior pituitary. Following cortisol secretion into the peripheral blood circulation, cortisol diffuses through the plasma membrane of cells in the pituitary, hypothalamus,



Corticotropin-Releasing Factor. Fig. 1. The hypothalamic–pituitary–adrenal axis. External stressors cause initiation of the HPA axis by first stimulating CRF neurons in the hypothalamus. Negative feedback inhibition loops return the system toward homeostasis (Adapted by permission from Krishnan and Nestler 2003).

and hippocampus where it binds to the ▶ glucocorticoid receptor (GR), a nuclear receptor transcription factor. Upon binding, the GR dissociates from a chaperone complex, which keeps it in an inactive state, and homodimerizes with another cortisol-bound GR. The homodimer translocates into the nucleus and binds to specific glucocorticoid response elements to cause the transcriptional regulation of CRF and POMC related genes, as well as many others, decreasing CRF and POMC production and release.

Metabolism

Unbound CRF is sequestered by a rather unique CRF-binding protein (CRF-BP), a 37 kDa protein characterized by Orth and Mount in 1987. CRF-BP and the CRF receptors bind CRF with similar affinity (0.2 nM). The protein also binds CRF fragments from residues 6–33 (designated as CRF 6–33) and residues 9–33 (CRF 9–33) with high affinity while the receptors bind these fragments with a lower affinity, supporting a role of the binding protein in modulating CRF ▶ bioavailability. Additionally, 40–60% of brain CRF is bound to CRF-BP, further supporting a role for this protein in CRF bioavailability. CRF-BP also binds peptides in the same family as CRF such as urocortin, sauvagine, and urotensin. In the brain, CRF-BP localization coincides with CRF and the CRF receptors in the ▶ amygdala and pituitary but is also distributed in the cerebral cortex and brain stem. Peripheral CRF-BP is highly expressed in only the human and primate placenta and to a lesser extent in the liver. These studies contribute to the theory that CRF-BP regulates CRF levels and acts as a reservoir for CRF when needed (Kemp et al. 1998). During the end of pregnancy, CRF-BP levels fall as placental CRF rises further implicating the protein as a CRF regulator. Novel treatments for mood and ▶ anxiety disorders (*vide infra*) may involve drugs targeting the CRF-BP in order to modulate free CRF concentrations without fully blocking the receptor as an antagonist might.

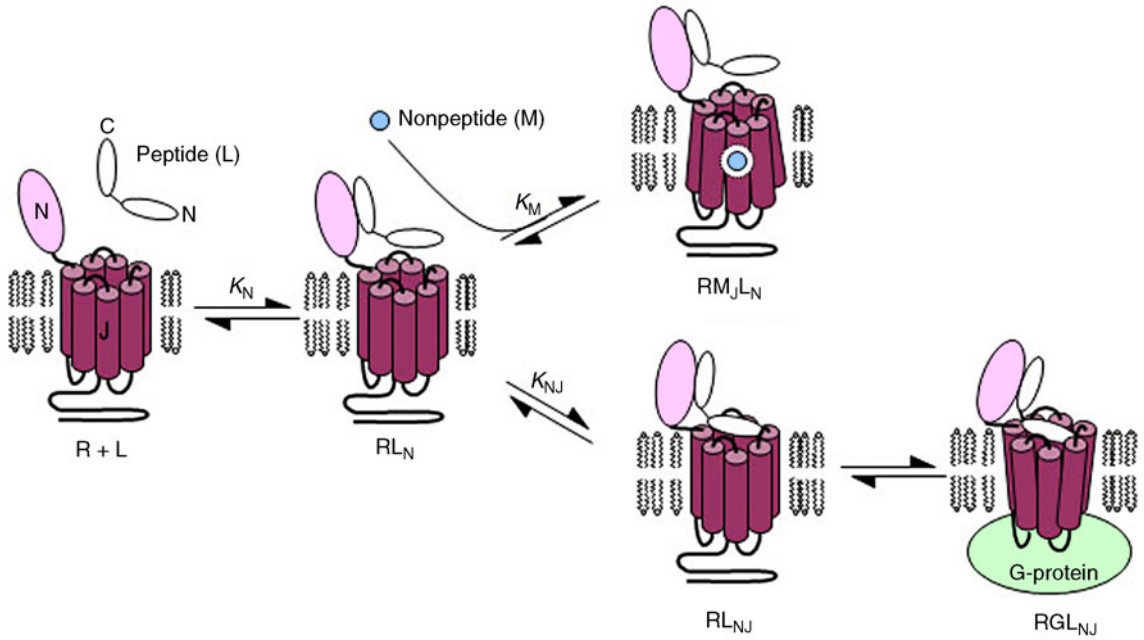
The endogenous enzyme(s) responsible for the degradation of CRF are unknown. However, experiments using purified endogenous ectopeptidases show that CRF is cleaved into smaller fragments. These fragments have reduced activity at CRF receptors.

Mechanism of Action

CRF binds exclusively to CRF_1 and CRF_2 receptors to produce its intracellular effects. Both CRF receptor ▶ subtypes are part of the Class B family of GPCRs, which also includes the calcitonin receptors and the parathyroid hormone receptor (De Souza 1995). Class B receptors contain an N-terminal extracellular ligand binding site (ECD), a seven transmembrane/juxtamembrane domain (JD), and a C-terminal binding site for the G protein (guanine nucleotide exchange protein). CRF binding has been proposed to proceed according to a "Two Domain Model" in which the C-terminus of CRF binds the N-terminus of the receptor (Fig. 2). This initial binding increases the affinity of the N-terminus of CRF for the J-domain of the CRF receptor. The N-terminus of the newly formed α-helical CRF binds the J-domain and initiates the activation of the CRF receptor, which can in turn activate adenylate cyclase via G-protein mediated signal transduction (Hoare 2005). This model explains some of the discrepancies in the loss of binding affinity observed in CRF fragments because the fragments may only be binding to one domain or blocking the binding pocket.

CRF_1 and CRF_2 receptor subtypes display 71% amino acid sequence homology to one another but mediate very different actions. CRF_1 receptors are implicated in the stress response while CRF_2 receptors are associated with feeding behaviors and, arguably, stress-coping behaviors. CRF_1 receptors are highly expressed in the anterior pituitary and mediate the pituitary–adrenal axis response to stress. It is also diversely expressed in the cerebral cortex, hippocampus, amygdala, cerebellum, and hypothalamus. Peripheral CRF_1 receptors are localized within the adrenal glands and the GI tract as well as the testis, ovaries, and immune system where they serve a variety of paracrine roles.

There are three separate ▶ isoforms of CRF_2 receptor delineated as CRF_{2A}, CRF_{2B}, and CRF_{2C}. These are produced from post-transcriptional mRNA processing of the same gene leading to splice variants, which produce different forms of the N-terminus and a single amino acid change at position 41. The exact importance of these changes is not clearly understood. However, binding studies have shown that the isoforms display slight changes in affinity for certain peptides in the CRF family (Dautzenberg and Hauger 2002). CRF_{2A} receptors are localized primarily in the lateral septum, raphe nucleus, and ▶ BNST. Unlike rodents, there is significant CRF_{2A} receptor density within primate cortex. Peptides that are CRF_{2A} selective antagonists have been shown to have some anxiolytic effects following stress conditions although transgenic studies in mice show that CRF_{2A} receptors may be involved in coping responses following stress. CRF_{2B} receptors are localized within ventricles and arterioles of the cerebrovasculature. There are detectable levels of mRNA expression in cardiac and skeletal muscles. Human CRF_{2C}



Corticotropin-Releasing Factor. Fig. 2. CRF receptor binding and activation. Binding of CRF and/or small molecule antagonist to CRF receptor. Non-peptide small molecule antagonist (M) can bind regardless of ligand but if bound, M will block binding of CRF N-terminus resulting in noncompetitive antagonism (Adapted by permission from Grigoriadis et al. 2009).

mRNA is localized in the septum and hippocampus with weak expression in the frontal cortex, amygdala, midbrain, and nucleus accumbens. A clear and significant role for the CRF_{2C} receptor has not been ascribed.

Behavioral and Endocrine Responses to CRF

Central administration of CRF into the CNS produces anxiety and fear-related behaviors in mice and rats nearly identical to those following exposure to a variety of experimental stressors. CRF antagonists also abolish or strongly attenuate stress-induced changes in physiology and behavior. Central administration also disrupts gastric and colonic motor systems, implicating CRF in the pathophysiology of irritable bowel syndrome. Numerous detailed reviews of the behavioral actions of CRF are available. Peripheral administration of CRF in the ▶ CRF stimulation test (with or without dexamethasone) is used to measure HPA axis dysregulation in MDD patients.

CRF is hypothesized to play a major role in many endocrine changes observed in patients suffering from psychiatric disorders. A significant subgroup of patients suffering from MDD exhibit elevated plasma cortisol concentrations as well as elevated cerebrospinal fluid CRF concentrations. Many MDD patients also exhibit a dysregulated glucocorticoid-mediated negative feedback mechanism. Depressed suicide victims show increased CRF mRNA expression in the ▶ hypothalamus as well as decreased CRF_1 receptor binding. There is also evidence that CRF plays a role in early life stress. Evidence suggests that early life trauma increases the sensitivity of the CRF system in adulthood, which may increase the risk of developing depression.

Although the data are limited, the genetic regulation and variation of components in the CRF system are associated with the pathophysiology of ▶ depression and ▶ anxiety. Specifically, single-nucleotide polymorphisms (SNPs) within the CRF_1 gene (CRHR1) support a link between these polymorphisms and the development of depression in patients with a history of child abuse (Bradley et al. 2008). Functional SNPs in the CRHR1 gene are also implicated in the susceptibility to ▶ panic disorder but only in conjunction with SNPs in the vasopressin receptor 1b gene (AVPR1B). Vasopressin receptors in the pituitary synergize with CRF to stimulate ACTH release. Some SNPs in the CRF-BP characterized in a Swedish population are comorbid with major depressive disorder, providing further evidence for the CRF system's role in depression. While there are no known polymorphisms in the CRF gene itself, SNPs in the CRF promoter region are associated with decreased sensitivity to

glucocorticoids and increased consumption of alcohol in Rhesus monkey.

Clinical Applications

Various peptides have been good tools for probing CRF receptor function *in vitro* and in laboratory animals; however, the lack of CNS penetrance renders them of no use for therapeutic applications. Research has focused on the development of non-peptide antagonists of the CRF_1 receptor for the treatment of stress-related disorders including depression and anxiety. High throughput screening and structure–activity relationship driven drug design has produced many small molecule antagonists. CP 316,311 failed in a clinical trial for depression in 2008 and pexacerfont was recently reported as ineffective for irritable bowel syndrome subjects. It should be noted that the extant literature suggests that, at least for major depression, only those individuals with dysregulated (hyperactive) CRF systems would be expected to benefit from CRF antagonists. We believe that this represents only a subgroup of depressed individuals. Therefore, only these individuals should be evaluated for efficacy in future trials. It is not at all clear how to best determine whether an individual has a CRF dysregulation. The use of CRF antagonists as anxiolytic medications might be expected to target a much larger population of individuals.

Cross-References

- ► Anxiety: Animal Models
- ► Arginine-Vasopressin
- ► Generalized Anxiety Disorder
- ► Hypothalamic–Pituitary–Adrenal Axis
- ► Neurosteroids
- ► Social Anxiety Disorder
- ► Social Stress
- ► Traumatic Stress (Anxiety) Disorder

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Corticotropin-Releasing Hormone

► Corticotropin-Releasing Factor

Cortistatin

Synonyms

CST; CST14; CST17; CST29

Definition

A rat ► neuropeptide with strong homology to SRIF was identified in the brain, cloned, and named cortistatin (CST). CST is also present in the periphery. In rodents, CST a tetradecapeptide (CST-14), sharing 11 amino acids with SRIF; the human homologue is a heptadecapeptide (CST-17). A longer isoform of CST has been identified, (CST-29). CST is produced as a prepropeptide that is processed to the final forms by peptide cleavage.

Cross-References

- ► Somatostatin
- ► SRIF

Cosmetic Psychopharmacology

Definition

The use of a psychotropic drug to ensure that a person who is not ill feels better than he or she already is.

Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study

► CUtLASS

CPP

► Conditioned Place Preference

CR

► Conditioned Response

Crack

Synonyms

Cocaine

Definition

Crack is the street name for cocaine processed to remove the hydrochloride (HCl) from the powder form of cocaine HCl. Cocaine HCl is mixed with ammonia or baking soda and the mixture is heated, allowed to solidify, and broken into small pieces ("rocks"). The crackling sounds made when the mixture is smoked give this freebase form of cocaine its street name.

Cross-References

► Freebase

Craving

Synonyms

Urge

Definition

The description of a strong urge and desire to drink alcohol or to take drugs, and its conceptualization to the construct of "craving" as a central downstream mechanism that initiates drug intake and precedes relapse, has a history of at least 60 years. Concepts of classical conditioning had a major impact on theories of alcohol and drug craving, suggesting that stimuli paired repeatedly with alcohol withdrawal could become conditioned stimuli that elicited conditioned positive and negative reinforcement which, in turn, would generate craving. For clinical use, craving was included in the international classification of diseases (ICD-10; WHO, 2003) as an optional diagnostic criterion for alcohol and drug dependence, defining the term as "a strong desire or sense of compulsion" to take the drug. In line with this, the majority of current conceptualizations of ► substance dependence define subjective craving as a sensory phenomenon that contributes the continuation of drug use.

CRF

► Corticotropin-Releasing Factor

CRF Stimulation Test

Definition

A test to determine HPA axis dysregulation. CRF is injected intravenously and serum levels of ACTH and cortisol are measured. In some patients with depression, ACTH and cortisol have a blunted response, leading to the conclusion that the HPA axis is dysregulated.

Cross-References

► Neuroendocrine Markers for Depression

CRH

► Corticotropin-Releasing Factor

Critical Flicker Fusion Frequency

Synonyms

CFFF; Flicker fusion rate; Flicker fusion threshold

Definition

Critical flicker fusion frequency (CFFF) is the frequency at which an intermittent light stimulus appears to be completely steady to the observer. This is often measured by exposing the subjects both to a low-frequency flicker, by increasing the frequency to the point the subject has the sensation that the flickering stops, and a

high-frequency flicker that decreases to the point where the flicker is detected. The CFFF is the mean of the two. If the frequency at which frames are displayed in a film falls below the CFFF then the image will be perceived as jerky.

Cross-Dependence

Synonyms
Substitution

Definition
When one drug is able to suppress the withdrawal signs and symptoms resulting from discontinued repeated administration of another drug, cross-dependence is said to occur. For example, methadone can be used to suppress withdrawal in persons physically dependent on heroin. This underlies one of the therapeutic bases for methadone treatment of opiate addiction. Cross-dependence is most readily seen among various opioids and is also seen among the CNS depressants such as the barbiturates, benzodiazepines, and alcohol.

Cross-References
- ▶ Abuse Liability Evaluation
- ▶ Alcohol
- ▶ Barbiturates
- ▶ Benzodiazepeines
- ▶ Opioid Dependence and Its Treatment
- ▶ Opioids
- ▶ Physical Dependence
- ▶ Sedative, Hypnotic, and Anxiolytic Dependence

Cross-Price Elasticity

Definition
Cross-price elasticity is the relationship between the price for one commodity and the demand for the alternative commodity.

Cross-References
- ▶ Behavioral Economics

Cross-Sectional Aspect

Definition
Concerning patterns and characteristics of a single episode of a disorder.

Cross-Tolerance

Definition
Animals and humans who have become tolerant on one drug are often tolerant to related drugs as well. This phenomenon is called cross-tolerance. For example, heroin abusers who are tolerant to heroin would also be tolerant to many other opioids, including methadone. This means that higher does of these other opioids would be needed to produce analgesia or intoxication than would be needed in a non-tolerant individual. Similarly, a patient treated with high doses of methadone would become cross-tolerant to heroin and other opioids, requiring higher doses to achieve intoxication. This serves as one of the pharmacological bases of methadone treatment.

Cross-References
- ▶ Abuse Liability Evaluation
- ▶ Opioid Dependence and Its Treatment
- ▶ Opioids
- ▶ Tolerance

Crying

- ▶ Distress Vocalization

CS

- ▶ Conditioned Stimulus

CSA

- ▶ Controlled Substances Act

5-CSRT

- ▶ Five-Choice Serial Reaction Time Task

5-CSRTT

- ▶ Five-Choice Serial Reaction Time Task

CST

► Cortistatin

CST14

► Cortistatin

CST17

► Cortistatin

CST29

► Cortistatin

Cue (in psychology)

► Discriminative Stimulus
► Drug Cues
► Stimulus Generalization

Cue Competition

► Overshadowing

Cued Fear

Definition

Conditioned fear of a discrete cue, usually a pure tone, white noise, or light stimulus.

Cueing Properties of Drugs

► Drug Discrimination

Cumulative Distance Moved

► Distance Traveled

Current Clamp

Synonyms

Membrane potential recording

Definition

Current-clamp recording is an intracellular recording modality where the experimenter records the voltage across the membrane of a cell while controlling the current flowing through the electrode, often holding it at zero.

Cross-References

► Intracellular Recording

Current Mood

► Affective State
► Decision Making

CUtLASS

Synonyms

Cost utility of the latest antipsychotic drugs in schizophrenia study

Definition

Study comparing an impact of the treatment with First Generation Antipsychotics and Second Generation Antipsychotics on quality of life. The main result is a lack of significant difference in this respect. The study also compares efficacy of predominately sulpiride with the SGA in the treatment of schizophrenia. In general, sulpiride was as effective and well tolerated as the SGA.

Cross-References

► First-Generation Antipsychotics
► Schizophrenia
► Second Generation Antipsychotics
► Sulpiride

Cyclic-Adenosine Monphosphate

► cAMP

Cycloheximide

Definition

A protein synthesis inhibitor isolated from *Streptomyces griseus* that exerts its effect by blocking translocation of the ribosome during the elongation phase of translation.

CYP

► Cytochrome P450

CYP450

► Cytochrome P450

Cytochrome P450

Synonyms

CYP; CYP450; P450

Definition

Cytochrome P450 is a large superfamily of hemoproteins that are essential to the enzymatic catalysis reactions involved in the metabolism of exogenous compounds (e.g., drugs) and endogenous (e.g., steroid hormones) substances. Usually, they form part of multicomponent electron transfer chains, called P450-containing systems. The most common reaction catalyzed by cytochrome P450 is a mono-oxygenase reaction.

Cross-References

► Sex Differences in Drug Effects

Cytokines

Definition

Cytokines are regulatory proteins involved in the intercell communication that are significant for the appropriate development and functioning of the immune system and that play a major role in a variety of immunological, inflammatory, and infectious disease in the CNS. The term includes interleukins, tumor necrosis factors (TNFs), interferons, transforming growth factor (TGF)beta, and colony-stimulating factors.

Cytotec

► Misoprostol

D

Δ^9-Tetrahydrocannabinol

► Cannabinoids
► Cannabinoids and Endocannabinoids

DA

► Dopamine

DARPP-32

Synonyms
Dopamine-and-cyclic-AMP-regulated-32KDa-phosphoprotein

Definition
Phosphoprotein enriched in the cytoplasm of medium-sized spiny neurons located in the caudate nucleus and receiving dopaminergic innervation. DARPP-32 critically influences the manifestation of ► dopamine receptor-mediated effects by regulating the signal cascade of adenylyl cyclase. Two isoforms of DARPP-32 exist that bear a phosphorilation at either of two distinct threonine residues: one of these isoforms is an inhibitor of the adenylyl cyclase cascade, while the other amplifies it. An equilibrium between the two isoforms of DARPP-32 exists under physiological conditions. Several centrally active substances, including ► opiates, addictive ► psychostimulants, and caffeine, can alter such an equilibrium, thus profoundly influencing the functionality of the dopaminergic transmission.

Cross-References
► Caffeine

DAT

► Dopamine Transporter

Davedax

► Reboxetine

db/db Mouse

Synonyms
Lep^{db}/*Lep*^{db} mouse

Definition
The *db/db* mouse is a genetically mutated *mouse* in which leptin receptors do not function properly. The *db/db mouse* is extremely obese and has many of the metabolic defects (hyperphagia, hyperglycemia, hyperinsulinemia, and infertility) found in *ob/ob* mouse.

Cross-References
► Hyperphagia

DBS

► Deep Brain Stimulation

2-DE

► Two-Dimensional Gel Electrophoresis

De Clerambault's Syndrome

► Delusional Disorder

Decision Making

Definition
Evaluation of costs and benefits of alternatives followed by the selection of one of them. The basis for evaluation is

Ian P. Stolerman (ed.), *Encyclopedia of Psychopharmacology,* DOI 10.1007/978-3-540-68706-1,

assumed to be the maximization of relative rate of net benefit gain though context-dependent factors may make this difficult to objectively verify. The neural substrates of decision making include reward valuation areas, including caudate, putamen, nucleus accumbens, as well as areas associated with emotion and cognitive processes, including dorsolateral prefrontal cortex, orbitofrontal cortex, amygdala, insula, anterior and posterior cingulate.

Cross-References

- ▶ Behavioral Economics
- ▶ Cognitive Enhancers
- ▶ Emotion and Mood
- ▶ Primate Models of Cognition
- ▶ Rodent Models of Cognition

Declarative and Non-Declarative Memory

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Synonyms

Consciously accessible and nonconsciously accessible memory; Explicitly and implicitly assessed memory.

Definition

Declarative memory and nondeclarative memory are two major classifications of long-term memory systems. Declarative memory allows us to consciously recollect events and facts. It is generally indexed by our ability to explicitly recall or recognize those events or facts. Nondeclarative memory, in contrast, is accessed without consciousness or implicitly through performance rather than recollection.

Impact of Psychoactive Drugs

Psychopharmacology of Declarative Memory

To embrace findings about the effects of pharmacological agents, it is helpful to distinguish between two key aspects of declarative memory. ▶ Episodic memory allows us to mentally travel back in time to re-experience personal events; it also helps us project into the future to pre-experience and plan for forthcoming events. ▶ Semantic memory, in contrast, stores language, concepts, and facts about the world.

Episodic memory is the most sensitive memory system to pharmacological disruption, and a range of drugs dose-dependently impairs our ability to mentally relive past experience. To date, the vast majority of research has involved single doses of drugs and we know correspondingly less about chronic effects, which are more relevant clinically for individuals who were prescribed repeated doses for treatment or those who addictively self-administer drugs. In terms of differentiating effects on long-term memory systems, the most intensively studied drugs are the ▶ benzodiazepines (BZDs), cholinergic blockers like ▶ scopolamine (SP), NMDA-receptor antagonists like ▶ ketamine, and, particularly in terms of emotional memories, beta-adrenergic antagonists like ▶ propranalol. This essay will provide a brief overview of the psychopharmacology of human declarative and nondeclarative memory, focussing on those compounds, which have been most extensively researched.

Anticholinergics, Benzodiazepines, and Declarative Memory

Interest in the cholinergic modulation of episodic memory was intrinsic to the development of the cholinergic hypothesis of ▶ Alzheimer's Disease (AD). All drug treatments currently available (e.g., tacrine, donepezil, rivastigmine) are designed to ameliorate or moderate this cholinergic depletion. Interest in the effects of BZDs on memory stemmed from anesthetists who value drugs that ensure a sufficient period and depth of anterograde amnesia so that even if the patient regained consciousness during an operation, they would not remember doing so. In this respect, BZDs proved to be ideal drugs. BZDs like ▶ diazepam, ▶ alprazolam, ▶ lorazepam, and 30 or more similar compounds act via specific $GABA_A$-BZD receptors to facilitate the transmission of ▶ GABA (γ-aminobutyric acid). BZD receptors are found throughout the brain, but the highest concentrations are in areas of known importance for memory functions: the cerebral cortex, limbic system, and cerebellar cortex.

Despite their differing pharmacological actions, SP and BZDs produce remarkably similar effects on episodic memory. Episodic impairments are anterograde, not retrograde such that information presented *after* the drug is administered is poorly remembered, whereas information studied *before* the drug is administered is retrieved intact. There is a general agreement that these drugs dose-dependently impair acquisition (encoding/consolidation) of new information and not retrieval. Once learning has been accomplished, the rate of forgetting is normal and there is no increased susceptibility to interference when initial acquisition levels on drug and placebo are matched.

When false recognition paradigms are used, these drugs acutely reduce false as well as veridical memories, a pattern similar to that seen in organic amnesia. Studies of metamemory suggest that people are unaware of having episodic memory deficits when they are intoxicated with a BZD.

Retrieval of material learned before a drug is ingested is not impaired and interestingly, can be improved when retrieval takes place on a BZD. This retrograde facilitation may be due to poor memory for material studied post-drug, which reduces interference on retrieval of material studied pre-drug. It could also reflect disinhibition of retrieval processes that may increase reliance on automatic rather than controlled processing. Retrograde facilitation is the opposite of notions of "► state-dependent retrieval" where performance is meant to be aided when encoding and retrieval taking place in the same drug state. In reality, state-dependent effects in humans are quantitatively very small and do not account for the marked effects of these drugs on acquisition.

The degree and duration of anterograde amnesia depends on the particular drug, its dose, and time curve of absorption and elimination. For example, following one oral dose of the BZD lorazepam, peak memory impairments occur from 1.5 to 5 h, after which effects slowly subside. Memory decrements also vary with task demands, so, for example, recall of information immediately after studying it is less impaired than recall tested several minutes or more after study; free recall deficits are greater than cued recall and recognition deficits. The degree of amnesia observed also varies with the characteristics of the tested individuals. Older healthy adults and Alzheimer patients show SP-induced memory impairments at lower doses of the drug than those needed to induce impairments in younger people. Further, the effects of a single dose of BZD are more pronounced in individuals who have never taken the drug before compared with those who have taken it occasionally or patients who take the drug daily for an ► anxiety or sleep disorder. As one would expect, neuroimaging studies show that BZD-induced dose-related decreases in memory performance are associated with dose-related decreases in activation in areas important for encoding information including the medial temporal lobe and prefrontal cortex.

In Endel Tulving's theory, the essence of episodic memory is the capacity to remember in the sense of re-experiencing events in subjective time. One way of evaluating episodic memory is therefore to tap into people's subjective awareness, which accompanies retrieval of a memory. Experiential approaches using the remember-know paradigm are based on a distinction between "remembering" in the sense of re-experiencing as a participant in an event and "knowing" in the sense of a personally detached observer of an event. BZDs, SP, and alcohol all acutely reduce "remember" responses at the same time as leaving "know" in tact, suggesting that they impair people's ability to mentally re-experience in subjective time (episodic memory) but do not affect semantic memory (reflected by "knowing").

Semantic memory has received less attention than episodic memory in terms of effects of BZDs and SP. Although some studies have assessed retrieval efficiency, acquisition of new semantic knowledge has been largely ignored. On the whole, these drugs do not appear to impede people's ability to *retrieve* items of general knowledge or other well-established memories. Conceptual priming in category generation tasks is intact even though a participant's explicit recall of studied category exemplars shows marked impairment, thus showing a differential effect of the drug on semantic and episodic memory assessed within the same task.

Glutamate, NMDA Blockers, and Declarative Memory

The excitatory amino acids, notably ► glutamate and aspartate, are the most prevalent excitatory neurotransmitters in the brain, and play an important role in cortico−cortical and cortical−subcortical interactions. Extensive research with animals has implicated the importance of glutamate, and especially the glutamatergic N-methyl-d-aspartate (► NMDA) receptor, in memory. Much of this research concerns ► long-term potentiation (LTP), an enduring form of synaptic plasticity that was initially identified in the hippocampus and more recently in the amygdala. LTP has been proposed as a mediator of learning and memory, although, it is not yet clear how LTP at the synaptic level relates to memory at a behavioral level. Drugs that block the NMDA receptor (e.g., ► ketamine) inhibit the induction of LTP in the ► hippocampus and there is considerable evidence that LTP is mediated by the NMDA receptor. In the human brain, NMDA receptors are densely localized in the cerebral cortex and the hippocampus.

Ketamine, like BZDs and ► scopolamine, disrupts acquisition of new information but not its retrieval. Acute ketamine dose-dependently impairs an individual's memory for the source – or contextual details – of information studied, reflecting a true episodic impairment. One study has suggested that interference from previously learned material may be increased acutely by ketamine. Preliminary evidence implies that ketamine may differ from classic amnesic drugs like BZDs and SP by adversely

impacting on semantic memory. Impairment of both episodic and semantic memory was suggested by one study showing that a single dose of ketamine produced similar impairments on both "remembering" and "knowing" states of subjective awareness in recognition. More recently, research using semantic priming tasks suggests that this drug has detrimental effects on aspects of semantic memory, although the degree to which this reflects in impairments from controlled rather than automatic processing are not clear.

Although ketamine is used clinically as an anesthetic, especially in vetinary and pediatric medicine, it is also a street drug, taken for its mood- and consciousness altering effects. Research with ketamine abusers has shown that the drug acutely impairs not only episodic memory but also retrieval from semantic memory on tasks such as semantic priming and sentence verification. Acute or chronic effects in recreational users mimic acute effects in healthy nonusers. There is now evidence that frequent, chronic use of ketamine may be associated with chronic episodic memory impairment, which persists for a period after stopping use of the drug.

Alcohol

Alcohol also produces its major amnesic effect on episodic memory and these range from mild impairment at low doses to total amnesia ("black-out") at high doses. ► Alcohol has NMDA-blocking as well as GABA-ergic properties, so it is not surprising that its effects are qualitatively similar to those of ketamine and BZDs.

Monoamines, Monaminergic Drugs, and Declarative Memory

Monoamines include the catecholamines (► dopamine, ► noradrenaline, adrenaline) and the indolamine, ► serotonin (5-hydroxytriptamine or 5-HT). Compared with SP or BZDs, there is relatively little research on the effects of monoaminergic drugs on memory for neutral information.

Dopaminergic compounds exert their most consistent effect on executive functions. A fairly consistent finding is that these drugs influence short-term or ► working memory (in ways which vary according to an individual's baseline level of functioning) and do not directly affect episodic memory. However, recent research using semantic priming paradigms has suggested dopaminergic modulation.

Our memory for personally experienced emotional events tends to be particularly vivid and durable. The neurobiological basis of enhanced episodic memory for emotional – as compared with neutral – information has been explored in an elegant series of studies by Cahill, McGaugh, and colleagues. They showed that drugs affecting adrenergic systems modulate emotional memory. Thus, the β-adrenergic antagonist, propranalol impairs healthy people's recall of emotionally arousing (but not neutral) elements of a storey, whereas stimulation of noradrenaline (with ► yohimbine) produces some enhancement of memory for emotional elements of the same story. Using the same task with two patients who had bilateral damage in the ► amygdala, they found a similar pattern of memory for the emotional and neutral storey elements. Together with the evidence that noradrenaline is released in the rat amygdala in response to learning to avoid an ► aversive stimulus, Cahill and others argue that adrenergic function in the amygdala mediates memory for emotional material. Within the basolateral amygdala and hippocampus, noradrenaline enhances glutamatergic ► synaptic plasticity, which is thought to underpin learning and memory. The profile of noradrenergic effects differs from that of BZDs, which acutely appear to impair memory similarly for both neutral and emotional elements.

Serotonin has been implicated in learning with some studies showing that rapid depletion of brain ► tryptophan (the amino acid precursor to serotonin) produces impaired learning and memory. However, manipulations that lead to serotonin depletion have not produced a consistent pattern of results. On the contrary, there is clear evidence that the drug "ecstasy" (3, 4-methylenedioxymethamphetamine ► MDMA), which produces marked serotonin *release* acutely impairs performance on tasks tapping episodic memory.

Other Compounds and Declarative Memory

A range of other drugs exert their primary effect on episodic memory. Cannabis and its main active ingredient Δ^9-tetrahydrocannabinol (THC) produce robust deficits for a time period after acute ingestion. However, the chronic effects of ► Cannabis on episodic memory appear more subtle and findings have been inconsistent. Opiates such as ► morphine and ► methadone can also exert detrimental effects on tasks tapping episodic memory, especially at high doses. Although tolerance rapidly develops in daily users, subtle episodic memory impairments have been observed following a daily dose or an increase in the prescribed dose.

Psychopharmacology of Nondeclarative Memory

Nondeclarative memory is an umbrella term, which covers our memory capacities that support skill and habit learning, perceptual priming, and other forms of behavior, which are expressed through performance rather than recollection. ► Procedural memory, such as knowing

how to ride a bicycle, is expressed indirectly through performance in riding a bicycle; perceptual representation memory, which underpins our ability to recognize words and other perceptual skills, is accessed implicitly; conditioning is generally seen as another type of nondeclarative memory.

In contrast to episodic memory, procedural memory is largely, although not always, resistant to drug-induced impairments. Often, though a drug may alter performance on a procedural learning task by disrupting physical coordination or arousal, it does not generally disrupt memory for previously acquired motor skills. Simple procedural learning tasks such as pursuit rotor or mirror reading tasks show very similar effects of BZDs and SP with learning curves on the drug generally being parallel to those for placebo. However, more complex tasks reveal differences. For example, one interesting study used the same sequential reaction time task to compare diazepam-induced amnesia with organic amnesia. Procedural learning in this task was preserved following ► diazepam in the same way as it was preserved in organic amnesia. However, the expression of that knowledge (priming) was impaired in both types of amnesia when contextual support was limited. This impairment of contextual priming was clearly dose-related in the diazepam condition. There is also some evidence from a single study that acutely, ketamine may impair procedural learning on the same task. Overall, findings suggest that whether impaired procedural memory is observed depends on the complexity of the task itself as simpler tasks generally show no drug-induced impairment.

Although conditioning has been traditionally seen as a nondeclarative memory capacity, its categorization varies according to whether successful conditioning occurs with or without conscious awareness. There is evidence that diazepam prevents the acquisition of fear conditioning in humans. However, the locus of this effect seems to be due to impairments in forming associations between the conditioned and unconditioned stimuli rather than the consolidation of fear memory per se. Enhancement of extinction of conditioned learning has been seen with drugs like D-cycloserine, which acts as a partial agonist at central glutamatergic NMDA receptors. This in turn suggests that D-cyloserine may be a useful therapeutic aid to psychological treatments which aim to extinguish conditioned responses (e.g., cue exposure in anxiety disorders). It may also have the potential as an adjunct to exposure treatment of drug dependency, a disorder in which both declarative memory and nondeclarative memory are intrinsically involved.

Perceptual ► priming studies have produced an intriguing finding that one particular BZD (lorazepam) but not others produces impairments on tasks tapping perceptual priming such as word stem, word fragment, or picture completion. Task purity criticisms can be applied to some earlier studies on the grounds that explicit impairments contaminated the performance on the "implicit" task. However, these could not explain findings of several studies, which compared lorazepam with another drug (a different BZD or SP) and found that although each drug produced the same impairment on an explicit task, only lorazepam impaired the perceptual priming. The fact that one BZD and not others suppresses priming supports a distinction between a system mediating perceptual priming (such as Tulving and Schacter's perceptual representational system) and other memory systems. The mechanism of this apparently unique effect of lorazepam is not yet known. One could speculate that there is a second population of BZD receptors, perhaps concentrated in posterior cortical areas, to which lorazepam but not other BZDs bind. Sub-types of BZD receptors have been identified by microbiological studies, but their functional significance is not yet known.

Specificity of Pharmacological Effects on Declarative and Nondeclarative Memory

In terms of neurocognitive specificity, clearly no drug *only* affects memory. Many drugs affect arousal and mood, and many alter aspects of executive functions. Changes in these functions may indirectly produce performance changes on a long-term memory task. Similarly, there is the fuzzy issue of neuropharmacological specificity, as drugs have diffuse effects on the central nervous system and changes in one neurotransmitter system will impinge on others. For example, acetylcholine interacts with other neurotransmitters and especially with the amino acids, ► GABA, and ► glutamate, which control basal forebrain cholinergic neurons. Such neurotransmitter interactions may underpin the similarity of amnesic effects of some of the different pharmacological compounds we have considered here.

There is now substantial evidence that the amnesic effects of benzodiazepines are not simply by-products of their sedative effects. Amnesic and sedative effects are differentially affected by (1) reversal by either a BZD antagonist or a stimulant like ► amphetamine; (2) ► tolerance over repeated dosage; (3) different dosages of BZDs and (4) amnesic effects of BZDs are seen even when their sedative effects are matched with other centrally acting compounds. The ► attentional effects of BZDs are less consistent than their memory effects. There is some evidence from dual task studies that reduced attentional resources cannot account for the amnesic effects of BZDs. With SP, the specificity debate has focussed more

on the attentional effects of the drug. Studies generally suggest that sedation may contribute to SP performance impairments on memory tasks but does not account for amnesia. On the other hand, studies of ▶ acetylcholinesterase inhibitors in patients with AD suggest amelioration of attentional function – rather than memory – may be the main route for cognitive change. Terms like attention, ▶ executive function, and arousal are umbrella concepts, which cover a range of differing systems, processes, or functions. There may be separate mechanisms responsible for different aspects of attention and arousal and these may be mediated by different neurobiological substrates.

Even with relatively specific task manipulations, tasks do not invoke/tap memory systems in isolation, and memory systems themselves are interacting, with considerable overlap in the neural machinery they engage. Acutely, although ketamine, SP, and BZDs do not impair the maintenance of information in working memory, they can all impair the manipulation of information in working memory. This means that elaborative encoding of information into episodic memory will be compromised as a by-product of working memory changes.

Conclusions

To date, the vast majority of research has involved single doses of drugs and we know correspondingly less about chronic effects, which are more relevant clinically for individuals prescribed repeated doses for treatment or those who addictively self-administer drugs. Further, research to date has focused almost exclusively on retrospective memory (memory for the past) and neglected "▶ prospective memory" (PM) – remembering to do something in the future – even though PM failures are the most frequent cause of forgetting in daily life. Some novel work on alcohol suggests that it globally impairs PM regardless of the specific type of PM task. It also suggests that engaging in "episodic future thinking" – mentally projecting oneself into the future to pre-experience an event – may overcome the deficit induced by acute alcohol and even play a role therapeutically in the treatment of alcoholism.

Taken as a whole, psychopharmacological studies support a differentiation between declarative and nondeclarative memory, and within declarative memory, between episodic and semantic systems. However, nondeclarative memory processes, such as perceptual priming, often contribute to the performance on declarative memory tasks such as recognition of words or pictures. Though this framework has clear benefits in describing psychopharmacological findings, one should be cautious of over-emphasizing differences at the expense of commonalities and interactions between different memory systems.

Cross-References

▶ Alcohol
▶ Cognitive Enhancers
▶ Inhibition of Memory
▶ Long-Term Potentiation and Memory
▶ Short-Term and Working Memory in Humans
▶ State-Dependent Learning

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Declarative Memory

Definition

Memory for facts, ideas, and events; is dependent on the hippocampus. Context fear is a model of declarative memory in rodents.

Decomposition

▶ Spectrograms

Deconvolution

▶ Spectrograms

Deep Brain Stimulation

Synonyms

DBS

Definition

A technique for activating specific brain regions by means of direct electrical stimulation delivered by electrodes

implanted in the brain that are powered by generators implanted in the upper chest. Introduced in the 1990s to treat ► Parkinson's disease, DBS may be beneficial in intractable cases of ► depression, ► obsessive-compulsive disorder (OCD), and ► Tourette syndrome, but such uses are still investigational. The main risks are those of brain surgery, which include hemorrhage, stroke, infection, and seizures.

Defensive Behaviors

Synonyms
Defensive responses; Defensive threat and attack

Definition
Defensive behaviors are a set of responses to threat stimuli and situations that have evolved on the basis of their adaptiveness in reducing harm to the threatened organism. These behaviors are highly conserved across mammals and rapidly conditioned to stimuli and situations associated with threat.

Cross-References
► Avoidance
► Freezing
► Risk Assessment

Defensive Responses

► Defensive Behaviors

Defensive Threat and Attack

► Defensive Behaviors

Deficit Symptoms Syndrome

► Negative Symptoms Syndrome

Degraded Contingency

► Relative Validity

Delay Discounting Paradigms

Synonyms
Delayed gratification; Delayed reward; Inter-temporal choice; Temporal discounting

Definition
Impulsive decision-making is commonly assessed using delay-discounting (DD) paradigms. In these tasks, impulsive choice is defined as preference for a small, immediate reward over a larger but delayed one. Various laboratories have used different versions of this family of paradigms, sometimes substituting the delays with probabilities (probability discounting procedure) or gradually adjusting the size of the reward instead of the delay to its delivery (adjusting amount procedure).

Cross-References
► Attention Deficit Hyperactivity Disorders: Animal Models
► Impulse Control Disorders
► Impulsivity
► Rodent Models of Cognition
► Translational Research

Delayed Gratification

► Delay Discounting Paradigms

Delayed Match-to-Sample Test

Synonyms
DMTS

Definition
In (variants of) this test, subjects are presented one or more stimuli to remember (spatial location, visual object, letter, etc.). These encoding stimuli are followed by a short delay, during which subjects have to maintain the stimuli "on-line." This delay is followed by a probe period, during which subjects reproduce the encoding stimuli (e.g., point to the spatial location), choose between two probe stimuli, or decide whether the probe stimulus was the same as one of the encoding stimuli. In some variants, intervening distractor stimuli are presented during the delay. In other "stimulus-reordering" versions, subjects

are required to reorder a sequence of letters presented to them during encoding. In these latter variants of the DMTS test, demands for executive components of working memory are increased.

Delayed (Non)Match-to-Sample Task

Definition

Derived from delayed-response principles, the delayed (non)match to sample task is a widely used test of working memory in animals. Typically, the animal is presented with a sample stimulus. After a short delay, the sample stimulus is shown again along with a novel alternative. In the nonmatching paradigm, the animal is rewarded for selecting the novel stimulus. In the matching paradigm, the animal is rewarded for selecting the sample stimulus thereby avoiding the novel stimulus. If different stimuli are used for every trial ("trial unique"), then the test specifically measures visual recognition memory. If the same stimuli are used on every trial ("trial nonunique"), then the test effectively measures the animal's ability to remember the most recent item. Delayed (non)matching tasks are considered tests of working memory because: (a) the information to be remembered on each trial is independent from the next and (b) the response is contingent upon the information that was presented at the beginning of the trial that must be discriminated from subsequently presented stimuli. Both rats and monkeys spontaneously select novel stimuli, thus the nonmatching version is usually preferred.

Delayed Onset of Drug Effects

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Synonyms

Delayed onset of action

Definition

According to the theory of delayed onset of action, the effects of antipsychotic or antidepressant drugs occur only after a delay of several weeks.

Current Concepts and State of Knowledge

The Concept

This chapter deals with the "delayed onset of action" hypothesis of ► antipsychotic and ► antidepressant drugs. This old theory states that antipsychotic or antidepressant drugs do not start to improve the symptoms immediately after administration, but that it rather takes several weeks until their effect sets in. It is shown that the "delayed onset of action" hypothesis is a myth and that the onset of action is early if not immediate. This article focuses on the evidence of ► antipsychotic drugs, but similar findings on ► antidepressants are briefly summarized at the end.

Historical Background

This theory probably emerged in the early 1970s, but there is no single author who could be quoted as its inventor and the statements in early textbooks were actually quite vague. For example, in 1969, Klein and Davis wrote in their seminal textbook: "Figs. 2–5 show that improvement takes place over long periods of time. In order to obtain maximum clinical effect, the patient must be treated with an adequate (antipsychotic) drug dose for an adequate time period" (Klein and Davis 1969). It then seems that the explanation of the effects of antipsychotic drugs by the ► depolarization block theory lent support to a delay of onset. The depolarization block theory was based on the studies on rats showing that antidopaminergic treatment leads to inactivation of dopamine firing and that it takes 3 weeks until the inactivation is in effect. This delay in the occurrence of the biological marker was thought to coincide with and explain the delay of onset of antipsychotic drug effects (Agid et al. 2003). Although the delay of onset of antipsychotic drug action had never been validated in clinical trials, it became widely recognized and was codified in many psychiatric textbooks (e.g., Gelder et al. 2000).

Refutation of the Delay of Onset of Action Hypothesis

Although the assumed delay of onset was a key concept in the mechanisms of action of antipsychotic drugs, it has only recently been systematically investigated. Two large, independent meta-analyses clearly refuted the theory (Agid et al. 2003; Leucht et al. 2005). A pivotal ► meta-analysis by Agid et al. (2003), based on 47 ► double-blind studies including 7,450 patients with schizophrenia, showed that the reduction of the overall ► positive

symptoms in the first 2 weeks was greater than that in the subsequent 2 weeks. Leucht et al. (2005) confirmed this finding using 1,708 original patient data from ▶ randomized controlled trials. In addition, they extended the analysis to 1 year and found that the largest part (68%) of the antipsychotic drug effect occurred in the first 4 weeks of treatment. Several subsequent analyses showed that the effects of antipsychotic drugs can be separated from that of placebo as early as within 24 h after the initiation of treatment (e.g., Kapur et al. 2005). In summary, these analyses clearly showed that the "delay of onset" was a myth, but that the onset of antipsychotic drug action rather sets in early.

Why Has the Delay of Onset Hypothesis Prevailed for such a Long Time?

There is an important distinction between a delay of "onset" and a delay of "development of full antipsychotic effects." While the recent studies have clearly refuted the concept of a delay of *onset* of drug action, it is very clear that it usually takes several weeks or even months until an antipsychotic drug develops its *full* effects or until a patient is in remission. It is likely that a confusion of these two concepts fueled the misunderstanding.

Consequences for the Understanding of the Mechanism of Action of Antipsychotic Drugs

The rejection of the delay of onset of action hypothesis has major implications for the explanation of the mechanism of action of antipsychotic drugs. The delay of onset of action suggested that the well-known effects of antipsychotic drugs on ▶ dopamine receptors are not directly responsible for the therapeutic effect, but rather postsynaptic mechanisms. As it is now clear that antipsychotic drugs start working without a delay, it is more likely that the blockade of dopamine receptors is also key in mediating the clinical response.

Does Early Improvement Predict Later Response?

The new "early onset of antipsychotic drug action" hypothesis also has major clinical implications. Due to a belief in the former theory of delay of onset, the treatment guidelines recommended to keep the patients for up to 6–8 weeks on the same drug before it should be considered ineffective and switched. As it is now clear that antipsychotic drugs can exert important effects in the first few weeks, it is possible that the degree of early improvement in 1 or 2 weeks predicts later treatment success. Already in the 1980s and 1990s, several studies showed that the degree of symptom reduction in 1 or 2 weeks strongly correlated with the degree of response after 4–8 weeks (e.g., Bartko et al. 1987). While these studies suggested that the degree of early improvement may be used as a predictor of later response, they were small and only correlational in design, that is, they did not come up with cutoffs of early improvement that could serve as predictors for later response or remission. A reliable measure such as a diagnostic test with high specificity, sensitivity, positive and negative predictive values is needed. Such a test would indicate whether a patient is an early improver or an early nonimprover, and would further predict whether a patient would develop a full response at later stages. Stimulated by the meta-analysis of Agid et al. (2003) several recent investigations have tried to develop such a test and usually based it on a minimum percentage reduction of the Brief Psychiatric Rating Scale (BPRS) or Positive and Negative Syndrome Scale (PANSS) total score in 1 or 2 weeks (e.g., Leucht et al. 2007). Although these analyses differed in populations (e.g., patients in registrational trials versus naturalistic settings), study duration (4–12 weeks), or definition of response (e.g., at least 20 or 50% BPRS/PANSS reduction or remission), they by and large found that minimal improvement (e.g., less than 25% BPRS/PANSS total reduction from baseline) in 1–2 weeks could serve as a predictor nonresponse at later time points (4–12 weeks).

In the Case of Nonresponse – Should Antipsychotic Drugs Be Switched Early On?

The fact that early improvement is a good predictor of later response suggests that the antipsychotic drug of early nonimprovers should be switched. But is this really true? It could also be that early nonimprovers have a poor outcome, irrespective of the antipsychotic drug used. It is necessary to find out whether an early switch to the antipsychotic drug really improves outcome from randomized studies in which early nonresponders are either switched to another antipsychotic or are kept on the same one. The first large double-blind study of this kind has been completed and it indeed showed that those patients who had not responded to 2-week treatment with ▶ risperidone were more likely to respond if they were switched to ▶ olanzapine than if they stayed on risperidone for another 10 weeks (Kinon et al. 2008). However, the gain was relatively small and the early nonimprovers never caught up with the early improvers, even if they were switched to olanzapine. As olanzapine and risperidone are both atypical antipsychotic drugs with similar receptor-binding profiles, studies on drugs with more different receptor-binding

profiles are now needed. Such studies could also investigate other strategies, for example, an early switch to the most efficacious antipsychotic drug ► clozapine, high dose strategies, or augmentation with other psychotropic compounds.

Delay of Onset of Antidepressants

As mentioned in the beginning of this article, the treatment of schizophrenia with antipsychotic drugs was used as an example, but there was also a delay of onset hypothesis in the treatment of depression which has recently been refuted. Taylor et al. (2006) published a meta-analysis of 28 randomized controlled trials including 5,872 participants and found that the effects of ► selective serotonin reuptake inhibitors (SSRIs) separated from those of placebo by the end of the first week of use and the rate of improvement decreased in the following 5 weeks. Szegedi et al. (2009) demonstrated in a large database of 6,562 patients from 41 randomized antidepressant drug trials that early improvement predicted later response with sufficiently good test values (Taylor et al. 2006; Szedegi et al. 2009).

Cross-References

► Antagonist
► Antidepressants
► Antipsychotic Drugs
► Atypical Antipsychotic Drugs
► Dopamine
► Double-blind
► First Generation Antipsychotics
► Placebo Effect
► Schizophrenia
► Second and Third Generation Antipsychotics

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Delayed Reward

► Delay Discounting Paradigms

Delay-Independent Deficit

Synonyms

Nonspecific memory impairment

Definition

In tests of working memory, the delay period is typically intermixed with short and long delays (~0–30 s) with long delays serving to increase the memory load of the task. Such tasks generally reveal a decline in performance accuracy as the delay interval between the sample and the choice phase is increased. The slope of the delay-performance curve (i.e., high accuracy at short delays and low accuracy at long delays) provides an index of the animals' rate of forgetting from working memory. Such delay-dependent gradients suggest that the disruptive effect of experimental or pharmacological treatments is attributable to a disturbance in the animal's working memory capacity. By contrast, a change in the slope of the curve that is *independent* of the delay whereby a decline in accurate performance is observed at the short "zero"-second delay as well as the long delays is generally interpreted as a nonspecific effect of attention. Thus, a delay-independent deficit suggests that the animals' failure to attend or encode the stimulus contributes to the overall memory deficit.

Cross-References

► Attention

Delirium

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Synonyms

Acute brain failure; Acute confusional state; Acute brain syndrome; Metabolic encephalopathy; Intensive care unit psychosis

Definition

Delirium is a common and often serious neuropsychiatric complication in the management of medically ill patients. It is associated with increased morbidity and mortality, causing distress in patients, family members, and staff (Breitbart and Alici 2008). It is characterized by an abrupt onset of disturbances of consciousness, attention, cognition, and perception that fluctuate over the course of the day. It is a sign of significant physiological disturbance, usually involving multiple medical etiologies, including infection, organ failure, and adverse effects of medication (APA 1999, 2000).

The Diagnostic and Statistical Manual of Mental Disorders (APA 2000) outlines the diagnostic criteria for delirium as follow (► DSM):

1. Disturbance of consciousness with reduced ability to focus, sustain, or shift attention.
2. Change in cognition that is not better accounted by a preexisting, established, or evolving dementia or development of a perceptual disturbance.
3. Development of the disturbance over a short period of time, usually hours to days, and fluctuation of symptoms during the course of the day.
4. Evidence from the history, physical examination, or laboratory tests that delirium is a direct physiological consequence of a general medical condition, substance intoxication or withdrawal, use of a medication, or toxin exposure, or a combination of these factors.

Role of Pharmacotherapy

Delirium is a medical emergency that needs to be prevented, identified, and treated vigorously. It is one of the most prevalent neuropsychiatric disorders in inpatient settings. The prevalence of delirium at hospital admission ranges from 14 to 24%, and the incidence of delirium during hospitalization ranges from 6 to 56% among general hospital populations (APA 1999; Breitbart and Alici 2008). Old age is a well-known risk factor for the development of delirium likely associated with increasing severity of medical comorbidities, dementia, and physical frailty. Postoperative patients and cancer and AIDS patients are also at greater risk for delirium. The highest prevalence and incidence of delirium is reported in terminally ill patients, occurring in up to 85% of patients in the last weeks of life (Breitbart and Alici 2008; Casarett and Inouye 2001).

Delirium is a syndrome of generalized dysfunction in higher cortical cerebral processes. Despite many different etiologies, symptoms of delirium are largely stereotypical, with a set of core symptoms. It appears that this diversity of physiological disturbances translates into a common clinical expression that may relate to dysfunction of a final common neuroanatomical and/or neurochemical pathway (Trzepacz 2000). It has been postulated that the final common pathway involves the ► prefrontal cortex, posterior parietal cortex (PPC), temporo-occipital cortex, anteromedial thalamus, and right basal ganglia with an imbalance in the neurotransmitters ► acetylcholine and ► dopamine (Trzepacz 2000). The acetylcholine–dopamine hypothesis explains the efficacy of dopamine antagonists in the treatment of delirium by regulating the imbalance between cholinergic and dopaminergic activity while the underlying etiology is being treated. Many other neurotransmitter systems including the serotonergic, noradrenergic, opiatergic, glutamatergic, and histaminergic systems, may contribute to delirium as a syndrome (Trzepacz 2000).

The clinical features of delirium are numerous and include a variety of neuropsychiatric symptoms as outlined above. Main features of delirium include prodromal symptoms (e.g., restlessness, anxiety, sleep disturbances, and irritability); rapidly fluctuating course; abrupt onset of symptoms; reduced attention (e.g., distractibility); altered level of alertness; increased or decreased psychomotor activity; disturbance of sleep–wake cycle; affective symptoms (e.g., emotional lability, depressed mood, anger, or euphoria); perceptual disturbances (e.g., misperceptions, illusions, and ► hallucinations); ► delusions; disorganized thinking; incoherent speech; and cognitive impairment (Breitbart and Friedlander 2006). On the basis of the psychomotor behavior and arousal levels, two subtypes of delirium have been described, including the hyperactive (or agitated, or hyperalert) subtype and the hypoactive (or lethargic, hypoalert, or hypoaroused) (► hyperactive

delirium; ▶ hypoactive delirium) subtype. A third subtype, namely the mixed subtype has been proposed with alternating features of each. Both hypoactive and hyperactive subtypes of delirium have been shown to cause distress in patients, family members, clinicians, and staff. There is evidence suggesting that the subtypes of delirium may be related to different causes, and may have different treatment responses. A ▶ randomized controlled trial of ▶ haloperidol and ▶ chlorpromazine found that both medications were equally effective in hypoactive and hyperactive subtypes of delirium. However, in an open label trial, the hypoactive subtype was associated with poorer treatment response to ▶ olanzapine. The hypoactive subtype of delirium is associated with higher mortality risk when compared with hyperactive delirium (APA 1999; Breitbart and Alici 2008; Breitbart and Friedlander 2006).

Many of the clinical features of delirium can also be associated with other psychiatric disorders, such as ▶ depression, ▶ mania, ▶ panic disorder, ▶ psychosis, and ▶ dementia. Acute onset, fluctuating course, disturbances of consciousness, and cognition in the presence of one or more etiological causes are characteristic in the diagnosis of delirium. The most challenging differential diagnostic issue is whether the patient has delirium or dementia. The temporal onset of symptoms in dementia is more subacute and chronically progressive. In delirium superimposed on an underlying dementia, such as in the case of an elderly patient, an AIDS patient, or a patient with a paraneoplastic syndrome, differential diagnosis becomes even more challenging. Delirium, unlike dementia, is by definition reversible, although in terminally ill patients, delirium may be irreversible (APA 1999; Breitbart and Friedlander 2006).

Clinically, the diagnostic gold standard for delirium is the clinician's assessment utilizing the DSM-IV-TR criteria as outlined above (APA 1999, 2000). Several delirium screening and evaluation tools have been developed to maximize diagnostic precision for clinical and research purposes and to assess delirium severity including the ▶ Delirium Rating Scale-Revised 98 (DRS-R-98), the ▶ Confusion Assessment Method (CAM), and the ▶ Memorial Delirium Assessment Scale (MDAS) (Breitbart and Alici 2008).

The standard approach to managing delirium includes a search for underlying causes, correction of those factors, and management of the symptoms of delirium. Treatment of the symptoms of delirium should be initiated before, or in concert with, a diagnostic assessment of the etiologies to minimize distress to patients, staff, and family members (APA 1999).

Nonpharmacologic and supportive therapies play an essential role in the treatment of delirium. Nonpharmacologic interventions have been shown to result in faster improvement of delirium symptoms and slower deterioration in cognition (Casarett and Inouye 2006). However, these interventions have not been found to have any effects on mortality or health-related quality of life when compared with usual care (Breitbart and Alici 2008). Nonpharmacologic interventions include oxygen delivery, fluid and electrolyte administration, ensuring bowel and bladder function, nutrition, mobilization, pain treatment, frequent orientation, use of visual and hearing aids, and environmental modifications (e.g., quiet, well-lit room with familiar objects, a visible clock or calendar) to enhance a sense of familiarity (Casarett and Inouye 2006). One-to-one nursing may be necessary for observation of agitated patients with delirium. Physical restraints should be avoided, when possible. The use of physical restraints has been identified as an independent risk factor for delirium persistence at the time of hospital discharge (Breitbart and Alici 2008).

Nonpharmacologic interventions and supportive measures alone are often not effective in controlling the symptoms of delirium. Symptomatic treatment with psychotropic medications is often essential to control the symptoms of delirium, although no medications have been approved by Food and Drug Administration (FDA) for the treatment of delirium.

Antipsychotic Medications

The American Psychiatric Association (APA) practice guidelines provide directions for the use of ▶ antipsychotics in the treatment of delirium and growing evidence supports their use (APA 1999) (Table 1).

Haloperidol (a "typical" antipsychotic) is often the gold-standard medication for the treatment of delirium, due to its efficacy and safety (e.g., few anticholinergic effects, lack of active metabolites, and availability in different routes of administration). ▶ Haloperidol in low doses (1–3 mg per day) is usually effective in targeting agitation and psychotic symptoms. In general, doses of haloperidol do not exceed 20 mg in a 24-h period; however, some clinicians advocate higher doses in selected cases. In severe agitation related to delirium, clinicians may add lorazepam to haloperidol. This combination may be more effective in rapidly sedating patients and may help minimize any ▶ extrapyramidal adverse effects of haloperidol (APA 1999; Breitbart and Alici 2008).

Oral or intravenous (IV) ▶ chlorpromazine is considered to be an effective alternative to haloperidol (with or without ▶ lorazepam) when increased sedation is required, especially in the intensive care unit (ICU) setting where close blood pressure monitoring is feasible, and for

Delirium. Table 1. Antipsychotic medications in the treatment of delirium.

Medication	Dose range	Routes of administration	Side effects	Comments
Typical antipsychotics				
Haloperidol	0.5–2 mg every 2–12 h	PO, IV, IM, SC	Extrapyramidal adverse effects can occur at higher doses. Monitor QT interval on EKG	Gold-standard treatment for delirium
Chlorpromazine	12.5–50 mg every 4–6 h	PO, IV, IM, SC, PR	More sedating and anticholinergic when compared with haloperidol	May be preferred in agitated patients due to its sedative effect
Atypical antipsychotics				
Olanzapine	2.5–5 mg every 12–24 h	PO*, IM	Sedation is the main dose-limiting side effect in short-term use	Older age, preexisting dementia, and hypoactive subtype of delirium have been associated with poor response
Risperidone	0.25–1 mg every 12–24 h	PO*	Extrapyramidal adverse effects can occur with doses >6 mg/day. Orthostatic hypotension	Clinical experience suggests better results in patients with hypoactive delirium
Quetiapine	12.5–100 mg every 12–24 h	PO	Sedation, orthostatic hypotension	Sedating effects may be helpful in patients with sleep–wake cycle disturbance
Ziprasidone	10–40 mg every 12–24 h	PO, IM	Monitor QT interval on EKG	Evidence is limited to case reports
Aripiprazole	5–30 mg every 24 h	PO*, IM	Monitor for akathisia	Evidence is limited to case reports and case series

*Risperidone, olanzapine, and aripiprazole are available in orally disintegrating tablets.

severe agitation in terminally ill patients to decrease distress for the patient, family, and staff. It is important to monitor chlorpromazine's anticholinergic and hypotensive side effects, particularly in elderly patients (Breitbart and Alici 2008).

A systematic review of the pharmacologic therapies for delirium in the terminally ill concluded that haloperidol was the most suitable medication for the treatment of patients with delirium near the end of life, with chlorpromazine being an acceptable alternative (Jackson and Lipman 2006).

FDA has issued a warning against the risk of QT interval prolongation and torsades de pointes with IV haloperidol, thus monitoring QT intervals daily among medically ill patients receiving IV haloperidol has become the standard clinical practice.

► Atypical antipsychotic agents (i.e., risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole) are increasingly used in the treatment of delirium due to lower risk of extrapyramidal adverse effects (Breitbart and Friedlander 2006).

A Cochrane review, comparing the efficacy and the incidence of adverse effects between haloperidol and atypical antipsychotics, concluded that, like haloperidol, selected newer atypical antipsychotics (risperidone, olanzapine) were effective in managing delirium. Haloperidol doses greater than 4.5 mg/day were more likely to result in increased rates of extrapyramidal symptoms when compared with the atypical antipsychotics, but low-dose haloperidol (i.e., less than 3.5 mg/day) did not result in a greater frequency of extrapyramidal adverse effects (Lonergan et al. 2007).

The APA guidelines for the treatment of delirium recommend use of low-dose haloperidol (i.e., 1–2 mg po every 4 h as needed or 0.25–0.5 mg po every 4 h for the elderly) as the treatment of choice in cases where medications are necessary (APA 1999).

On the basis of the existing literature, ► risperidone may be used in the treatment of delirium, starting at doses ranging from 0.25 to 1 mg and titrated up as necessary with particular attention to the risk EPS, orthostatic hypotension, and sedation at higher doses. ► Olanzapine can be started between 2.5 and 5 mg nightly and titrated up with the sedation being the major limiting factor, which may be favorable in the treatment of hyperactive delirium. The current literature on the use of ► quetiapine suggests a starting dose of 25–50 mg and a titration up to 100–200 mg a day (usually at twice-daily divided doses). Sedation and orthostatic hypotension are the main dose-limiting factors. Case reports suggest a starting dose of 10–15 mg daily for ► aripiprazole, with a maximum dose of 30 mg daily (Breitbart and Alici 2008; Breitbart and Friedlander 2006).

Despite the availability of intramuscular formulations of olanzapine, aripiprazole, and ziprasidone, none of these medications have been studied in the treatment of delirium.

Important considerations in starting treatment with any antipsychotic for delirium may include EPS risk, sedation, ► anticholinergic side effects, cardiac arrhythmias, and possible drug–drug interactions. The FDA has issued a "black box" warning of increased risk of death associated with the use of typical and atypical antipsychotics in elderly patients with dementia-related psychoses (Breitbart and Alici 2008). A retrospective study comparing the mortality risk among elderly patients with delirium who were treated with antipsychotics to those who did not receive antipsychotics did not find an increased risk of mortality with the use of antipsychotics in this patient population (Elie et al. 2009).

Psychostimulants

Some clinicians have suggested that the hypoactive subtype of delirium may respond to ► psychostimulants such as ► methylphenidate, or combinations of antipsychotics and psychostimulants or antipsychotics and wakefulness agents such as modafinil (Breitbart and Alici 2008). However, there have been no randomized controlled trials supporting the use of psychostimulants in the treatment of delirium. The risks of precipitating agitation and exacerbating psychotic symptoms should be carefully evaluated when psychostimulants are considered in the treatment of delirium.

Cholinesterase Inhibitors

Impaired cholinergic function has been implicated as one of the final common pathways in the neuropathogenesis of delirium (Trzepacz 2006). Despite case reports of beneficial effects of ► donepezil and ► rivastigmine in the treatment of delirium, a Cochrane review concluded that there is currently no evidence from controlled trials supporting the use of ► cholinesterase inhibitors in the treatment of delirium (Breitbart and Alici 2008).

Dexmedetomidine

Dexmedetomidine, an alpha-2-adrenergic agonist, is used in the ICUs for its central sedative effects through inhibition of noradrenergic cortex activation (Riker et al. 2009). The use of dexmedetomidine in the treatment of delirium among mechanically ventilated ICU patients has been associated with an increased number of delirium-free days when compared with lorazepam-treated patients in a randomized controlled trial (Lonergan et al. 2009). Dexmedetomidine has also been associated with a lower incidence of delirium when compared with ► midazolam among ICU patients (Riker et al. 2009). However, the expense of dexmedetomidine treatment limits its routine use in ICU patients despite encouraging results with this agent.

Benzodiazepines

Benzodiazepines are commonly used in the treatment and prevention of ► alcohol-withdrawal delirium. A systematic review of the use of ► benzodiazepines in the treatment of nonalcohol-withdrawal delirium has concluded that there are no controlled trials to support the use of benzodiazepines, and a controlled trial comparing the effectiveness of lorazepam, haloperidol, and chlorpromazine has shown increased confusion associated with the use of lorazepam among HIV-patients with delirium.

Prevention of Delirium

Several researchers have studied both pharmacologic and nonpharmacologic interventions in the prevention of delirium among older patient populations, particularly in surgical settings (Breitbart and Alici 2008). Antipsychotic medications (i.e., haloperidol) and cholinesterase inhibitors (donepezil and rivastigmine) have been studied in randomized controlled trials for their effectiveness in the prevention of postoperative delirium. Both groups of medications have failed to reduce the incidence of delirium in patients undergoing elective cardiac or joint replacement surgery (Breitbart and Alici 2008). Geriatric consultations and nonpharmacologic interventions such as a multicomponent intervention program have reported reduced number and duration of episodes of delirium among hospitalized older patients. However, a systematic review of all the existing delirium-prevention studies concluded that the current evidence on effectiveness of

interventions to prevent delirium was limited (Breitbart and Alici 2008).

Conclusion

Clinicians commonly encounter delirium as a major complication of medical illness and its treatments, particularly among hospitalized patients. Proper assessment, diagnosis, and management of delirium are essential in improving quality of life and minimizing morbidity in the medically ill.

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Delirium Tremens

Definition

Delirium tremens is the most severe phase of alcohol withdrawal and occurs in individuals with a history of constant, long-term alcohol intake. Five percent of cases of acute ethanol withdrawal progress to delirium tremens. Main symptoms are disorientation, confusion and agitation, and signs of severe autonomic instability (fever, tachycardia, hypertension). It commonly includes intense visual hallucinations. Delirium tremens often also includes symptoms of anxiety and paranoia. If untreated, mortality ranges up to 35%.

Cross-References

▶ Alcohol Abuse and Dependence

Delirium-Rating Scale

Synonyms

DRS

Definition

The DRS is a numerical rating scale that specifically integrates DSM-III-R diagnostic criteria for delirium. It is a 10-item scale, with items scored from 0 to 3 or 0 to 4 in the following domains: (1) temporal onset, (2) perceptual disturbance, (3) hallucinations, (4) delusions, (5) psychomotor behavior, (6) cognitive status, (7) physical disorder, (8) sleep–wake cycle disturbance, (9) lability of mood, and (10) variability of symptoms. A score of 12 or greater is diagnostic of delirium. DRS-R-98 is the revised version of the DRS. The summation of the first 13 item scores allows for a total severity score (range 0–39), while the last three (temporal onset and fluctuation of symptoms, and the presence of a physical disorder) can be exclusively used for diagnostic purposes. It includes more items than the DRS and is designed for phenomenologic and treatment research although it may be used clinically. The DRS-R-98 is a valid, sensitive, and reliable instrument for rating delirium severity.

Delorazepam

▶ Benzodiazepines

Delta Activity

▶ Function of Delta Waves

Delta-Receptor

Definition

The term δ-opioid peptide receptor represents the ▶ G-protein coupled receptor protein that responds

selectively to a group of largely experimental opioid drugs and endogenous opioid peptides. It is usually named the δ-receptor or DOR. It is homologous with the MOR receptor and is expressed in areas of the nervous system that moderately mediate analgesia with a side-effect profile distinct from μ-opioids. The DOR receptor protein is produced by a single gene. When activated, the DOR receptor predominantly transduces cellular actions via inhibitory G-proteins. The electrophysiological consequences of DOR receptor activation are usually inhibitory.

Delusion of Interpretation

► Delusional Disorder

Delusions of Infestation

► Delusional Disorder

Delusional Disorder

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Synonyms

Capgras syndrome; De Clerambault's syndrome; Delusional halitosis; Delusions of infestation; Delusion of interpretation; Delusional parasitosis; Dermatophobia; Erotomania (also known as De Clerambault's syndrome); Ekbom's Syndrome; Inventors delusion; Inventors' psychosis or "inventors" delusion (in German: "Erfinderwahn" or "Erfindungswahn"); Megalomania; Michael Kohlhaas' syndrome; Koro; Othello syndrome; Paranoid delusions; Paranoid psychosis; Paranoia; Persecutory delusions; Querulous paranoia; Sensitive delusion of reference; Psychose passionelle.

Definition

Paranoia/paranoid psychosis was renamed by Winokur (1977) as delusional disorder. Different forms of the disorder have been well described since the early nineteenth century (Grover et al. 2006). Delusional disorder is characterized by the presence of one or more delusions, which are not bizarre. These delusions may occur in real life and last at least 1 month according to the fourth Edition of the Diagnostic and Statistic Manual (► DSM-IV) of Mental Disorders and at least 3 month according to the Tenth Revision of International Classification of Diseases and Related Health Problems (ICD-10) (American Psychiatric Association 2005). Bizarre and nonbizarre delusions may be difficult to differentiate. However, delusions of control, thought broadcasting, thought insertion, and thought withdrawal are described as bizarre delusions, while persecutory, somatic, grandiose, and religious delusions, as well as most delusions of jealousy are described as nonbizarre. Examples of nonbizarre delusions include false beliefs of being followed or loved, of having special abilities, power or wealth, etc.

Delusional disorder can be diagnosed if diagnostic criteria for ► schizophrenic disorder have never been met and organic mental disorders and psychoactive/drug-induced psychotic disorders can be excluded. Delusions are the leading symptoms of this disorder even if some hallucinations are present. Patients suffering from delusional disorder may have well-preserved social and work functions in spite of complete or almost complete lack of insight.

Role of Pharmacotherapy

Phenomenology of Delusional Disorders

Delusional disorder is a rare condition, the lifetime morbidity risk is estimated to be less than 0.2%, the annual incidence is 1–3 new cases per 100,000 persons. The types of delusional disorder are defined based on the predominant delusional theme (Sadock and Sadock 2003). They are:

Erotomanic Type: having a delusion of a secret lover; the "lover" is often a famous person, a celebrity. The person with this type of delusional disorder may or may not contact the person, who is object of the delusion. The characteristics of this disorder have been excellently described by de Clerambault (1921): "Fundamental postulate: *It is the Object who began it and who loves the most or is the only one to love.* (N.B.: Object usually of high birth, classic notion." Some of the derived themes are: "The Object cannot achieve happiness without the suitor. . . . The Object is free. His marriage is invalid."

Grandiose Type: having delusion/s of one's own extreme greatness, goodness, knowledge, power, and/or wealth, having special relationship to famous persons, having famous ancestors.

Jealous Type: having a delusion of unfaithfulness of the spouse/sexual partner. It includes accusations of infidelity/testing the fidelity, searches for evidence

of infidelity, questioning/interrogation of the partner, and also stalking. As Shakespeare described in his play "Othello," delusions of jealousy can be very dangerous and result in homicide and suicide.

Persecutory Type: having a delusion of persecution – it is one of the most known delusional disorders. Being followed by the police, Mafia, FBI, KGB, etc., are frequent contents of persecutory delusions.

Somatic Type: having a delusion of somatic disorder/pathology, such as Ekbom syndrome (delusional parasitosis), which is characterized by delusions about the skin being infected (e.g., the skin is infected with parasites, "small bugs"). Some patients with Ekbom syndrome may have unusual delusions, which may qualify for bizarre delusions, e.g., claiming that invisible "small houses" are in the skin. Another example is koro, which is characterized by delusions of penis shrinkage and retraction into the body or a delusion that the genitals have been stolen. Koro has been more frequently reported from Asia, but also described internationally for hundreds of years. Somatic defects may lead these patients to plastic surgeons. Some patients claim having a specific disease, e.g., AIDS in spite of the fact having negative laboratory findings. The delusions (e.g., the patient may claim that the laboratory values were falsified) differentiate it from hypochondriasis. Current diagnostic systems classify individuals with dysmorphic delusions into two groups: delusional body dysmorphic disorder and delusional disorder, somatic type. The differentiation may be difficult: a good example is the delusional complaint about ugliness.

Mixed Type: persons have more than one delusional theme.

Religious delusions are not included in the diagnostic systems as a type of delusional disorder, but they are frequent in some parts of the world (e.g., in the city of Jerusalem) and their differential diagnosis may be rather difficult. It can be part of ▶ schizophrenia, manic episode of ▶ bipolar disorder, delusional disorder, or of other psychotic disorder, however it may be a shared belief of a religious community. The consensus of the given community can help in understanding the difference between their religious beliefs, practices, and delusions.

Querulous paranoia has rarely been reported from some parts of the world (e.g., China), which may have been related to the underdetecting and underreporting of this disorder. Querulous paranoia has practically disappeared from the psychiatric literature; however, it seems to be flourishing in modern complaints organizations and the courts (Lester et al. 2004). Thus, social and cultural factors have a major influence on the detection and diagnosis of some forms of delusional disorders.

Delusion of reference is often part of the above mentioned types of delusional disorder. Delusion of reference is characterized by false beliefs about remarks, events, or objects unrelated to the person by giving them person related meaning and significance. Mistrust and hypersensitive personality are typical features of the syndrome.

Cotard delusion or Cotard's syndrome, is also known as nihilistic or negation delusion. Patients may claim having no arms or legs, in severe cases may even deny to exist. This delusion is part of other psychiatric disorders, such as schizophrenia or most often of severe (melancholic) depression.

Genealogical delusions are characterized by false beliefs about the descent of a person through an aristocratic or famous ancestral line. Genealogical delusions are part of other psychiatric disorders and interestingly the theme of the delusions changes over time, e.g., nowadays no patient claims being related to the Habsburg emperors.

Shared paranoid disorder (also known as shared psychotic disorder, induced psychotic disorder, folie á deux, and double insanity) is characterized by the transfer of delusions from one person to the other. They "share" the same false beliefs. Persons involved are close to each other, mostly have lived together for a long time. Shared paranoid disorder is considered to be a separate psychiatric disorder; it is not included in the group of delusional disorders.

The aetiology of delusional disorder is not known. Most probably it includes different conditions which share the presence of nonbizarre delusions; however, the available literature indicates substantial heterogeneity of this diagnostic category. Neurobiological and neuropsychological correlates of delusions suggest dysfunctions of the prefrontal, limbic, and subcortical regions, however further studies are needed (Kunert et al. 2007). Toxic and organic origin of the disorder has been repeatedly described in the literature. Delusions of patients with ▶ organic brain syndromes are looser and simpler, and often temporary. Patients with complex and systematized delusions showed only slight cognitive impairment, which may indicate that largely intact cognitive functions are an important prerequisite for elaborate delusional processing (Kunert et al. 2007).

The female:male ratio in delusional disorder is around 3:1. Recent studies found only a slightly increased prevalence in females, and could not confirm the 3:1 ratio. The grandiose type affects almost only men, while the erotomanic type is more frequent in women. The most frequently encountered type is the persecutory type, followed by the somatic type and jealous type. The age at onset is around 40 years, however, there are differences described according

to the type of delusional disorder, the oldest age at onset being associated with the persecutory type, and the youngest with the somatic type (Yamada et al. 1998). The onset is often insidious. Key experiences may facilitate the development of this disorder. Delusions may have an interpretative character related to the key experience – in this case the disorder starts with a real event/sensation followed by delusional interpretation and an uncontrollable drive to relate everything to himself. Other delusions, (e.g., most erotomanic delusions) are autonomous, not related to any experience.

Treatment

Delusional disorders are difficult to treat; to our knowledge no drug has been approved for its treatment until April 2009, when this chapter was written. Publications about the pharmacological treatment of delusional disorders are focusing on the use, actually on the ► off-label use, of ► antipsychotic drugs. The off-label status of antipsychotics in delusional disorders is a very severe limitation in prescribing them with this indication. Before considering pharmacotherapy the diagnosis has to be confirmed, other disorders and conditions that may cause delusions have to be excluded, such as schizophrenic disorder and organic brain syndromes. It may be difficult to differentiate between delusions/paranoid development and inappropriately rigid, unwavering demands to receive that which is due to us, whether such action is practical or not and leads to catastrophic consequences or not (e.g., the case of Michael Kohlhaas as described in the novel of Heinrich von Kleist).

The treating personnel need some training in psychiatry. Two major problems may arise with untrained staff members: (1) arguing with the patient about the delusions, trying to convince him about the unreality and senselessness of his delusions; (2) submission to the delusions, deal with delusions as with part of reality. In the first case the patient may leave the treatment immediately, in the second case the patient sooner or later will realize that the physician (or other staff member) is lying. While most patients with delusional disorder are treated as outpatients, in case of danger to himself or to others (see Othello syndrome above) urgent and even involuntary hospitalization is indicated. Due to lack of insight, which is a core feature of delusional disorder, patients do not seek psychiatric treatment. With somatic type of delusional disorder patients may turn to other specialists, such as dermatologists in the case of Ekbom syndrome, which gives the opportunity to provide these patients with appropriate treatment. Well-organized consultation – liaison psychiatric services could improve psychiatric treatment, including the treatment of these patients.

Since we are dealing with a rare disorder, which even if diagnosed is still rarely treated and difficult to treat and there is no approved drug for its treatment, it is not surprising that there is a dearth of strong evidence-based data. However, the available data support the usefulness of both first and second generation antipsychotic drugs (Smith and Buckley 2006) antipsychotic drugs, ► first-generation antipsychotics, and ► second and third generation antipsychotics. Early publications on antipsychotic treatment of delusional disorders focused on the efficacy of ► pimozide, a first generation antipsychotic drug. This finding supported the ► dopamine hypothesis of delusions. The use of pimozide significantly decreased partly because of the increasing use of second generation antipsychotics and partly because of safety concerns (ECG changes) with pimozide. Among the second generation antipsychotics, most experience in the treatment of delusional disorders is with ► risperidone and ► olanzapine (Freudenmann and Lepping 2008). The reported full or partial remission rates were high, around 70%. It is important to note that the doses used were lower than those used in schizophrenia. To our knowledge there are no dose-response data for any antipsychotic drug in the treatment of delusional disorder. Treatment data on one type of delusional disorder – such as delusional parasitosis – may not be generalized to other types of delusional disorders. Lack of treatment compliance is a major obstacle in the treatment of delusional disorders. Adherence to treatment in schizophrenia seems to be higher with second generation antipsychotics. Long acting intramuscular injection formulations of first generation antipsychotics and the availability of choices and formulations (liquid, dissolvable, acute intramuscular, and long-acting intramuscular) with second generation antipsychotics may offer an opportunity to improve treatment adherence in patients with delusional disorder. The efficacy, safety, and tolerability, as well as the advantages and the limitations of antipsychotic drugs are described in the other chapters of this book on ► antipsychotic drugs, ► first generation antipsychotics, and ► second and third generation antipsychotics.

Pharmacotherapy of delusional disorders needs major development, since the available options have very limited value.

Cross-References

► Antipsychotic Drugs
► Bipolar Disorder
► First-Generation Antipsychotics
► Schizophrenic Disorder
► Second and Third Generation Antipsychotics
► Somatoform and Body Dysmorphic Disorders

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Delusional Halitosis

► Delusional Disorder

Delusional Parasitosis

► Delusional Disorder

Delusions

Definition

Delusions are false beliefs that are held with complete conviction, unaffected by clear evidence to the contrary and implausible or bizarre. For a belief to be considered a delusion, it should additionally not be shared by other members of the culture from which the individual who holds it originates.

Cross-References

► Delusional Disorder
► Hallucinations

Demand

Definition

The *demand* for a commodity is the amount of a commodity that is consumed at a particular price.

Cross-References

► Behavioral Economics

Dementia

Definition

Dementia is the significant loss of intellectual abilities such as memory capacity, severe enough to interfere with social or occupational functioning. Criteria for the diagnosis of dementia include impairment of attention, orientation, memory, judgment, language, motor and spatial skills, and function. It often includes disturbances in many cognitive domains including executive function (decision making), language, object recognition, and spatial navigation. By definition, dementia is not due to major depression or schizophrenia.

Dementia Praecox

► Schizophrenia

Dementia with Lewy Bodies

► Lewy Body Dementia

Dementias and Other Amnestic Disorders

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Definition

Amnestic disorders in general are characterized by memory impairment based on the inability to learn new information or recall previously learned information or past events, which causes marked impairment in social or occupational functioning. Dementia (from Latin, de- "apart, away" + mens- "mind") is a syndrome in which multiple cognitive deficits develop that include memory impairment, as well as impairment of attention, orientation, judgment, language, motor and spatial skills, or executive functioning. In addition to cognitive deficits, patients present behavioral and psychological signs and symptoms of dementia (► BPSD), as well as impairments of functional, instrumental, and social activities of daily living. Patients clearly display a decline from a previous higher level of functioning.

Role of Pharmacotherapy

Dementia may be due to the direct physiological effects of a general medical condition, the persisting effects of a certain substance or may have multiple etiologies (Table 1).

Dementia of the ► Alzheimer's type (DAT) is the most frequent type of dementia, accounting for 60% of cases. The prevalence of DAT has been estimated at about 10% among people aged 65 years or more, and 40% among people aged 85 or more. DAT is by its prevalence and nature an important burden on the life of patients, their immediate family, and caretakers. This essay will, therefore, mainly focus on the pharmacological treatment options for DAT.

Currently, several symptomatic treatment options are available for DAT in routine clinical practice. While not healing the disease, symptomatic treatment may contribute during a limited time period to slowing down the evolution of the symptoms. The mode of action is mainly based on ► neurotransmitter (Neurotransmitter synthesis, turnover, and uptake) replacement therapy. Given the cholinergic deficit typical of DAT, current drugs are based on acetylcholine replacement by inhibition of the catalytic enzyme ► acetylcholinesterase (AChE) (► Acetylcholinesterase inhibitors as cognitive enhancers). Though mainly aiming at improvement of cognitive function, these compounds were also shown to positively affect activities of daily living and BPSD. Until now, five cholinesterase inhibitors (Acetylcholinesterase inhibitors as cognitive enhancers) have been marketed: tacrine, metrifonate, donepezil, rivastigmine and galantamine. Currently, four are still available (not metrifonate), and tacrine sees its use steadily decreasing because of important cholinergic side effects, mainly of gastrointestinal origin, and the complex multiple daily dosing. ► Donepezil, ► rivastigmine, and ► galantamine currently form the cornerstone of

Dementias and Other Amnestic Disorders. Table 1. Dementia types and subtypes according to the American Psychiatric Association (2000).

Dementia type	Subtypes
Dementia of the Alzheimer's type (DAT)	Early-onset with age of onset $\leq$65 years
	Late-onset with age of onset >65 years
Vascular dementia	With delirium superimposed on dementia
	With delusions as the predominant feature
	With depressed mood as the predominant feature
	Uncomplicated
	In addition, the presence of behavioral disturbances can be specified
Dementia due to other general medical conditions	The underlying medical condition may be, e.g., HIV infection, traumatic brain injury, Parkinson's disease, Huntington's disease, Pick's disease, Creutzfeldt-Jakob disease, normal-pressure hydrocephalus, hypothyroidism, brain tumor, vitamin B12 deficiency
	Dementia may present with and without behavioral disturbances
Substance-induced persisting dementia	
Dementia due to multiple etiologies, e.g., mixed dementia which is the coexistence of vascular dementia and DAT	
Dementia not otherwise specified	

symptomatic treatment of DAT. Donepezil was the second cholinesterase inhibitor which became available for the symptomatic treatment of DAT. It is a noncompetitive, reversible AChE inhibitor (► Acetylcholinesterase inhibitors as cognitive enhancers) with a high central versus peripheral cholinomimetic specificity and a long duration of inhibitory action. In large-scale clinical studies it was shown to be a well-tolerated drug that causes improvement of cognitive and global function in mild to moderate DAT. Rivastigmine is a noncompetitive, pseudoirreversible AChE and butyrylcholinesterase inhibitor indicated for treatment of mild to moderately severe DAT. It has a long-lasting inhibitory effect, and besides being brain-selective, rivastigmine acts brain region-specific being most effective in hippocampus and cortex, which are in the main associated with cholinergic dysfunction in DAT. Rivastigmine significantly ameliorates cognitive function, activities of daily living and disease severity. Galantamine enhances central cholinergic activity through a dual mode of action. Besides its action as a brain-selective, competitive, reversible AChE inhibitor, galantamine is an ► allosteric potentiating ligand of the nicotinic acetylcholine receptor (nAChR). Clinical efficacy if this compound is based on improvement of cognitive function, as well as functional and behavioral symptoms of mild to moderate DAT.

Although the second-generation AChE inhibitors have a better safety and tolerability profile compared with the first-generation compounds, e.g., tacrine, on an average, approximately 75% of participants randomized to active AChE inhibitor treatment reported at least one adverse effect. The most frequently reported adverse events are of gastrointestinal origin, including nausea, diarrhea, vomiting, weight loss, as well as dizziness. For memantine, the most frequently reported adverse events in placebo-controlled trials included agitation, falls, dizziness, accidental injury, influenza-like symptoms, headache and diarrhea.

Although a substantial relation has not been established between sex and responsiveness to the second-generation cholinesterase inhibitors, some indications toward sexual dimorphism in response to these agents warrant further investigation, especially in regard to its role in the development of novel DAT therapies.

In focusing on DAT, it is useful to note that conclusions drawn from DAT studies, will frequently apply to other dementia entities. Cerebrovascular dementia consists mainly of patients with DAT and notable concomitant cerebrovascular disease (mixed dementia or DAT with cerebrovascular disease). Cerebrovascular disease is now believed to represent a continuum of relevance for DAT as well as cerebrovascular dementia. Lewy body dementia is frequently noted to be accompanied by DAT neuropathology and is sometimes seen to be a Lewy body variant of DAT. These latter clinical entities have also been shown to benefit – at least to a certain degree – from treatment with AChE inhibitors as has also been demonstrated for Parkinson's disease dementia. Nevertheless, additional clinical evidence is required since studies have reported contradictory efficacy levels. Cholinesterase inhibitors and memantine produce (although sometimes limited) benefits in cognition, including executive functioning, but often not in activities of daily living, as is the case in DAT.

Besides neurotransmitter replacement therapy, several routinely available treatment strategies for DAT are based on knowledge of underlying pathophysiological mechanisms. Their potential disease modifying efficacy is, however, in many cases still a matter of debate.

The therapeutic use of enzyme inhibitors in treatment of neurodegenerative diseases has its origin in the anti-Parkinson action of the selective, irreversible monoamine oxidase (MAO) B inhibitor, ► selegiline, thus preventing the breakdown of monoamine neurotransmitters and thereby increasing their availability. Clinical evidence for therapeutic efficacy in DAT is controversial with few studies showing improvement of cognitive function, mood, and behavior. Recently, selegiline was demonstrated to have a synergistic cognition-improving effect with donepezil, whereby selegiline potentiates the effect of donepezil on the cognitive impairment presumably through both the cholinergic and dopaminergic systems.

Dysfunction of the excitatory glutamatergic neurotransmitter system has been implicated in neurodegenerative disorders, including DAT. Under physiological conditions, *N*-methyl-D-aspartic acid ► (NMDA) receptors are blocked by Mg^{2+} in the absence of their ligand, glutamate. Excitatory toxicity is based on the permanent activation of NMDA receptors by continuous presynaptic release of low glutamate levels, and subsequent toxic Ca^{2+} influx. ► Memantine is a noncompetitive, voltage-dependent NMDA receptor antagonist that blocks the ion channel in the presence of sustained release of low glutamate quanta, thereby inhibiting a toxic Ca^{2+} influx. Symptomatic efficacy of memantine treatment is presumably based on the brief removal of memantine from the channel in case of transient high glutamate release into the synaptic cleft during learning and memory processes. Memantine is indicated for treatment of moderate-to-severe DAT, where it improves cognitive, functional and behavioral parameters. Given the fact that based on its mode-of-action, memantine may prevent glutamatergic excitotoxicity, it has been proposed as a neuroprotective agent with disease-modifying potential.

Although originally developed as symptomatic treatment agents, neuroprotective effects have been allotted to the cholinesterase inhibitors as well. For donepezil this is presumably based on the inhibition of AChE-induced ► amyloid-β (Aβ) aggregation and fibrillogenesis, since it is the only AChE inhibitor currently marketed that targets both the catalytic site of the enzyme and the peripheral anionic site, with latter triggering amyloid-β fibril formation. Galantamine's dual mode of action is supposed to underlie its neuroprotective capacities. Galantamine distinctively operates upon the α4β2 nAChR subtype, which upon stimulation inflicts neuroprotective effects. In addition, neuroprotective efficacy of both donepezil and galantamine seems to be linked to the α7 nAChR. Rivastigmine favorably modulates the human cellular response to injury through potentiating of heat–shock transcriptor factor-1, which elevates heat–shock protein 70 levels leading to cell protection. Advanced studies are required to further scrutinize action mechanisms underlying presumed neuroprotective mechanisms of cholinesterase inhibitors.

Based on the cholinergic hypothesis of DAT, the use of nicotinic agonists has incited a large research endeavor. There are significant numbers of nicotinic receptors within the brain, both pre- and postsynaptically, that are known to be important in learning and memory. DAT patients exhibit a loss of some subtypes of nicotinic receptors and the degree of loss correlates with the severity of the symptoms. There is a large body of evidence to indicate that nicotinic drugs indeed affect learning and memory. ► Nicotine and other ► nicotinic agonists can improve cognitive and psychomotor function, whereas nicotinic antagonists lead to cognitive impairment. Nicotine is reported to improve attention and information processing in DAT patients and small short-term studies have been carried out looking at the use of nicotine skin patches. Nicotine or nicotinic agonists are likely to have marked vascular effects and this may limit their use. In addition, direct stimulation by nicotinic agonists may induce desensitization of nicotinic receptors reducing the efficacy of such compounds in the longer term. Receptor modulation, as is the case for the allosteric potentiating ligand galantamine, may therefore be a better approach to overcome this hurdle.

The main drug target of commercially available neuroprotectants is oxidative stress by oxygenized free radicals. *Ginko biloba* extract has been used for treatment of memory problems for many years despite the lack of proven clinical efficacy. Its presumed mode of action is based on the presence of flavonoids, terpenoids and organic acids in the extract acting as free radical scavengers. A recent randomized controlled clinical trial found that it was not effective in reducing either the overall incidence rate of dementia or DAT incidence in elderly individuals with normal cognition or those with MCI. Vitamin E or α-tocopherol is another free radical scavenger used for treatment of DAT, despite of insufficiently proven clinical efficacy.

Given the central role of amyloid-β pathology in the DAT disease process, future treatment strategies should mainly focus on the prevention or reversal of amyloid-β peptide deposition. Several experimental strategies focusing on amyloid-β are presently under intense preclinical and clinical investigation, including interventions modulating proteolytic amyloid precursor protein processing with e.g., secretase inhibitors, passive or active immunization against amyloid-β, and treatments blocking amyloid-β aggregation. Data from animal models suggests that antibodies raised against the amyloid-β can decrease Aβ deposition through several mechanisms, as well as decrease amyloid-β associated damage such as dystrophic neurite formation, and improve behavioral performance. Data from human studies suggests that active immunization can result in plaque clearance and that passive immunotherapy might result in slowing of cognitive decline. Despite this, a recent analysis from a phase I trial evaluating active immunization with $A\beta_{1-42}$, while not powered to determine efficacy, suggested no large effect of active immunization despite the fact that plaque clearance was very prominent in some subjects. An important issue to consider is when active or passive immunization targeting amyloid-β has the chance to be most effective. Pathological and biomarker studies have shown that amyloid-β deposition probably begins about 10–15 years prior to DAT symptom onset. By the time the earliest clinical signs of DAT emerge, amyloid-β deposition may be close to reaching its peak and tangle formation and neuronal cell loss is substantial, though still not at its maximal extent. Since immunization targeting amyloid-β does not appear to have major effects on tangle pathology, for immunization to have the most chance for success, performing clinical trials in individuals who are cognitively only very mildly impaired or even in those with preclinical DAT would likely offer a much better chance for success. Current work with DAT biomarkers suggests that such individuals can now be identified and it seems likely that targeting this population with antiAβ immunization strategies is likely to be successful.

Epidemiological data collected between the mid 1980s–late 1990s suggested that prolonged exposure to ► nonsteroidal antiinflammatory drugs (NSAIDs) in conditions like arthritis entailed a reduced risk and delayed onset of

DAT. NSAIDs exert antiinflammatory, analgesic and antipyretic activities and are involved in the suppression of prostaglandin synthesis by inhibiting cyclo-oxygenase, a key mediator of the inflammatory cascade. Initially, the diminishing effect of prolonged usage of NSAIDs on the risk of DAT was attributed to a reduction of inflammation. Several subsequent clinical trials testing NSAIDs in DAT patients based on this rationale, however, yielded negative results. In recent years, several studies have proven that a subset of NSAIDs (e.g., ibuprofen, indomethacin, flurbiprofen) reduce $A\beta_{1-42}$ production in cultured cells and mouse brain, whereas other NSAIDs do not affect Aβ metabolism (e.g., aspirin, sulindac, ketoprofen), and others (e.g., celecoxib) even increase $A\beta_{1-42}$ production. The use of NSAIDs may prove efficacious in other protein-misfolding disorders besides DAT, given the fact that some of these compounds may exhibit antifibrillogenic and fibril-destabilizing activities for other proteins that can aggregate and form amyloid-like fibrils besides amyloid-β, including alpha-synuclein in Lewy body dementia. Nevertheless, a large body of preclinical and clinical research is required to underpin these presumed disease-modifying effects of certain NSAIDs.

Until a therapy is developed that can prevent or reverse the disease, the optimal goal for effective DAT management is to develop a treatment regimen that will yield maximum benefits for individual patients across multiple domains, including cognition, daily functioning, and behavior, and to provide realistic expectations for patients and caregivers throughout the course of the disease.

Besides focusing on cognitive symptomatology, treatment of DAT should also include managing BPSD and related behavioral alterations, especially given their major impact on patients, caretakers, and society at large. Behavioral symptoms, particularly aggression, agitation and circadian rhythm disturbances, or sundowning behavior, have been described as the primary predictor of caregiver burden and often motivate institutionalization in specialized care facilities. In addition, the presence of BPSD in DAT is associated with more rapid cognitive deterioration.

A variety of pharmacological agents has been evaluated for the treatment of BPSD, including cholinomimetics, antidepressants, anticonvulsants, anxiolytics, hormonal preparations and antipsychotic (neuroleptic) drugs. Unfortunately, clinical evidence is rather anecdotal or based on open-label clinical trials for most of these substances. In addition, although the categories of BPSD are superficially similar to symptoms in, for example, the psychosis of schizophrenia or depression in major affective disorders, the specific nature of these symptoms in DAT and related disorders may be different based on DAT-specific neurochemical alterations and the interaction with psychological, cognitive and functional factors.

Neuroleptics are implemented most frequently, although the use of classic neuroleptics in an elderly population implicates the risk of irreversible movement disorders, extrapyramidal side effects, anticholinergic effects and adverse drug interactions. Novel (atypical) antipsychotic agents should be screened in placebo-controlled randomized double-blind clinical trials assessing efficacy and safety profile. Two atypical antipsychotic agents, ▶ risperidone and ▶ olanzapine, are presently the most optimal treatment options for BPSD and have been evaluated in a series of placebo-controlled randomized clinical trials, albeit with rather variable results. Nevertheless, the increased risk of cerebrovascular accident in patients taking risperidone or olanzapine may limit their use in demented subjects. Risperidone is a strong dopamine antagonist with high affinity for D_2 dopaminergic receptors, as well as serotonin ($5\text{-}HT_2$) receptors. It is well absorbed after oral administration and peak plasma levels are reached in 1 h. Olanzapine has a higher affinity for $5\text{-}HT_2$ serotonin receptors than D_2 dopamine receptors. Peak plasma levels are reached within 5–8 h following oral administration. Taking into account the rather limited efficacy and the importance of side effects observed with psychotropic agents overall in this indication, the majority of existing guidelines underline the importance of nonpharmacological strategies.

The proportion of dementia patients experiencing major or minor depression is estimated to be around 25%, and 20–50% in patients diagnosed with DAT. The etiology of depression in DAT is heterogeneous as indicated by the four subtypes identified: adjustment disorder, recurrence of earlier depressive episode, vascular depression and depression associated with neurodegeneration. Given the symptom overlap between nondepressed DAT patients and depression associated with dementia, including psychomotor retardation and difficulty thinking and concentrating, as well as depression-like symptoms in case of DAT-associated apathy, diagnosing depression in DAT may be complex. Beyond the inherent burden on patients and caretakers, comorbid depression may cause a decline in quality of life, impairment in functionalities of daily living and has been linked to greater and faster cognitive decline. In addition, controlled pharmacological treatment trials of depression in DAT yielded conflicting results. DAT-associated depression has been treated with ▶ tricyclic antidepressants (TCAs) (e.g., imipramine, clomipramine) or ▶ selective serotonin reuptake inhibitors (e.g., setraline, citalopram). SSRIs increase the extracellular level of serotonin by inhibiting its reuptake into the presynaptic cell,

increasing the level of serotonin available to bind to the postsynaptic receptor. SSRIs are currently the first choice for treatment of comorbid depression in dementia because of a superior safety and tolerability profile compared to TCAs, as well as the fact that worsening of cognitive impairment with TCAs has been observed. Interestingly, some DAT patients experienced significant improvement of cognitive and emotional functioning with ► citalopram compared to placebo (<*individual items on the Gottfries–Bråne–Steen Dementia rating scale*).

Treatment goals clearly change with the severity of DAT. In patients with mild to moderate disease, goals are to improve or maintain baseline performance through the administration of disease-modifying drugs targeting crucial etiological processes that thereby are neuroprotective. As the disease progresses, the goal of treatment is to slow the rate of decline in performance, mainly through highly efficacious symptomatic therapeutics improving cognitive and behavioral deficits that impair the well being of patients and caregivers. Symptomatic therapies, however, do not address the cause of the disease. If predisposition for the development of DAT should become predictable in the future, for example based on biomarker profiling in patients with mild cognitive impairment, the development of truly preventive therapies will become mandatory.

Cross-References

► Acetylcholinesterase Inhibitors as Cognitive Enhancers
► Antipsychotic Drugs
► Cognitive Enhancers

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Dementias: Animal Models

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Definition

A laboratory animal that has undergone a manipulation, for example a pharmacological challenge, surgical procedure or genetic modification(s) so that it models aspects of human dementia.

Current Concepts and State of Knowledge

There are over 50 described causes of dementia but the most common among these are ► Alzheimer's disease, vascular dementia, Lewy body dementia, frontotemporal dementia, and HIV-associated dementia. Dementia is also associated with diseases such as Parkinson's, Huntington's, progressive supranuclear palsy, Creutzfeldt–Jakob disease, Gerstmann–Sträussler–Scheinker syndrome, other prion disorders and ► dementias and other amnestic disorders but for the sake of brevity, this essay will focus on animal models of dementia caused by Alzheimer's disease (AD).

AD is characterized by a progressive, age-dependent decline in cognitive functioning including, but not restricted to gross impairments in memory, speech, visuospatial skills, and behavior. The clinical symptoms of AD are the result of significant neuronal and synaptic loss in selected brain regions, including the temporal and parietal lobes and restricted regions within the frontal cortex and cingulate gyrus. In addition to neurodegeneration, the two main histopathological hallmarks of AD are

extracellular plaques comprising predominately of ► β-amyloid derived from the amyloid precursor protein (APP), and intraneuronal ► neurofibrillary tangles (NFT's), comprising of a hyperphosphorylated form of the microtubule associated protein Tau. β-amyloid and ► Tau show distinct regional distribution throughout the brain with amyloid plaques predominately found in the neocortex, temporal and entorhinal cortices, ► amygdala, and ► hippocampus, while Tau NFT's are primarily localized to the entorhinal and limbic cortices but also the CA1 region of the hippocampus.

During the mid-1970s, a detailed biochemical analysis of brains from Alzheimer's patients demonstrated that there were significant neocortical reductions in the enzyme responsible for the synthesis of the neurotransmitter ► acetylcholine (ACh). Later studies then went on to show reduced uptake of choline, ACh release, and significant cell loss in the primary cholinergic cell body that projects to the neocortex (nucleus basalis of Meynert). In addition to the pronounced deficits of the cholinergic system, more subtle deficits to other neurotransmitter systems including the noradrenergic, serotonergic systems and neuropeptides such as substance P and somatostatin were also reported, whereas the dopaminergic system and several other neuropeptides appeared to be unaffected. Degeneration of the primary noradrenergic cell body (locus coeruleus) is perhaps the best documented with studies reporting up to 68% cell loss.

It was from these seminal histological and biochemical studies and the subsequent connection between emerging data demonstrating a role for ACh in learning and memory, that the "Cholinergic Hypothesis of AD" was formed (for review see Bartus 2000). Essentially this hypothesis states that the degeneration of cholinergic neurons in the basal forebrain and associated loss of cholinergic transmission in the cerebral cortex and other areas associated with cognition are responsible for the decline in cognitive functioning observed in AD. While providing the first starting point for AD animal model development, the cholinergic hypothesis also forms the theoretical basis for cholinergic therapy with ► acetylcholinesterase and cognitive enhancement, which are still the most effective in the treatments for AD.

Primarily driven by the cholinergic hypothesis, a variety of experimental approaches were developed that aimed to establish dysfunctional cholinergic systems in animals. The most commonly utilized of these is the ► scopolamine challenge model. Scopolamine and atropine are naturally occurring compounds found in the nightshade (Solanaceae) plant family. When administered to animals, including man, they potently block both central and peripheral cholinergic muscarinic receptors, ► muscarinic agonists and antagonists. The resulting cholinergic dysfunction causes pronounced, albeit reversible cognitive impairments. The first studies that determined the effects of scopolamine on normal human cognitive functioning were performed in the early 1970s. When administered to healthy human volunteers, scopolamine was shown to cause reversible learning and memory deficits similar to those observed in elderly and dementia patients. Due to its procedural simplicity and distinct lack of safety concerns, the human scopolamine challenge model is still occasionally used today for the evaluation of novel drugs postulated to improve cognitive functioning of ► cognitive enhancers: novel approaches.

In addition to the human studies, the effects of scopolamine in pre-clinical species were first reported in the 1950s. While these studies focused primarily on the general impairing effects of scopolamine on operant test responding ► operant behavior in animals, considerable efforts over the last 50 years have led to a comprehensive characterization of scopolamine's effects on most aspects of animal cognition. Although a review of this work is beyond the scope of this article (for review see Blokland 2005), it is worth mentioning that while there is irrefutable evidence for scopolamine-induced amnesia in animals, there has also been some considerable debate as to whether the impairments are specifically learning- and memory- related. This is because scopolamine also elicits multiple effects on other non-cognitive related processes including gross animal behavior (i.e., locomotor activity), pupil diameter, salivation, perception, and anxiety responses. These effects are caused by the lack of selectivity that scopolamine displays across all the muscarinic receptor subtypes (m1–m5) located in the body.

While most of the confounding effects of scopolamine are typically associated with higher doses of scopolamine, it can be still extremely difficult to experimentally separate scopolamine effects on cognition from its non-specific effects (Blokland 2005). Moreover, there is now considerable evidence suggesting that scopolamine effects on learning and memory are likely to be secondary to its effects on attentional processes. Even with these caveats, there is no doubt that the scopolamine challenge model is an important tool for both the pre-clinical and clinical assessments of novel cognitive enhancing compounds and is perhaps one of the clearest examples of a CNS translational model for ► translational research.

As a direct parallel to the scopolamine model, alternative approaches were developed that aimed to address the selectivity issues mentioned earlier, but also to establish

more permanent cholinergic deficits similar to that observed in AD. Both of these objectives were partially achieved by lesioning discrete cholinergic brain nuclei and/or pathways. The basal forebrain contains two groups of cholinergic neurons: (1) the medial septal nuclei (medial septal nucleus and vertical diagonal band) that project to the ▶ hippocampus and parahippocampal gyrus (2) the nucleus basalis nuclei (nucleus basalis, substantia innominata and horizontal diagonal band) that project to the neocortex, limbic cortex, and ▶ amygdala. The nucleus basalis magnocellularis (nbm) is the rodent equivalent to the human nucleus basalis of Meynert that undergoes degeneration in AD.

Early brain lesioning techniques were limited by available technology, and therefore relied upon either electrolytic probes or direct injection of ▶ excitotoxins. Electrolytic-induced lesions are generated by stereotaxically placing an anodal electrode into the brain region of interest. A small electrical current is then passed through the electrode and cells that are in close proximity to the electrode undergo degeneration. Although far from precise, lesion size can be manipulated by altering either the current amplitude and/or length of current application. Electrolytic lesioning techniques are now rarely used because they have been shown to cause considerable damage to adjacent fiber tracts which can cause neuronal degeneration at sites distal to the lesion.

The use of excitotoxins to cause brain lesions was a considerable improvement on the electrolytic approach. Excitotoxins are receptor ligands that directly act on the glutamatergic system (e.g., NMDA, ibotenic acid, and quisqualic acid). These ligands once directly infused into the brain region of interest bind to their appropriate receptor and open calcium channels. The resulting calcium influx leads to hyperpolarization and ultimately, cell death. Excitotoxic lesions are generally thought to spare axons (fibers) that run adjacent to the injection site and thus avoid the issues associated with electrolytic lesions.

Further improvements in lesion specificity was achieved when a monoclonal antibody raised to the nerve growth factor (NGF) receptor "192IgG" was coupled to the cytotoxin, "saporin," forming a "192 IgG-saporin" complex. When administered intracranially, the 192 IgG-S complex binds to the low-affinity neurotrophin receptor ($p75^{NTR}$) on cholinergic cells and the receptor complex is internalized. Once in the cell, ▶ saporin enzymatically disables ribosomes and shuts down protein synthesis, resulting in the selective death of cholinergic neurons. This widespread, yet selective degeneration of cholinergic neurons including those in the nucleus basalis of Meynert and septum causes pronounced learning and memory deficits.

There is no doubt that animals with lesions in the forebrain cholinergic nuclei have proved useful as a model of cholinergic hypofunction. They have provided information on cortical cholinergic innervations and how changes to this system can affect neuronal functioning and cognitive processes. They have also proved useful in determining the effects of novel compounds designed to restore/preserve cholinergic functioning, for example acetylcholine esterase inhibitors. However, as a model of AD, they show a number of serious limitations. The main concern is that the resulting cholinergic hypofunction is not associated with amyloid ▶ plaques or NFT's, and there is no progressive worsening of the hypofunction but on the contrary some recovery may take place (for review see Toledano and Alvarez 2004).

As briefly mentioned earlier, AD is also associated with significant degeneration of the primary noradrenergic cell body (locus coeruleus) with resulting downstream alterations in noradrenergic receptor expression. DSP-4 is a potent and selective neurotoxin of noradrenergic neurons and when injected systemically, produces long-lasting reductions in basal noradrenaline levels and uptake capacity in the brain and spinal cord. The most consistent effects of DSP-4 lesions are disruptions in behavioral tasks designed to measure attention-related processes (for review see Sara 2009). Interestingly, most studies have shown no effect of noradrenaline depletion on learning and memory tests that are otherwise dramatically altered by either cholinergic blockade or aging. Due to these caveats, the time and associated costs in generating lesioned animal models, but primarily the concern that these models fail to predict for clinical efficacy, they are very rarely used in the modern drug discovery process.

Aged animals have been and are still occasionally used for investigating drugs postulated to be active in treating AD. While aged rodents (mice and rats) are the most frequently used since they are relatively easy and cheap to obtain, occasionally old primates are used and may form the last preclinical step before evaluation in humans. There are two main limitations of the aging animal model. First, aged animals do not develop the neuropathological picture of AD. While extremely rare, plaques have been described in the primate, but none of the histopathological alterations typical of AD occur in aging rodents. Second, in aged animals, it is relatively easy to improve the cholinergic hypofunction and associated cognitive deficits with drugs whose efficacy has proved difficult to demonstrate in clinical trials.

Studies of amyloid plaques in the 1980s showed that they predominantly consisted of a long peptide with

40–42 amino acids that is formed into a beta-pleated structure. The subsequent sequencing of the isolated β-amyloid peptide identified a 90 Kd single transmembrane protein termed the APP, whose cleavage leads to the production of β-amyloid peptides. The amyloid cascade hypothesis postulates that the aberrant accumulation of β-amyloid is the primary abnormality in AD and that its deposition leads to disturbed axonal transport and neuronal cell death, ultimately causing deficits in synaptic plasticity and cognition, ► long-term potentiation and memory. The supporting evidence for the amyloid cascade hypothesis derives from a number of observations (for review see Tanzi and Bertram 2005), but can be broadly classified into three strands: (1) an association of AD with Down's syndrome, (2) APP mutations on chromosome 21, and (3) experiments demonstrating that β-amyloid is neurotoxic both in-vitro and in-vivo.

Animal models based on the amyloid cascade hypothesis of AD can be simply divided into two groups: transgenic models ► genetically modified animals and non-transgenic models. The non-transgenic amyloid animal model involves acutely injecting or continuously perfusing β-amyloid peptide directly into the brains of normal animals. The first in-vivo data showing that injection of β-amyloid into the frontal cortex of rats causes neurodegeneration and cell loss was reported in 1991 (Kowall et al. 2001). Since then there have been a large number of in-vitro and in-vivo studies clearly showing that β-amyloid peptides are neurotoxic and can lead to learning and memory impairments in rodents and primates (for review see Harkany et al. 1999).

With respect to transgenic models, the first APP transgenic mouse that deposited β-amyloid similar to that observed in AD patients was generated in the mid 1990s. As a platelet-derived growth factor promoter was used to express the mutant human APP gene, this transgenic mouse is referred to as the "PDAPP" mouse (Games et al. 1995). Shortly after, a variety of novel APP transgenic mice were developed including the Tg2576 mouse (Hsiao et al. 1996) and the APP23 mouse (Sturchler-Pierrat et al. 1997). The Tg2576 and APP23 mice both express human APP with the AD Swedish mutation, whilst the PDAPP mice express human APP with the Indiana AD mutation.

Simply because the Tg2576 strain was made freely available to both profit and non-profit research organizations, the Tg2576 mouse is the most widely investigated of the APP transgenic lines. The histopathogical characteristics of Tg2576 mice are similar to that seen in AD in that they show amyloid plaques, dystrophic neurites, astrogliosis, microgliosis, increased oxidative stress and inflammatory ► cytokines. β-amyloid levels generally begin to increase in Tg2576 mice at approximately 6 months of age and plagues begin to develop at around 9–12 months (Hsiao et al. 1996).

In the same year that the PDAPP transgenic mouse was described, mutations in the presenilin (PS1) gene were found to be responsible for some cases of familial AD (Sherrington et al. 1995). Soon after a mouse line overexpressing the mutated PS1 gene was generated and when later crossbred with the APP mouse, the new strain showed pronounced increases in amyloid levels with earlier onset of plaque deposition. Within a short period, numerous mouse lines were created that carried either single or multiple mutations in the APP and presenilin genes. Whilst APP and PS1 transgenic mice showed elevated levels of β-amyloid and increased amyloid plaque deposition, the lack of robust neuronal loss and NFT's pathology raised serious debate on the validity of the amyloid hypothesis as a model for AD (for review see McGowan et al. 2006).

In 1998, mutations of the Tau gene on chromosome 17 was linked to frontotemporal dementia with Parkinson's disease confirming that Tau dysfunction is linked to neurodegeneration (Hutton et al. 1998). Subsequent phenotyping of the rapidly generated Tau transgenic mice revealed age-dependent expression of insoluble hyperphosphorylated Tau and intraneuronal NFT inclusions. Whilst some NFT's were present in the brain, greater expression was seen in spinal cord neurons. The spinal cord also showed considerable axonal degeneration ultimately leading to paralysis of the hind limbs. Whilst slightly more problematic, the Tau transgenic mice were crossed with APP mice to determine if there was synergy between β-amyloid and Tau pathogenesis. The double transgenic mouse line showed considerably more neuropathology than the Tau mutation alone, but because these mice were extremely poor breeders and developed severe motor deficits, long term studies were not feasible.

A relatively recent development in the AD transgenic mouse field has been the generation of the triple transgenic mouse line. To avoid potential issues associated with the cross breeding of APP, PS1, and Tau lines, the two transgenes encoding APP and Tau were injected into single cell embryo's harvested from a PS1 mouse line. The resulting 3X TG-AD mouse shows: age-dependent increases in β-amyloid levels, amyloid and Tau pathology, reduced long-term potentiation and significant deficits in both spatial and contextual learning (for reviews see McGowan et al. 2006; Sankaranaarayanan 2006). Whilst cognitive analysis of AD transgenic animals has certainly yielded fascinating results, cautious interpretation is always recommended as cognitive testing in mice is not as straight

forward as the rat and the published reports on the mice have certainly caused some controversy (Routtenberg 1997).

Bearing in mind the above caveats, the transgenic and non-transgenic models described above have proved useful in reproducing the pathological phenotype associated with amyloid and Tau expression, and to a lesser extent the neurodegeneration and synaptic deficits found in AD. As a consequence, a number of late stage therapeutic compounds designed to lower β-amyloid load have been tested in these models and some look promising ► neuroprotectants: novel approaches for dementias. As these molecules progress through clinical trials, the amyloid hypothesis of AD will be tested. This should hopefully lead to a clear conclusion that reducing β-amyloid in the CNS will lead to either stabilization or more preferably an attenuation of the cognitive decline in AD.

Although cognition tests are discussed in more detail within other essays, for example see, operant behavior in animals, ► rodent models of cognition and ► short-term and working memory in animals, it is worth briefly mentioning some of the classical rodent cognition tests that have been used in the characterisation of AD animal models. Due to the pronounced hippocampal abnormalities in AD patients, rodent cognition tests that are hippocampal-dependent have been the tests of choice. The most popular of these has been the ► Morris water maze which was developed nearly 30 years ago to measure ► spatial learning and memory capabilities in rodents. The water maze consists of a large circular water filled tank with a submerged escape platform. The animals are required to learn and remember the location of a hidden platform using spatial cues positioned within the testing room. Aged, lesioned, pharmacologically challenged and AD transgenic animals have all shown performance deficits, sometimes reversible in the water maze.

Another widely used test for rodent cognition involves the acquisition and retention of ► passive avoidance behavior. Here a rodent is punished when it engages in a spontaneous behavior, typically receiving a mild foot shock when it enters a dark compartment from a brightly lit holding chamber. Later, the animal is tested for its "memory" of the aversive event by determining the latency to reenter the compartment where the shock was delivered. Taken at face value, changes in entry latencies can be interpreted as measures of the animal's memory for the aversive event. However, there are considerable confounding factors that must be taken into account when interpreting data from passive avoidance studies. For example, treatments that cause motor impairments, changes in anxiety responses, pain sensitivity, and motivation can all impact entry latencies and potentially be misconstrued as cognitive effects. Perhaps the most significant concern with passive avoidance has to be its lack of predictive validity as numerous novel cognitive enhancers which have shown efficacy in this test have failed to deliver in the clinic. In addition to these tests, other examples of cognition tests that have been used to characterize AD animal models and assess potential efficacy of AD therapies include cued/contextual learning, operant-based (lever pressing) tasks, object recognition tests and the five choice serial reaction time test.

To conclude, animal models and appropriate tests have been and still will be pivotal in our attempts to understand the complex biology found in AD and other related dementias. Furthermore, they also serve as indispensable tools in the drug discovery and development process. Data generated in these models not only provides additional confidence in the likely therapeutic utility of novel compounds, but also confirms whether the identified molecular target is linked to the disease process and whether its modulation will lead to beneficial effects. Whilst there is no single animal model that can fully recapitulate all of the cognitive, biochemical and histopathological abnormalities observed in AD patients, partial reproduction of AD neuropathology and cognitive deficits have been achieved with the AD models described above. AD and other dementia research will continue to depend on the use of thoroughly validated animal models but to increase clinical success researchers are now combining new technologies such as biomarker and genetic profiling so that improved treatments may be identified and hopefully delivered to the patients.

Cross-References

► Acetylcholinesterase and Cognitive Enhancement
► Cognitive Enhancers: Novel Approaches
► Dementias and Other Amnestic Disorders
► Five-Choice Serial Reaction Time Task
► Genetically Modified Animals
► Long-Term Potentiation and Memory
► Muscarinic Agonists and Antagonists
► Neuroprotectants: Novel Approaches for Dementias
► Operant Behavior in Animals
► Rodent Models of Cognition
► Short-Term and Working Memory in Animals
► Translational Research

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Demerol

► Pethidine

Demoralization Syndrome

► Chronic Disappointment Reaction

Dendritic Spine

Definition

A protrusion in neuronal dendrites that contains the postsynaptic part of a neuronal synapse. The vast majority of dendritic spines is found in glutamatergic neurons and form asymmetrical synapses.

Deoxyglucose

Synonyms

2-deoxyglucose; 2-DG

Definition

A glucose molecule where the 2-hydroxyl group is replaced by a hydrogen, preventing further glycolysis following cellular uptake and hence accumulation in the cell. Deoxyglucose can be administered to living organisms where it competes with glucose uptake into the cell. Consequently, cells with higher glucose uptake, such as activated neurons, have a higher uptake of deoxyglucose. Deoxyglucose can be radiolabeled with tritium [^{3}H], carbon-14 [^{14}C], or fluorine-18 [^{18}F] and used as a ligand to measure brain activation in animals or man, either by autoradiography, mPET, or PET.

Cross-References

► Imaging
► PET
► μPET

Depakine

► Valproic Acid

Dependence

Definition

Synonymous with addiction. The World Health Organization defined it as a state, psychic and sometimes also physical, resulting from the interaction between a living organism and a drug, characterized by behavioral and other responses that always include a compulsion to take the drug on a continuous or periodic basis in order to

experience its psychic effects, and sometimes to avoid the discomfort of its absence. Tolerance may or may not be present. A person may be dependent on more than one drug because a range of withdrawal symptoms are experienced. Other definitions are also in use.

Cross-References

- ▶ Addiction
- ▶ Agoraphobia
- ▶ Physical Dependence
- ▶ Sedative, Hypnotic, and Anxiolytic Dependence

Depersonalization

Definition

Experiencing changes of oneself or parts of the body.

Cross-References

- ▶ Alcohol Abuse and Dependence
- ▶ Cannabis Abuse and Dependence
- ▶ Cocaine Dependence
- ▶ Cross Dependence
- ▶ Hallucinogen Abuse and Dependence
- ▶ Nicotine Dependence and Its Treatment
- ▶ Opioid Dependence and Its Treatment

Depolarization Block Theory

Definition

A theory based on studies in rats showing that antidopaminergic treatment leads to inactivation of dopamine firing which was thought to be the mechanism of antipsychotic drug action. As it took 3 weeks until this inactivation was in effect, it was believed that this delay explained the delay of onset of antipsychotic drug effects.

Depression

Synonyms

Major and minor and mixed anxiety-depressive disorders

Definition

An emotional state characterized by persistent feelings of sadness, loss of energy and interest, thoughts of death or suicide.

Depression: Animal Models

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Definition

Animal models for ▶ depression refer to experimental procedures or animal preparations which model the aspects of Major Depressive Disorder (MDD) in humans. These animal models are broadly subdivided into screening models, used primarily for identifying potential therapeutic effects of established and novel compounds, and simulation models, where the emphasis is on understanding the theoretical basis for MDD. General reviews of animal models of depression are available (Cryan et al. 2002; Nestler et al. 2002; Willner and Mitchell 2002a,b) and specific models are described in a special issue of *Neuroscience & Biobehavioral Reviews* (2005, vol. 29, No. 4–5).

Current Concepts and State of Knowledge

Symptoms of MDD

The clinical symptoms required for diagnosis of an episode of MDD are depressed mood, markedly diminished interest or pleasure in activities, significant weight loss or weight gain, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue, or loss of energy, feelings of worthlessness or excessive or inappropriate guilt, diminished ability to think or concentrate, and recurrent thoughts of death or suicide (DSM IV) (American Psychiatric Association 1994). The symptoms must be persistent, at least 2 weeks in duration. Some of the clinical symptoms can be modeled directly by behavioral studies in rodents and are marked in the italicized rows of Table 1. These behaviors form the basis for some of the tests and animal models of the predisposition or treatment of mood disorders.

Symptoms outside of the DSM IV criteria, such as anxiety, loss of control, and irritability, may also form the basis for animal models of depressive behavior because they are part of a dimension of similar behavior clusters described for MDD. Symptoms of depressed mood and recurrent thoughts of death and suicide cannot be modeled in rodents because they are internal or private states experienced by the patients.

Behavioral Screening Tests for Antidepressant Treatments

The most common use of animal screening tests for depressive behaviors (Table 2) is to predict the therapeutic

Depression: Animal Models. Table 1. Comparison of DSM IV symptoms of major depressive disorder in humans and behavioural tests in rodents that model those symptoms (italicized area).

Clinical symptoms of depression (humans)	Behavioral model of symptoms in rodents
Markedly diminished interest or pleasure (anhedonia)	*Intracranial self-stimulation, operant responding for positive reward, ingestion of sucrose, social withdrawal*
Significant changes to appetite or weight gain	*Loss in body weight after exposure to chronic stress*
Insomnia or excessive sleeping	*Abnormal sleep architecture*
Psychomotor agitation or retardation	*Agitation: irritability on handling; Retardation: reduction of motor activity or speed*
Fatigue or loss of energy	*Reduced activity in home cage, activity tests, nest building*
Indecisiveness or diminished concentration	*Deficits in woking or spatial memory, learning, sustained attention*
Difficulty in performing even minor tasks, such as personal hygiene	*Poor coat condition and impaired grooming*

Depression: Animal Models. Table 2. Pharmacological and behavioural screening tests for antidepressant drugs.

Screening tests for antidepressant drugs
Pharmacological tests Reserpine and tetrabenazine reversal (reversal of catecholamine insufficiency) 5-HTP potentiation (augmentation of serotonin function) Yohimbine potentiation (α2 receptor blockade) Apomorphine (dopamine) and clonidine (α2) autoreceptor antagonism 8-OH-DPAT (5-HT_{1A} autoreceptor) antagonism Potentiation of apomorphine and clonidine-induced aggressive-defensive behaviour Cytokine-induced depression or illness
Behavioral tests Behavioral despair Forced swim test Tail suspension test Hyponeophagia DRL behaviour Waiting behavior or delayed discounting

effects of novel drugs. The rationale for the prediction is to reproduce the pattern of response of antidepressant drugs that have already been shown to be clinically effective, a criterion of success defined as ► predictive validity. Predictive validity for antidepressant treatments has grown more complex with the introduction of compounds and somatic treatments with a wide array of pharmacological and physiological effects. Initially, ► TCAs and ► MAOIs were the principal classes of antidepressant drugs. Subsequently, other classes of antidepressant drugs were introduced, including ► SSRIs, NRIs, ► SNRIs, and atypical antidepressants. In addition, some effective somatic treatments for depression are in widespread use, including ► electroconvulsive shock, exercise, ► transcranial magnetic stimulation, and stimulation of the vagus nerve. Different antidepressant treatments (SSRIs, SNRIs, novel compounds) may produce similar behavioral effects, though they may produce their effects through different mechanisms.

Pharmacological screening tests may be based on a particular theoretical rationale, but the particular theoretical rationale used in the screen may also limit the range of compounds that can be detected with the test. For example, reversal of the effects of ► reserpine or ► tetrabenazine ptosis, motor activity or hypothermia is based on the catecholamine hypothesis of affective disorders, because reserpine and tetrabenazine deplete catecholamines and the clinical use of reserpine was reported to cause depression. However, these screening tests cannot be used to detect SSRIs or other compounds that do not involve catecholamine mechanisms. Behavioral screening tests may differ from pharmacological tests because they are not limited to identifying drugs from a particular class. Thus, the forced swim test, based on a theoretical rationale involving ► learned helplessness (LH) as a contributor to the development of depression, can detect all of the major pharmacological and somatic classes of antidepressant treatments.

Behavioral tests of depressive behavior are not true animal models of MDD. They do not attempt to reproduce multiple components of depression and they do not induce symptoms for a prolonged duration. Screening tests are usually a behavioral characteristic, or an ► endophenotype, that can be measured quantitatively and is associated with a single dimension of emotional behavior related to depression. Tests of ► behavioral despair involve the reaction of animals to inescapable stress and the loss of control, hyponeophagia involves anxiety associated with novelty, and DRL or waiting behavior are tests of impulse control.

Another important dimension is whether screening tests or models respond to acute or chronic

antidepressant treatment. There is a temporal delay between the initiation of clinical treatment and the appearance of full or even partial recovery. Some behavioral and pharmacological effects require chronic treatment to develop and may bear a closer temporal correlation with the time course of clinical treatments. Tests such as the forced swim test, tail suspension test, DRL behavior, and waiting behavior can respond to acute treatment with antidepressants, particularly at high doses. However, these tests may respond or demonstrate sensitization upon chronic treatment, particular if lower doses are used that produce plasma levels of drug that are similar to those in humans. Some behaviors, such as reduction of hyponeophagia, are produced only following chronic treatment and are associated with increases in ►brain-derived neurotrophic factor and hippocampal neurogenesis.

Depression Models Based on Environmental Adversity

A number of animal models of depression use environmental stress to produce long-term changes in behaviors associated with depression. The models of environmental adversity are based on the rationale that exposure to stress is a known precipitate of MDD (Table 3).

Learned Helplessness

►Learned Helplessness (LH) is based on an influential theory that exposure to uncontrollable stress leads animals to learn that voluntary actions will not be effective in coping with stress. LH produces changes in affective, cognitive, and motor functions, although controversy has centered on whether the effects of LH represent cognitive impairment or motoric inactivity. In LH, animals that are exposed to inescapable stress will subsequently fail to escape from a situation where escape is possible. Usually, rodents are tested for escape from electric shock in a shuttle box. Animals are compared to several control groups, including yoked control animals that receive the same amount of shock but are allowed to terminate the shock through a response. Differences are then attributable to control over shock termination.

LH animals show several neurovegetative changes that are similar to depression, such as rapid eye movement sleep alterations, reduced body weight, diminished sexual behavior, and elevated levels of corticotropin releasing factor and corticosterone. Repeated treatment with antidepressants reduces the latency to escape and decreases the number of animals that develop LH.

It remains unclear whether LH is a better model of posttraumatic stress disorder and other conditions where acute stress is a clear etiological factor than of depression. Since there is variability in the susceptibility of different animals to LH, some studies have used the variability to segment vulnerable populations from resilient populations. The effects of LH training depend on genetic background, and lines of rodents have been bred with increased vulnerability that may amplify its effects (Table 4). Nevertheless, the effects of LH training are usually not long-lasting.

Depression: Animal Models. Table 3. Models of depression as a response to environmental adversity (i.e., stress).

Models of depression as a response to environmental adversity (i.e., stress)	
Chronic stress	Learned helplessness
	Chronic mild stress
Social dominance models	Social defeat in resident-intruder test
	Social hierarchy
Social separation	Isolation from parents, peers or social bond

Depression: Animal Models. Table 4. Models of genetic predisposition to stress.

Models of genetic predisposition to depression	
Genetic models	
Rats	Selective breeding for muscarinic hypersensitivity
	Roman low-avoidance strain
	Fawn-hooded strain
	Wistar-Kyoto
	High DPAT sensitive – 5-HT1A receptor sensitivity
	Swim high (SwHi) and low active (SwLo)
	Learned helplessness – Henn
Mouse	Learned helplessness – helpless versus nonhelpless lines
	Behavioral despair – long versus short immobility times
Genomic models	
	5-HT transporter knockout
	CRF-R2 knockout
	BDNF knockout
Developmental models	
	Neonatal antidepressant treatment
	Prenatal/neonatal stress
	Maternal separation
Lesion model	
	Olfactory bulbectomy

Chronic Mild Stress

The ► chronic mild stress procedure causes behavioral changes in rodents that parallel the symptoms of depression by continuous exposure to a variety of mild stressors, such as periods of food and water deprivation, cold, changes of cage mates or isolation, and alterations of the light cycle (Willner 2005). An assortment of heterogenous stressors is used to avoid adaptation to repeated exposure to a single stressor. Over weeks of chronic exposure, rodents gradually reduce their consumption of a preferred dilute sucrose solution. The deficit of sucrose consumption persists for weeks until the cessation of the stress. These effects appear to reflect a generalized insensitivity to reward, as also shown by reduced ► brain stimulation reward or place preference conditioning. Other behavioral signs of chronic stress include reduction of body weight, altered sleep patterns, decreased sexual and aggressive behavior, and abnormal grooming behavior.

Chronic treatment of rodents with antidepressant drugs restores the normal preferential intake of sucrose and other indices of stressed behavior, such as abnormal grooming or place conditioning. Chronic treatment is required for behavioral effects, and nonantidepressants are ineffective. Giving antidepressant drugs chronically to unstressed animals did not alter these behaviors. The chronic mild stress procedure has been used to measure the potential antidepressant activity of a number of novel targets. The major disadvantage of this model has been its variable outcome across laboratories.

Social Dominance Models

There are parallels between the symptoms of MDD and behaviors of animals of low social rank. Such comparable behaviors form the basis for attempts to model MDD using species-specific subordinate behaviors evoked by social conflict. The rationale for these models generates from the greater pathology risk of individuals in subordinate roles or those who have lost social status as a result of defeat in social conflict. One of the attractive features of models using ► social stress is that they employ naturalistic and ethologically relevant situations to evoke and measure depressive behavior. Many models involve rodents but these have been extended to nonhuman primates.

In chronic social defeat, a rodent is exposed briefly but repeatedly to an aggressive and dominant animal. In continuous subordination stress, rodents are exposed to defeat and then held in close contact with the dominant animal from a protected enclosure on a daily basis. Modified procedures expose dominant pair-housed rats to defeat by an intruder from a more aggressive strain, resulting in the loss of their dominant status. Rodents exposed to chronic social defeat show reduced body weight, reduced sucrose drinking, increased corticosterone levels, increased immobility in the forced swim test, and suppression of BDNF activity in the VTA. Rodents exposed to social defeat will demonstrate avoidance of other rodents in a social choice situation that will persist for weeks after the cessation of social contact. Chronic administration of antidepressant drugs has been shown to restore social approach behavior and the other behavioral effects of chronic social defeat. Subordinate rats or tree shrews often need to be rescued, however, because they will not maintain subordinate status without morbidity.

Social Hierarchy

A way to measure social status is to house rats in closed social groups of 2 or 3 animals per cage to develop a stable social hierarchy. Their relative social rank can be assessed by tests of competitive behavior, usually involving food consumption. The hierarchy can be disrupted by treating the subdominant animal chronically with antidepressant drugs, where the subdominant animal demonstrates increased assertiveness during social encounters.

A similar competitive situation has been used to examine social competition between stable pairs of rodents contesting over access to food. Chronic administration of antidepressant drugs to the subordinate member of the pair has been shown to increase their competitiveness for food to the extent where the hierarchy is no longer maintained. There is a great deal of variation in the behavior of rodents involved in daily social competition, and a stable hierarchy must be maintained over many weeks for antidepressant drug testing. In laboratory rodents, winning or losing in a competitive situation is limited to the specific test and does not readily transfer to other competitive situations. A separate control group (treated with vehicle) is needed to assess whether drug treatments change the behavior significantly beyond the level expected from normal variation.

Social Separation

The loss of important social support, either loved ones or peers, contributes to the development of depression. A number of animal models are based on the separation of social groups, either infants separated from parents, juveniles separated from a peer group, or two life-long mates in the case of voles. One of the most well-known primate models is the development of depressive behaviors by separating infants from parents, decreased activity, appetite, failure to play, and sad facial expressions, that are strikingly similar to human depression. Maternal

separation in rodents also produces life-long vulnerability to changes in depressive and anxiety behaviors.

Models of Genetic Predisposition to Stress

MDD is a highly heritable disorder with genetic factors estimated to comprise at least 50% of the risk for developing the disorder. Genetic factors also determine an animal's biological and behavioral responses to stress that are reflected in vulnerability to tests of depressive behavior. Different inbred strains of rats and mice show variations in responses to stress, along with sets of behaviors that comprise models of exaggerated depression-related behaviors similar to humans (see Table 4). Understanding the genetic factors underlying these behavioral differences using techniques such as quantitative trait locus analysis could facilitate human genetic studies by suggesting individual genes and gene maps that may contribute to mood disorders in humans. Inbred strains also display variations in the response to antidepressant drugs that can be used to model factors contributing to treatment resistance (Crowley and Lucki 2005).

Despite acknowledgement of a genetic etiology, no specific genetic abnormalities that confer risk have been identified. Targeted genetic mutations can be produced by removing or replacing a selected sequence of DNA within the genome with a different sequence. When genetic factors for MDD are identified or hypothesized, rodent models of depression may be developed to study the effects of homologous genetic mutations. Until that time, many lines of rodent mutations have been studied using depression-related behaviors, mostly using the mouse forced swim test. Some mouse lines have been identified that show exaggerated depressive behaviors associated with genetic deficiency of endocrine function (aromatase, CRF-R2), neurotrophic factors (BDNF), or neurotransmitter function (5-HT transporter). Other lines of rodents have been identified as genetic models of depression because they demonstrate a consistent pattern of exaggerated depressive-like behaviors, although the genetic mechanisms underlying these changes have not been identified.

Aside from genetic predisposition, developmental and lesion models have also been used to produce long-lasting predispositions to depressive behavior. Rodents as neonates given antidepressants develop exaggerated signs of depressive-like behavior when tested as adults. Rodents exposed to higher levels of stress prenatally also demonstrate behavioral abnormalities associated with depression and anxiety when tested as adults. Lesions of the olfactory bulb produce a complex of abnormal emotional behaviors, not due to anosmia, that are normalized by the chronic administration of antidepressant drugs.

Depression: Animal Models. Table 5. Models of depression involving medical comorbidity.

Models of medical comorbidity
Cardiovascular illness
Diabetes
Stroke
Gonadal insufficiency
Withdrawal from psychomotor stimulants

Medical Comorbidity

MDD has frequently been reported to occur coincidentally with the development of medical illness, such as cardiovascular illness, diabetes, or stroke (see Table 5). When MDD develops, it has been shown to worsen the trajectory of recovery from medical illness. Pre-existing depression also increases the vulnerability for developing serious consequences of medical illnesses, such as myocardial infarction or stroke. Insufficient secretion of major gonadal hormones developed through progressive aging has been associated with increased incidence of MDD. Pre-existing addictions, principally to psychomotor stimulants or nicotine, can convey residual vulnerability to MDD after clinical treatment for substance abuse. Rodent models of depression have been developed for studying these comorbid conditions. Altered vulnerability to stress or immunological factors could convey comorbidity between depression and medical illness. Comorbid illness may also respond to different sets of antidepressant medications than other depression models.

Cross-References

- ▶ Animal Models for Psychiatric States
- ▶ Antidepressants
- ▶ Behavioral Despair

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Depression Medications

► Antidepressants: Recent Developments

Depression NOS

► Postpsychotic Depressive Disorder of Schizophrenia

Depression Superimposed on Residual Schizophrenia

► Postpsychotic Depressive Disorder of Schizophrenia

Depressive Disorder and Schizophrenia

Definition

Schizophrenic patients frequently suffer from ► comorbid depressive syndromes. These can either be part of the acute manifestation of the illness or occur during the prodromal period, or as post-psychotic depression. The latter is diagnosed after the symptoms of acute psychosis have subsided and is sometimes interpreted as an adjustment disorder related to the disabilities caused by schizophrenia. Lastly, depression and ► schizophrenia can occur in parallel in patients suffering from schizoaffective disorder.

Depressive Disorders in Children

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Synonyms

Childhood depression

Definition

Depressive disorders in children and adolescents include major depressive disorder (MDD), depressive disorder not otherwise specified (► depressive disorder nos) and ► dysthymic disorder. Discussion in this essay will be limited to major depressive disorder because there are no controlled trials for the treatment of dysthymic disorder or depressive disorder nos. However, in clinical practice, treatment recommendations for MDD are successfully used in the management of dysthymic disorder and depressive disorder nos.

MDD in children and adolescents is characterized by one or more major depressive episodes, defined as at least 2 weeks of persistent change in mood manifested by either depressed or irritable mood or loss of interest or pleasure and at least four additional symptoms of depression, including changes in appetite or weight, sleep, psychomotor activity, decreased energy, feelings of worthlessness or guilt, difficulty thinking or concentrating, or recurrent thoughts of death or suicidal ideation, plans, or attempts. The symptoms must persist for most of the day nearly every day, must be associated with an impairment in functioning (social, academic or other), must not represent the direct physiologic effect of a substance or a general medical condition and must not be better accounted for by bereavement (American Psychiatric Association 1994).

Role of Pharmacotherapy

Depressive disorders in children are common, recurrent, and impairing. Depression is prevalent in 1–2% of children and 3–8% of adolescents. By the end of adolescence, approximately 1 in 5 adolescents will have experienced at least one depressive episode. After the onset of puberty, girls have twice the risk of developing depression that boys do, and risk is closely correlated with levels of testosterone, estradiol, and follicular stimulating hormone (Lewinsohn et al. 1998). Depression is a recurrent condition in children and adolescents, with 40% of patients experiencing a second episode within 2 years, and nearly 75% within 5 years. Almost all will experience another episode in their adult life. Untreated depression is associated with substantial impairment both during and after the episode, with difficulties in school, interpersonal relationships, and occupational adjustment, tobacco and ► substance abuse, suicide attempts, and a 30-fold increased risk of completed suicide.

When depression presents with psychotic symptoms, especially in adolescents with family history of bipolar

disorder, it is usually resistant to treatment and is associated with increased risk for bipolar disorder. Atypical depression presents with atypical symptoms such as lethargy (► leaden Paralysis), increased appetite, ► hypersomnia and increased sensitivity to rejection. While the major symptoms of depression persist across all ages, manifestations of depression may vary with age. Preschoolers may exhibit irritability, withdrawal, or regression as symptoms of depression (Luby et al. 2003). School-age children may display irritable or depressed mood, crying spells, or somatic complaints such as headaches and stomachaches. Adolescents often present with extreme irritability or atypical depressive symptoms such as increased appetite, hypersomnia, and excessive fatigue.

Clinical guidelines for the acute management of child and adolescent depression recommend the prescribing of antidepressant medications, psychotherapy, or both, with the best-studied psychotherapy being cognitive behavioral therapy (CBT) (Birmaher et al. 2007).

Antidepressants

It is important to personalize the selection of a specific medication to each patient by taking into consideration the relative safety for the particular patient, comorbid psychiatric diagnoses, side-effect profiles, and the patient's other medical conditions. Physicians need to discuss risks and benefits of the medication and available alternative treatments, and obtain informed consent prior to starting treatment.

The ► selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed class of antidepressants. They work by inhibiting reuptake of serotonin by presynaptic neurons, with at least 70% reuptake inhibition required to result in clinical improvement. They include ► fluoxetine (Prozac), ► sertraline (Zoloft), ► paroxetine (Paxil), ► fluvoxamine (Luvox), ► citalopram (Celexa), and ► escitalopram (Lexapro). Currently, fluoxetine and escitalopram are the only antidepressants approved by the U.S. Food and Drug Administration for the treatment of depression in patients under the age of 18, although other SSRIs are often prescribed based on factors such as side-effect profile or personal or family history of response to a specific medication. Depressed patients treated with SSRIs have a relatively good response rate (40–70%), but placebo response rate in ► randomized controlled trials of pediatric depression is also high (30–60%), resulting in an overall ► number needed to treat (► NNT) of 10 (Bridge et al. 2009). Baseline depression severity was an inverse predictor of treatment response in these studies (i.e., less severely ill children were more likely to respond) (Curry et al. 2006). Antidepressants are more efficacious in adolescents than in children (NNT of 7 vs. 15), except for studies of fluoxetine, in which the effects are equal in children and in adolescents and are stronger than in most other studies of pediatric depression (NNT = 5). The half-lives of paroxetine, sertraline, citalopram, and ► venlafaxine are shorter in children and adolescents than in adults, which may explain the superior efficacy of fluoxetine vs. these other agents in prepubertal youth. While response and sustained improvement occurs in well over half of treatment-naive depressed adolescents, complete symptomatic ► remission rates are considerably lower, on the order of 20–37% after 12 weeks of treatment.

To date, no non-SSRI medication – except for venlafaxine in treating resistant depression – has demonstrated clear efficacy in treating pediatric depression, but a number of newer non-SSRI antidepressants are available (Brent et al. 2008). These agents preferentially affect a variety of different receptor sites, and they include ► bupropion (Wellbutrin, Zyban), a primarily noradrenergic agent with some dopaminergic effect; ► trazodone (Desyrel) and nefazodone (serzone), serotonin receptor blockers; ► mirtazapine (Remeron), a serotonergic and adrenergic receptor blocker; venlafaxine (Effexor) and ► duloxetine (Cymbalta), serotonin and norepinephrine reuptake inhibitors; and ► atomoxetine (Strattera), a selective norepinephrine reuptake inhibitor (which is marketed for ► attention deficit hyperactivity disorder [ADHD], but not as an antidepressant). These are in addition to the older ► tricyclic antidepressants (TCAs), mixed serotonergic and noradrenergic agents that include ► amitriptyline (Elavil), ► clomipramine (Anafranil), desipramine (Norpramin), ► imipramine (Tofranil), ► nortriptyline (Pamelor, Aventyl), and protriptyline (Vivactil).

► Randomized control trials (RCTs) conducted with nefazodone are contradictory, with one trial demonstrating positive efficacy on some measures while the other was negative. Trials conducted with mirtazapine were negative. Conversely, in a study comparing response to an alternative SSRI or venlafaxine in adolescents who had failed to respond to an adequate trial of an SSRI, both classes of antidepressants were equally effective in reducing depressive symptoms, although venlafaxine has resulted in more side effects. Small open-label studies have suggested bupropion's efficacy in treating adolescent MDD with and without ADHD but no RCTs have been conducted. In a study of adolescents with ADHD and comorbid MDD, atomoxetine was shown to improve ADHD symptoms but not depression compared to placebo. RCTs, as well as a ► meta-analysis, have shown that TCAs are no more efficacious than placebo for the

treatment of child and adolescent depression and should not be used as a first-line medication. Moreover, they are associated with more side effects than the SSRIs and are potentially lethal in overdose.

Side Effects

Suicidal Ideation/Attempts

Antidepressants increase the risk of spontaneously reported suicidal adverse events by about twofold, with estimates of the risk difference ranging between 9 to 2% (Bridge et al. 2007). Most of these suicidal adverse events were increases in suicidal ideation, with relatively few attempts and no completions. Twelve times more depressed youths show a clinical response than experience a suicidal event. Those depressed youth with high suicidal ideation, irritability or anger, family conflict, and drug and alcohol use have been reported to be at higher risk for a suicidal adverse event. While disinhibition, switch to ► mania, onset of ► akathisia, increased irritability, and non-adherence followed by withdrawal from medication have all been posited to be related to suicidal adverse events, none of these hypotheses have been tested in pediatric samples. The ability to identify those who are most likely to respond and least likely to have adverse events is critical given the current level of concern about the associated risk of suicidality (Brent and Maalouf 2009).

Other Side Effects

SSRIs and other newer antidepressants are associated with side effects that are dose dependent and that may subside with time. The most common side effects include gastrointestinal symptoms, sleep changes (e.g., insomnia, somnolence or nightmares), restlessness, headaches, changes in appetite, and ► sexual dysfunction. Approximately 5% of youths, mainly young children, may have behavioral activation characterized by increased agitation and irritability or silliness. It is clinically important to differentiate these symptoms from mania or hypomania that may be induced by the antidepressant in children and adolescents with bipolar disorder or a family history of bipolar disorder. Other rare side effects include ► serotonin syndrome, ► extrapyramidal syndrome and increased bleeding time.

Side effects that are specific to some newer antidepressants include elevated blood pressure and tachycardia with venlafaxine; increased appetite, weight gain and somnolence with mirtazapine; risk of priapism in males taking trazodone; risk of fulminant hepatitis with nefazodone (which has led to its removal from some markets as a result); and risk of seizure with immediate-release formulations of bupropion, especially in doses higher than 400 mg/day and in patients with a history of eating disorders.

Treatment of Resistant Depression

Issues to consider in treating a child or adolescent who is not responding to treatment include misdiagnosis, undetected bipolar disorder, untreated comorbid medical or psychiatric disorder and non-adherence to treatment. Evidence shows that for the treatment of depressed adolescents who have not responded to an initial adequate trial with an SSRI, a switch to another SSRI is just as efficacious as a switch to venlafaxine, with fewer side effects (Brent et al. 2008). Small studies using ► lithium augmentation in resistant depression in adolescents have shown contradictory results. Studies in adult depression suggest that augmentation with atypical antipsychotics (such as ► aripiprazole), lithium, or thyroid hormone (T3) is efficacious and well-tolerated, but such studies have not been conducted in younger populations. Finally, some reports have suggested that ► electroconvulsive therapy (ECT) may be efficacious in treating resistant depression in adolescents, especially those with bipolar depression, although further research in this area is needed.

Cross-References

► Adolescence and Responses to Drugs
► Antidepressants
► Antidepressants: Recent Developments
► Bipolar Disorder in Children
► Dysthymic Mood Disorder
► NARI Antidepressants
► SNRI Antidepressants
► SSRIs and Related Compounds
► Suicide

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Depressive Disorders Not Otherwise Specified

Definition

A ► DSM IV diagnostic category that includes disorders with depressive features that do not meet the criteria for major depressive disorder, dysthymic disorder, or adjustment disorder.

Derealization

Definition

The environment seems surreal and changed.

Dermatophobia

► Delusional Disorder

Desensitization

Definition

The inhibition of the receptor caused by sustained exposure to an agonist.

Desoxyephedrine

► Methamphetamine

Desvenlafaxine

Synonyms

Desvenlafaxine succinate

Definition

The new SNRI, desvenlafaxine, is the major active metabolite of venlafaxine. In the USA, it became available under the brand name Pristiq in 2008. Its efficacy for acute treatment of MDD and for relapse prevention has been demonstrated in several randomized, double-blind, placebo-controlled studies.

Desvenlafaxine Succinate

► Desvenlafaxine

Detector

Definition

The detector is where identification and quantification of the separated components of the sample is carried out. Different types of detection (e.g., ultraviolet (UV) absorption spectroscopy, fluorescence spectroscopy, electrochemical detection) are used, depending on the nature of the compound(s) to be measured.

Detoxification

Definition

Detoxification is a process involving the discontinuation or tapering of a substance that an individual has been consuming on a regular basis usually because he/she is suffering from an addiction to this substance. Detoxification usually requires medical management and the administration of ancillary medication to ease withdrawal symptoms.

Developmental Neurotoxins

► Perinatal Exposure to Drugs

Developmental Programming

Definition

Long-term effects of early experiences on later neurobehavioral function in offspring.

Developmental Toxicology

Definition

The study of the effects of drugs, poisons, environmental contaminants, and other chemicals on development of the organism.

Dexmethylphenidate

► Methylphenidate

DF-118

► Dihydrocodeine

2-DG

► Deoxyglucose

DHC

► Dihydrocodeine

Diacetylmorphine

► Diamorphine

Diamorphine

Synonyms

Diacetylmorphine; Heroin

Definition

Diamorphine is more commonly known as heroin. It is a semisynthetic opioid drug synthesized from morphine, obtained from the opium poppy. It reaches the brain rapidly, where it is deacetylated into 6-monoacetylmorphine (6-MAM) and then into morphine, which binds to μ-opioid receptors to produce the drug's euphoric, analgesic, and anxiolytic effects. Diacetylmorphine itself exhibits relatively low affinity for the μ receptor. It has an extremely high potential for abuse and only limited medical uses, due to the wide range of other substances available. Frequent and regular administration is associated with tolerance, physical dependence, and severe psychological dependence.

Cross-References

► Addiction
► Analgesics
► Morphine
► Physical Dependence
► Tolerance

Diazepam

Definition

Diazepam is a classical benzodiazepine drug with sedative, hypnotic, anxiolytic, amnestic, muscle-relaxant and anticonvulsant activity. It produces these effects by potentiating the effects of ► GABA at $GABA_A$ receptors. Diazepam, like other ► benzodiazepines, binds to a distinct site within the $GABA_A$ receptor ion channel complex causing a conformational change in the receptor ion channel that potentiates the effects of GABA. Thus, the channel passes more current in a given time and produces greater neural inhibition. Diazepam itself has a ► half-life of approximately 30 h but there are several active metabolites that considerably increase the active half-life (range 20–100 h). It is used widely for sedation and as an anxiolytic, in particular, as a premedication before surgery, and sometimes for inducing brief anesthesia during minor investigative or surgical procedures. It is also used as an adjunct treatment for the relief of skeletal muscle spasm, for

convulsive disorders especially *Status epilepticus*, and for the treatment of alcohol withdrawal. Diazepam is also used recreationally either alone as a sedative or to enhance the effects of alcohol or opioids, for example, diazepam reportedly produces an augmented high when administered with methadone. Diazepam is also used by cocaine users to reduce the risk of seizures and by heroin users to enhance the effects of heroin. In addition, it is often used by cocaine and heroin users and alcoholics to reduce withdrawal symptoms between doses. The main adverse effect associated with the long-term clinical administration of diazepam is tolerance and dependence.

Cross-References

► Alcohol Abuse and Dependence
► Sedative, Hypnotic, and Anxiolytic Dependence

Dietary Tryptophan Depletion

► Tryptophan Depletion

Diethyl Barbituric Acid

► Barbiturates

Digital EEG Nomenclature

Synonyms

Electroencephalography; qEEG; Spectrograms

Definition

Digitization is carried out at sampling rates that are often called "sampling frequency." To avoid confusion with frequencies in EEG signals, this will be expressed in samples/s units. High-pass section is mostly carried out by digital filters and expressed in Hertz, normally set at 0.3–0.5 Hz. In the old literature, this section was determined by RC-circuits, and its characteristics are expressed in time constants t s, the shorter its value, the faster the relaxation is dampened. A t of 0.6 corresponds roughly with 0.3 Hz high pass. EEG frequency bands are also expressed in Hertz, but one can still find the expression cycles-per-second, cycles/s or cps.

Dihydrocodeine

Synonyms

DHC; DF-118; Paracodeine

Definition

Dihydrocodeine is a semisynthetic opioid analgesic developed in Germany in 1908 and released on the market in 1911. Dihydrocodeine is a powerful cough suppressant like all other members of the immediate codeine family and their cousins hydrocodone and oxycodone. It is also an analgesic, but the antitussive dose tends to be less than the analgesic dose. It is prescribed either alone or compounded with aspirin or paracetamol. In some countries, controlled-release dihydrocodeine is used as an alternative to methadone in treatment of opioid dependency and addiction.

Cross-References

► Addiction
► Analgesics
► Dependence
► Hydrocodone
► Opioids
► Oxycodone
► Pain
► Tolerance

Dihydrocodeinone

► Hydrocodone

Dihydromorphinone

► Hydromorphone

1,3-Dihydro-7-Nitro-5-Phenyl-2H-1,4-Benzodiazepin-2-One

► Nitrazepam

l-3,4-Dihydroxyphenylalanine

► Levodopa

N-[(3-Dimethylamino)Propyl]-N-[(Ethylamino)Carbonyl]-6-(2-Propenyl)-Ergoline-8b-Carboxamide

► Cabergoline

N,N Dimethyl-2[α-(o-Tolyl)Benzyloxy] Ethylamine HCl or Citrate

► Orphenadrine

Dimension

Definition

In relation to ► behavioral flexibility, a dimension is a category of attributes, within which multiple stimuli may be discriminated. The attributes might be visual features (such as color or shape) or another perceptual feature (such as odor or texture). Alternatively, a discriminative dimension might be based on non-perceptual attributes, such as grammar (part of speech) or emotional valence.

Dimorphone

► Hydromorphone

2-[(Diphenylmethyl)Sulfinyl]acetamide

► Modafinil

Dipipanone

Definition

Dipipanone is an opioid analgesic that is prescribed for relief of moderate to severe pain. Chemically, it closely resembles methadone, the only structural difference being the N,N-dimethyl moiety of ► methadone being replaced with a piperidine ring. Its usage is now officially discouraged because of the abuse risk. It is sometimes used as Diconal, a mixture of Dipipanone with an antihistamine, cyclizine. The combination with cyclizine produces a very strong rush if injected.

Cross-References

► Addiction
► Analgesics
► Dependence
► Opioids
► Pain
► Tolerance

Disability Scales

► Impairment of Functioning; Measurement Scales

Discontinuation Symptoms

Definition

Symptoms that emerge or worsen markedly, following either the withdrawal or a reduction in prescribed dosage of medication, seen with most classes of psychotropic drug but perhaps most visibly with benzodiazepines and some SSRIs. Symptoms are typically at their worst within the first week, although some patients report symptoms persisting over longer periods.

Discrete-Cue-Induced Reinstatement

Definition

In this procedure, laboratory animals are first trained to self-administer a drug or nondrug reinforcer; each reinforcer delivery is temporally paired with a discrete cue (e.g., tone, light). Lever pressing is then extinguished in the absence of the reinforcer and the cue. During reinstatement testing, exposure to the cue, which is earned contingently during testing, reliably reinstates responding.

Discriminative Cue

► Discriminative Stimulus
► Stimulus Generalization

Discriminative-Cue-Induced Reinstatement

Definition

In this procedure, rats are trained to self-administer a reinforcer in the presence of distinct discriminative stimuli; one set of stimuli signals reinforcer availability (S+) and the other signals unavailability (S−). Lever pressing is then extinguished in the absence of the discriminative stimuli. During the reinstatement test, re-exposure to the S+ reinstates lever responding.

Discriminative Stimulus

Synonyms

Cue (in psychology); Discriminative cue

Definition

A discriminative stimulus is an environmental event that sets (signals) occasions during which a behavioral response has a significant consequence such as the presentation or withholding of a reinforcer. Discriminative stimuli may be present either in the external environment (exteroceptive stimuli) or the internal environment (interoceptive stimuli).

Cross-References

► Drug Discrimination

Disease Modification

Definition

A process that alters the expected natural course of the disease other than by improving symptoms. It may work via a neuroprotective mechanism or may alter the response to other drugs.

Dishabituation

Definition

Dishabituation refers to an increase of a previously habituated response to the original stimulus following the presentation of a different stimulus in the same or different modality.

Disruptive Behavior Disorders

► Externalizing Disorders

Dissociated Learning

► State Dependence of Memory

Dissociative Anesthetics

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Definition

Dissociative anesthesia is a form of anesthesia characterized by ► catalepsy, ► catatonia, analgesia, and amnesia. It does not necessarily involve loss of consciousness, and thus does not always imply a state of ► general anesthesia. Dissociative anesthetics probably produce this state by interfering with the transmission of incoming sensory signals to the cerebral cortex and by interfering with communication between different parts of the central nervous system.

Pharmacological Properties

History

Most dissociative anesthetics are members of the phenyl cyclohexamine group of chemicals. Agents from this group were first used in clinical practice in the 1950s. Early experience with agents from this group, such as ► phencyclidine and cyclohexamine hydrochloride, showed an unacceptably high incidence of inadequate anesthesia, convulsions, and psychotic symptoms (Pender 1971). These agents never entered routine clinical practice, but phencyclidine (phenylcyclohexylpiperidine, commonly referred to as PCP or "angel dust") has remained as drug of abuse in many societies. In clinical testing in the 1960s, ► ketamine (2-(2-chlorophenyl)-2-(methylamino)-cyclohexanone) was shown not to cause convulsions, but was still associated with anesthetic emergence phenomena, such as ► hallucinations and agitation, albeit of shorter duration. It became commercially available in 1970. There

are two optical isomers of ketamine: S(+) ketamine and R(−) ketamine. The S(+)-isomer is approximately three to four times as potent as the R(−)-isomer, probably because of higher affinity of the S(+)-isomer to the phencyclidine binding sites on NMDA receptors (see subsequent text). The S(+) enantiomer may have more pschotomimetic properties (although it is not clear whether this simply reflects its increased potency). Conversely, R(−) ketamine may preferentially bind to opioid receptors (see subsequent text). Although a clinical preparation of the S(+)-isomer is available in some countries, the most common preparation in clinical use is a racemic mixture of the two isomers.

The only other agents with dissociative features still commonly used in clinical practice are ► nitrous oxide, first used clinically in the 1840s as an inhalational anesthetic, and dextromethorphan, an agent used as an antitussive in cough syrups since 1958. Muscimol (a potent $GABA_A$ agonist derived from the amanita muscaria mushroom), and salvinorin A (a κ-opioid receptor agonist derived from the plant salvia divinorum), are also said to be dissociative drugs, and have been used in mystic and religious rituals (► Ritual uses of psychoactive drugs).

Mechanisms of Action

The primary direct molecular mechanism of action of ketamine (in common with other dissociative agents such as nitrous oxide, phencyclidine, and dextromethorphan) occur via an antagonist effect at the ► N-methyl-D-aspartate (NDMA) receptor. It may also act via an agonist effect on ► κ-opioid receptors (► Opioids). (Sharp 1997) ► Positron emission tomography (PET) imaging studies suggest that the mechanism of action does not involve binding at the ► γ-amino butyric acid ► GABAA receptor. (Salmi et al. 2005)

Indirect, downstream effects are variable, and somewhat controversial. The subjective effects of ketamine appear to be mediated by increased release of ► glutamate, (Deakin et al. 2008) and also by increased dopamine release mediated by a glutamate-dopamine interaction in the posterior cingulate cortex. (Aalto et al. 2005) Despite its specificity in receptor-ligand interactions noted earlier, ketamine may cause indirect inhibitory effects on GABA-ergic interneurons, resulting in a disinhibiting effect, with a resulting increased release of serotonin, norepinephrine, and dopamine at downstream sites.

The sites at which dissociative agents (such as subanesthetic doses of ketamine) produce their neurocognitive and psychotomimetic effects are partly understood. ► Functional MRI (► fMRI) (► Magnetic resonance imaging functional studies) in healthy subjects who were given low doses of ketamine have shown that ketamine activates a network of brain regions, including the prefrontal cortex, striatum, and anterior cingulate cortex. Other studies suggest deactivation of the posterior cingulate region. Interestingly, these effects scale with the psychogenic effects of the agent, and are concordant with functional imaging abnormalities observed in patients with ► schizophrenia (Fletcher et al. 2006; Pomaral-Clotet et al. 2006). Despite these data, it remains unclear whether these fMRI findings directly identify the sites of ketamine action, or whether they characterize the downstream effects of the drug. In particular, direct displacement studies with PET, using ^{11}C-labeled *N*-methyl-ketamine as a ligand, do not show clearly concordant patterns with fMRI data. Further, the role of direct vascular effects of the drug remain uncertain, since there are clear discordances in the regional specificity and magnitude of changes in cerebral blood flow, oxygen metabolism, and glucose uptake, as studied by PET in healthy humans. (Langsjo et al. 2004)

The neurophysiological effects of anesthetic doses of ketamine are different from those of most other anesthetic agents. When used as the sole anesthetic agent, ketamine results in maintained or increased global cerebral metabolism and cerebral blood flow, whereas most anesthetic agents reduce cerebral blood flow and metabolism. The regional cerebrovascular and metabolic effects of anesthetic doses of ketamine have been studied in animal models, and are broadly concordant, but no data are available in humans. However, the global increases in cerebral blood flow and volume produced by ketamine mean that, in patients with poor intracranial compliance, ketamine can cause increases in intracranial pressure. ► Electroencephalography shows that electrical activity during ketamine-induced anesthesia is maintained, with alternating periods of high amplitude delta activity and periods of fast activity. Again, when there are regional variations in such effects, their relationship to regional physiology and metabolism, and their neurochemical specificity, are poorly studied in man.

Pharmacokinetics

For medical use, a 10 mg/ml or 50 mg/ml solution is administered by intramuscular injection or, more commonly, by intravenous injection. Being a lipophilic drug, the onset of clinical effects is rapid and the time to peak effect after a bolus intravenous dose is short, suggesting that the drug crosses the ► blood-brain barrier rapidly. No estimates of the blood-effect-site equilibration rate constant have been published.

The initial volume of distribution is 60–80 L. Ketamine undergoes extensive re-distribution – two and three compartment ▶ pharmacokinetic models have been described. Fast re-distribution results in a short duration of action after a bolus dose (half-life 11–17 min). Lipophilicity results in accumulation in the fatty tissues. Published volumes of distribution at steady state are in the range 200–350 L (Reilly 1994; Sinner and Graf 2008).

Ketamine undergoes hepatic metabolism. Demethylation results in the major metabolite, norketamine, which possesses sedative and analgesic properties (potency is ~20% of ketamine). After hydroxylation and conjugation, norketamine is excreted by the kidneys. ▶ Elimination half-life is 2.5–4 h. Total clearance is ~1,200 mL/min. Despite accumulation, the relatively fast rate of metabolism makes ketamine an ideal agent for use by infusion.

Ketamine in powder form is rapidly absorbed via the mucosal surfaces of the upper airway, and so when used for recreational purposes (▶ Self-administration of drugs) it is usually administered by insufflation. Oral administration is seldom used since mean bioavailability is ~16%, and drug absorbed through the gut mucosa is rapidly metabolized to norketamine, resulting in sedation, which limits the dissociative effects.

Efficacy/Doses

Ketamine is used in clinical practice in two main indications. At moderate doses, it is a powerful analgesic, whereas at higher doses it is used as an anesthetic agent in specific situations (see below). Its ability to block NMDA-receptors has prompted studies investigating its role as a ▶ neuroprotective agent, and as a treatment for refractory status epilepticus. Intriguingly, in other settings (particularly in the developing brain and in aged animals) ketamine has been shown to be neurotoxic. Very low doses of ketamine have found a substantial research role in producing human models of ▶ schizophrenia. For analgesia without unconsciousness, intravenous dose requirements are 0.25–0.75 mg/kg, whereas intramuscular dose requirements are ~0.5–2 mg/kg. Bolus doses toward the upper end of the above ranges will result in a dissociated state with sometimes profound psychiatric symptoms (such as the "▶ k-hole"). The plasma levels at which psychotomimetic symptoms develop range between 50 and 300 ng/mL, analgesic effects are observed at about 200 ng/mL, whereas anesthesia is achieved at plasma levels above 1,000 ng/mL.

For anesthesia, an intramuscular dose of 8–10 mg/kg will produce loss of consciousness within 5 min, and anesthesia lasting for approximately 30 min. An intravenous dose of 1–2 mg/kg will produce loss of consciousness within 2 min, and anesthesia lasting 10–15 min. After an initial intravenous bolus dose, anesthesia can be maintained with additional bolus doses of 0.5 mg/kg or by an infusion at 1–2 mg/kg/h.

Safety/Tolerability

Ketamine increases in upper airway secretions, which can be attenuated by prior treatment with an anticholinergic agent. It can cause post-operative nausea and vomiting, and is associated with unpleasant dreams and hallucinations on emergence, with nightmares on subsequent days. These psychiatric phenomena can be attenuated by concomitant administration of a ▶ benzodiazepine or propofol, an intravenous anesthetic agent that acts at GABA receptors.

When used for recreational purposes, ketamine causes hallucinations, and a dissociative state characterized by depersonalization and derealization. At higher doses, users may experience a constellation of symptoms colloquially known as a "k hole." In clinical studies, infusions of subsedative doses produce several of the negative symptoms of schizophrenia, producing a reversible model for studying its pathogenesis. Such studies have shown that low doses of ketamine can produce impairments in ▶ working memory and ▶ episodic memory functions found in patients with schizophrenia. (Corlett et al. 2006)

Compared with other anesthetic agents, respiratory drive, airway reflexes, and ventilation are well maintained with ketamine, although at higher doses respiratory depression and apnoea will eventually occur. Ketamine possesses sympathomimetic properties, resulting in bronchodilation, increases in heart rate, and maintained or increased blood pressure in normovolaemic patients. Very low doses may cause favorable effects on immune functions. Ketamine is a potent analgesic. Subanesthetic doses have been shown to produce postoperative analgesia and to have antihyperalgesic activity. These powerful analgesic properties make it useful in occasional patients with severe chronic pain, unresponsive to first line analgesics. Ketamine may have a role in the prevention of chronic pain when used as an analgesic for acute (typically post-operative) pain, possibly by preventing ▶ central sensitization in neural systems. Ketamine has also been used for the treatment of chronic pain, by the oral, parenteral, and spinal routes.

The paucity of cardio-respiratory depressant effects makes ketamine an ideal anesthetic agent for use in poorer countries, where facilities for ventilation and airway management may be limited, and also in trauma situations, where patients may have suffered significant blood loss resulting in hypovolaemia (and in whom other anesthetic agents may result in significant falls in blood pressure).

In children, it is sometimes used by intramuscular injection for sedation where intravenous access is difficult to achieve. The analgesic properties can make ketamine a useful agent for short-term sedation or dissociative anesthesia for painful procedures, such as burns dressing changes.

Conclusion

Recreational use of ketamine is common in many countries. In contrast, the use of dissociative anesthesia is becoming increasingly rare in the first world, since adequate sedation, analgesia, and anesthesia can be achieved with one or more newer agents with fewer adverse effects. However, ketamine is being used increasingly as an adjuvant analgesic during general anesthesia. The adverse psychiatric effects that limit its use in clinical practice do, however, provide a useful model for investigating the cognitive deficits and pathogenesis of schizophrenia. Functional imaging studies can identify the neuroanatomical sites at which altered cognitive function occurs in subjects receiving ketamine, and may thus identify the areas where altered function results in the behavioral and cognitive changes common to schizophrenia and low-dose ketamine administration. Finally, in chronic pain studies, ketamine may provide insights into the pathogenesis of chronic pain, and may have a role in the prevention and treatment of chronic pain.

Cross-References

- ► Benzodiazepines
- ► Blood-Brain Barrier
- ► Electroncephalography
- ► Magnetic Resonance Imaging (Functional)
- ► Opioids
- ► Pharmacokinetics
- ► Positron Emission Tomography (PET) Imaging
- ► Ritual Uses of Psychoactive Drugs
- ► Schizophrenia
- ► Self-Administration of Drugs

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Dissociative Reaction

Definition

A psychological reaction characterized by such behavior as amnesia, fugues, sleepwalking, and dream states.

Distance Traveled

Synonyms

Cumulative distance moved

Definition

Distance traveled is the sum of the distances between successive *x*–*y* coordinate pairs that define an animal's momentary position on the horizontal plane that forms the floor of the instrument that is used to quantify locomotor activity. Video tracking systems, photobeam actometers, and force-plate actometers all provide *x*–*y* coordinate pairs with varying degrees of spatial and temporal resolution. Because of a lack of calibration standards as well as a multiplicity of recording methods, it is difficult to compare distance traveled measures across laboratories, unless they happen to use the same instruments, software, and summing intervals.

Cross-References

- ► Motor Activity and Stereotypy
- ► Open Field Test

Distress Vocalization

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Synonyms

Alarm calls; Crying; Isolation calls; Separation calls; Ultrasonic vocalizations

Definition

Mammalian vocalizations are the product of respiratory and laryngeal activities under the direct control of brain stem cranial and spinal motor neurons and modulated by higher brain processes (Miczek et al. 1995; Newman 2007). Distress vocalizations are sounds produced in the presence of painful, stressful, or threatening stimuli. Vocalizations are a particularly attractive candidate for psychopharmacological research because they represent species specific and ethologically relevant behaviors spontaneously expressed in response to unique provocation. Vocalizations offer the further promise of unique informational content about the emotional state of the subject. Finally, there is evidence that the form, contexts, and neural processes which modulate distress vocalizations are highly conserved between species (Newman 2007). This makes them a particularly attractive candidate for translating findings from animal models to human clinical conditions.

Pharmacological studies of distress vocalizations can be predominantly clustered according to the maturity of the subjects examined – infant or adult.

Types of Distress Calls

Infant distress vocalization: The production of vocalizations by infant mammals during parental separations has been detected in virtually every known mammalian species including humans (Newman 2007). Rat and mouse infant vocalizations have been the most vigorously studied by psychopharmacologists and are expressed in the ► ultrasonic frequency range. Drug effects on the vocalization by several nonhuman primate species have also been examined including rhesus, squirrel, and marmoset monkeys. Across species, infant vocalizations share remarkable structural as well as contextual similarities (Newman 2007) (Fig. 1).

Adult distress vocalization: Adult animals also produce intense vocalizations when provoked by painful, threatening, or stressful stimuli or during drug withdrawal. Like infant vocalizations, these too share remarkable structural similarities between species, and in rodents they are also predominantly ultrasonic (Miczek et al. 1995; Sanchez 2003).

Vocalizations in both age groups have been proposed to reflect emotional states of fear or anxiety. Consequently, they have been primarily the target of research related to ► anxiolytic drugs and/or neural substrates of emotional behavior. The separation vocalizations of infant animals have also been proposed to reflect frustration of attachment bonds and consequently a further focus of pharmacological research has examined neural processes associated with the formation and maintenance of social bonds.

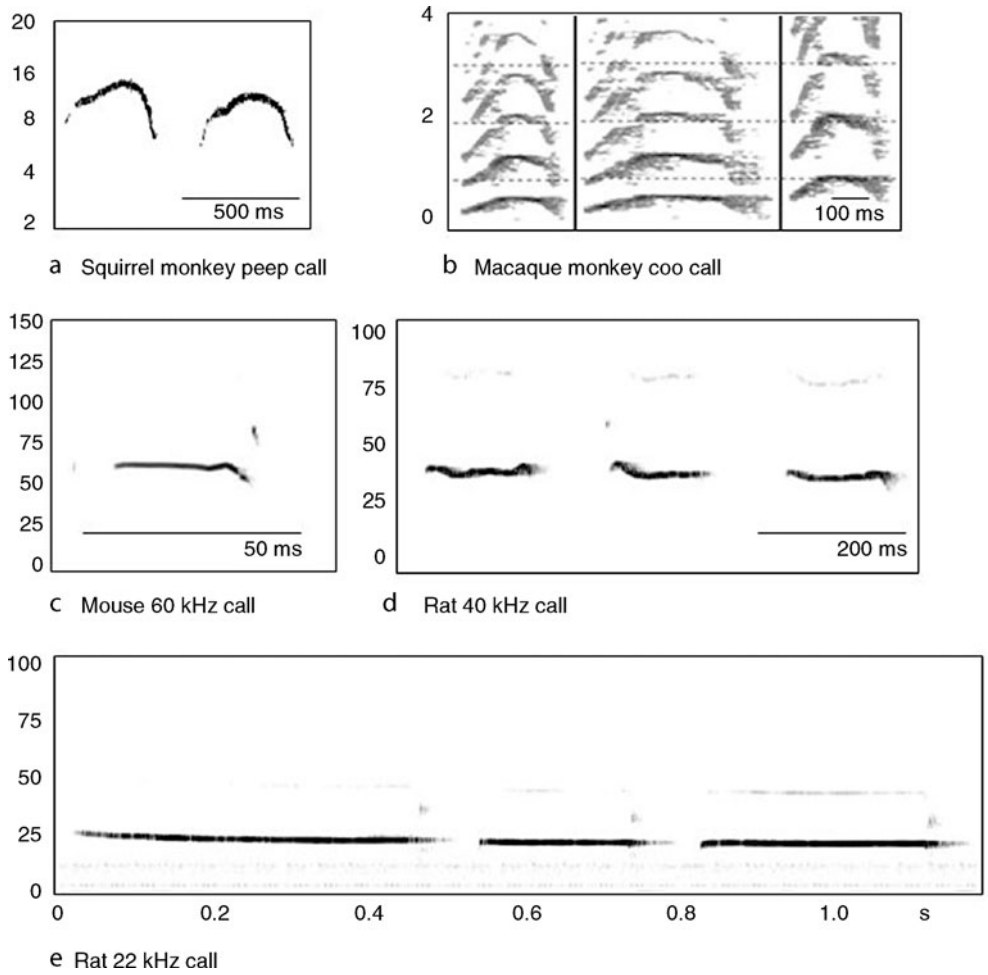
In the ensuing essay, we will focus our discussion on the ultrasonic vocalizations of rodents since the preponderance of pharmacological study has likewise been examined primarily in rodents. Nevertheless, the basic principles of measurement and many of the pharmacological findings have been replicated in nonhuman primates (Levine and Mody 2003; Winslow et al. 2007).

Measurement of Calls

Vocalizations are typically audio recorded and then defined and quantified using sound ► spectrographic techniques which also allow automated detection for some call types. For rodent species, specialized recording equipment capable of detecting ultrasonic frequency ranges is required and commercial systems are available (see Hofer et al. (2002) for an excellent guide).

Rodent infants emit ultrasonic (30–50 kHz in rat and 50–80 kHz) vocalizations ranging from 100 to 500 ms in duration virtually from the day after birth to the time of weaning. It is notable that the rate and intensity of calling varies systematically by age. Separation of a pup from its home cage, littermates, and dam into a novel test chamber elicits high rates of ultrasonic calls, and is the most frequently used eliciting stimulus in pharmacological studies.

Adult rats produce "distress" ultrasonic vocalizations in the 20–30 and 50–70 kHz range during encounters wherein they are attacked or threatened by a conspecific. 22 kHz calls are also emitted by rats in the presence of painful or stressful (e.g., startle or air-puff stimuli) stimuli as well as during opioid and cocaine withdrawal. Taken together these results suggest that distress vocalizations, particularly the 22 kHz of rats may convey an anxious or fearful emotional state common to multiple contexts. Adult mice also emit ultrasonic vocalizations; however, so far these have been detected only in reproductive encounters and not, notably, in the stressful or aversive conditions typical of rats.



Distress Vocalization. Fig. 1. Depicts distress calls expressed by infant, juvenile, and adult animals including (**a**) the isolation peep call of the juvenile squirrel monkey; (**b**) the coo call of the macaque monkey (Japanese); (**c**) the mouse pup ultrasonic separation call; (**d**) the rat pup ultrasonic separation call; and (**e**) the 22 kHz ultrasonic distress call of the adult rat. The call shows remarkable similarities in form. (Adapted from Ceugniet and Izumi 2004; Miczek et al. 1995; and www.avisoft.com/rat.)

Measurements of duration of ultrasonic vocalization, inter-ultrasonic vocalization interval, bout structure, and detailed acoustic analysis of calls have been performed, but have not been systematically studied in relation to eliciting conditions, regulation by sensory cues, or neural control though initial efforts suggest important information may be available in these parameters (Scattoni et al. 2008).

Caveats and Controversies

Developmental changes in vocalization: Infant vocalizations show a pronounced change in the pattern of calling as animals mature. Ultrasonic vocalization responses of infant rodents follow a fairly predictable developmental pattern. The first ultrasonic vocalization response to isolation occurs in a day or two after birth at a moderate rate at typical ambient temperatures (32–35°C), then rises to a peak in the first week at about 100/min, finally beginning a gradual decline until approximately the same age they obtain ▶ homeothermy, at which point few or ultrasonic vocalizations may be detected within a 10 min separation test. Conversely, adult-type vocalizations in appropriate contexts once established in puberty remain remarkably stable though not without variability between individuals.

Role of thermoregulation: The ambient temperature of the test chamber is the most easily manipulated regulator of ultrasonic vocalization rate in rat and mouse pups during their first two weeks of postnatal life (Hofer 2002). Ultrasonic vocalization rates expressed by isolated pups can be systematically varied from 10 or less calls per

minute at typical ambient temperatures up to 200 calls/min in cooler environments. The relationship between ultrasonic vocalization and temperature has led some to hypothesize that ultrasonic vocalization emissions might also play a role in pups' physiological thermoregulatory capacity (Blumberg and Alberts 1991). According to this view ultrasonic vocalization could be considered, at least in part, a byproduct of thermoregulatory physiology rather than an affective expression in a communicative system (Blumberg and Alberts 1991). Indeed, correlations have been found between ultrasonic vocalization production and thermoregulatory and cardiovascular changes. Similar proposals have been offered to account for adult rodent ultrasonic vocalizations. Nevertheless, a clear physiological role for ultrasonic vocalization in thermoregulation has yet to be demonstrated except perhaps during recovery from severe hypothermia (Hofer and Shair 1992). In contrast, there are several lines of evidence that the physiological changes involved in the act of ultrasonic vocalization emission do not play a functionally significant role in the thermoregulation of young rats, at least under typical test conditions (Hofer 2002).

Species and strain differences: As noted earlier, while there appear to be many similarities between species in context, form, and neural processes, there are nevertheless important differences between species that are evident – not the least being the frequency range within which the calls are expressed. In addition, there are differences in the sensitivity of the rodent species to the modulation of calling by social stimuli (e.g., comforting upon return of the mother to her infant) or the type and intensity of provocation by some stimuli in adult animals (Hofer 2002). These are even more evident in the wide range of differences in the rate of calling that can be obtained when comparing between various strains of mice used in genetic modeling research (Wohr et al. 2008).

Impact of Psychoactive Drugs

Pharmacological studies of distress vocalizations have been undertaken for various reasons, from aiding the development of animal models of clinical anxiety to demonstrating the functional efficacy of a system in development, or to examining the neural processes related to the formation and maintenance of social attachment – particularly infant–mother bonds.

Infant distress vocalizations have proven to be remarkably sensitive to both the anxiolytic-like effects of GABAergic, serotonergic, and glutamatergic receptor subtype selective ▶ ligands as well as the ▶ anxiogenic-like effects often reported for ligands with complementary actions at the same or related receptor subtypes (Winslow and Insel 1991). Thus, for example, GABA-A agonists such as ▶ diazepam reduce vocalizations while antagonists such as pentylenetetrazol increase vocalizations (Miczek et al. 1995). Conversely glutamate receptor antagonists such as MK801 decrease while agonists such as NMDA increase calling (Winslow et al. 1990). Similarly, serotoninergic drugs with putative anxiolytic properties such as the 5HT-1A receptor agonist ▶ buspirone reduce calling in infant rats while 5HT-1B receptor agonists appear to increase call rates, although the dose relationship may be complex (Winslow and Insel 1991). Similarly, studies of adult distress vocalizations indicate comparable predictive validity for GABAergic, glutamatergic, and serotonergic ligands as anxiolytic or anxiogenic compounds depending on the subtype of the receptor affected (Sanchez 2003; Takahashi et al. 2008).

A number of systems have been proposed to have important roles in the formation and maintenance of attachment bonds between social animals. Prominent among these are the opioid system because social attachment has some similarities to drug dependence. Oxytocin and vasopressin have also been implicated in the formation and maintenance of mother–infant bonds as well as between adults with monogamous mating strategies. Studies of the effects of ligands active in these systems have generally demonstrated that distress vocalizations provoked by maternal loss are predictably modulated. For example, oxytocin or ▶ morphine administration effectively quiets infant mice, rats, and young monkeys separated from their social companions.

Distress vocalizations are a prominent feature of withdrawal from chronic administration of a variety of pharmacological drugs of dependence including opiates, benzodiazepines, ▶ alcohol, and ▶ psychomotor stimulants (Covington and Miczek 2003). While distress vocalizations during withdrawal are evident in a variety of species, systematic study has been thus far limited to rats. These few studies have demonstrated that the rate of calling is independent of an audience and directly related to key parameters of chronic administration such as how much drug is administered, for how long and whether the drug is self-administered or administered by a researcher (Covington and Miczek 2003).

Cross-References

▶ Aggression
▶ Animal Models for Psychiatric States
▶ Anxiety: Animal Models
▶ Autism: Animal Models
▶ Benzodiazepines
▶ Emotion and Mood

- ▶ Ethopharmacology
- ▶ Excitatory Amino Acids and their Antagonists
- ▶ Inverse Agonists
- ▶ Panic Disorder
- ▶ Phenotyping of Behavioral Characteristics
- ▶ SNRI Antidepressants
- ▶ Social Stress
- ▶ SSRIs and Related Compounds
- ▶ Translational Research
- ▶ Traumatic Stress (Anxiety) Disorder

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Distribution

Definition

Distribution is the dispersion of a drug throughout the fluids and tissues of the body or the reversible transfer of drug from one location to another within the body.

Cross-References

- ▶ Absorption
- ▶ Excretion
- ▶ Liberation
- ▶ Metabolism
- ▶ Pharmacokinetics

Disulfiram

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Synonyms

Tetraethylthiuram disulphide

Definition

Disulfiram is one of several aldehyde dehydrogenase (ALDH) inhibitors that increase the plasma level of ▶ acetaldehyde in the body following the ingestion of ethanol. Disulfiram is currently used in the treatment of alcoholism.

Pharmacological Properties

History

As early as 1937, it was realized that exposure to disulfiram (tetraethylthiuram disulphide) resulted in abstinence from alcohol. Tetraethylthiuram disulphide has been used since the 1880s in the manufacturing process of rubber (Suh et al. 2006). E. E. Williams, an American physician working at a chemical plant, was the first to observe that workers who were exposed to disulfiram experienced unpleasant effects after drinking alcohol and, as a result, involuntarily abstained from alcohol. Williams (1937) sent a letter to the editor of the *Journal of the American Medical Association* (*JAMA*) suggesting that the compound could be beneficial as a cure for alcoholism. The discovery remained overlooked until 1945 when Hald, Jacobsen, and Larsen, experimenting with disulfiram as

an antihelminthic drug, ingested the drug and alcohol and experienced the unpleasant side effects firsthand. Realizing the potential of the drug, they went into collaboration with a clinician, Martensen-Larsen, to expand the research of disulfiram to alcoholics (Petersen 1992). The results were promising, pointing to disulfiram as a potential pharmacological treatment for alcoholism.

► Pharmacokinetics

Absorption and Biotransformation

Following oral administration, disulfiram is rapidly absorbed from the gastrointestinal tract and is distributed across the mucosa into the blood. Endogenous thiols and the glutathione reductase system of erythrocytes then reduce disulfiram to its monomer, diethyldithiocarbamic acid (DDC). DDC, while unstable in the extremely acidic environment of the stomach, is a strong metal-chelating agent that has an affinity for cupric ions, forming a bis (diethyldithiocarbamato) copper complex ($Cu(DDC)_2$). $Cu(DDC)_2$ is rapidly degraded after its formation during the simultaneous reformation of DDC. DDC is itself unstable in biological tissues and is degraded into diethylamine (DEA) and CS_2, both of which are eliminated without further degradation.

Another metabolite of disulfiram, diethylthiomethylcarbamate (Me-DTC), is formed by oxidative desulfuration, which is mediated by microsomal ► cytochrome P450 mono-oxygenases. The last oxidative biotransformation of disulfiram produces formaldehyde, inorganic sulfate, and methanethiol (Johansson 1992).

Distribution, Protein Binding, and Excretion

Following absorption, disulfiram and its metabolites are evenly distributed throughout the body in a variety of tissues including the kidney, heart, liver, thyroid gland, adrenal gland, pancreas, and muscle, with lesser amounts observed in blood and the brain. Disulfiram and its metabolite DDC are bound to proteins by an interaction with protein-free thiol groups, while, in the blood, disulfiram and its metabolite Me-DTC are extensively bound to plasma albumin.

The metabolites of disulfiram are excreted by means of the lungs, kidney, and feces. Less than a quarter of the intact drug is excreted in the feces. The majority of metabolites, especially DDC, are eliminated by the kidneys. Although no excretion data are available for Me-DTC, the CS_2 produced from the degradation of DDC in tissues is eliminated from the lungs. Only minor amounts of DDC, Me-DTC, CS_2, and DEA are detectable in urine (Johansson 1992).

Aldehyde Dehydrogenase (ALDH) Inhibition – Mechanism of Action

Following consumption of ethanol, the first oxidation metabolite produced is ► acetaldehyde. Because acetaldehyde is toxic to cells, it is essential that it is metabolized further. The next step in the elimination of ethanol is made possible by the enzyme ALDH, which almost instantaneously metabolizes the toxic acetaldehyde to the nontoxic acetate. There are four different ► isozyme forms of ALDH although the two main forms involved in the oxidation of acetaldehyde are ALDH1 and ALDH2, both of which are found mainly in the liver.

Disulfiram has a preference for ALDH1, and this preferential inhibition causes a marked increase in acetaldehyde following the ingestion of ethanol. The rapid accumulation of acetaldehyde occurs not only because the enzyme that degrades it is inhibited, but also because the enzyme that degrades ethanol into acetaldehyde, ► alcohol dehydrogenase (ADH), has a faster turnover rate than ALDH. Not only does disulfiram block ALDH1, but its metabolites play a role in inhibiting ALDH as well. Specifically, Me-DTC has been characterized as an irreversible inactivator of ALDH1. The overall inhibition of ALDH by disulfiram and its metabolites is via a quick competitive inactivation, which is then followed by the irreversible inhibition of the enzyme, halting its activity (Johansson 1992).

The consequential buildup of acetaldehyde from blocking its metabolism by ALDH is responsible for the negative effects associated with combining disulfiram and ethanol. These negative effects are proportional to the amount of ethanol ingested. Immediately after drinking, the person experiences facial flushing, a mild headache, and sweating. The effects may then worsen to include nausea, vomiting, palpitation, hyperventilation, and hypotension. The most severe effects may include respiratory depression, arrhythmias, unconsciousness, convulsions, congestive heart failure, cardiovascular collapse, and even death (Suh et al. 2006).

Drug Interactions

There are a large number of reported compounds that adversely interact with disulfiram. Those drugs that interfere with the dopamine/norepinephrine system should not be administered with disulfiram because this may cause sleeplessness, paranoia, and even ► psychosis. Examples of drugs that interfere with the dopamine/norepinephrine system include ► bupropion, ► amphetamines, ► methylphenidate, and ► cocaine. Interestingly, the pesticide thiram acts as a disulfiram analog, and its use should be avoided by anyone taking disulfiram. The *Coprinus atramentarius* species of mushroom should also

be avoided since it is an ALDH inhibitor (Johansson 1992).

Drugs that use cytochrome P450 for oxidative metabolism have been found to change their biotransformation rate when coadministered with disulfiram. In particular, warfarin and some of the ► tricyclic antidepressants such as ► amitriptyline and ► imipramine have prolonged plasma clearance rates when given with disulfiram.

Other drugs that do not utilize cytochrome P450 for metabolic oxidation still show a prolonged clearance rate when coadministered with disulfiram. These drugs include ► barbiturates, many of the ► benzodiazepines including diazepam. ► Caffeine metabolism is also prolonged in persons taking disulfiram. Patients on the bronchodilator theophylline should also be aware that concurrent use with disulfiram will cause them to experience a prolonged effect of the bronchodilating methylxanthine (Johansson 1992).

Efficacy

While disulfiram is a useful aversion therapy drug, there are other variables at work. The efficacy of disulfiram is more dependent on compliance than only on the drug itself. When patients are closely monitored during the course of treatment, the efficacy of disulfiram is quite good. In fact, a review by Brewer et al. (2000) reported that 17 out of 18 disulfiram studies demonstrated the effectiveness of disulfiram when subjects were directly supervised. Without supervision, the adherence rate can be as low as 20% (Suh et al. 2006).

Another factor that influences the efficacy of disulfiram is the patient. When patients have stability in the home and family, are not uncontrolled heavy drinkers, and are motivated to abstain from alcohol, they display better adherence to disulfiram treatment. Although disulfiram no longer holds the key to a cure for alcoholism, it can be a very helpful tool when combined with appropriate supervision and support (Johnson 2008).

Safety/Tolerability

When disulfiram was first being evaluated as a treatment for alcoholism, the dose range was between 1,000 and 3,000 mg/day. At such high doses, severe ► adverse effects were not uncommon. Such adverse effects included psychosis, sudden circulatory collapse, and sudden respiratory collapse. It is important to note, however, that most of the patients who suffered a fatal disulfiram-ethanol reaction were reported to have consumed large amounts of alcohol following disulfiram administration, a combination that undoubtedly contributed to their deaths (Suh et al. 2006).

Besides the high doses of disulfiram, early treatments also involved an initial aversion trial in which the patient would purposefully be given disulfiram and ethanol. The point was to demonstrate to the patient, under controlled medical conditions, how the disulfiram-ethanol interaction would feel and thus prevent patients from drinking while being treated with disulfiram. The practice of the initial aversion trial was later discontinued, and patients were only given verbal descriptions of the side effects of the disulfiram-ethanol reaction. This change in practice ushered in the use of disulfiram as strictly a psychological deterrent to drinking while reinforcing the importance of close supervision during treatment.

Current treatment guidelines state that the lowest possible dose of disulfiram should be given in order to obtain the required result. The FDA recommends a daily dose of 250 mg, but some patients can take as little as 125 mg or up to as much as 500 mg. At these doses, disulfiram is safe and well tolerated for both short- and long-term treatment of alcoholism (Suh et al. 2006).

The most frequently reported side effects of disulfiram in the absence of alcohol include headache, drowsiness, dermatitis, and a garlic-like aftertaste. Another less common side effect is ► hepatotoxicity, especially in persons with liver disease. This adverse effect can, however, be avoided by providing the patient with educational materials and by conducting frequent liver function testing.

Disulfiram is contraindicated in persons with cardiovascular as well as cerebrovascular disease. Patients with severe liver function abnormalities should also refrain from taking disulfiram. Disulfiram is a pregnancy category C compound and should not be given to women who are or may become pregnant during the course of treatment.

Conclusion

In conclusion, disulfiram continues to play an important role in helping people who abuse alcohol to achieve abstinence. Although disulfiram is in no way a panacea, its use as an aversion therapeutic in conjunction with appropriate supervision can help people to effectively abstain from alcohol consumption. It is up to the clinician to determine whether the patient would be successful in adhering to the disulfiram course of treatment and to make sure that the patient has all the necessary resources to be successful.

Cross-References

► Alcohol
► Alcohol Abuse and Dependence
► Drug Interactions
► Pharmacokinetics

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Diuretics

Definition

A diuretic is any drug that elevates the rate of urination and thus provides a means of forced diuresis.

Diversion

Definition

Diversion refers to a prescribed drug being given or sold to other people instead of being consumed by the person for whom it was prescribed.

Cross-References

► Abuse Liability
► Addiction

Divided Attention

Definition

This is the ability to concentrate on a number of different things in the environment simultaneously.

DLB

► Lewy Body Dementia

DMTS

► Delayed Match-to-Sample Test

DNA-Marking

► Epigenetics

DNA Methylation

Definition

DNA methylation is one of the most characterized epigenetic modifications and is associated with gene silencing. It refers to the addition of methyl groups to the number 5 carbon of the pyrimidine ring of the DNA base cytosine, due to activation of enzymes known as DNA methyltransferases. This usually results in a reduction in expression of the associated gene.

Cross-References

► Epigenetics
► Gene Expression and Transcription

DNA Methyltransferase Inhibitors

Definition

DNA methyltransferase inhibitors are drugs that prevent the action of a family of enzymes that normally catalyze the transfer of a methyl group to DNA. The action of these drugs means that DNA remains unmethylated resulting in gene expression.

Cross-References

► Gene Expression and Transcription

Dominance Aggression

Definition

It is defined as the display of aggressive acts and postures for the purpose of securing access to preferred resources and transmitting genes into the next generation. This type of aggression is frequent and intense when the

dominance hierarchy is formed, and the displays become more ritualized during the maintenance of the hierarchy. Dominance aggression is particularly intense when females are sexually receptive.

Dominant Negative Antagonist

Definition

A protein, which by itself is inactive biologically, inhibits the activity of another endogenous protein.

Donepezil

Definition

Donepezil is a drug marketed for treating the cognitive impairments (learning, memory, and attention) in ► Alzheimer's disease. It has mainly been used in patients in the mild to moderate stages of the disease and according to some has modest effects in treating symptoms in Alzheimer's patients. It is an anticholinesterase, working by enhancing brain levels of ► acetylcholine, a neurotransmitter that is reduced in Alzheimer's disease, and is known to be relevant to cognition.

Cross-References

► Cognitive Enhancers: Neuroscience and Society
► Dementias and Other Amnestic Disorders

Dopamine

Synonyms

DA

Definition

A major modulatory brain monoamine neurotransmitter released by axons of cell groups located in the midbrain and other deep brain areas, and synthesized in the brain from the amino acid tyrosine. It is an intermediate step in the synthesis of ► norepinephrine and epinephrine. Four dopaminergic pathways have been localized in the central nervous system: mesolimbic, mesocortical, nigrostriatal, and tuberoinfundibular. Furthermore, five receptors have identified (D_1–D_5) within two families: D_1 (D_1, D_5), D_2 (D_2, D_3, D_4). Extracellular dopamine levels are regulated by at least two mechanisms: the ► dopamine transporter, which recycles dopamine into the presynaptic terminal, and the enzyme catechol-*O*-methyltransferase, which degrades extracellular dopamine and norepinephrine.

Dopaminergic projections reach many regions of the brain, especially the dorsal striatum, where dopamine participates in the selection of motor actions; the ventral striatum or nucleus accumbens, involved in motivation and prediction of future rewards; the amygdala, processing emotional reactions, and the cerebral cortex (especially prefrontal), where dopamine regulates executive functions like attention and working memory. Thus, via its interactions with ► glutamate and ► GABA-based synaptic transmission in these regions, dopamine plays a key role in attention, cognition, motivation, and both pharmacological and biological rewards, as well as in sensory and motor functions. Dopamine is implicated in ► Parkinson's disease, ► schizophrenia, and drug ► dependence. It has long been hypothesized that at least the positive symptoms of schizophrenia (e.g., delusions, hallucinations) reflect hyperdopaminergic activity. The dopamine D_2 receptor has been tied to this effect and all available ► antipsychotics demonstrate some degree of dopamine D_2 blockade. The D_3 receptor has also been implicated in ► psychosis, while the D_1 receptor is involved in cognitive processes. The majority of abused drugs target dopaminergic synapses in the ventral striatum, inducing an increase of dopaminergic signaling.

Cross-References

► Cognitive Enhancers
► First Generation Antipsychotics
► Second- and Third-Generation Antipsychotics
► Short-Term and Working Memory in Animals
► Short-Term and Working Memory in Humans

Dopamine Agonist

Definition

A drug that has chemical properties similar to dopamine, stimulating some or all of the dopamine receptors.

Dopamine-and-Cyclic-AMP-Regulated-32KDa-Phosphoprotein

► DARPP-32

Dopamine Hypothesis

Definition

The dopamine hypothesis of schizophrenia and other psychoses – including ► delusional disorders – states that these disorders are related to a dysfunction of the dopamine system in the brain. Positive symptoms, such as delusions and hallucinations are linked to dopamine "hyperfunction" (to hyperactive signal transduction).

Dopamine Reward Systems

► Mesotelencephalic Dopamine Reward Systems

Dopamine Transporter

Synonyms

DAT

Definition

The dopamine transporter is the plasma membrane-bound protein that is responsible for removing dopamine from the synaptic cleft, transporting it back into the dopaminergic neurons from which it originated, thereby terminating its signaling activity on postsynaptic neurons. It is a target for the action of psychostimulant medications.

Cross-References

► Transporter

Dosulepin

Definition

Dosulepin is a ► tricyclic antidepressant with a tertiary amine chemical structure. It acts by inhibiting the reuptake of serotonin and norepinephrine. Its primary use is in the treatment of ► depression, but it is also occasionally used in treating ► anxiety disorders. Usage of dosulepin has declined in recent years in conjunction with the general decline in the use of tricyclics. Dosulepin has a side-effect profile similar to that of other tricyclics, including drowsiness, cardiovascular effects, and anticholinergic effects (e.g., constipation, dry mouth, blurred vision, urinary retention). As with other tricyclics, its potential for lethality in overdose is high.

Cross-References

► Antidepressants
► Tricyclic Antidepressants

Double-Blinded Study

Synonyms

Double-blind study; Double-masked studies

Definition

Blinded studies are part of a scientific method to prevent research outcomes from being influenced by various biases such as patient expectations (placebo effect) and experimenter expectancy (observer bias). The term blind is a figurative extension of the literal idea of blindfolding someone. The opposite of a blinded trial is an open trial. An open trial or open-label trial is a clinical trial in which both the researchers and participants know which treatment is being administered. There can be varying degrees of blinding such as single-blind, double-blind, triple-blind, etc. Double-blinded study is a term used to described a study in which both the investigator or the participant are blind to (unaware of) the nature of the treatment the participant is receiving. In a double-blind experiment, neither the individuals nor the researchers know who belongs to the control group and the experimental group. Double-blind trials are thought to produce objective results, since the expectations of the researcher and the participant about the experimental treatment such as a drug do not affect the outcome. Double-blinded studies are often chosen when a treatment shows particular promise and the illness involved is serious. It can be hard to recruit human subjects for a blinded study of a promising treatment when one group will receive only a placebo or an existing medicine.

Cross-References

► Clinical Antipsychotic Trials
► Randomised Controlled Trial
► Relaps Prevention Study Design

Double-Masked Studies

► Double-Blinded Study

Downregulation

Definition

Can refer to a reduction of total cellular protein of a receptor or, alternatively, a loss of receptor expression on the cell surface. The latter can arise from redistribution of receptor from surface to intracellular pools.

Doxepin

Definition

Doxepin is a ► tricyclic antidepressant with a tertiary amine chemical structure. It acts by inhibiting the reuptake of serotonin and norepinephrine. Its primary use is in the treatment of depression, but it is also occasionally used in treating anxiety disorders and insomnia. Usage of doxepin has declined in recent years in conjunction with the general decline in the use of tricyclics. Doxepin causes marked sedation; otherwise, its side effect profile is similar to that of other tricyclics, including cardiovascular effects and anticholinergic effects (e.g., constipation, dry mouth, blurred vision, urinary retention). As with other tricyclics, its potential for lethality in overdose is high.

Cross-References

► Antidepressants
► Tricyclic Antidepressants

Driving and Flying Under Influence of Drugs

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Synonyms

Traffic safety and medicines.

Definition

Driving and flying under the influence of drugs are common, since most people who use psychoactive medication are outpatients who participate fully in society. Psychoactive medication may produce adverse effects that impair driving and flying such as reduced alertness, psychomotor impairment, and impaired vision. Most commonly prescribed psychoactive drugs include hypnotics, antidepressants, antihistamines, analgesics, and stimulant drugs. Within these categories of medicines, significant differences concerning their impact on driving and flying ability are evident. For example, benzodiazepines and tricyclic antidepressants (TCAs) significantly impair driving and flying, whereas selective serotonin reuptake inhibitors (SSRIs) do not. These differences should be taken into account when prescribing psychoactive medication to patients who are willing to drive a car or fly a plane.

Current Concepts and State of Knowledge

Introduction

In modern society, driving and flying are common modes of transportation. The majority of adults in Western society drive a car on a daily basis and worldwide over 50,000 commercial flights are performed daily. Unfortunately, driving and flying are not without risk: accidents can happen that may result in injury or even death. The World Health Organization is concerned about the worldwide increase in traffic accidents and launched various campaigns to enhance traffic safety (Peden et al. 2004). Traffic accidents are often caused by human error, distraction, and reduced alertness.

Psychoactive medication may cause sedation and reduce alertness. Therefore, these drugs can impair performance and increase the risk of traffic accidents. It is estimated that alcohol and psychoactive drugs are involved in 5–35% of road accidents (Verster et al. 2009). These percentages seem high, but one should consider that most people who use psychoactive medication are outpatients who are therefore likely to participate in traffic.

Driving

Alcohol

Experimental studies have shown that ► alcohol impairs driving performance in a dose-dependent manner. Since alcohol is the most frequently used psychoactive substance, this is of great concern. About 50 years ago, Borkenstein and colleagues performed a landmark study that showed the relationship between ► blood alcohol concentration (BAC) and the risk of becoming involved in traffic accidents. After the results of this study became public, many countries enforced laws to limit driving after alcohol consumption. Most commonly applied legal limits to drive a car are 0.05% (e.g., the Netherlands), 0.08% (UK and USA). During the last decade, many countries are lowering their legal limit to further reduce traffic accidents.

For example, for novice drivers in The Netherlands, the legal limit is lowered to BAC 0.02%. The main reason for this is the fact that young novice drivers are inexperienced drivers and often overestimate their driving skills. Despite returning public campaigns and intensified police controls, a minority of people still drive a car while intoxicated, putting themselves and others at risk. Currently, alcohol is still the number one cause of traffic accident death among young drivers.

Sleep medication

Insomnia and sleep apnea are examples of common sleep disturbances. People who suffer from these sleep complaints do not wake up refreshed and this is reflected by daytime sleepiness. The reduced alertness and distraction produced by sleepiness is the cause of many traffic accidents. This is one of the reasons that throughout the European Union, current traffic safety campaigns specifically warn against sleepy driving. The use of sleep medication is meant to help patients fall asleep or maintain sleep during the night. Unfortunately, many hypnotic drugs produce residual effects after the patient has woken up. That is, patients feel sedated and drowsy after waking up. Particularly, the traditional hypnotic drugs, i.e., the ▶ benzodiazepines, have shown this unfavorable adverse effect profile. A number of these hypnotics, including ▶ flurazepam, ▶ oxazepam, and ▶ temazepam, were studied applying the on-the-road driving test in real traffic (Verster et al. 2004). In this test, subjects drive a car over a 100-km public highway. They are instructed to maintain a constant speed (95 km/h) and steady lateral position within the right slower traffic lane. Primary parameter of the test is the Standard Deviation of Lateral Position (SDLP), i.e., the weaving of the car. A camera mounted on the roof of the car records the SDLP (see Fig. 1).

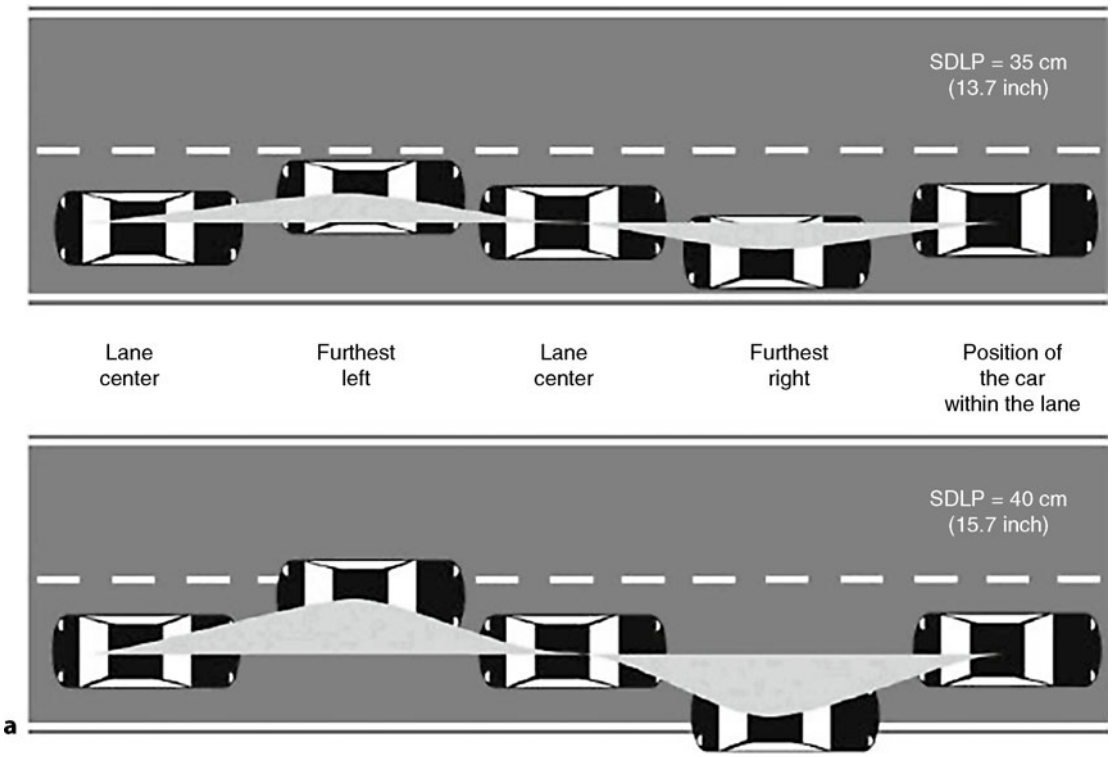
Benzodiazepine hypnotics were administered at bedtime and driving performance was tested the following morning (10–11 h after intake) and afternoon (16–17 h after intake). In the morning test, benzodiazepine hypnotics significantly impaired driving performance in a dose-dependent manner. Using twice the recommended dose (which is common in practice), driving was also significantly impaired in the afternoon. Epidemiological evidence confirmed these findings by revealing increased traffic accident risks for those using benzodiazepine hypnotics. ▶ Tolerance to the impairing effects develops slowly: increased traffic accident risks have been reported in chronic users (>1 year) as well. ▶ Zopiclone, a nonbenzodiazepine hypnotic, showed no improvement relative to the benzodiazepines. Significant increased weaving in the driving tests showed that driving was impaired and epidemiological evidence revealed a fourfold increased traffic accident risk for drivers who use zopiclone. ▶ Zolpidem and ▶ zaleplon, two other nonbenzodiazepines, did not impair driving performance when used as recommended. Future research should develop new hypnotics, preferably with a different mechanism of action, that do not produce residual effects on driving ability.

Anxiolytics

Benzodiazepines are also used for the treatment of anxiety. It is not surprising that these anxiolytics impair driving performance similar to benzodiazepines that are used as hypnotics (Verster et al. 2005). In fact, driving impairment is often much more profound because the time between drug intake and driving is much shorter when compared with hypnotics. On-the-road studies have shown significant impairment with benzodiazepine anxiolytics such as ▶ alprazolam, ▶ diazepam, and ▶ lorazepam. Epidemiological evidence shows that tolerance develops slowly when using these drugs. Driving studies confirmed that after 1 week of treatment, benzodiazepine anxiolytics also significantly impair driving performance and even after 4 weeks of treatment SDLP was significantly increased in patients treated with diazepam. TCAs such as ▶ imipramine and ▶ amitriptyline also significantly impair driving performance. Although tolerance develops more quickly when compared with benzodiazepines, in terms of traffic safety TCAs were no improvement. In contrast, a newer class of antidepressants, the SSRIs such as ▶ paroxetine and ▶ fluoxetine, and related compounds such as venlafaxine showed no impairing effects on driving performance. Also, ritanserin and ondansetron (both 5-HT antagonists), and ▶ buspirone do not affect driving ability. Thus, in terms of traffic safety, SSRIs and related compounds seem first-choice treatments.

Antidepressants

About 15% of the population suffers from ▶ depression at least once during their life and the disease is 2–3 times more common among females. Research has shown that both treated and untreated depression may impair driving performance (Ramaekers 2003). Traditionally, depression was treated with TCAs, ▶ mianserin, and ▶ mirtazapine. The first week after treatment initiation, these drugs significantly impair driving performance. Thereafter tolerance develops. Nocturnal treatment increases the time between drug use and driving and may be a solution for patients who want to drive a car. Research showed no driving impairment the morning following bedtime



Driving and Flying Under Influence of Drugs. Fig. 1. SDLP and the instrumented vehicle. (**a**) The Standard Deviation of Lateral Position (SDLP). SDLP represents the weaving of the car and is a measure of overall vehicle control. With increased SDLP, driving becomes unsafe. (**b**) The instrumented test vehicle. A camera, mounted on the roof of the car, continuously records the position of the car within the right traffic lane, by tracking the relative distance of the car from delineated stripe in the middle of the road.

administration of these antidepressants. SSRIs (e.g., ► escitalopram) and ► moclobemide are also used to treat depression and do not affect driving performance. The World Health Organization expects depression to be the second highest cause of mental disability by 2030. By that time, many outpatients will be treated with antidepressants. Therefore, it is of great importance that pharmaceutical companies continue the search for new antidepressants without negative effects on driving ability.

Antihistamines

The first-generation antihistamines such as diphenhydramine and triprolidine are effective against hay fever but had the disadvantage to produce significant sedation. Patients using these antihistamines often report sleepiness and reduced alertness. Driving studies showed significant impairment, both after acute and subchronic use (Verster and Volkerts 2004). Second-generation antihistamines such as cetirizine and loratadine produce much less sedation and driving tests have not consistently shown impairment. The magnitude of impairment, if any, differed between individuals and depended on the administered dose, time between drug intake and driving, gender, and age. Tolerance usually develops after 4–5 days of treatment, but a subgroup of patients shows increased vulnerability to the potential sedative effects of antihistamines and continues to experience adverse effects that may impair driving.

The third-generation antihistamines (fexofenadine, desloratadine, and levocetirizine) were developed to establish treatment options devoid of sedative effects. Driving studies showed that these antihistamines are a considerable improvement: with similar or improved clinical efficacy, these compounds do not affect driving ability.

Analgesics

Pain significantly impairs driving performance (Veldhuijzen et al. 2006a). Common pharmacological treatment of pain includes ► non steroid anti-inflammatory drugs (NSAIDs) and opioids. Laboratory tests of cognitive functioning and psychomotor skills generally do not show significant performance impairment in patients using NSAIDs or acetaminophen. Laboratory studies failed to find consistent results when testing ► opioids such as ► morphine and ► oxycodone (Zacny 1996). Up to now, one driving study examined the effects of bromfenac (an NSAID no longer marketed) and oxycodone. Neither analgesic affected driving performance. Chronic pain patients are often treated with antidepressants such as amitriptyline instead of opioids and NSAIDs. A driving study showed that 13 h after treatment administration, amitriptyline (25 mg) significantly impaired performance in neuropathic pain patients (Veldhuijzen et al. 2006b). After 2 weeks of daily use, tolerance developed to the impairing effects of amitriptyline. More driving research is needed to examine the effects of analgesics on driving ability.

Stimulant drugs

Stimulant drugs are used to improve attention and daytime alertness in the treatment of ADHD and narcolepsy. The effects of 3,4-methylenedioxymethamphetamine (► MDMA) and ► methylphenidate on driving performance have been studied in recreational MDMA users. Methylphenidate has been studied in patients with ADHD as well. Driving performance after using methylphenidate and MDMA was significantly improved when compared with placebo.

Summary

Table 1 gives an overview of most commonly used psychoactive drugs and their effects on driving ability. Classification is conducted according to the categorization of the International Council on Alcohol, Drugs and Traffic Safety (ICADTS). Drugs are allocated to one of the following categories:

1. Presumed to be safe or unlikely to produce an effect
2. Likely to produce minor or moderate adverse effects
3. Likely to produce severe effects or presumed to be potentially dangerous

To make the categories understandable, a comparison with BAC is made. Driving impairment for the categories I, II, and III are equivalent to BAC $<$ 0.5 g/l ($<$0.05%), BAC 0.5–0.8 g/l (0.05–0.08%), and BAC $>$ 0.8 g/l ($>$0.08%).

It is evident from Table 1 that for many diseases, a number of treatment options are available. These treatments differ greatly on how and if they affect driving ability. Physicians should take this into account when prescribing psychoactive medication for patients who want to drive a car.

Flying

Flying is an example of complex behavior. Alcohol and psychoactive medication may affect skills and abilities to fly a plane, especially during take-off and landing maneuvers. In addition, radio communication and following instructions during the flight require efficient use of working memory and decision-making processes.

Alcohol

Aircraft personnel have specific guidelines for alcohol use. The US Federation Aviation Administration (FAA)

Driving and Flying Under Influence of Drugs. Table 1. International Council on Alcohol, Drugs and Traffic Safety (ICADTS) categorization of commonly used psychoactive medication. For a complete listing, see Verster et al. (2009).

ICADTS Category	Sleep medication	Anxiolytics	Antidepressants	Antihistamines	Analgesics
Category I (Presumed to be safe or unlikely to produce an effect)		Buspirone	Fluoxetine, Paroxetine, Venlafaxine, Reboxetine	Levocetirizine, Fexofenadine, Desloratadine, Ebastine, Azelastine, Loratadine	Acetylsalicyclic acid, Paracetamol
Category II (Likely to produce minor or moderate adverse effects)	Zolpidem	Medazepam, Clobazam	Desipramine, Imipramine, Clomipramine, Nortriptyline, Citalopram, Sertraline, Fluvoxamine, Escitalopram, Nefazodone, Moclobemide	Chlorpheniramine, Mequitazine, Meclozine, Cetirizine, Mizolastine	Oxycodone, Codeine, Hydromorphone
Category III (Likely to produce severe effects or presumed to be potentially dangerous)	Flurazepam, Nitrazepam, Flunitrazepam, Estazolam, Triazolam, Lormetazepam, Temazepam, Midazolam, Brotizolam, Quazepam, Loprazolam, Zopiclone	Diazepam, Chlordiazepoxide, Oxazepam, Lorazepam, Bromazepam, Ketazolam, Alprazolam	Amitriptyline, Doxepin, Mianserin, Mirtazapine, Trazodone	Diphenhydramine, Clemastine, Prometazine, Triprolidine	Morphine, Tramadol, Fentanyl, Pentazocine, Buprenorphine

applies a BAC limit of 0.04% and European regulations apply a BAC limit of 0.02%. Pilots may not drink within 8 h of flying a plane or when they feel impaired. Research shows that flight personnel often underestimate the risk of alcohol use and admit that they sometimes disobey these rules (Verster 2007). This is of concern because over the past decade, approximately 8% of flight crashes have been associated with alcohol use. Studies performed in flight simulators have shown dose-dependent impairment in flying performance. In addition, other studies have pointed at significant impairment when BAC was below 0.04% or even zero. Alcohol hangover studies revealed that flying was significantly impaired in pilots who consumed alcohol the evening before flying, also when a sobering period of more than 8 h preceded flying. Flight personnel have the responsibility for the lives of hundreds of passengers. Therefore, a zero alcohol policy is preferable. Flight personnel should be educated about the risks of flying after drinking and their alcohol use should be monitored on a regular basis.

Psychoactive medication

When compared with driving, much less research has been devoted to examine the effects of psychoactive medication on flying. Most information about the capability to fly an airplane comes from general studies testing the effects of psychoactive medication on cognitive and psychomotor functioning. Based on these studies, FAA has composed guidelines about medical conditions and psychopharmacological treatments that prohibit pilots to fly a plane. These include ► insomnia, ► bipolar disorder, epilepsy, ► substance abuse, ► psychosis, and personality disorder. More recent studies tested pilots in advanced flight simulators whereas older studies tested flying-related skills and abilities in isolation.

Pilots diagnosed with depression are often not allowed to fly a plane, with or without antidepressant treatment. This is understandable when treated with TCAs. Nevertheless, several studies showed that SSRIs (e.g., ► sertraline, citalopam, escitralopam) and buproprion do not affect flying performance.

Antihistamines are commonly used to treat hay fever or motion sickness. Various first- and second-generation antihistamines including ► promethazine, meclizine, diphenhydramine, and triprolidine impair flying performance up to several hours after intake. In contrast, no significant effects were found for loratadine and desloratadine. After a couple of days, tolerance develops to the impairing effects of antihistamines.

Conclusions

Psychoactive medication may impair the ability to drive a car or fly a plane. However, for various medical conditions, different treatment options are available, and for some treatments it has been shown that it is safe to drive a car. Patient willing to drive a car should always ask their physician if these alternative treatments are available.

Much more research is necessary to examine flight simulator performance after intake of psychoactive medication. For alcohol, public health campaigns have proven to be effective. The general public is much less aware of the possible impairing effects of psychoactive medication. Therefore, educating patients about the possible side effects of medication is important to prevent impaired driving and flying.

Disclaimer: Although the information presented has been gathered and evaluated with great care, the author will not accept any liability after use of the information by patients taking the medicines discussed. Patients should always consult their physician concerning whether or not it is safe to drive a car.

Cross-References

► Alcohol
► Analgesics
► Antidepressants
► Benzodiazepines
► Hypnotics
► Insomnias
► Methylphenidate and Related Compounds
► Opioids
► SSRIs and Related Compounds

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Dronabinol

Definition

Dronabinol is a synthetic form of Δ^9-tetrahydrocannabinol, the main psychoactive substance in marijuana/cannabis. It is a cannabinoid agonist acting on cannabinoid CB1 and CB2 receptors. The cannabinoid CB1 are mostly located in the brain and involved in addictive properties of marijuana; the CB2 receptors are located in the periphery notably in the immune system, but may be also located in the brain. Dronabinol has been used in AIDS-related anorexia associated with weight loss and in nausea and vomiting associated with cancer chemotherapy. It has the potential to be abused and is a controlled substance.

Cross-References

- ▶ Appetite Stimulants
- ▶ Cannabinoids
- ▶ Cannabinoids and Endocannabinoids
- ▶ Δ^9-Tetrahydrocannabinol

DRS

- ▶ Delirium-Rating Scale

Drug

- ▶ Medicine

Drug Abstinence

- ▶ Withdrawal Syndromes

Drug Abuse

Definition

A maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by one (or more) of the following, occurring within a 12-month period:

1. Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home
2. Recurrent substance use in situations in which it is physically hazardous
3. Recurrent substance-related legal problems
4. Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance

Drug Addiction

- ▶ Dependence
- ▶ Opioid Dependence and Its Treatment
- ▶ Substance Abuse

Drug as Cues

- ▶ Drug Cues
- ▶ Drug Discrimination
- ▶ Occasion Setting with Drugs

Drug Augmentation

- ▶ Drug Interactions

Drug Combinations

- ▶ Drug Interactions

Drug Cues

Synonyms

Cue; Drug stimuli; Drug as cues

Definition

This is a generic term referring to drug-related stimuli. These are stimuli previously experienced during self-administration of that drug and it is generally assumed that these stimuli have been paired in some way with the drug effect. The stimuli can comprise external, internal, and cognitive stimuli; they can occur just before or long before drug intake. In the human, they can be described subjectively and usually increase the desire for the drug. The term is often used in clinical work to refer to stimuli that increase the risk for drug relapse in abstinent persons or the risk of continued drug intake in an active drug consumer. The actual word "cue" can be traced to its use in theatrical or musical pieces to indicate when an artist is to start playing part. In the learning literature, a cue is usually a signal that leads to reinforcement in one of two different ways: The cue can simply set the occasion for a reaction or act as a ► discriminative stimulus. The cue can also elicit a reaction, which is said to be an appetitive response or ► conditoned reinforcement. These are analogous to the use of cue in the literature on cognitive processes of drug intake where a cue is seen to produce variations in different forms of activation (memories, feeling, arousal, etc.) or to elicit selectively particular responses (cue reactivity). The term is often replaced by words such as secondary reinforcer, conditioned stimulus, context stimuli, and so on.

Cross-References

► Conditioned Drug Effects
► Conditioned Place Preference and Aversion
► Conditoned Reinforcer
► Conditioned Taste Preferences
► Discriminative Stimulus

Drug Discontinuation

► Withdrawal Syndromes

Drug Discrimination

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Synonyms

Cueing properties of drugs; Drugs as cues

Definition

Drug discrimination refers to behavioral paradigms in which the subjects learn to recognize the effects of a drug and report its presence by behavioral responses emitted to obtain reward or to avoid aversive stimuli. More formally, the presence of a drug generates an interoceptive ► discriminative stimulus (cue) signaling that an appropriate behavioral response will be reinforced. Drugs belonging to a wide range of pharmacological classes can serve as discriminative stimuli, and the subjects participating in a study may be either animal or human.

Principles and Role in Psychopharmacology

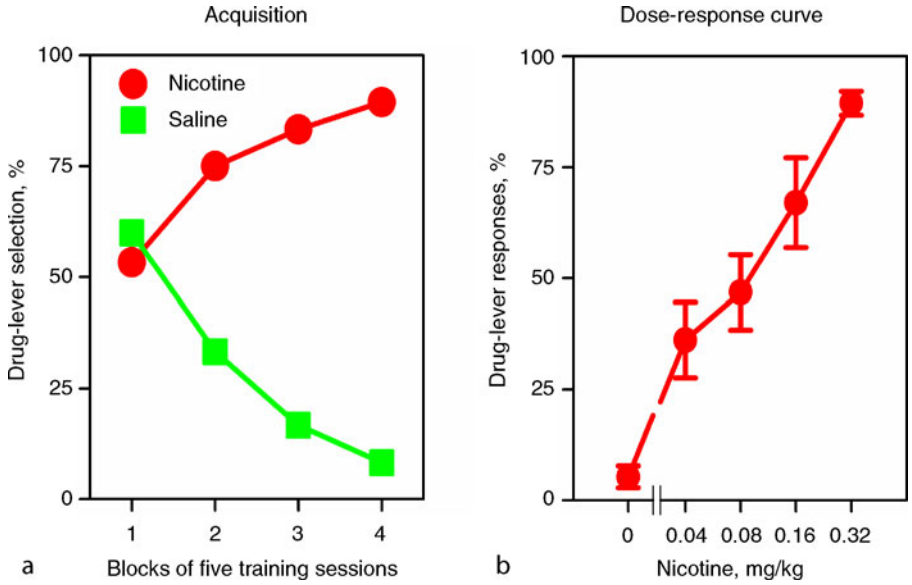
Most psychoactive drugs have effects that can be recognized and reported by people who have consumed them. Such self-reports may be seen conceptually as a consequence of an individual's natural history of learning to describe moods during his or her lifetime. Responses acquired during drug discrimination experiments with human subjects also reflect the reporting of subjective states, but under more carefully controlled conditions and with known drugs given in defined doses (Schuster and Johanson 1988). By imposing a analogous history of conditioning upon animal subjects, it is possible to implement drug discrimination experiments that establish responses that are similarly controlled by the recognition of drug effects. The development of the field owed much to the pioneering work of Donald Overton and was initially documented in a series of books (e.g., Colpaert and Rosecrans 1978; Glennon et al. 1991; Lal 1977), after which the area has become more fully integrated in the broader field of behavioral pharmacology. The experimental paradigms that emerged assist the development of novel drugs for treating psychiatric conditions, for characterizing the receptors and neurotransmitter systems through which psychoactive drugs act, and for evaluating the ► abuse liability of substances that might produce dependence or addiction (Ator and Griffiths 2003; Solinas et al. 2006; Stolerman 1992). Drug discrimination should be considered not as one technique but as a family of closely related methods. One of its distinctive features is a unique bibliographic database (www.drugrefs.org).

Simple Drug Versus Vehicle Discrimination

Simple, drug versus vehicle discrimination studies using two-lever ► operant conditioning methodology and food reinforcers account for about three-quarters of all reports of original investigations in the field (www.drugrefs.org). In a typical animal discrimination study with exteroceptive stimuli, the subject is placed in a test chamber and lever pressing responses result in the delivery of food. If a

stimulus light is turned on only during periods when lever presses produce food pellets, then lever pressing occurs at a high rate when the light is on and at a relatively low rate when it is off. The light is thereby established as a discriminative stimulus that controls the lever-pressing behavior. In drug discrimination, the effects of a drug serve a discriminative function in relation to behavior that is similar to that of the light in the preceding example. Thus, animals are trained to press one of two levers to obtain food after receiving drug injections, and to press the other lever after control injections in which no drug is given. Intermittent schedules of reinforcement facilitate the development of optimal performance. After learning the discrimination, the animal identifies the presence or absence of the drug effect and reliably selects the appropriate lever. Discriminative stimulus effects of the drug are distinguished from those of the food by using data from test sessions where differential reinforcement of responses on the two levers is temporarily withheld. Figure 1a illustrates the acquisition of drug discrimination behavior in a typical study using animal subjects. Human studies are carried out in a functionally equivalent way but with responses appropriate for the species and with monetary reinforcers instead of food or water.

Once a subject has been trained with a given drug, further investigations are possible, where the dose of the substance is varied, or other drugs are administered. Figure 1b shows a typical dose–response curve, from which the potency of the drug can be estimated by the ► ED_{50} value. These dose-response curves are also psychophysical generalization gradients along the dimension of stimulus intensity, through which the subjects indicate how they perceive similarities between the test stimuli (drug doses) and those used for training. When a different drug is given during test sessions, a dose–response curve similar to that for the training drug may be obtained (► stimulus generalization); this typically occurs when the two substances belong to the same pharmacological class and therefore have similar psychoactive effects. For example, ► amphetamine is generalized with ► cocaine because both drugs act as psychomotor stimulants. In contrast, if an ► anxiolytic or sedative-hypnotic drug is administered to rats trained to discriminate cocaine, then they do not identify any psychomotor stimulant effects,



Drug Discrimination. Fig. 1. (**a**) Typical pattern of acquisition of simple drug discrimination by a group of eight rats. Initially responding was at the chance level of 50% regardless of drug or saline injection. Over 20 saline training days responding on the drug-appropriate, lever decreased progressively. In the 20 randomly interspersed training days with nicotine (0.4 mg/kg) responding on the drug-appropriate, lever increased progressively. Data shown as percentage of sessions in which rats initially chose to press the drug-appropriate lever averaged across successive blocks of five sessions. (**b**) Typical dose-response curve for nicotine obtained in a group of eight trained rats. Different doses of nicotine and saline were given in random order before test sessions that took place twice weekly, with normal training on intervening days. Results shown as percentage of responses on the drug-appropriate lever during 5-min sessions when no food was available (means ± s.e.m.).

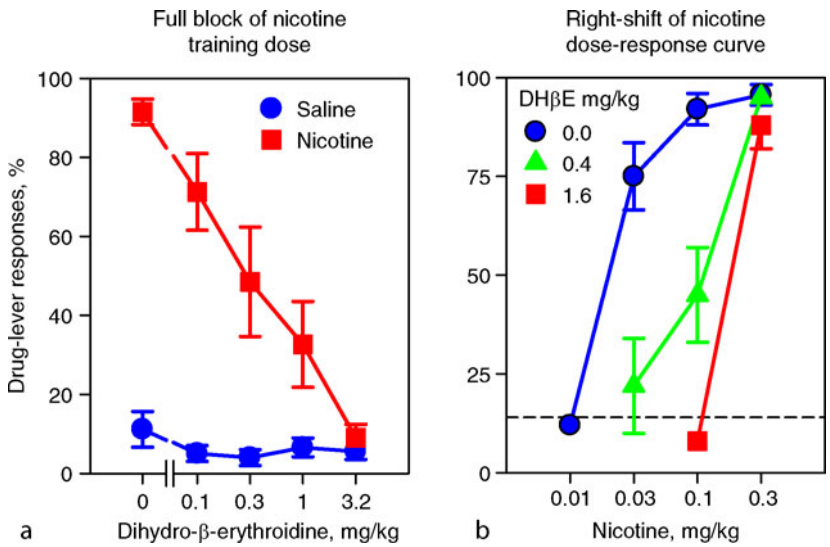
and they press predominantly upon the nondrug lever. Such observations show that in typical two-lever drug discrimination experiments, the discrimination that is acquired is not between abnormal and normal states, but between the presence and absence of the specific pharmacological effects of the training drug. Thus, the trained rats can serve as a "litmus-paper" for a test drug that has pharmacological effects shared with those of the training drug. In such cases, the generalization gradient (dose–response curve) reflects the extent of qualitative similarity between training and test drugs as well as the intensity of the drug stimuli.

Discriminative stimuli produced by drugs with well-defined actions at known receptors are blocked by the appropriate specific antagonists (e.g., Fig. 2) and agents that influence the release, reuptake, and degradation of neurotransmitters can show orderly and comprehensible profiles of generalization according to the drug used for training. The influence of variables such as drug dose used for training, timing, and route of drug administration and ▶ schedule of reinforcement have been studied and are well understood. Such information has established the validity of the approach for investigating the neuropharmacological mode of action of drugs. The simple, drug versus vehicle discrimination using two-lever operant conditioning methodology and food reinforcers accounts for about three-quarters of all reports of original investigations in the field. Drug discrimination may be related to ▶ state-dependent learning, but some experts argue on theoretical and empirical grounds that the two phenomena are fundamentally dissimilar.

Discriminative drug effects nearly always originate within the central nervous system, as has been shown by the typical lack of generalization to agents that share the peripheral actions of psychoactive substances but do not penetrate into the central nervous system. Similarly, receptor antagonists that penetrate poorly into the brain are rarely effective. However, generalization and blockade can be seen with agonist and antagonist drugs that are poorly brain-penetrant if they are administered intracerebrally.

Applications

Drug discrimination methodology has been much used in the later stages of searches for new and improved pharmaceuticals. It may be used to identify compounds with specific actions at novel receptor sites when there is a prototypical agonist available for use as the training drug. Alternatively, putative antagonist drugs can be evaluated against a range of agonists to determine whether they produce full or partial block and whether the effect is specific for the targeted agonist. By such means it is possible to verify that substances initially identified



Drug Discrimination. Fig. 2. (**a**) Dihydro-β-erythroidine (DHβE) blocked the discriminative stimulus effect of a 0.1 mg/kg training dose of nicotine in a group of eight rats. The nicotine stimulus did not generalize to DHβE when the antagonist was administered alone. (**b**) DHβE shifted the dose–response curve for the nicotine (0.1 mg/kg) discriminative stimulus to the right in a dose-related manner (nine-fold increase in the nicotine ED_{50} after 1.6 mg/kg of DHβE). Horizontal dashed line represents performance after saline. All results shown as means ± s.e.m. for a group of eight rats. (Redrawn from Stolerman et al (1997) Psychopharmacology 129:390–397.)

mainly by in vitro methods or with quicker but less specific in vivo approaches have the intended effects. The 5-HT_2 antagonist drugs are an example of such substances, some of which have proven valuable as ► antipsychotics. It was shown that whereas older compounds such as ► methergoline acted as ► partial agonists in relation to ► LSD, novel agents such as ► risperidone and ritanserin, acted as pure antagonists (Colpaert 2003).

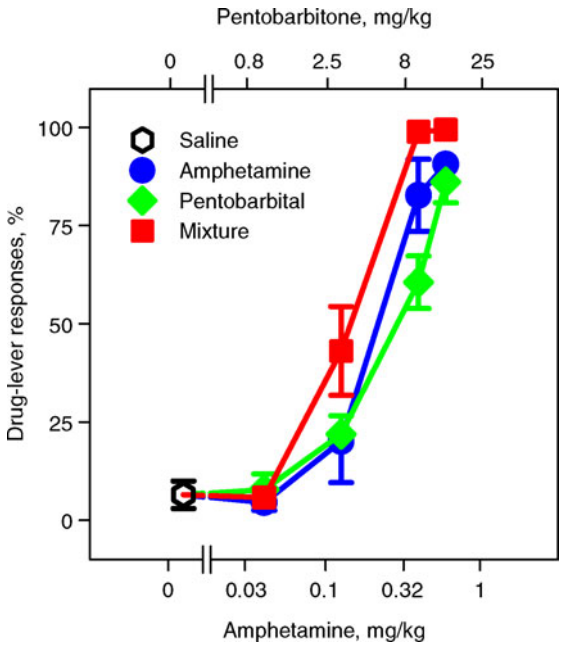
Academic researchers have also made very extensive use of discrimination methodology in studies of the mode of action of an extraordinarily wide range of drugs. Prior to the development of robust ► self-administration techniques for ► nicotine in the 1980s and for ► cannabinoids from 2000 onwards, drug discrimination was the main approach for studying their dependence-related effects in animals. Thus, discrimination studies using a variety of agonist and antagonist drugs suggest that the nicotine discriminative stimulus is mediated mainly through high-affinity heteromeric nicotinic receptor subtypes and this is verified by studies with knockout mice lacking different nicotinic-receptor subunits; the findings are concordant with results of studies on nicotine self-administration. However, improvements in self-administration techniques and the increased range and sophistication of such approaches are contributing to a decline in use of discrimination methods in the current millennium.

Both American and European authorities regard drug discrimination as a key technique in the evaluation of ► abuse liability. The fact that a substance supports discrimination learning is not by itself evidence for abuse potential because some non-abused substances have that ability. The key principle underlying its use in assessing abuse liability is stimulus generalization; only if a test compound generalizes with a known abused compound is there evidence for abuse (Ator and Griffiths 2003). Tests may be made by training with the test compound itself and then testing for generalization to prototypical agents of each class of abused substance. This is the more cost-efficient approach as less work and fewer subjects are required, but it may fail if the test substance does not produce a robust discriminative stimulus. Alternatively, separate groups of subjects are trained with abused drugs from different classes and then generalization to the novel compound is examined.

Complex Drug Discrimination Paradigms

Diverse models for drug discrimination broaden its applicability. Three variants are discussed here and others are known (Stolerman 1993). In drug versus drug discrimination procedures one response is associated with administration of one psychoactive drug and a second response is associated with a different substance. This procedure facilitates finer distinctions between closely related substance, such as full and partial agonists acting at the same receptor site. In practice the most useful model is a three-response variant in which the third response is associated with the undrugged state; although training takes longer, it avoids a problem with the simpler procedure in which test results for substances different from each of the training drugs are not readily interpretable.

Discrimination experiments where mixtures of dissimilar drugs were used as stimuli have shed light on how subjects process the different elements in a complex drug-induced stimulus. These studies have shown that in most cases the stimuli produced by the component drugs in binary mixtures are perceived and processed independently. Figure 3 illustrates such findings for a mixture of stimulant and depressant drugs that



Drug Discrimination. Fig. 3. Identification of the components of a drug mixture. Dose-response curves for a group of ten rats trained to discriminate a mixture of (+)-amphetamine (0.5 mg/kg) plus pentobarbitone (12 mg/kg) from saline. Each drug administered alone increased drug-appropriate responding in a dose-related manner, and at the largest doses tested their effects were not significantly below those of the drug mixture. Results shown as mean percentage of responses on the drug-appropriate lever (±s.e.m.) during 5-min sessions when no food was available. (Redrawn from Mariathasan et al (1991) Behav Pharmacol 2:405–415.)

produce unique effects in less refined procedures; the drug mixture did not produce a distinctive, novel discriminative stimulus.

Finally, novel-response procedures for drug discrimination in human subjects facilitate the interpretation of placebo-appropriate response choices (Bickel et al. 1993). In standard procedures placebo-appropriate responding indicates either the absence of any drug effect or a drug effect unlike the training drug. Instructions to subjects exposed to novel-response procedures inform them that responses on a novel-appropriate device should be made if an active test substance unlike the training drug is detected. This methodology increases the selectivity of placebo-appropriate responding and has been used in studies with psychomotor stimulants, opioids, nicotine, sedative-hypnotics, and other agents.

Advantages and Limitations of Drug Discrimination Procedures

The major advantages of discrimination procedures have resided in (1) applicability to an extremely wide range of psychoactive substances; (2) typically excellent pharmacological specificity as shown in generalization tests between agents from different classes; (3) the robust, highly reproducible nature of effects seen in many studies; (4) relative ease of collecting high-quality quantitative data. On the other hand, the time taken to train animals militates against use in primary screens or in combination with procedures that cannot be carried out repeatedly in the same subjects, such as those involving intracerebral drug administrations. Intermediate results from generalization tests can be difficult to interpret. Although a strong case has been made on both theoretical and empirical grounds that drug discrimination is functionally equivalent to the self-reporting of drug-induced subjective states, attempts to link discriminative drug effects to specific changes such as relief of anxiety, as distinct from sedation, have not been successful. Perhaps paradoxically, the greatest success with the procedures has been attained in analyses of the neuropharmacological mode of action of drugs where in many cases drug action at the molecular level has been firmly related to behavior.

Cross-References

- ▶ Abuse Liability
- ▶ Antipsychotics
- ▶ Discriminative Stimulus
- ▶ ED_{50}
- ▶ LSD
- ▶ Methergoline
- ▶ Nicotine
- ▶ Risperidone
- ▶ Self-Administration
- ▶ State-Dependent Learning

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Drug Discriminative Stimulus

- ▶ Drug Discrimination
- ▶ Occasion Setting with Drugs

Drug (Dose)-Effect Function (Curve)

Definition

It is obtained when the effects of multiple doses of a drug on a measure are obtained; generally presented as a graph showing the effect as a function of dose.

Drug–Drug Interactions

Synonyms

Drug interactions

Definition

A phenomenon in which one drug affects the pharmacokinetic or pharmacodynamic properties of another drug. This is commonly mediated by effects on protein binding in the circulation, or on liver-mediated metabolism of the second drug, and can give rise to changes in the levels of circulating drug, changing the effects of a given dose on therapeutic efficacy or side effects.

Drug Effects

► Environmental Enrichment and Drug Action
► Rate-Dependency Theory

Drug Facilitator

► Occasion Setting with Drugs

Drug Interactions

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Synonyms

Drug–drug interactions; Potentiation

Definition

When multiple drug therapy is prescribed, there is a possibility of drug interactions. They occur when the effectiveness or toxicity of a drug is altered by the concomitant administration of another drug. This may have beneficial effects such as increasing therapeutic efficiency or reducing risk of side effects. Often, however, they are critical because the outcome is diminished therapeutic efficacy or enhanced toxicity. Mechanisms of drug interactions are usually divided into two categories: ► pharmacodynamic and ► pharmacokinetic. Pharmacodynamic interactions occur when two drugs act at the same or interrelated receptors. This may lead to additive, synergistic, or antagonistic effects. Additive effects may be useful in case of ► lithium ► augmentation under insufficient response to a ► selective serotonin reuptake inhibitor or a ► tricyclic antidepressant. Another useful indication of a combination therapy may be the treatment of unwanted drug effects such as the use of biperiden to alleviate extrapyramidal symptoms induced by ► antipsychotic drugs. Additive effects, however, can also lead to intoxication, e.g., when combining two drugs with QT interval prolongation. Pharmacokinetic interactions consist of changes in the absorption, distribution, metabolism, or excretion of a drug and/or metabolites. This has consequences for the amount of the drug that reaches the site of action. In clinical practice metabolic drug interactions in the liver are most relevant. Since ► polypharmacy is commonly used and frequently required in psychopharmacotherapy, it is important to understand the mechanisms of drug–drug interactions and how to use polypharmacy as rationally and safely as possible.

Current Concepts and State of Knowledge

Since the accidental discovery of lithium, ► chlorpromazine, iproniazid, and ► imipramine as effective drugs for the treatment of major psychiatric diseases, more than 100 psychoactive drugs have become available – ► antipsychotics, ► antidepressants, ► anxiolytics, ► cognitive enhancers, ► hypnotics, ► mood stabilizers, and ► psychostimulants. The drugs have been approved for many psychiatric diseases, and controlled ► randomized clinical trials have proved their therapeutic efficacy. Intensive basic and clinical research during the last 50 years has built up a detailed knowledge base of the mechanisms of the actions of psychoactive drugs, which is summarized in Table 1. Enzymes involved in metabolic degradation were characterized in vitro and in vivo, and enzymes of the ► cytochrome P450 (CYP) family were found to be highly active in detoxifying the mostly lipophilic psychotropic drugs (Table 1). Target structures and clinical consequences following inhibition or stimulation in the central nervous system have been identified (Table 2). Taken together, this wide knowledge has become the basis of rational psychopharmacotherapy.

Regarding actual guidelines for pharmacological treatment of psychiatric disorders, monotherapy is the mainstay. In clinical practice, however, polypharmacy is more common than monotherapy, despite limited information on the efficacy of combination treatments (Glezer et al. 2009; Goodwin et al. 2009). Psychiatric patients need concomitant medication when monotherapy fails to achieve sufficient improvement. Moreover, incomplete remission, chronic symptoms, or drug-induced side effects may give rise to the need for additional drugs. Another significant reason for polypharmacy is comorbidity. When

Drug Interactions. Table 1. Enzymes and mechanisms of action involved in the pharmacokinetics and pharmacodynamics of psychoactive drugs.

Drug	Enzymes[a]	Mechanisms of action (targets)
Acamprosate	Not metabolized	NMDA receptor antagonist
Agomelatine	**CYP1A2**, CYP2C19	M1 and M2 melatonin receptor agonist, $5HT_{2C}$-receptor antagonist
Alprazolam	**CYP3A4**	Allosteric $GABA_A$ receptor stimulation
Amisulpride	Not metabolized	Dopamine D2 and D3 receptor antagonist, potassium channel blockade
Amitriptyline	**CYP1A2**, CYP2C9, CYP2C19, **CYP2D6**, CYP3A4	Inhibition of noradrenaline and serotonin reuptake, antagonist of acetylcholine, noradrenaline and histamine receptors
Aripiprazole	CYP3A4, CYP2D6	Antagonist and agonist of dopamine D2 receptors, antagonist of 5-HT_{2A} and 5-HT_{2C} and 5-HT_{1A} receptors
Atomoxetine	**CYP2D6**	Inhibitor of noradrenaline uptake
Bupropion	**CYP2B6**	Inhibitor of dopamine and noradrenaline uptake
Buspirone	**CYP2B6, CYP3A4**	Antagonist of 5-HT_{1A} receptors
Carbamazepine	CYP3A4, CYP2B6, CYP1A2, CYP2C8	Inhibitor of hyperactive neurons
Citalopram	**CYP2C19**, CYP3A4, CYP2D6	Inhibitor of serotonin uptake
Clomipramine	**CYP2C19,** CYP1A2, CYP3A4, **CYP2D6**	Inhibitor of serotonin (clomipramine) and noradrenaline (norclomipramine), antagonist of acetylcholine receptors and α_1-adrenoceptors
Clozapine	**CYP1A2**, CYP3A4, CYP2D6, CYP2C19	Antagonist of dopamine D4, D2, D3 and D1, 5-HT_2, acetylcholine M1 and histamine H1 receptors
Desipramine	**CYP2D6**	Inhibitor of noradrenaline uptake and acetylcholine receptors
Diazepam	CYP2B6, **CYP2C19,** CYP3A4	Allosteric $GABA_A$ receptor stimulation
Donepezil	**CYP2D6**, CYP3A4	Inhibitor of acetylcholine esterase
Doxepin	**CYP2C19**, CYP2D6	Inhibitor of histamine receptors, noradrenaline and serotonin uptake, acetylcholine receptors and α_1-adrenoceptors
Duloxetine	**CYP1A2**, CYP2D6, Catechol-O-methyltransferase	Inhibitor of noradrenaline and serotonin uptake
Escitalopram	**CYP2C19**, CYP3A4, CYP2D6	Inhibitor of serotonin uptake
Flunitrazepam	CYP3A4, CYP2C19	Allosteric $GABA_A$ receptor stimulation
Fluoxetine	CYP2D6, CYP2B6, CYP2C9, CYP2C19	Inhibitor of serotonin uptake
Flupentixol	**CYP2D6**	Inhibitor of dopamine D2, 5-HT_2 receptors and α_1-adrenoceptors
Flurazepam	**CYP3A4**	Allosteric $GABA_A$ receptor stimulation
Fluvoxamine	**CYP2D6**, CYP1A2	Inhibitor of serotonin uptake
Galantamine	CYP2D6, CYP3A4	Inhibitor of acetylcholine esterase, allosteric stimulation of nicotine receptors
Haloperidol	**CYP3A4**, CYP2D6	Antagonist of dopamine D2 receptors and α_1-adrenoceptors
Imipramine	**CYP1A2**, **CYP2D6**, CYP2C19, CYP3A4	Inhibitor of noradrenaline and serotonin uptake, acetylcholine receptors and α_1-adrenoceptors
Lamotrigine	Glucuronyl transferase	Inhibitor of excitatory neurons
Levomepromazine	**CYP1A2**, CYP2D6	Antagonist of dopamine D2, acetylcholine, histamine receptors and α_1-adrenoceptors
Lithium	Not metabolized	Stimulation of monoaminergic second messengers
Loprazolam	**CYP3A4**	Allosteric $GABA_A$ receptor stimulation
Lorazepam	Glucuronyl transferase	Allosteric $GABA_A$ receptor stimulation

Drug Interactions. Table 1. (continued)

Drug	Enzymes[a]	Mechanisms of action (targets)
Lormetazepam	Glucuronyl transferase	Allosteric $GABA_A$ receptor stimulation
Maprotiline	**CYP2D6**	Inhibitors of noradrenaline, histamine receptors and α_1-adrenoceptors
Melatonin	**CYP1A2**, CYP3A4	Agonist of M1, M2 und M3 melatonin receptors
Methylphenidate	CYP2D6	Inhibitor of dopamine uptake
Midazolam	**CYP3A4**	Allosteric $GABA_A$ receptor stimulation
Mirtazapine	CYP3A4, CYP1A2, CYP2D6	Stimulation of noradrenaline and serotonin release, antagonist of histamine H1 receptors
Moclobemide	CYP2C19, CYP2C9	Reversible inhibitor of monoamine oxidase A
Modafinil	CYP1A2, CYP2C9, CYP2C19, CYP3A4	Inhibitor of noradrenaline uptake and other mechanisms (unclear)
Naltrexone	Dihydrodiol dehydrogenase	Antagonist of μ-opiate receptors
Nicotine	**CYP2A6**	Agonist of nicotinic acetylcholine receptors
Nitrazepam	CYP2D6, CYP3A4, **Glucuronyl transferase**	Allosteric $GABA_A$ receptor stimulation
Nordazepam	**CYP2C19, CYP3A4**	Allosteric $GABA_A$ receptor stimulation
Nortriptyline	**CYP2D6**	Inhibitor of noradrenaline uptake, acetylcholine receptors and α_1-adrenoceptors
Olanzapine	Glucuronyltransferase, Flavine monooxigenase, **CYP1A2,** CYP2D6	Antagonist of dopamine D2, 5-HT_2, acetylcholine M1 and histamine H1 receptors
Oxazepam	**Glucuronyl transferase**	Allosteric $GABA_A$ receptor stimulation
Paliperidone	CYP3A4	Antagonist of dopamine D2 and 5-HT_2 receptors and adrenoceptors
Paroxetine	**CYP3A4**, CYP2D6, Catechol-O-methyltransferase	Inhibitor of serotonin uptake
Perazine	CYP3A4, CYP2C19, Flavine monooxigenase	Antagonist of dopamine D2, histamine H1, 5-HT_2, acetylcholine receptors and α_1-adrenoceptors
Perphenazine	**CYP2D6**	Antagonist of dopamine D2 and histamine H1 receptors
Pimozide	**CYP1A2**, CYP3A4	Antagonist of dopamine D2 receptors, potassium channel blockade
Prazepam	**CYP2C19, CYP3A4**	Allosteric $GABA_A$ receptor stimulation
Pregabalin	Not metabolized	Presynaptic inhibition of hyperactive neurons
Promethazine	**CYP2D6**	Antagonist of histamine receptors
Quetiapine	**CYP3A4**	Antagonist of dopamine D2 and 5-HT_2 receptors
Reboxetine	CYP3A4	Inhibitor of noradrenaline uptake
Risperidone	**CYP2D6**, CYP3A4	Antagonist of dopamine D2, 5-HT_2 receptors and adrenoceptors
Rivastigmine	Acetylcholine esterase	Inhibitor of acetylcholine and butyrylcholine esterase
Sertindole	**CYP3A4**, CYP2D6	Antagonist of dopamine and 5-HT_2 receptors, blockade of potassium channels
Sertraline	CYP2B6, CYP2C19, CYP2C9, CYP2D6	Inhibitor of serotonin uptake
Sulpiride	Not metabolized	Antagonist of dopamine D2 receptors
Temazepam	Glucuronyl transferase	Allosteric $GABA_A$ receptor stimulation
Thioridazine	**CYP2D6**, CYP1A2, CYP2C19	Inhibitor of acetylcholine, dopamine D2, 5-HT_2 receptors and α_1-adrenoceptors
Trimipramine	**CYP2C19, CYP2D6,** CYP2C9	Inhibitor of histamine H1 and dopamine D2 receptors
Tranylcypromine	Monoamine oxidase	Irreversible inhibitor of monoamine oxidase

Drug Interactions. Table 1. (continued)

Drug	Enzymes[a]	Mechanisms of action (targets)
Trazodone	**CYP3A4**	Inhibitor of serotonin uptake and agonist of serotonin receptors
Triazolam	CYP3A4	Allosteric $GABA_A$ receptor stimulation
Trifluprom azine	Unclear	Inhibitor of dopamine D2 and 5-HT_2 receptors and α_1-adrenoceptors
Valproic acid	**Glucuronosyl-transferase**, CYP2A6, CYP2B6, CYP2C9, beta-oxidation	Inhibitor of hyperactive neurons
Varenicline	Not metabolized	Agonist of nicotinic acetylcholine receptors
Venlafaxine	**CYP2D6**, CYP3A4	Inhibitor of serotonin and noradrenaline uptake
Zaleplone	CYP3A4	Allosteric $GABA_A$ receptor stimulation
Ziprasidone	Aldehyde oxidase, CYP3A4	Antagonist of dopamine D2, 5-HT_2 and histamine H1 receptors and inhibitor of noradrenaline and serotonin uptake
Zolpidem	**CYP3A4,** CYP1A2, CYP2C9	Allosteric $GABA_A$ receptor stimulation
Zopiclone	**CYP3A4**, CYP2C8, CYP2C9	Allosteric $GABA_A$ receptor stimulation
Zotepine	**CYP1A2**, CYP3A4	Antagonist of dopamine D2, 5-HT_2 and histamine H1 receptors
Zuclopenthixol	**CYP2D6**	Antagonist of dopamine D2, acetyl choline, histamine receptors and α_1-adrenoceptors

[a]Inhibition or induction of enzymes indicated in bold can lead to clinical relevant drug–drug interactions

Drug Interactions. Table 2. Clinical consequences of inhibition or stimulation of target structures affected by drugs actually used for the treatment of psychiatric disorders.

Target structure	Therapeutic effects	Adverse effects[a]
Acetylcholine esterase	Inhibition decreases clinical deterioration in Alzheimer's disease and has positive effects on cognition, mood, behavior, and the ability to perform daily activities	Inhibition may effect gastrointestinal disturbances, confusion, dizziness, drowsiness, headache, insomnia, agitation, and/or hallucinations
Adrenoceptors, α_1		Inhibition may effect orthostatic hypotension, reflex tachycardia
Adrenoceptors, α_2	Inhibition effects contraction of male genitalia during ejaculation and antagonizes hyperalgesia	Facilitation of ventricular tachycardia
Dopamine D_2 receptors	Inhibtion has antipsychotic effects	Inhibition may effect extrapyramidal symptoms, prolactin release, sexual dysfunction, disturbed thermoregulation, neuroleptic syndrome. Stimulation induces akathisia, nausea, vomiting, enhanced sexual drive
Dopamine transporter	Inhibition enhances vigilance and attention and reduces hyperactivity in patients with an attention deficit syndrome	Inhibition may effect headache, euphoria, psychosis, drowsiness, dizziness, dyskinesia, abdominal pain, nausea and vomiting, tachycardia, palpitations, arrhythmias, changes in blood pressure and heart rate, disturbed sleep, decreased appetite
$GABA_A$ receptors	Stimulation effects anxiolysis, muscle relaxation, hypnosis, analgesia and has anticonvulsive properties	Stimulation may lead to ataxia, apathy, weakness, hyperactivity, hyperreagibility, respiratory or cardiovascular depression. Inhibition may induce convulsions

Drug Interactions. Table 2. (continued)

Target structure	Therapeutic effects	Adverse effects[a]
Glutamate receptors, NMDA	Inhibition decreases clinical deterioration in Alzheimer's disease and has positive effects on cognition, mood, behavior, and the ability to perform daily activities	Inhibition may effect confusion, dizziness, drowsiness, headache, insomnia, agitation, and/or hallucinations. Stimulation may induce convulsions and affect multiple CNS functions
Histamine receptors, H_1	Inhibition effects sedation and sleep	Inhibtion effects sedation, delirium, weight gain
Potassium channels		Inhibition effects QT time interval prolongation, torsades de pointes, arrhythmia
Monoamine oxidase	Inhibition has antidepressant effects	Inhibition effects sleep disturbances, agitation, anxiety, restlessness, dizziness, headache, paraesthesia, visual disturbances, flushing, dry mouth, nausea, vomiting, diarrhea, constipation
Muscarinic acetylcholine receptor, M_1		Inhibition effects disturbed accommodation, dry mouth, sinus tachycardia, obstipation, urinary retention, glaucoma, cognitive disturbances, delirium, seizures
Nicotinic acetylcholine receptors	Stimulation relieves nicotine withdrawal symptoms, improves cognition	Stimulation effects headache, dizziness, nausea, vomiting, indigestion, heartburn, increased salivation, muscle ache
Noradrenaline uptake	Inhibition has antidepressant potential	Inhibition effects insomnia, vertigo, tachycardia, palpitation, vasodilatation, postural hypotension, abnormality of accommodation, dry mouth, constipation, urinary hesitancy, sensation of incomplete bladder emptying
Opiate receptors, μ	Stimulation effects euphoria. Inhibition maintains opioide dependence after detoxification, reduces alcohol consumption and craving behavior	Stimulation effects drowsiness, headache, miosis, dry eyes, nausea, vomiting, constipation, dry mouth, confusion sleep disturbances, euphoria, restlessness, decreased libido, dependence. Inhibition effects difficulty in sleeping, anxiety, nervousness, abdominal pain, nausea, vomiting, low energy, joint and muscle pain, headache
Serotonin receptors, 5-HT_2	Inhibition affects anxiety, negative symptoms, sleep, appetite	Inhibition affects weight gain, gastrointestinal functions, regulation of body temperature
Serotonin uptake	Inhibition has antidepressant effects and delays ejaculation	Gastrointestinal disturbances, nausea, vomiting, serotonin syndrome (increased heart rate and blood pressure, confusion, agitated delirium, muscular rigidity and tension)

[a]The occurrence of adverse events depends on the dose and the disposition of the individual patient

the patient is still not doing well and the clinician is afraid to withdraw any of the drugs, the list of drugs becomes longer and longer and the pharmacology becomes more and more complex. Drug–drug interactions, especially, complicate the treatment (Rothschild et al. 2007). Polypharmacy is reportedly associated with an increased risk of adverse events and medication errors (Paterno et al. 2009).

Pharmacodynamic Interactions

Pharmacodynamic interactions are those where the effects of one drug are changed by the addition of another drug. The drugs may compete for the same receptor or interact indirectly by interfering within a common physiological pathway (Table 1). Pharmacodynamic interactions are often based on the intention to enhance a therapeutic effect; such strategies are termed "► add on,"

"potentiation," or "synergistic" therapy, and for most of these combination strategies more or less well-designed clinical trials give evidence if they are effective and safe. When clinical trials on a distinct drug combination are lacking, an experimental combination therapy must consider the pharmacodynamic profile of the combined drugs to predict the add on effect. Based on the target profiles summarized in Table 1, it seems likely that the combination of ▶ clozapine and ▶ olanzapine makes little sense, as the receptor profiles of the two atypical antipsychotic drugs are very similar. The expected add on effect should also be attained by increasing the dose of a single compound. It would be more appropriate to use ▶ haloperidol or ▶ risperidone in addition to clozapine. There are, however, also combination strategies that are helpful in one group of patients and harmful in other patients. Wellknown examples are augmentation therapies in antidepressant drug treatment. A ▶ serotonin syndrome that includes mental, autonomic, and neuromuscular dysfunctions is the result of over-stimulation of serotonin receptors. It may occur by combining a selective serotonin reuptake inhibitor and lithium. Enhancement of the serotonergic activity, however, can also be a strategy to overcome treatment refractory depression in an individual patient. Therefore, each combination treatment that uses pharmacodynamic interactions must be well supervised to maximize benefits and minimize risks.

Pharmacokinetic Interactions

Pharmacokinetic interactions are those that affect the absorption, distribution, metabolism, or excretion of a drug. Most psychoactive drugs are given orally. Interactions during absorption through the gastrointestinal tract are rare. One example is ▶ ziprasidone; its ▶ bioavailability is increased when taken with food. Most psychotropic drugs, however, are rapidly absorbed. Independent of the absence or presence of food, maximal concentrations in blood are attained at 1–3 h after drug intake. For some drugs bioavailability is limited by the action of drug transporter proteins such as P-glycoprotein (Pgp), which eject drugs that have diffused across the gut. Risperidone is a substrate of Pgp, and Pgp limits its availability. So far, however, evidence is lacking that Pgp in the gut plays a significant role as a target for drug interactions. Following absorption, drugs are rapidly distributed in the body by circulation. Due to high lipid solubility, most psychotropic drugs are bound to transport proteins, primarily albumin. The binding is reversible, and only the unbound drug is pharmacologically active. Drug interactions may occur by displacement from transport proteins. With the exception of anticonvulsant drugs, however, displacement interactions are not relevant for combinations with psychiatric drugs.

The vast majority of clinically important pharmacokinetic interactions of psychoactive drugs result from the induction or inhibition of drug metabolizing enzymes (Spina et al. 2003), primarily isoenzymes of the cytochrome P450 family (CYP).

Enzyme Induction

▶ Carbamazepine, ▶ phenobarbital, and a number of drugs shown in Table 3 are "inducers." In addition, constituents of food or herbal drugs may contain inducers. They stimulate the activity of a variety of CYP enzymes by enhancing the synthesis of proteins such as CYP1A2, CYP2C9, CYP2C19, and CYP3A4. Moreover, smoked or

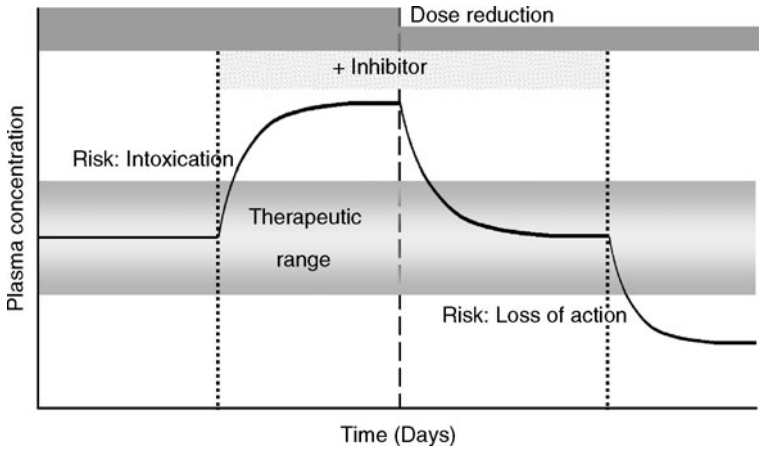
Drug Interactions. Table 3. Inducers of cytochrome P450 (CYP) isoenzymes.

CYP	Psychoactive drugs	Other drugs	Food, herbal drugs and life style
1A2	Carbamazepine, modafinil	Omeprazole, rifampicin, ritonavir	Smoking, charcoal-broiled food, broccoli
2B6		Cyclophosphamide, phenobarbital, phenytoin, rifampicin	
2C9	Carbamazepine	Cyclophosphamide, ifosfamide, phenobarbital, phenytoin, primidone, rifabutine, rifampicin, ritonavir	
2C19	Carbamazepine, phenytoin	Felbamate, modafinil, topiramate, rifampicin	
2D6	Unknown		
2E1	Ethanol	Isoniazide, smoking	
3A4	Carbamazepin, hyperforin, modafinil, oxcarbazepin, phenobarbital, phenytoin	Efavirenz, dexamethasone, lovastatine, oxybutynin, rifabutin, rifampicin	St. John's wort, Echinacea, green tea

charcoal-broiled food that contain polyaromatic carbohydrogens most effectively induce CYP1A2. As these enzymes are involved in biotransformation of many therapeutic agents, patients take enzyme inducers that quickly metabolize a wide range of concomitantly administered drugs. Depending on the therapeutic range, dosages must be increased to avoid the risk of loss of therapeutic effects (Fig. 1). One example is the combination of ▶ quetiapine and carbamazepine. Quetiapine blood levels will markedly decrease when combined with carbamazepine. Therefore, this combination is not recommended. It must also be considered that doses have to be reduced after discontinuation of inducers. Decreased enzyme activity may lead to high drug concentrations and thus bear the risk of intoxications (Fig. 1). The latter has been reported in patients who underwent treatment with the antipsychotic drugs olanzapine or clozapine after discontinuation of smoking. For drugs that are converted to active or toxic metabolites, ▶ enzyme induction may result in enhancement of the activity of the affected drug. An example is the induction of primidone metabolism by ▶ phenytoin, which results in increased concentrations of the active metabolite phenobarbital.

Enzyme Inhibition

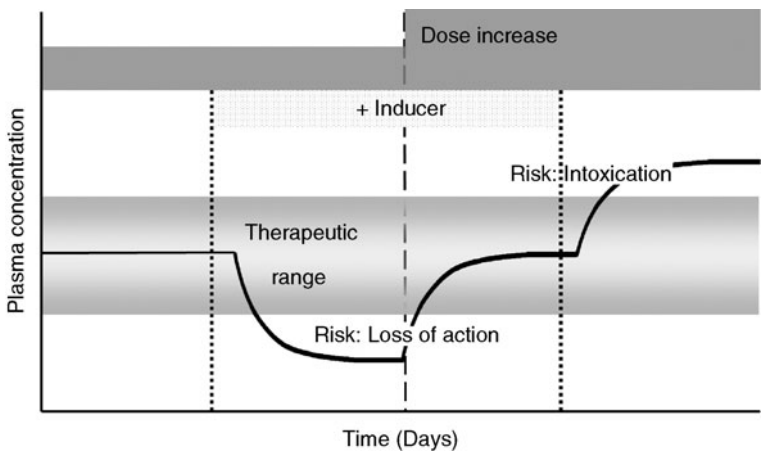
▶ Enzyme inhibition is rather common in psychotropic drugs (Lynch and Price 2007). Among the five selective serotonin reuptake inhibitors, ▶ paroxetine, ▶ fluoxetine, and ▶ fluvoxamine are potent inhibitors of CYP enzymes (Table 4). Combining two drugs of which one is an inhibitor and the other a substrate of the same enzyme, the concentration of the substrate will increase as shown in Fig. 2. Whether this increase has clinical consequences by inducing a toxic reaction, will depend on the therapeutic range of the drug. This may be controlled by determining drug concentrations in blood through therapeutic drug monitoring (TDM). Pharmacokinetic drug interactions are therefore an important indication to use TDM (Baumann et al. 2004; Bengtsson 2004). Considering the enzymes involved in the metabolism, it may be predicted whether plasma concentrations increase after the addition of another drug (Fig. 2). Using TDM and dose reduction it is possible to avoid toxic reactions. TDM may also be useful after discontinuation of the inhibiting drug, as plasma concentrations may decrease to low levels, leading to the risk of loss of action. Considering the pharmacokinetic profile of the combined drugs, it is possible to use interacting drugs safely. However, prediction is not always easy. Psychoactive drugs can be metabolized by a single enzyme such as ▶ atomoxetine by CYP2D6 or by several enzymes such as amitriptyline by CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. A drug can also be a substrate and inhibitor of the same enzyme such as paroxetine for CYP2D6 or fluvoxamine for CYP1A2. Therefore, it is advisable to control drug concentrations in blood to measure the effect of the comedication. This is especially useful when combining a drug with a CYP inhibitor (Hiemke 2008). The therapeutic index of the affected drugs is also of great concern. In combination with an inhibiting or inducing drug, plasma levels of a given substrate are more likely to reach toxic or subtherapeutic values when the substrate has a narrow therapeutic index. This is of importance for ▶ tricyclic antidepressants, clozapine, and also some new antipsychotic drugs (e.g., loss of action of quetiapine after addition of St John's wort).



Drug Interactions. Fig. 1. Pharmacokinetic behavior of a drug before and after addition of a drug metabolizing enzyme inducer and before and after dose increase.

Drug Interactions. Table 4. Inhibitors of CYP isoenzymes.

CYP	Psychotropic drugs	Other drugs	Food, herbal drugs and life style
1A2	Fluvoxamine, perazine	Cimetidine, ciprofloxacine, enoxacine, norfloxacine	Echinacea
2B6		Clopidogrel, clotrimazole, itraconazole	
2C9	Fluvoxamine	Amiodarone, metronidazole, fluconazole, ritonavir, sulfaphenazol	
2C19	Fluvoxamine, moclobemide	Omeprazole	
2D6	Bupropion, fluoxetine, levomepromazine, melperone, moclobemide, norfluoxetine, paroxetine, ropinirole, thioridazine	Amiodaron, quinidine, cimetidine, metoclopramide, metoprolol, propanolol, ritonavir	
2E1	Disulfiram		
3A4/5/7	Norfluoxetine	Cimetidine, cisapride, clarithromycine, diltiazem, erythromycine, indinavir, itraconazole, ketoconazole, mifepriston, nelfinavir, ritonavir, saquinavir, simvastatine, troleandomycin	Grapefruit juice, Kava kava



Drug Interactions. Fig. 2. Pharmacokinetic behavior of a drug before and after addition of an inhibitor and before and after dose reduction.

Clinical Evaluation of Drug Interactions

Information on the pharmacodynamic and pharmacokinetic profile of the combined drugs suggests possible interactions. Because of the understanding of the relevance of pharmacokinetic drug interactions during the last 15 years, it is today necessary that preclinical drug development include not only characterization of the pharmacodynamic profile of the drugs and its metabolites but also identification of the enzymes involved in the metabolism. Substrate and inhibitor properties of the drugs and the major metabolites must be clarified in the preclinical phase of drug development. Based on this knowledge, risks of concomitant use of co-medication can be defined. Because of possible risks due to pharmacodynamic or pharmacokinetic interactions, relevant co-medications are normally not allowed during the phases of clinical evaluation. Therefore, systematic clinical testing of drug combinations is rare or even lacking, and it is difficult or even impossible to evaluate the clinical relevance of combination treatments, especially the consideration of safety aspects. This information is normally raised when the drugs are used under naturalistic conditions. For this purpose, pharmacovigilance programs are most important (Grohmann et al. 2004). In the past, many interactions of psychoactive drugs were observed

accidentally, especially pharmacokinetic interactions of TDM controls. An increasingly important help is the use of computer-based drug interaction programs (e.g., https://www.medicinescomplete.com/mc/stockley/current/login.htm, http://www.medscape.com/druginfo/druginterchecker, http://www.psiac.de, http://www.mediq.ch/). Their quality has improved during the last years. However, only a few systems provide adequate information about the clinical effects of drug interactions or use medical advice.

Practical Issues

Combination treatment should be used as a last resort. One must be aware of drug–drug interactions. Computerized systems have shown that drug–drug interactions are among the most frequent alerts presented to clinicians writing medication orders (Paterno et al. 2009). The choice of particular drugs for individual patients requires a balancing of efficacy and side effects. This holds true for monotherapies and even more for polypharmacy. Risks of adverse effects increase under polypharmacy, and valid data on safety and efficiency of combinations are mostly lacking. Polypharmacy can be a validated or an empirical strategy. Whenever available, validated combinations should be used. When an empirical treatment lacking research-based evidence is used, objective symptom ratings should be applied to evaluate the result of the treatment.

Whenever a combination treatment is required, the following should be considered to make polypharmacy as effective and safe as possible:

- Combination therapies should be used only when preceding therapeutic trials with a single agent were of sufficient length, sufficient dose, and sufficient drug concentrations in blood.
- For most combination therapies, effectiveness or efficacy data are rare or even lacking.
- Combination therapies increase the risk of morbidity and mortality.
- Combination treatments must consider possible pharmacodynamic and pharmacokinetic interactions.
- Ineffective or minimally effective medications should be discontinued.
- Pharmacodynamic drug interactions require careful clinical supervision.
- Pharmacokinetic drug interactions should be controlled by determining drug concentrations in blood plasma or serum (TDM), especially for drugs with a narrow therapeutic range.
- To evaluate the results of a combination treatment, objective symptom ratings should be used.
- Computer programs should be used to check the medication orders to control for possible drug–drug interactions.

Cross-References

- ▶ Anticonvulsants
- ▶ Antidepressants
- ▶ Antipsychotic Drugs
- ▶ Benzodiazepines
- ▶ Monoamine Oxidase Inhibitors
- ▶ Pharmacokinetics
- ▶ SSRIs and Related Compounds

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Drug Licensing

▶ Licensing and Regulation of Medicines

Drug Modulator

► Occasion Setting with Drugs

Drug Occasion Setter

► Occasion Setting with Drugs

Drug Pellet

Definition

Capsule made to slowly release drug subcutaneously over 2 weeks (at the level of the lower back) and to avoid repetitive injection schedules. These drug pellets provide researchers with a convenient and reliable method for controlled agent delivery *in vivo*.

Drug Plasma Level Determination for Therapy Optimization

► Therapeutic Drug Monitoring

Drug Preferences

► Drug Taste Preference Conditioning

Drug Seeking

► Self-Administration of Drugs

Drug Self-Administration

Definition

In the drug self-administration procedure, animal or human subjects perform an operant response (e.g., lever press, nose-poke) to receive abused drugs that serve as appetitive unconditioned stimuli, paralleling effects of palatable food, or other non-pharmacological rewards. The drug is often administered via a chronically indwelling venous catheter although other routes are also used (e.g., oral). The premise of these studies is that the drug rewards control behavior by functioning as a positive reinforcer. A stimulus is defined as a positive reinforcer if its presentation following a response increases or maintains the likelihood that the response will reoccur.

Cross-References

► Conditioned Place Preference
► Drug Dependence
► Self-Administration of Drugs

Drug Stimuli

► Drug Cues
► Drug Discrimination

Drug Taking

► Self-Administration of Drugs

Drug Taste Preference Conditioning

Synonyms

Drug preferences; Oral self-administration

Definition

This is a term used to describe situations where taste conditioning takes place while an organism learns to drink a sapid drug solution. Except in the cases of drinking solutions prepared with highly potent drugs (e.g., etorphine) the solution is usually given its flavor by the drug itself. Different ways can be used to extract information on taste preferences, such as consumption of a single drug solution, intake of the drug solution as choice with water or other taste, and measurement of consumption of a solution that has the same taste as the drug solution but does not contain the drug. This would be accomplished by flavoring the drug solution, but in ► morphine taste preference conditioning, a conditioned morphine taste preference can be shown by substituting a solution of quinine for the morphine.

Cross-References

► Alcohol Preference Test
► Appetitive Responses
► Conditioned Taste Preferences
► Self-Administration of Drugs

Drug Tolerance

Definition

Drug tolerance is when an individual's reaction to a drug decreases so that larger doses are required to achieve the same effect. Drug tolerance can involve both psychological drug tolerance and physiological factors. Characteristics of drug tolerance: it is reversible; the rate depends on the particular drug, dosage, and frequency of use; differential development occurs for different effects of the same drug. There are three major mechanisms for tolerance:

- Dispositional tolerance: occurs because of a decreased quantity of the substance reaching the site it affects.
- Reduced responsiveness: the response to the substance is decreased by cellular mechanisms.
- Conditioned tolerance

Cross-References

► Area Under the Curve
► Behavioral Tolerance
► Bioavailability
► Conditioned Drug Effects
► Elimination Half-Life

Drug Toxicity

Synonyms

Side effects

Definition

Drug toxicity refers to the level of damage that a compound can cause to an organism. The toxic effects of a drug are dose-dependent and can affect an entire system as in the CNS or a specific organ such as the liver. Drug toxicity usually occurs at doses that exceed the therapeutic efficacy of a drug; however, toxic and therapeutic effects can occur simultaneously. It can be assessed at the behavioral or physiological level. Behaviorally, drug toxicity can be exhibited in a variety of ways, for example, decreases in locomotor activity, loss of motor coordination, cognitive impairment. Examples of physiological effects include lesions to tissue, neuronal death, and disrupted hormonal cycles.

Drug Vulnerability

► Addictive Disorder: Animal Models

Drug-Induced Motor Syndromes

► Movement Disorders Induced by Medications

Drugs as States

► State Dependence of Memory

Drugs of Abuse

Synonyms

Dependence-forming drugs

Definition

A varied group of mainly nonprescription drugs that cause dependence primarily by activating the mesocortical dopaminergic system.

DSM

Definition

Diagnostic and Statistical Manual of Mental Disorders (currently in its fourth edition). Diagnostic criteria for psychiatric/mental disorders, published by the American Psychiatric Association (APA).

Dual Diagnosis

Definition

Term most commonly used in psychiatric care and research communities to describe the high rates of mental illness and substance use disorder comorbidities within individuals and whole patient populations. Neurobiological explanations for dual diagnosis seek to understand the interactions between the brain effects of psychoactive drugs and brain abnormalities that generate mental illness. Sometimes dual diagnosis is used to refer to the comorbidity of psychiatric illness with other biomedical conditions (e.g., mental retardation).

Dual-Process Mechanism

Definition

A hypothetical explanation for the ability for a drug or any stimulus to produce one effect initially and the precise opposite effect at a later time period. With chronic administration of the drug, the initial effect may decrease while the secondary effect increases, with the concomitant development of apparent tolerance.

Duloxetine

Synonyms

Duloxetine hydrochloride

Definition

Duloxetine was the second ► SNRI approved by the United States Food and Drug Administration; it is available under the brand name Cymbalta. Duloxetine has been approved in the USA for the treatment of ► major depressive disorder, ► generalized anxiety disorder, fibromyalgia, and for painful diabetic peripheral neuropathy in adults.

Duloxetine Hydrochloride

► Duloxetine

Dynorphins

Synonyms

Endogenous opioids

Definition

Dynorpins include dynorphin-A, dynorphin-B, α-neodynorphin, and "big-dynorphin." All are endogenous opioids derived from the large peptide precursor, prodynorphin. Although they are the only endogenous opioids that interact significantly with ► κ-receptors (KOR), they also interact with other opioid receptors, particularly the ► μ-receptor (MOR).

Dysbindin

Synonyms

Dystrobrevin-binding protein 1

Definition

Dysbindin is a protein constituent of the dystrophin-associated protein complex of skeletal muscle cells. Dysbindin is found in neural tissue of the brain, especially in axon bundles and particularly in certain axon terminals, notably mossy fiber synaptic terminals in the cerebellum and hippocampus. Pedigree-based family-association studies of families with a history of schizophrenia have shown a strong association between expression of a particular dysbindin allele and a clinical expression of schizophrenia. However, the exact link between dysbindin and schizophrenia remains highly controversial.

Cross-References

► Schizophrenia

Dyskinesia

Definition

This term refers to abnormal, involuntary bodily movements, which are characteristically spasmodic or repetitive.

Dysmorphology

Definition

Anomalies in whole body shape and contour, that is, hands, feet, rib cage, and spine.

Dysphoric State

Definition

It is an unpleasant or uncomfortable mood, such as sadness (depressed mood), anxiety, irritability, or restlessness. Etymologically, it is the opposite of euphoria.

Dysthymia

► Dysthymic Disorder

Dysthymic Disorder

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Synonyms

Chronic low-grade depression; Dysthymia; Neurotic Depression

Definition

Dysthymic disorder is a ► mood disorder that is characterized by chronic mild depression. To meet DSM-IV criteria of dysthymic disorder, an individual must have "depressed mood for most of the day, for more days than not" for at least 2 years. In addition, there must be two or more of the following symptoms: poor appetite or overeating; insomnia or hypersomnia; low energy or fatigue; low self-esteem; poor concentration or difficulty making decisions; and feelings of hopelessness. There cannot have been any periods of normal mood lasting more than 2 months during the most recent 2-year period. In addition, there cannot have been an episode of major depression during the first 2 years of the disorder, and there cannot be a history of manic or hypomanic episodes. The disorder must cause distress or impaired social functioning. Onset before or after 21 years is specified as "early onset" or "late onset," and the disorder can also be described as having (or not having) atypical features such as lethargy, increased sleep, and increased appetite.

Role of Pharmacotherapy

Individuals may present with a variety of forms of chronic depression. In 1980, the DSM-III (American Psychiatric Association 1980) recategorized what had previously been called "neurotic depression" into the diagnosis of dysthymia, a condition that was placed among the mood disorders. Renamed dysthymic disorder (DD) in the 1994 DSM-IV, this condition is characterized by the presence of chronic low-grade depressive symptoms that last for a minimum of 2 years (American Psychiatric Association 2000). In clinical settings, patients often present for care after having depressive symptoms for decades rather than just for a few years. Some have been depressed since childhood; others describe onset in adolescence, adulthood, or even in geriatric years. Some patients may have milder forms of symptoms commonly seen in major depression, such as decreased sleep, weight loss, or insomnia, whereas others may have more "atypical" depressive symptoms such as weight gain, lethargy, and increased sleep. In addition, many patients present for treatment in the context of having both dysthymic disorder and major depression, or what is called "double depression."

DD has been called a paradoxical disorder because on a cross-sectional basis it appears to be mild, whereas on a longitudinal basis it has major consequences on quality of life and can justly be described as a "severe" disorder (Klein et al. 2000). Individuals with DD have been shown to have impairment in psychosocial functioning, marital and intimate relationships, and work functioning (including increased absenteeism and greater disability). They have an increased level of health care utilization, though their depression may be ignored by care providers. They also may have a greater risk for suicidal behavior than patients with acute major depression. Of note, in some cases chronic depression may result from other causes than a primary "unipolar" mood disorder. Causes may include psychiatric (such as ► bipolar disorder or psychotic illness), medical (such as thyroid disease), and chronic ► substance use (such as alcohol or marijuana use). In those situations, the patient would not meet DSM-IV criteria for DD, and treatment of the primary disorder is essential in addition to addressing depressive symptoms. Importantly, some patients presenting with mild depression may have conditions that do not meet criteria for DD. For instance, if the depression is of relatively brief duration, the appropriate diagnosis might be an adjustment disorder with depressed mood.

Stressful experiences in early life, including experiences of neglect and abuse, increase the risk of developing DD. The biological underpinnings of DD have not been well ascertained; data suggest that individuals with DD resemble those with major depression in measures such as sleep architecture and changes in stress-induced skin conductivity, as well as by family history, but in other ways are distinct (for instance, having lower rates of dexamethasone nonsuppression). On a broader level, many authorities believe that DD is likely to be a heterogeneous condition, resulting from a variety of causes ranging from genetic to environmental, and that there is unlikely to be a single underlying pathophysiology or a single mechanism for effective treatment (Griffiths et al. 2000).

Efficacy of Medications

Numerous classes of medication have been demonstrated to be effective in the treatment of dysthymic disorder (Hellerstein 2001; Lima et al. 2005; Thase et al. 1996; Vanelle et al. 1997). These include major classes of

antidepressant medications, such as ▶ tricyclic antidepressants, ▶ monoamine oxidase inhibitors (MAO), ▶ serotonin reuptake inhibitors, and other medications (such as the atypical antipsychotic ▶ amisulpride and the 5HT2 antagonist ritanserin). At the time of the most recent Cochrane review, there were approximately 17 ▶ double-blind placebo-controlled studies of DD in the literature, with a duration of 6–12 weeks. Generally, studies suggest that about half of the people with DD respond to any single medication trial. Forms of psychotherapy such as interpersonal psychotherapy and cognitive behavioral therapy have also been shown to be effective in small studies. Nonetheless, as various authors have pointed out, the number of high-quality studies of treatments of dysthymic disorder is small, and most existing studies suffer from a variety of defects, including small sample size and methodological deficiencies. In particular, because there are few studies of long-term treatment of dysthymic disorder, there is only a limited understanding of whether treatment can achieve long-term remission of this disorder. Furthermore, there are few studies of medication treatment for patients who have not responded to an initial trial. Finally, the literature on combined psychopharmacology and psychotherapy treatments of DD is extremely limited, and it is not clear whether one can justifiably extrapolate from such studies in major depression to the treatment of DD.

Typically, antidepressant treatment of DD uses doses of medication similar to those used in the treatment of major depression, e.g., the equivalent of 20–80 mg/day of fluoxetine. Studies of antidepressant medications in DD use criteria for treatment response similar to those used in the treatment of major depression: responders are generally defined as having a 50% or greater improvement in depressive symptoms (typically measured by the ▶ Hamilton Depression Rating Scale [Ham-D] or specific dysthymia rating scales such as the Cornell Dysthymia Rating Scale), and remitters are defined in various ways, such as having a score less than 7 on the Ham-D, or a score of 0 on Ham-D item 1 (depressed mood) and no longer meeting DSM criteria for DD. In studies using such criteria, response rates are generally higher in open-label than in double-blind studies. In the absence of long-term data, duration of antidepressant treatment needed in DD is unclear; the few follow-up studies indicate that medication improvement generally persists over a year or more when medication is continued, and that depressive symptoms tend to return after medication is discontinued. However, it is not clear whether lifetime medication treatment is needed, or whether some patients may remain in remission after a period of medication treatment. Some clinicians attempt to gradually taper medications after DD has been in remission for a year or more.

Studies indicate that social function improves following effective treatment of depressive symptoms of DD (Kocsis et al. 1997). This suggests that a broader process of recovery may be initiated in many patients. However, despite such improvement, studies have shown that only 24% of dysthymics who have responded to treatment have returned to psychosocial functioning in the normal range (as measured by the Social Adjustment Scale [SAS]) after 6 months (Friedman et al. 1999). Therefore, augmenting medication or psychotherapy treatments may be indicated.

Side Effects and Advantages and Disadvantages of Various Agents

Because DD is a chronic disorder and may often require many years of medication treatment, it is important to consider the long-term tolerability of any medication chosen. Side effects such as weight gain or sexual dysfunction may have a major effect on quality of life and medication compliance. In current practice, ▶ selective serotonin reuptake inhibitors (SSRIs) are most commonly used as first choice medications in the treatment of DD; they have the advantage of broad efficacy on a variety of depressive and anxiety symptoms, high tolerability, and low levels of toxicity. In addition, a number of studies provide evidence for their efficacy. Other medications are widely used in treatment of DD despite limited evidence of benefit. These include ▶ bupropion, a medication hypothesized to work through dopamine and norepinephrine reuptake inhibition, and which is associated with low levels of sexual dysfunction and weight gain. The serotonin–norepinephrine reuptake inhibitors (▶ venlafaxine, desvenlafaxine, ▶ duloxetine, etc.) are also used despite a lack of efficacy data in DD, but with the thought that they may alleviate a broader range of dysthymic symptoms than SSRIs. Older classes of medications, such as the ▶ tricyclic antidepressants (TCAs) and ▶ monoamine oxidase inhibitors (MAOIs) have been shown to be effective in the treatment of DD, but are less frequently used as first-line agents because of their greater side effects and potential toxicity. The reversible MAOI ▶ moclobemide may have lower risks for adverse events such as tyramine-induced hypertension than other medications in its class, and has been shown to be effective in DD. Moclobemide is not available in the USA. Still other classes of medications have demonstrated some benefit in the treatment of DD, including the atypical antipsychotic ▶ amisulpride, possibly via dopamine modulation. In some instances, where there is inadequate response to a single medication, medication

combinations are used. Examples include bupropion combined with an SSRI, or augmentation of antidepressants with stimulants. However, data are lacking on the efficacy of such approaches in DD.

Cross-References

- ► Antidepressants
- ► Antipsychotic Drugs
- ► Major and Minor and Mixed Anxiety and Depressive Disorders
- ► Monoamine Oxidase Inhibitors
- ► SNRI Antidepressants
- ► SSRIs and Related Compounds

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Dystonia

Definition

This is a movement disorder characterized by abnormal muscle tone. It manifests as sustained, repetitive muscle contractions cause twisting and jerking movements or abnormal postures.

Dystrobrevin-Binding Protein 1

- ► Dysbindin

E

E

► Methylenedioxymethamphetamine (MDMA)

EAAT

► Glutamate and EAA Transporters

Early Onset Schizophrenia

► Pediatric Schizophrenia

Early Ventral Hippocampal Lesion Model

Definition

An animal model in which the ventral hippocampal region in rats is lesioned using an excitotoxic agent. This lesion is performed at an early age (typically postnatal day 7). These animals develop several schizophrenia-like phenomena in adulthood. Interestingly, most of the symptoms occur after puberty in accordance with the clinical literature on schizophrenia.

Cross-References

► Schizophrenia: Animal Models
► Simulation Model

Eating and Appetite

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Synonyms

Energy Intake

Definition

Feeding reflects the behavioral response necessary for replenishing energy substrates critical for the survival, whereas appetite refers to the motivational component of this behavior.

Impact of Psychoactive Drugs

Feeding can be defined as the behavioral response necessary for replenishing energy substrates to maintain energy balance and, ultimately, the survival of all humans. Predictably, a shortage of food sources is associated with increased motivational states that promote food seeking, as well as metabolic changes that allow for energy stores to be amassed in the form of adipose tissue. In general, increases in these motivational states are commonly referred to as appetite (Berthoud and Morrison 2008). Feeding can also be elicited by the mere presence of food and, in the absence of negative energy state, possibly as an adaptive behavioral response directed at storing excess energy in anticipation of future shortages. Clearly, the mechanisms regulating feeding behavior are complex and involve both regulatory and nonregulatory processes.

Peripheral signals regulating energy balance. Both food intake and appetite are influenced by multiple neural

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and peripheral signals. These include energy substrates such as glucose, free fatty acids, and amino acids; hormones such as ▶ leptin, ▶ cholecystokinin (▶ CCK), insulin, and ghrelin; and neurotransmitters, including ▶ dopamine (DA), ▶ serotonin (5HT), ▶ norepinephrine (NE), and ▶ endocannabinoids. Moreover, drugs that affect these systems are currently used as a mean to curb obesity and treat Type II diabetes or to increase feeding in pathological conditions that lead to anorexia and cachexia (e.g., cancer and chronic renal disease). Finally, drugs used to treat other conditions have side effects that include abnormal feeding behaviors (▶ anorexia or overeating) (Berthoud and Morrison 2008).

Pharmacological agents affecting feeding and appetite. The complexity of neural mechanisms underlying feeding behavior is reflected by the number of pharmacological agents that are known to affect this behavior. Commonly, these actions are identified as side effects of treatments to other pathological conditions and, subsequently, are used to control feeding behaviors. In some cases, these medications are used to stimulate feeding in circumstances where patients are anorexic, but the great majority of drugs aimed at modulating feeding behavior are aimed at reducing caloric intake. It is difficult, however, to identify a single neurotransmitter system as critical for food intake, as many have been implicated in the regulation of feeding (Bray and Greenway 2007).

Most ▶ appetite suppressants are drugs that modify the release of monoamine and catecholamine neurotransmitters in the brain. The most successful of these is ▶ sibutramine, a drug approved by the United States Drug and Food Administration (FDA) for the treatment of obesity and one that primarily inhibits the reuptake of 5-HT and NE and, to a lesser extent, dopamine. Sympathomimetics had also been approved by the FDA and include ▶ amphetamine, ▶ phentermine, benzphetamine and phendimetrazine, although these are only prescribed for short-term use given their potential addictive properties. Finally, some ▶ antidepressant medications have anorectic effects, including drugs such as ▶ fluoxetine, which is a selective serotonin reuptake inhibitor (SSRI), and ▶ bupropion, a dopamine and norepinephrine reuptake inhibitor (Bray and Greenway 2007).

There are a number of appetite suppressants that act through physiological mechanisms other than direct action onto aminergic neurotransmitters. ▶ Rimonabant, a compound that blocks the CB1 ▶ cannabinoid receptor has been recently rejected as an anti-obesity medication and has some appetite suppressant properties. Leptin, a hormone produced by white fat cells, also lowers food intake and body weight and continues to be considered as a potential drug to treat obesity and metabolic syndrome (Bray and Greenway 2007). All of these drugs have been reported to be effective in reducing appetite, but their effects are short-lived possibly because of the development of ▶ tolerance (Fernstrom and Choi 2008).

It is well known that typical (▶ haloperidol) and some ▶ atypical antipsychotic drugs (▶ clozapine, ▶ olanzapine, and ▶ risperidone) increase appetite and body weight significantly. Conversely, some atypical antipsychotic drugs like ▶ ziprasidone decrease appetite. Similarly, ▶ tricyclic antidepressants, ▶ monoamine oxidase inhibitors, and some atypical antidepressants also cause weight increases that range from moderate to high (more than 10%) over the treatment period. These medications include ▶ Imipramine, phenazine, ▶ mirtazapine, and ▶ trazodone. Selective serotonin reuptake inhibitors are commonly associated with weight decreases early in treatment, but with body weight increases after prolonged use. Treatment with the atypical antidepressant ▶ bupropion results in decreased body weight (Jensen 2008).

Central Regulation of Feeding and Appetite. Feeding and appetite are both regulated by multiple brain regions (Berthoud and Morrison 2008; Bray and Greenway 2007). The ▶ hypothalamus plays a predominant role in eliciting feeding responses as a means of achieving a homeostatic state. Early studies using hypothalamic lesions emphasized the role of the mediobasal hypothalamus in mediating satiety responses, and that of the lateral hypothalamus in mediating appetitive responses. More recently, however, it has become clear that the hypothalamus contains a massive peptidergic network that regulates food intake and energy expenditure in response to hormonal and nutritional signals. One current idea is that the hypothalamic arcuate nucleus (ARC), a bilateral hypothalamic structure that surrounds the ventral portion of the third ventricle, plays a fundamental role in regulating feeding and energy homeostasis (Cone 2005). Indeed, the ARC contain cells that are sensitive to all peripheral signals that convey information about energetic state, and produce a number of peptides that influence food intake and appetite. A subset of neurons in the ARC produce the ▶ α-melanocyte stimulating hormone (α-MSH), a cleaved product of the proopiomelanocortin (POMC) precursor that decreases food intake and increases energy expenditure. A second subset of ARC neurons release two peptides that have a strong orexigenic effect: ▶ Neuropeptide Y (▶ NPY) and the ▶ agouti related peptide (▶ AGRP). Both α-MSH and AGRP compete for the same receptors (the melanocortin receptors 3 and 4, or MCR3, and MCR4) at target regions, with AGRP being

a natural antagonist and ► α-MSH being an agonist to these receptors (Cone 2005). Given these properties, the cells in the ARC and the MCR3 and MCR4 receptors at their target brain sites are referred to as the melanocortin system of energy regulation. In addition to NPY and melanocortin, peptides secreted by other hypothalamic nuclei also play an important role in modulating feeding and appetite. For example, cells in the lateral hypothalamus produce ► orexins/hypocretin or melanin concentrating hormone (MCH), both of which stimulate food intake and appetitive responses. In contrast, cells in the paraventricular nucleus (PVN) of the hypothalamus release corticotrophic and thyrotropin releasing hormone (► CRH and TRH respectively), which have an anorectic effect and stimulate metabolic rate (Berthoud and Morrison 2008).

Although the hypothalamus is important for the regulation of energy balance, integration of circulating metabolic signals occurs in several brain stem nuclei (Grill 2006). These nuclei are intimately associated with autonomic responses that follow the activation of the stress axis by psychogenic, metabolic or immunological challenges. Within the brain stem, the three divisions of the dorsal vagal complex (DVC) play a key role in integrating metabolic signals, interoceptive afferent signals relaying information from the digestive system via the vagus nerve, and information transmitted from cranial nerves that carry taste, texture, and sensory-motor signals from the mouth. Within the DVC, the nucleus of the solitary tract (NTS) is the main target for information ascending from the gut via the vagus nerve and the enteric nervous system. The NTS contains noradrenergic neurons that target and modulate the activity of hypothalamic and limbic structures implicated in feeding, including the PVN and central nucleus of the ► amygdala (CeA). The area postrema (AP), a second division of the DVC, lies outside of the blood brain barrier and is thus especially sensitive to blood borne nutritional signals, including those that are relayed by hormones like leptin, insulin, ► cholecystokinin (CCK), and ghrelin, as well as being sensitive to changes in circulating plasma levels of glucose. The AP transduces these signals and conveys them primarily to the NTS where they are integrated with ascending visceral signals, but also directly onto the PVN, where they may elicit feeding and autonomic responses. In addition to the regulation of feeding responses, the brain stem plays a key role in the generation of the autonomic responses, being involved in blood pressure regulation, respiration, glucose release from the liver, vasoconstriction, lipolysis, and thermogenesis (Grill 2006).

Recent evidence has highlighted the role of the midbrain in the regulation of feeding and appetite (Volkow and Wise 2005). The midbrain contains a number of cell groups implicated in brain functions underlying reward seeking, learning and memory processes, affective states and the generation of locomotor responses (Wise 2004). Their role in the modulation of feeding responses is considered within the context of these processes. Moreover cells in these midbrain nuclei release neurotransmitters commonly implicated in the regulation of feeding and appetite. For example, Dopamine (DA) cells of the ventral tegmentum (VTA) and substantia nigra have been implicated in the modulation of food intake through their projection to the striatum, prefrontal cortex, hippocampus, and amygdala. Destruction of these pathways results in hypophagia similar to that reported in animals with lateral hypothalamic (LH) lesions, and DA deficient mice die of starvation unless they are given exogenous L-DOPA (Palmiter 2007). In addition to DA-related processes, serotonergic components of the raphe nuclei have been implicated in the regulation of food intake. Indeed, there are 5-HT projections to hypothalamic and limbic centers involved in the regulation of food intake and several lines of evidence demonstrate that 5-HT has an inhibitory effect on food intake, including clinical and experimental data on the anorectic effects of SSRIs. The effects of 5-HT on food intake and metabolic function are mediated, at least in part, through the stimulation of POMC cells in the hypothalamic ARC, as well as through direct effects of 5-HT onto cells of the PVN (Zhou et al. 2005).

Circuits in the midbrain and brain stem are often viewed as either secondary or connected in series with the hypothalamus. In effect, their role in food intake regulation is that of an accessory to the function of the hypothalamus. The fact that these centers are sensitive to the same peripheral signals affecting the hypothalamus, however, suggests that feeding regulation occurs via the parallel activation of these circuits. In addition, activation of brain stem or midbrain pathways may override regulatory signals from hypothalamic homeostatic centers to modulate appetite.

The relative contribution of these brain pathways in mediating the effects of most drugs regulating feeding and appetite has not been fully elucidated, and continues to be a primary focus of investigation. Moreover, alterations in the activity of these circuits are thought to underlie ► eating disorders such as ► anorexia nervosa, bulimia, binge eating disorder, and obesity. Undoubtedly, better knowledge of these brain circuits and the way in which drugs affect them will improve their effectiveness, and minimize side effects ultimately producing better appetite suppressants and orexigenic drugs.

Cross-References

- ▶ Anorexia Nervosa
- ▶ Antidepressants
- ▶ Antipsychotics
- ▶ Appetite Stimulants
- ▶ Appetite Suppressants
- ▶ Eating Disorders
- ▶ Endocannabinoids
- ▶ Hipocretins/Orexins
- ▶ Leptin
- ▶ Melanin Concentrating Hormone
- ▶ α-Melanocyte Stimulating Hormone

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Eating Disorder: Anorexia Nervosa

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Synonyms

Anorexia; Eating disorder

Definition

Anorexia nervosa is a mental disorder characterized by extremely low body weight (▶ BMI 17.5 kg/m^2 or less in ▶ ICD-10 and 85% of expected weight for height and age in ▶ DSM IV), body image distortion, and an obsessive fear of gaining weight and becoming fat. Individuals with anorexia control their body weight by voluntary starvation, excessive exercise or other weight control behaviors such as self-induced vomiting, or the misuse of ▶ laxatives, ▶ diuretics, or ▶ enemas. Women with this disorder develop ▶ amenorrhea.

Role of Pharmacotherapy

Diagnostic Categories

Anorexia nervosa primarily affects adolescent females and young women, and only about 5–10% of people with the diagnosis are male. Two subtypes have been specified:

- *Restricting Type*: the person does not regularly engage in binge-eating or purging behavior (i.e., self-induced vomiting, excessive exercise, or the misuse of laxatives, diuretics, or enemas)
- *Binge-Eating Type or Purging Type*: the person regularly engages in binge-eating or purging behavior (i.e., self-induced vomiting, excessive exercise or the misuse of laxatives, diuretics, or enemas).

Anorexia nervosa is a serious and potentially life-threatening disorder with the highest standardized mortality rate among all psychiatric disorders, due to the chronic course, the associated medical complications, and the mental comorbidity. The cumulative lifetime prevalence is estimated to be 0.6% in the general population (Hudson et al. 2007) with an onset peak around 15–19 years. Anorexia nervosa is frequently associated with other psychological symptoms including ▶ depression, ▶ anxiety, and ▶ obsessive–compulsive features. Therapy typically includes nutritional rehabilitation and psychotherapeutic interventions, inpatient treatment is frequently required.

Drug Treatment

There is no officially approved medication for the treatment of anorexia nervosa. A variety of agents have been examined with mostly discouraging results with regard to facilitating weight gain or reducing associated cognitive and emotional symptoms such as body image distortion or fear of weight gain. In addition, only very few randomized controlled studies exist, usually with inadequate sample sizes and high drop out rates. Poor medication compliance seems to be a particular prominent problem in the treatment of anorexia nervosa most likely due to the patients' ambivalence about treatment in general

(Crow et al. 2009). Medication should not be used as the sole or primary treatment for anorexia nervosa (APA 2006; NICE 2004). ► Antidepressants and other psychiatric medications may be used to treat associated symptoms of depressive, anxiety, obsessive-compulsive, and other co-morbid disorders; however, these symptoms may resolve with weight gain alone. When medication is used to treat people with anorexia nervosa, the side effects of drug treatment (in particular, cardiac side effects) should be carefully considered. Bupropion is contraindicated in patients with eating disorders because of the increased seizure risk in these patients. Adverse reactions to ► tricyclic antidepressants and ► monoamine oxidase inhibitors (MAOIs) might be more pronounced in underweight individuals (Roerig et al. 2009).

Recently, ► second-generation antipsychotics, particularly ► olanzapine, have been used in small controlled trials. There is some evidence that olanzapine in a dose of 2.5–15 mg daily might increase the rate of weight gain and might reduce obsessive symptoms in patients with anorexia nervosa. If olanzapine is used, it is recommended that the patients be carefully monitored for ► extrapyramidal symptoms as well as for insulin resistance, abnormal lipid metabolism, and prolongation of the QTc interval.

Conclusion

There is a very limited evidence base for the pharmacological treatment of anorexia nervosa and there is no convincing evidence to date of efficacy for any drug treatment for anorexia nervosa in either the acute or chronic phase of the disorder.

Cross-References

► Antipsychotic Drugs
► Eating and Appetite
► SSRIs and Related Compounds

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Eating Disorders: Animal Models

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E

Synonyms

Anorexia nervosa; Binge-eating disorder; Bulimia nervosa

Definition

► Animal models have been developed for the study of each of the three most common eating disorders listed in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (► DSM-IV): anorexia nervosa, bulimia nervosa, and binge-eating disorder. These models attempt to mimic the altered patterns of food intake that comprise the core behavioral features of the human disorders. Some models also seek to mimic motivational, endocrine or morphometric aspects of eating disorders.

Current Concepts and State of Knowledge

Applicability of Current Models to Human Eating Disorders

In addition to replicating the core symptoms defined in the DSM-IV (see Table 1), animal models of eating disorders should address three key elements: gender bias, ► comorbidity with other psychiatric disorders, and adolescent onset. ► Anorexia and bulimia affect three times as many women as men (Hudson et al. 2007). The gender bias of binge-eating disorder is only slightly less pronounced, with 1.75 times as many women as men affected during their lives. Given this differential risk, animal models should incorporate the study of females whenever possible. Animal models should also address the high ► comorbidity with anxiety disorders, mood disorders, impulse control disorders, and ► substance abuse. For example, anxiety- or depression-related variables might be conceived as experimental end points or as means to initiate disordered eating behavior. Finally, because the median age of onset for all three disorders ranges from the late teens to early twenties in humans, models should prioritize the use of juvenile and young adult animals.

An ideal animal model would possess face, construct, and predictive validity, but eating disorders present significant challenges to the development of such a model. Because the causes of anorexia, bulimia, and binge-eating disorder in humans remain unclear, assessing the

Eating Disorders: Animal Models. Table 1. Summary of eating disorder diagnostic criteria.

Anorexia nervosa	Refusal to maintain body weight above 85% of the expected value for age and height
	Intense fear of weight gain
	Disturbed perception of body shape or denial of seriously low body weight
	Amenorrhea (in females) for three consecutive months
Bulimia nervosa	Recurrent episodes of binge eating
	Recurrent compensatory behaviors to prevent weight gain (e.g., vomiting, laxative use)
	Binging and compensatory behaviors occur at least twice weekly for 3 months
	Self-evaluation excessively influenced by body shape
	Does not meet criteria for anorexia nervosa
Binge-eating disorder[a]	Recurrent episodes of binge eating
	Feelings of distress about binge eating
	Binges occur at least twice weekly for 6 months
	Does not meet criteria for anorexia or bulimia nervosa

[a]Binge-eating disorder is currently listed in the Appendix of the DSM-IV as a potential eating disorder for full inclusion in the next edition

► construct validity is difficult. The dearth of pharmacological agents effective for the treatment of eating disorders also hinders assessment of ► predictive validity. No FDA-approved treatment currently exists for the treatment of anorexia or binge-eating disorder, and ► fluoxetine is the only medication currently approved by the FDA for the treatment of bulimia. Due to these issues, animal models have sought to achieve ► face validity. Animal models are further limited, however, by their inability to mimic certain psychological or social components of eating disorders. Despite these limitations, animal models can serve as powerful hypothesis generators for further study in humans of the biological underpinnings or consequences of eating disorders. Current models have focused overwhelmingly on rodents and can be broadly divided into anorexia-like and binge-like paradigms.

Models of Anorexia Nervosa

An effective model of anorexia nervosa should mimic the core symptoms of a voluntarily low body weight (less than 85% of normal), reduced food intake, and ► amenorrhea in females. Hyperactivity with high levels of energy expenditure (e.g., compulsive exercise), though not part of the core diagnostic criteria, is also extremely common. Efforts to recreate these symptoms have included both genetic and environmental models. As mentioned previously, animal models are not suited to address the intense fear of weight gain and distorted body image seen in anorexics.

The *anx/anx* Mouse

The most commonly studied genetic model is the *anx/anx* mouse. Additional, less widely studied genetic models of anorexia include the contactin-deficient mouse and the dopamine-deficient mouse; others too have studied the hypophagic phenotypes of knockout mice, including the MCH, Crh2, and M3 receptor null mutants, as modeling aspects of the anorexia nervosa syndrome. The *anx* mutation, which arose spontaneously at Jackson Laboratories, is an autosomal recessive trait that results in a dangerously low food intake. *Anx/anx* mice are emaciated and exhibit motor symptoms including body tremors, hyperactivity, headweaving, and uncoordinated gait. The *anx* mutation is lethal within 3–4 weeks of birth depending on the genetic background. The gene product of *anx* is unknown, but the mutation has been localized to a 0.2-cM interval corresponding to 1.28 Mbp on mouse chromosome 2 (Johansen et al. 2003). The model is valuable due to its ability to reduce food intake without forced starvation or use of a pharmacological agent as an appetite suppressant. It has been simultaneously criticized, however, because appetite itself, if not hunger, appears intact in human anorexics. Moreover, based on gene expression profiling, the *anx/anx* mouse has been recently suggested to model ► cachexia, rather than anorexia nervosa or starvation.

The *anx/anx* mouse shows several neurobiological abnormalities that may underlie its phenotype. Two cell populations in the arcuate nucleus of the hypothalamus exert opposing influences on food intake in normal individuals. One population produces the ► orexigenic signals ► neuropeptide Y (NPY) and agouti gene-related protein (AgRP). A second population that produces proopiomelanocortin (POMC) and cocaine- and amphetamine-related transcript (CART) yields ► anorexigenic signals. In *anx/anx* mice, NPY and AgRP accumulate in the cell body but are reduced in axon terminals. Decreased NPY receptor mRNA levels have also been seen, as well as possible compensatory responses to starvation, including reduced POMC and CART levels and low serum ► leptin levels. Serotonergic hyperinnervation of several forebrain structures, including the arcuate nucleus, has also been observed. This hyperinnervation may be behaviorally relevant given the anorectic influence of ► serotonin. Outside the ► hypothalamus, the *anx/anx* mouse also exhibits

reduced striatal dopamine levels and reduced sensitivity to dopamine's action to reduce Na^+,K^+−ATPase activity.

Activity-Based Anorexia

The most widespread nongenetic model of anorexia nervosa is activity-based anorexia, also known as starvation-induced hyperactivity. Rodents receiving time-limited daily access to food will increase intake during that time to maintain a stable body weight. In the activity-based anorexia model, this compensatory feeding behavior is disrupted by providing access to a running wheel. Details of food and wheel availability vary between investigative groups, but wheel access typically exceeds food access in duration. Under these conditions, animals dramatically reduce food intake while increasing wheel running, such that energy expenditure surpasses energy intake. Body weights decline, and animals will eventually die without experimenter intervention. This paradigm thus jointly models the hyperactivity and voluntary decrease in food intake seen in human anorexics. Female rats also escalate their running more rapidly than males and stop estrous cycling. Unlike human anorexia, however, body weights recover under activity-based anorexia conditions if food access is increased or if palatable, high-fat food is provided.

As in the *anx/anx* mouse, several neurochemical abnormalities have been observed in the hypothalamus following activity-based anorexia. Rodents subjected to activity-based anorexia show increased NPY and AgRP mRNA in the arcuate nucleus after 3 days of hyperactivity combined with lower levels of POMC and CART mRNA. Leptin levels drop rapidly during activity-based anorexia, and leptin administration can rescue low body weights. Hypothalamic levels of β-endorphin are elevated when animals on this paradigm lose 25% of their normal body weight, and serotonin levels are elevated in the medial basal hypothalamus (Hillebrand et al. 2008). In this respect, activity-based anorexia may parallel the human condition, as reduced CSF levels of the serotonin metabolite 5HTIAA are observed in anorexic patients. Perhaps lending some predictive validity, the atypical antipsychotic olanzapine appears to attenuate hyperactivity in both activity-based anorexia and human subjects. Further work is necessary to characterize fully any causal relationship between the neurochemical changes and the hyperactivity and starvation seen in the model.

Models of Bulimia Nervosa and Binge-Eating Disorder

Both bulimia nervosa and binge-eating disorder are characterized by recurrent episodes of ► binge eating – consuming more within a given time than a normal individual would eat under the same circumstances – and animal models have sought to replicate this core symptom. Several factors believed to contribute to or precipitate binges in humans have been used to elicit binge eating in rodents, including food restriction followed by free feeding, intermittent access to highly palatable food, and stress. As in anorexia nervosa, animal models cannot mimic several psychological features of the disorder, including preoccupation with body image.

Sham Feeding

Bulimia can be differentiated from binge-eating disorder by the presence of compensatory behaviors including purging, laxative abuse, fasting, or compulsive exercise. Rodents lack a vomiting reflex, but sham-feeding models have been used to mimic purging in rodents. In sham feeding, a gastric fistula is used to drain the recently ingested meal from the stomach before it reaches the intestine. The animal thus experiences gustatory feedback while consuming the meal, but receives minimal postingestive ► satiety signals from the digestive tract. Sham-fed animals increase their meal size and consume meals more rapidly, analogous to human bulimics. A limitation of the sham-feeding model is that compensatory behaviors in humans are voluntary and thought to occur despite homeostatic regulation, whereas sham feeding is experimentally induced and results from homeostatic processes.

Restriction and Refeeding Cycles

Binge-like behavior can be elicited in rodents by restricting food access for an extended period and then returning the animals to *ad libitum* food access for a refeeding period. This cycle of restriction and refeeding may be repeated numerous times. Animals typically increase their intake during the refeeding period relative to animals without a history of restriction, a phenomenon known as rebound ► hyperphagia. A normal individual would be expected to increase consumption after forced restriction; thus, this hyperphagia is not a perfect analog of human binges, which frequently occur even in the absence of ► hunger. Additional factors such as palatable foods and stress can be added, however, to increase the validity of the model. Rats allowed to refeed on palatable food, such as a high-fat cookie diet or sucrose, have greater hyperphagia than those allowed to refeed on chow. Such palatable foods share greater similarity to the high-fat, high-sugar foods typically consumed during human binges. Rats with a history of restriction and refeeding on palatable food also show depressive-like and anxiety-like symptoms, suggesting that such models might be useful for studying the high comorbidity of binge eating with mood and anxiety disorders. Alterations in monoamine function in these animals have also been observed. Changes include

reduced extracellular dopamine accompanied by increased acetylcholine in the ▶ nucleus accumbens shell when fasting (Avena et al. 2008), reduced hypothalamic dopamine, and reduced serotonin and dopamine in the medial prefrontal cortex (Chandler-Laney et al. 2007).

Palatable Food

Palatable foods high in sugar or fat can promote binge-like intake with little or no food restriction. It has been proposed that limiting access to these "forbidden foods" contributes to their overconsumption during episodes of human binge eating or when dieters "cheat" on a diet. Several animal models alternate between access to a standard chow diet and access to a preferred diet to mimic this cyclical pattern of restraint and relapse. As access to a palatable food is decreased in rodents, the rate at which it is consumed when it becomes available again increases. Corwin and Wojnicki (2006) have developed a model using a pure fat (vegetable shortening), provided for only 1–2 h three times per week while chow remains available ad lib at all times. After approximately four weeks on this schedule, intake of the pure fat increases dramatically, eventually comprising approximately 70% of normal total daily intake in ad lib chow-fed rats. Fat intake under these limited access conditions is unaffected by administration of galanin or enterostatin, two peptides involved in regulating fat consumption, but can be reduced with the GABA-B agonist baclofen. Baclofen does not alter the intake of chow, suggesting that the binge-like intake of the fat is driven by some property of the high-fat diet, perhaps its palatability.

Further restricting palatable food access can produce binge-like behavior more rapidly. Cottone et al. (2008) have developed a model of binge eating where a daily 2-h period of food deprivation is followed by access to a high-sucrose diet for only 10 min. Chow is available ad lib at all other times. On this schedule, rats rapidly increase their intake of the high-sucrose diet beginning on the second day of exposure, eventually consuming 40–50% of total daily intake during the 10-min limited-access session. Binge magnitude is reduced by administration of the mu- and kappa-opioid antagonist nalmefene (▶ endogenous opioids).

Anxiety appears to be increased on both the 2-h and 10-min binge schedules. Heightened anxiety may reflect a dysphoric state (▶ affective state) induced by withdrawal from the preferred diet. Rats alternating between 5 days of access to standard chow and 2 days of access to a palatable high-sucrose diet show an increase in anxiety-like behavior only when tested on days when the palatable food is unavailable.

▶ Benzodiazepines, known for their potent anxiolytic effects, increase palatable food consumption in nondeprived animals and humans. These orexigenic effects are dissociable from effects on anxiety, as not all benzodiazepine ▶ partial agonists that are anxiolytic also stimulate food intake. Benzodiazepines may instead act to enhance hedonic responses to palatable foods. They enhance preferences for sweet or salty tastes and increase motivation to obtain a food reinforcer in rats trained on a ▶ progressive ratio schedule. In contrast, benzodiazepine ▶ inverse agonists attenuate taste preferences and reduce palatable food intake by reducing the length of feeding bouts (Cooper 2005).

Stress

Acute ▶ stress typically reduces food intake in rodents, but Boggiano et al. (2005) have developed a model that combines restriction–refeeding cycles with palatable food and stress to cause binge-like behavior. In this model, rats are placed on food restriction (67% of normal intake) and are allowed to refeed on chow or palatable food ad lib, then are exposed to a foot shock stressor. Rats placed on this restriction/stress schedule increase their intake of palatable food after the foot shock relative to rats exposed to either restriction or stress alone, indicating that a synergistic effect of restriction and stress drives the binge. Binges can be attenuated with ▶ naloxone (▶ opioid antagonist) treatment, suggesting that the drive to consume the palatable food is related to reward seeking. If chow alone is available during the refeeding phase, binge-like behavior is absent. Other stressors can also precipitate a binge. Rebound chow hyperphagia is enhanced if rats with a history of 2-h time-limited daily food access are allowed to refeed in cages that severely restrict movement (Inoue et al. 1998). This cycle of restriction, stress, and binging on a rewarding stimulus bears a remarkable similarity to drug addiction, and it has been suggested that binge eating should be examined from the same perspective as substance abuse disorders. As with addiction, humans with bulimia or binge-eating disorder report a loss of control during a binge despite feelings of shame or guilt. Uncovering further similarities in the mechanisms of substance use and binge eating may help refine existing models of both categories.

Cross-References

▶ Abstinence
▶ Addictive Disorder: Animal Models
▶ Animal Models for Psychiatric States
▶ Appetite Stimulants
▶ Appetite Suppressants
▶ Craving
▶ Eating and Appetite
▶ Eating Disorder: Anorexia Nervosa
▶ Energy Balance

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EBM

► Evidence-Based Medicine

Eccie

► Methylenedioxymethamphetamine (MDMA)

Echolalia

Definition

The involuntary repetition, usually immediate, of words, phrases, or other vocalizations made by another person; usually seen in psychotic and pervasive developmental disorders (e.g., autism).

Echo-Planar Imaging

Synonyms

Gradient-echo EPI; Spin-echo EPI

Definition

Echo-planar imaging (EPI) is a magnetic resonance imaging (MRI) technique that permits the rapid collection of entire two-dimensional MR images (slices) in only a fraction of a second (40–100 ms). It has been fundamental to the development of BOLD fMRI.

Cross-References

► Magnetic Resonance Imaging (Functional)

Echopraxia

Definition

The involuntary imitation or mirroring, usually immediate, of the movements made by another person; usually seen in Tourette syndrome and in psychotic and pervasive developmental disorders (e.g., autism).

Ecogenetics

Synonyms

Ecological genetics

Definition

Ecogenetics is a branch of genetics that studies how the genetic makeup affects the way organisms respond to all kind of environmental substances. This field deals with the genetic basis of environmental toxicity to develop methods for the detection, prevention, and control of environmentally related disease. According to the environmental agents involved, one may distinguish infection ecogenetics, nutritional ecogenetics, physical ecogenetics, and chemical ecogenetics.

Cross-References

► Pharmacogenetics
► Pharmacogenomics

Ecological Genetics

► Ecogenetics

Ecstasy

► Methylenedioxymethamphetamine (MDMA)

ECT

► Electroconvulsive Therapy

ED

► Extradimensional

ED_{50}

Definition

The ED_{50} is a commonly used abbreviation that denotes the Effective Dose of a drug needed to produce a particular response in 50% of a population of test samples. It is a quantitative measure of the potency of a drug; the smaller the ED_{50} value, the more potent is the substance in the test system used. The original use of the term related to drug effects of an all-or-none (quantal) nature and it was assumed that the full range of effect frequencies from 0% to 100% actually occurred. Subsequently the term was adapted to a wider range of test situations including those where quantitative (graded) data were obtained for drug effects did not necessarily reach the extremes of a percentage scale. For example, in drug discrimination experiments using graded scales, the ED_{50} value is often defined as the dose of the drug that produces a mean of 50% drug-appropriate responding, as estimated from dose-response data by an appropriate statistical method. The ED_{50} is a valuable index for comparing potency in a series of related substances.

Cross-References

► Drug Discrimination

Edronax

► Reboxetine

EEG

► Electroencephalography
► Electroencephalogy

Effect Inversion

Synonyms

Opposite effect

Definition

Inversion in the nature of the effect(s) exerted by a biologically active substance. This phenomenon may be triggered, on the one hand, by the intake (or administration) of a dose much higher than the one capable of exerting the required effect. On the other hand, effect inversion may emerge as a consequence of the prolonged consumption (or administration) of low to moderate doses of an active substance. In the latter case, effect inversion is distinct from tolerance and leads to the manifestation of effects that are opposite to those exerted by the substance upon its single intake (or acute administration).

Cross-References

► Caffeine

Effect Size

Synonyms

Standardized mean difference

Definition

Effect size (ES) is a term given to a family of indices that measure the magnitude of a treatment effect. Unlike significance tests, effect size is independent of sample size. Effect sizes are used when treatment effects are defined over a continuous measure. For a given treatment, effect size is usually defined as the mean improvement over the course of a trial divided by the standard deviation for the treatment group. Based on convention, a small effect size is considered less than 0.3, medium effect size 0.3–0.7, and a large effect size greater than 0.7.

Effectiveness

Synonyms

Pragmatic outcome; Usefulness

Definition

The beneficial effect of a medicinal product seen in everyday clinical practice, in relatively unselected patients who may have psychiatric or medical comorbidities, who may be taking concomitant medication, whose compliance

with medication is unsupervised and where the outcome is useful to the patient in terms of quality of life.

Effectiveness of Antipsychotic Drugs in First-Episode Schizophrenia and Schizophreniform Disorder

► EUFEST

Effectiveness Studies

Definition

Efficacy trials in psychopharmacology examine the performance of an agent under "ideal" conditions. They are routinely short-term (e.g., 4–8 weeks), with strict inclusion/exclusion criteria and placebo and/or comparator drug control groups. Such trials are integral to regulatory approval in drug development. In contrast, effectiveness trials evaluate the performance of an agent in the "real world" of actual clinical practice, unencumbered by the same restrictive criteria and required control groups.

Efficacy does not ensure effectiveness, as has been demonstrated recently with development of the atypical antipsychotics. Numerous efficacy trials with individual agents demonstrated their superiority when compared to placebo, as well as a typical or conventional antipsychotic. However, subsequent effectiveness studies tempered these findings; in the more naturalistic surroundings of actual clinical practice, the atypical antipsychotics failed to distinguish themselves from conventional agents in the manner reported in efficacy trials.

These findings highlight the need for both efficacy and effectiveness studies in drug evaluation. Proven efficacy is necessary, but not sufficient, to guarantee effectiveness in actual clinical practice.

Cross-References

► Second- and Third-Generation Antipsychotics

Efficacy

Synonyms

Clinical outcome; Therapeutic benefit

Definition

In pharmacological investigations, efficacy is the property of an agonist drug at its receptor that reflects its ability to produce a response. Drugs that act at the same receptor can vary in their efficacies. Efficacy also depends on whether a drug acts as a full, partial, or inverse agonist. Pure antagonist drugs occupy receptors but have no efficacy.

In clinical situations, efficacy refers to the beneficial effect of a medicinal product under ideal conditions – usually phase 2 or 3 clinical trials conducted at least partially in a hospital setting and involving a selected subsample of the population for which the medicine will eventually be indicated, and where outcome is typically measured by symptom ratings.

Effort Cost

Definition

The subjective appraisal of the physical exertion required to procure a reward.

Egocentric

Definition

In terms of spatial cognition, an egocentric frame of reference is centered on the ego or navigator. Thus, object location can be described in terms of angle subtended from the head direction and distance from the navigator.

Ejecting Current

Definition

A current (either positive or negative) that causes the exit of charged transmitters, drugs, or other compounds of interest from the iontophoretic pipette into the extracellular environment.

Ekbom's Syndrome

► Delusional Disorder

Elasticity

Synonyms

Adjustability; Flexibility; Malleability; Plasticity; Pliancy

Definition

The *elasticity* is the degree to which a change in price or income changes the demand for a commodity.

Cross-References

► Behavioral Economics

Eldepryl

► Selegiline

Electrochemical Techniques and Advances in Psychopharmacology

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Synonyms

Amperometry; Fast-scan cyclic voltammetry; High-speed chronoamperometry

Definition

Electrochemical Techniques: A group of analytical methods based on measuring the current produced by oxidation or reduction of electroactive molecules at an electrode or microelectrode surface. Loss or gain of electrons, respectively, occurs in response to varying the applied potential at the working electrode with respect to a reference electrode: commonly called voltammetry, amperometry, chronoamperometry, or fast-scan cyclic voltammetry due to the way the voltage is applied. The resulting current produced by the oxidation/reduction of analytes is proportional to analyte concentration at the electrode surface. Historically, electrochemical techniques have been utilized to study chemical reactions, but more recently, they have been used to measure the concentrations of neurotransmitters and other endogenous substances in biological systems. Considerable work has been carried out over the last three decades to develop and to modify electrodes and recording techniques to make these methods selective and sensitive for biogenic amine neurotransmitters. Newer versions of microelectrodes are modified with enzyme layers, such as oxidases, that allow for the formation of reporter molecules for neurotransmitters and neurochemicals that cannot be directly oxidized or reduced at microelectrode surfaces. This has increased the capabilities of electrochemical techniques so that neurotransmitters such as glutamate and acetylcholine can be measured. At this time, measurement of ► neuropeptides is not within the scope of this methodology.

Principles and Role in Psychopharmacology

Introduction: Electrochemical techniques are widely used in many varied research arenas, including the disciplines of chemistry, physics, and biology. Here, we focus on the application of electrochemical methods to the field of neuropsychopharmacology and recent advances in this field. In particular, we illustrate some of the breakthroughs made in our understanding of brain ► neurotransmitter transporters. These highly regulated transmembrane proteins are critical for clearance of released neurotransmitters from the extracellular milieu. Transporters are also primary targets for numerous psychotherapeutic and addictive drugs. Moreover, neurotransmitter transporters are implicated in the pathophysiology of psychiatric disease states including depression, anxiety disorders, schizophrenia, autism, and addiction, as well as Parkinson's and Alzheimer's diseases. The following sections focus on the basic principles of chronoamperometry and amperometry coupled with microelectrodes as they have been applied to advances in the field of psychopharmacology.

High-Speed Chronoamperometry to Measure Biogenic Amines Using Carbon Fiber Microelectrodes: Chronoamperometry is based on methods originally described by Cottrell in 1902. Modern electronics and digital data acquisition have led to the ability to measure current at rapid sampling intervals (1 Hz or faster) permitting high-resolution measurements of neurotransmitter transport. To investigate the uptake of ► biogenic amines, such as serotonin (5-HT), norepinephrine (NE), or dopamine (DA), a carbon fiber microelectrode (CFE), which is often coated with ► Nafion to repel interfering anions, and a reference electrode are positioned in a suitable buffer solution, cell suspension, synaptosomal preparation, tissue section, or directly into the brain (Daws and Toney 2007; Perez et al. 2007). The CFE is held at a constant resting potential (typically 0 V) versus a Ag/AgCl reference electrode. A 1–10 Hz square wave step potential (typically +0.55 V) is applied. This voltage step is selected to encompass the

range at which most biogenic amines are oxidized, i.e., lose electrons, histamine being a notable exception, as it requires a voltage of +1.0 V for oxidation. The applied voltage is held for 100 ms and this produces a change in oxidative current (typically in the range of pA to low nA) recorded at the CFE. Initially, the current decays quickly as a function of time, which reflects the capacitive or charging current at the surface of the electrode. The remaining Faradaic current produced by each step potential can be integrated and used to calibrate the CFE against known concentrations of neurotransmitter prior to use in an experimental setting. The voltage is then returned to the resting potential and held for 100–900 ms (depending on the neurotransmitter being measured). This gives rise to a reductive current. The ratio of the oxidative and reductive currents can be used to aid in identification of biogenic amines. Currents that result from repeated step potentials are measured as a function of time to determine the rate of change in neurotransmitter concentrations resulting from the action of neurotransmitter transporters. The limit of detection for most biogenic amines by chronoamperometry is in the nanomolar range and this technique has found its greatest successes in measuring the uptake of exogenously applied neurotransmitters. A limitation of this approach is that basal concentrations of neurotransmitter are not readily determined because microelectrodes have limited selectivity, and other oxidizable species in brain tissue that contribute to the measured current are not easily distinguished from basal neurotransmitter levels. One of the advantages of chronoamperometry is that the high frequency at which recordings are made (1–10 Hz) enhances signal-to-noise because small changes in current due to the detection of biogenic amines are not masked by large and potentially varying background current (see Daws and Toney 2007). Additional advantages include the spatial (micrometer) resolution at which recordings are made. There are many variations of this approach and these are described in detail in "Electrochemical Methods for Neuroscience (2007)."

Applications in Psychopharmacology: Chronoamperometry approaches used by us, and others, stem from the pioneering work of Ralph Adams in the late 1970s and 1980s. In brief, Nafion-coated CFEs, precalibrated to the neurotransmitter of interest, are exposed to brain tissue or implanted stereotaxically into the brains of anesthetized mice or rats. By coupling CFEs to glass, multibarrel micropipettes, drugs, or neurotransmitters can be exogenously applied directly to the brain with excellent spatial resolution (e.g., the typical active recording areas of CFEs range from 50 to 300 μm in length and from 5 to 30 μm in diameter, and micropipettes can be closely positioned within 300 μm). Bath application or direct pressure-ejection of exogenous neurotransmitter provides a straightforward but powerful means to determine the kinetic parameters associated with transporter function and to tease apart contributions from different transporters, enzymes, and diffusion to the clearance rates of individual neurotransmitters. Likewise, factors regulating transporter function, such as kinases and growth factors, can be studied *in vivo*. The following section provides some examples of how this approach has been used to advance psychopharmacology.

Transporter Kinetics: High-speed chronoamperometry and other electrochemical techniques have given us the unprecedented ability to investigate the kinetics of biogenic amine transport mechanisms on a second-by-second basis in vitro, ex vivo, and in vivo, the latter in both anesthetized and freely moving animals. One of the findings that have emerged is that uptake rates may be significantly higher and affinities substantially lower than previously thought based on radiochemical studies of neurotransmitter transporters (Perez et al. 2007). For example, 5-HT uptake rates measured by chronoamperometry in synaptosomes (Perez and Andrews 2005) or in vivo (Daws 2009) are up to 100 times higher than those determined radiochemically. Likewise, the affinity of the 5-HT transporter (SERT) for 5-HT is 1 μM by chronoamperometry compared with values in the low nanomolar range determined by uptake of [^{3}H]5-HT. The reasons for these discrepancies are complex; however, some of the contributing factors have been elucidated and involve loss of transported neurotransmitter during the filtration process used for synaptosomes, which is necessary for radiometric assay, but not for direct chronoamperometric measurements of uptake ex vivo or in vivo (Perez et al. 2006). Additionally, chronoamperometry is typically carried out in synaptosomes or cells incubated in oxygenated buffer or in intact respiring brain tissue. Finally, because changes in neurotransmitter concentration due to transporter activity are resolved on a second-by-second timeframe by chronoamperometry, compared with a single measurement obtained over minutes by radiochemical methods, the entire nonlinear kinetics associated with transport can be resolved using chronoamperometry, including initial uptake rates.

Biogenic Amine Promiscuity: Studies carried out in the 1960s and 1970s using in vitro uptake assays of tritiated neurotransmitters gave rise to the notion that transporters for the biogenic amines, for example the 5-HT, NE, and DA transporters (SERT, NET, and DAT, respectively), take up not only their native neurotransmitter, but are capable, albeit with lower affinity, of taking up other neurotransmitters (see Daws 2009 for review). However, this concept

of neurotransmitter transporter promiscuity has only recently become more widely accepted in our thinking about central neurotransmission. Studies using chronoamperometry have played a significant role in advancing this idea (see Daws 2009). A recent example comes from studies in mice lacking one intact copy of the SERT gene. These SERT-deficient mice are a useful model for humans carrying variants of the SERT gene that confer constitutively lower SERT expression and function. Interestingly, humans with lower expressing SERT alleles show somewhat greater susceptibility to ▶ depression and other stress-related disorders on average and may be less responsive to treatment with 5-HT selective reuptake inhibiting antidepressants (SSRIs), such as ▶ fluoxetine (Prozac), which act to inhibit SERT. One possible explanation for SSRI resistance is upregulation of other transporters capable of taking up 5-HT. These transporters thereby buffer the ability of SSRIs to increase extracellular 5-HT, presumably the first step necessary for triggering the cascade of events leading to therapeutic benefit. One such promiscuous transporter is the organic cation transporter type-3 (OCT3), for which SERT-deficient mice have higher expression levels (Baganz et al. 2008). Like 5-HT, histamine is also a substrate for OCT3; however, it is not a substrate for SERT. Using high-speed chronoamperometry, histamine clearance from the extracellular fluid in the hippocampus was found to be significantly faster in SERT-deficient mice than in wild-type mice, a relationship opposite to that for 5-HT clearance in these animals (Baganz et al. 2008). Blockers of OCT3 were found to inhibit 5-HT clearance more efficaciously in SERT-deficient mice than in wild-type mice, suggesting the possibility of using OCT3 antagonists as novel antidepressants or adjuvant therapy (Baganz et al. 2008). Preliminary studies assessing the antidepressant-like activity of the OCT3 blocker, decynium-22, suggest that this is an avenue for further research and potential drug development. This example of transporter promiscuity is one of many that have been revealed using electrochemical approaches (see Daws 2009) and it has wide-ranging implications for understanding treatment responses in numerous psychiatric disorders, as well as sensitivity to abused drugs.

Regulation of Biogenic Amine Transporters: Biogenic amine transporters were once thought to be relatively invariant regarding their expression and function; however, research over the past 15 years has shown that these transporters are highly regulated at a number of different levels (Blakely et al. 2005). Our understanding of the underlying signaling pathways and neuroadaptive scenarios that regulate transporters has grown substantially and much research in this area has been carried out using in vitro systems. Amperometry has been employed in transfected cell lines to reveal that biogenic amine transporters can operate in different modes e.g., similar to a gate in an alternating access turnstile, or under other circumstances, like an open channel (Blakely et al. 2005). Furthermore, chronoamperometry has demonstrated that signaling pathways regulating biogenic amine transporters, as identified in vitro, are also at work in vivo. These regulatory pathways include those coupled to 5-HT_{1B} autoreceptors, alpha_2-adrenoceptors, adenosine receptors, and dopamine D_2 autoreceptors (Daws and Toney 2007). In the future, in vivo electrochemical techniques can also be used to investigate the therapeutic potential of drugs targeted to sites downstream of receptors, such as second messengers and kinases.

Regulation of transporters by other signaling molecules, including brain-derived neurotrophic factor (BDNF), neurotrophic growth factor (NGF), corticosterone, and insulin, have also been studied in vivo using amperometric approaches. Results from these studies are providing vital clues into how stress, nutrition, and aging influence biogenic amine transporter function, as well as individual variations in response to therapeutics that target these transporters. In addition, future studies using in vivo electrochemical techniques aimed at answering questions such as determining how psychotherapeutics exert their effects on brain neurochemistry, why their therapeutic actions might be delayed (as is the case with current antidepressant medications), and what compensatory changes might occur in other transporter systems, have the potential to provide new information leading to the development of novel pharmacologic approaches for the treatment of psychiatric and neurodegenerative disorders.

Summary: This section has focused primarily on chronoamperometry to measure biogenic amine clearance. A brief description of the principles underlying this technique and examples of its applications to psychopharmacology are described. For more comprehensive information on fundamental principles and applications, the reader is referred to *Electrochemical Methods for Neuroscience* (2007). Notably, electrochemical techniques, such as amperometry, provide the only means currently available for the study of the time-resolved kinetics of neurotransmitter release and clearance in vivo, in both anesthetized and freely moving animals. The following section focuses on technological advances that enable the study of fast synaptic neurotransmission of nonelectroactive transmitters, such as glutamatergic signaling, using electrochemical techniques.

Real-Time (2 Hz) Measurements of Neurotransmission In Vivo Using Enzyme-Based Microelectrode Arrays: Numerous advances in electrochemical techniques have

now allowed the measurement of fast excitatory neurotransmission using enzyme-modified microelectrodes (Hascup et al. 2007). This was not previously possible using standard electrochemical techniques because neurotransmitters, such as glutamate, cannot be oxidized or reduced at electrode/microelectrode surfaces at usable working potentials (typically <1 V). ▶ Microelectrode array (▶ MEA) technology can now be used for direct in vivo determination of basal or resting levels of ▶ glutamate and other neurotransmitters, as well as evoked overflow due to stimulation or behaviorally induced events (Hascup et al. 2007). These MEAs are microfabricated using photolithographic techniques. The design employs Al_2O_3 substrates patterned with Pt or Ir electrode surfaces, which are coated with polyimide layers for insulation (Burmeister et al. 2000). The resulting 4–16 recording site arrays are modified with enzymes and organic molecules to make them sensitive and selective for the reproducible and rapid measurement of L-glutamate (▶ Glutamate MEAs), which is the major excitatory neurotransmitter in the CNS. Recently, MEAs have been manufactured by the thousands and routinely exhibit limits of detection for L-glutamate <0.2 μM, with response times of 2 Hz. Early designs employing Nafion coatings have now been replaced with ▶ meta-phenylenediamine (▶ m-PD) to greatly increase the selectivity of the measurements, which can detect changes in glutamate from 0.2 to 500 μM with Pearson's coefficients >0.99. Despite these advances, weaknesses in the designs still include: in vivo lifetimes limited to 30 days, enzyme coatings that require 2 days for curing, response times limited to 2 Hz, and the fact that MEAs have higher fabrication costs than CFEs.

Applications in Psychopharmacology: MEA technology has recently been applied to study changes in the CNS in normal aging (see Hascup et al. 2007) and in mice that lack the D_4 dopamine receptor (Thomas et al. 2008), which is a receptor possibly implicated in ▶ attention deficit hyperactivity disorder (ADHD). Reliable measures of basal glutamate have been determined in awake rats, mice, and monkeys in striatum and ▶ prefrontal cortex. Using self-referencing recording methods, extracellular glutamate can be reliably measured and generally ranges from 5 to 10 μM. In rats, extracellular levels of glutamate are diminished by >50% with transient application of tetrodotoxin, a sodium channel blocker, and >50% with local application of α-conotoxin, a calcium channel blocker, supporting the idea of neuronal origin of these extracellular glutamate signals. Local application of the glutamate transporter inhibitors, DL-*threo*-beta-benzyloxyaspartate (TBOA) or DL-*threo*-beta-hydroxyaspartate (THA), increases extracellular glutamate concentrations. Reproducible potassium-evoked release (1–2 s pressure ejection of 50–150 nL of 70 mM KCl) of glutamate ranging typically from 5 to 40 μM has been recorded in regions of the ▶ hippocampus, frontal cortex, striatum, and cerebellum of anesthetized rats, mice, and monkeys. These signals have average rise times of 1–3 s with total time courses of typically 5–12 s. Signals appear to be governed by Michaelis–Menten-like kinetics, with the rate of decay of the signals increasing as the maximum amplitude of the signals increases. Typical rates of clearance of glutamate range from 1 to 10 μM/s when measured by MEAs. Potassium-evoked release of glutamate can be repeated at 30 s intervals in most brain areas. In addition, MEAs have been modified with different enzymes and polymer coatings to measure a number of nonelectroactive neurotransmitters, metabolites, and drugs, including but not limited to choline, acetylcholine, glucose, aspartate, lactate, peroxide, GABA, dopamine, and ethanol in CNS tissues. Interestingly, the MEA technology is the first to allow in vivo measures of resting or basal levels of neurotransmitters by virtue of the ability to carry out self-referencing recordings with this microelectrode, in addition to stimulus-evoked release of neurotransmitters.

In summary, the electroanalytical techniques described here can be used to address a large number of pharmacological questions in anesthetized and freely moving experimental animals. In addition, the rapid recording capabilities of MEAs allow for the assessment of the kinetics of electroactive and nonelectroactive neurotransmitter release and clearance in vivo, analogous to the aforementioned studies of biogenic amines investigated using chronoamperometry in combination with CFEs.

Cross-References

▶ Biogenic Amines
▶ Carbon Fibre Amperometry
▶ Electrochemical Techniques
▶ Glutamate MEAs
▶ Meta-Phenylenediamine (m-PD)
▶ Microelectrode Arrays (MEAs)
▶ Nafion
▶ Neurotransmitter Transporters

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Electroconvulsive Therapy

Synonyms
ECT

Definition
A procedure in which electrical current is administered via scalp electrodes to induce a brief seizure. Originally introduced in the 1930s, ECT is now used primarily to treat severe ► depression, and less frequently for mania or catatonia that is refractory to medication. Treatments are given under light anesthesia, with a usual course of 6–12 treatments given two or three times a week. In addition to the risks of anesthesia, the major adverse effect is memory loss, which can be mitigated by electrode placement.

Electroencephalogram

Definition
Recording of the brain's global electrical activity, obtained using electroencephalography.

Cross-References
► Event-Related Potentials

Electroencephalography

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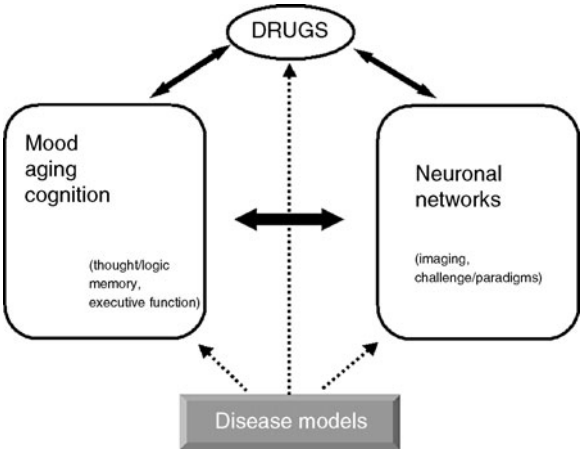
Synonyms
Cortical or brain waves; Digital EEG nomenclature; EEG; Network oscillations; Surface (or deep) field potentials

Definition
The Electroencephalogram (EEG) is a classical method to study dynamic properties of brain circuits; the EEG reflects a summation of extracellular potentials of synchronized populations of neurons with high temporal resolution (Niedermeyer and Lopes Da Silva 2005). Electroencephalography is used to passively record continuous electrical brain activity. Electrodes are either positioned on the surface of the scalp to record the activity emanating from the underlying cortex or inserted through the skull and positioned to record the activity from deeper brain structures both in animals and humans. After appropriately amplifying and filtering the signals, they are displayed as an EEG. The EEG shows the spontaneously generated aperiodic as well as slow and fast oscillatory brain activity recorded by the electrode(s). The fields of application of electroencephalography range from performance in activated states, quiet waking or ► wakefulness, normal and pathological ► sleep, as well as ► general anesthesia. EEG is widely used for the detection and diagnosis of epilepsy and other seizure disorders.

Early hopes that brain wave recording would allow one to understand how the human brain operates and help solve the mind–brain problem are yet too ambitious. Nevertheless, behavioral state changes in a certain context (or pathology) are believed to correlate with the neuronal events, which are quantifiable in the EEG (Fig. 1). This chapter emphasizes that many drugs acting on neurotransmitter systems (reversibly) perturb the EEG, which can then be used during clinical trials to indicate if and when a given drug has successfully reached its target in the brain and to quantify its duration of action.

Principles and Role in Psychopharmacology
To record a typical EEG from humans, multiple surface recording electrodes are glued to the scalp and one ► reference electrode is positioned preferably over an isoelectric part (linked earlobes, nose, and mastoid bone). The signals of interest are in the microvolt (millionths of a volt) range and sensitive to extracerebral



Electroencephalography. Fig. 1. Diagram summarizing common straightforward relationships in brain physiology, behavior, and psychopharmacology research and applications.

noise-sources. Although there exists no ideal zero-reference, scalp electrode recordings are improved by subtracting the common reference signal. Artifacts due to muscle activity or movement occur in EEG recordings, and they must be removed. Such artifacts are frequently caused by eye movements, blinks, heart beating/blood circulation, facial/scalp muscle activity, breathing, and swallowing. To help with artifact removal, polygraphic recordings are often performed alongside the EEG recording in both humans as well as animals, by the placement of additional sensors for monitoring, e.g., eye movements (EOG), postural/neck muscles (EMG), heart activity (EKG), thoracic expansion, and blood pressure. In practice though, the eye of the expert, who examines the entire multichannel EEG recording in addition to the accessory records, is the best means for artifact removal and epoch selection for the analyses in both wakefulness and ▶ polysomnography.

Sleep pattern characterization is usually carried out by visual inspection (see scoring rules in Iber et al. 2007) on cleaned traces in the temporal domain. Digital EEGs in animals and humans are nowadays nearly always obtained (as recommended, e.g., Penzel and Conradt 2000) with commercially available equipment. This has promoted the field of quantified wake EEG or ▶ qEEG which uses the fast fourier transform to calculate power spectra of the EEG segments and thus to quantify changes in the various frequency bands. Multivariate EEG-analysis by way of ▶ spectrograms provides valuable biomarkers for the endogenous modulation (by speeding or slowing) of the level of arousal, for the continuum in the change of patterns from adolescence, adulthood to normal brain aging, or for occasional EEG-changes related to life style, but also pathological states. Importantly, multivariate EEG-analysis also allows the study of perturbations induced by drugs.

Pharmaco-EEG is a technique to evaluate the effect of drugs on electrical brain activity in a defined context and implicitly makes use of qEEG. A large number of currently available therapeutics act on receptors/channels/▶ neurotransmitter transporters/enzymes in the brain, which take part in or influence synaptic transmission. Many of these drugs also influence the EEG power spectra, thus pharmaco-EEG has become a useful research tool in psychopharmacology; it is most commonly (but not exclusively) used in preclinical and early phase I ▶ randomized controlled trials for novel drugs. This technique allows to evaluate the cerebral ▶ bioavailability of compounds in man in comparison to animals (▶ translational research). qEEG provides a high-dimensional biomarker with the potential to perform systematic ▶ classification of psychoactive drugs, drug "finger-printing" (Saletu 1987), and risk evaluation. The versatility of EEG parameters lies in the fact that it provides a metric which is objective and can be expressed as (single subject or group) "raw" data, either as predose-adjusted value or as placebo-adjusted value. EEG data with good test–retest reliability are obtained when the volunteer is awake but with the eyes closed, whereas in freely-moving animals, the exact behavioral state and other confounding factors are more difficult to control.

Cortical Basis of EEG

Neurons firing action potentials generate extracellular electromagnetic gradients (▶ extracellular recording) in the cortex. When the timing is sufficiently coherent, synchronous activity gives rise to the microvolt signals named ▶ field potentials that make up the EEG by volumic summation of these elementary (neuronal) events; optimal geometry is an arrangement in the form of a "palisade-like" array. The macroscopic EEG signals switch polarity in a cyclic manner, and zero-crossings for the alternating waveforms can be as fast as 20 ms for a particular structure, or up to >1,000 ms for a different structure. The technique does not allow to reconstruct the individual ▶ firing patterns of neurons. Exactly which type of neurons and interactions contribute to the EEG and from where in the brain the different characteristic rhythms originate are the subjects of intensive research. The present view of the cellular aspects of generators of EEG is that particular neuron types, which are located in different parts of the CNS, have membrane properties that

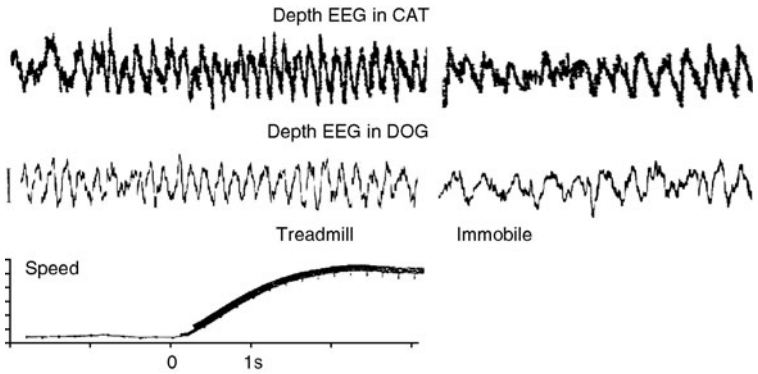
enable them to rhythmically fire action potentials and to participate in generating network oscillations in some frequency range. These membrane properties can be measured by performing ► intracellular recordings or patch clamp recordings. These neurons are, by virtue of their synapses from and onto other neurons, embedded in local network loops and the balance of net interactions determines the composite frequencies. Indeed, remotely located pacing structures, as is the case for thalamocortical loops, are necessary to entrain alpha and beta frequencies as described (e.g., Steriade 2001) by correlating signals from depth electrodes with cortex recordings; in practice, the net result of cortical generator events in the crown of sulci (cells with dendrites oriented radially to the skull) are most likely to be detected on the scalp of e.g., human or rat skull.

Similarly, impinging volleys via afferent septohippocampal pathways drive/impose the theta rhythm that arises primarily from the ► hippocampus (Buszaki et al. 1983). In animals, the pharmacology of the hippocampal theta rhythm is well studied. Theta rhythm is largely abolished by the muscarinic acetylcholine receptor antagonist atropine, whereas muscarinic agonists, like carbachol, induce "theta-like" rhythmic network activity in isolated hippocampal slice preparations. Hence there is a neurochemical basis for oscillatory brain potentials. The study of scopolamine-induced deteriorations in EEG (see ► Dementias: Animal Models and also ► scopolamine) helps in the development of ► Acetylcholinesterase inhibitors and ► Cognitive Enhancers or drugs for ► Dementias and Other Amnestic Disorders.

Neuropharmacology is applied to study the organization of brain rhythms. Systemically administered ► benzodiazepines modify beta-activity in the cortex of rats. EEG effects, when plotted as a function of blood concentration of ► midazolam (PK–PD), follow a sigmoidal curve evidencing a relationship of beta waves and the enhancement of the functions of ► $GABA_A$ receptors; moreover, the position of curves for e.g., drug-analogs with comparable EEG-effects reflect potency differences (Mandema and Danhof 1992). Experimental conditions can be refined (topic application of drugs) and pharmacology is useful for the understanding of how brain structures presumed to play a role in the generator process do cooperate with other regions to make up the EEG, but also to understand the normal equilibrium state in neural circuitry in general.

Components of the EEG

There is consensus to divide EEG (quasi-sinusoidal) waves into the following frequency bands: delta (1–4 Hz), theta (5–8 Hz), alpha-1 (9–10 Hz), alpha-2 (10–12 Hz), beta-1 (13–17 Hz), beta-2 (18–20 Hz), beta-3 (21–30 Hz), and gamma (31–100 Hz) in accordance with the International Pharmaco EEG Group (IPEG). To study the role of these waves, EEG experiments have been performed in numerous animal species, making use of conditioning paradigms. Repeated walking on a treadmill (see ► operant behavior in both animals and humans and ► instrumental conditioning) was used by Lopes Da Silva to establish empirically behavioral correlates of EEG components. Figure 2 shows examples of performance-related

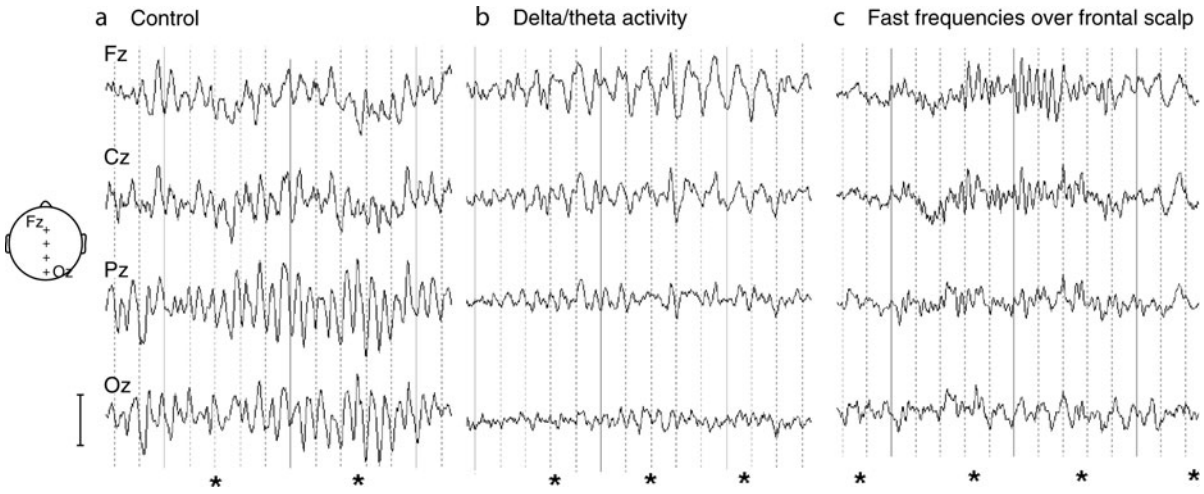


Electroencephalography. Fig. 2. Functional correlates of EEG rhythms. Examples of EEG traces from the hippocampal formation for two mammalian species. The animals were conditioned to perform treadmill-walking and to remain alert, resting wakefulness. Note the presence of regular quasi-sinusoidal waves when the animals are moving, which disappear under immobility. Calibration bar 250 μV; speed in arbitrary units (remastered own unpublished ink-on-paper recordings from a Siemens ELEMA Mingograf® 16-channel EEG-machine (mfi-TNO); the author acknowledges P Dalenconte, a professional photographer, for image processing).

hippocampal theta in two animal species; 4–5 Hz dominant activity is more synchronized during walking than during rest or eating. The result fits in with the concept that theta rhythm, also named ► RSA (Vanderwolf 1969), is related to voluntary movement. The hippocampal formation is believed to play an important role in memory updating. J O'Keefe, L Nadel and collaborators, have produced evidence that the theta rhythm serves as a reference framework for a higher mental function, namely spatial navigation (http://www.congnitivemap.net/). Interestingly, subpopulations of individual neurons have properties like place-specific firing at a given location in e.g., a foraging task on an ► elevated plus-maze, and the moment of firing displays a phase relationship with hippocampal electrical field potentials in the theta frequency band suggesting that theta rhythm plays a role in navigation (Lisman 2005) and ► Spatial Learning in Animals. This finding can be extrapolated to ► Spatial Learning in Humans.

Examples of human EEG-components from four midline scalp locations in normal quiet resting state with eyes closed, show clearcut alpha spindles (Fig. 3 *left panel*) and correlates of hypovigilance or psychotropic drug states give changes in slow wave (Fig. 3 *middle panel*) and beta frequency bands (Fig. 3 *right panel*). What is known about the functional correlates of the frequency bands in man during waking and/or sleep? In brief, high power in the alpha band can be seen during certain attention tasks and/or when the subject is awake with the eyes closed and mixed beta frequencies are associated with active thinking and concentration. Gamma frequency activity is associated with higher mental function and can be generated in many different brain regions. EEG segments characterized by ongoing activity in the theta frequencies may indicate that the subject is involved in active exploration of the environment. Paradoxically, sleep stage N1 is associated with low amplitude 4–7 Hz activity (mostly theta frequency band, Iber et al. 2007). EEG segments with a preponderance of large amplitude waves in the delta frequency band (see ► function of delta waves), in particular, during polysomnography recordings (one or few EEG-channels) are scored according to the latest guidelines from the American Academy of Sleep Medicine as sleep stage N3, slow wave sleep (SWS) which makes part of ► NREM sleep and distinguishes from the ► REM sleep stage. The translational value from animal to human (and vice versa) is evident. The EEG montage along with an EMG from a postural (usually neck) muscle and a motion detector and/or a video monitor are used together to discriminate the different stages in animal studies. In drug development, it is well known that e.g., rat sleep-EEG has predictive value for the efficacy of new ► hypnotics and possibly for the development of ► antidepressants, in particular by studying REM-suppression.

Digital EEGs and related analyzes in the frequency domain are performed more frequently in animal and in



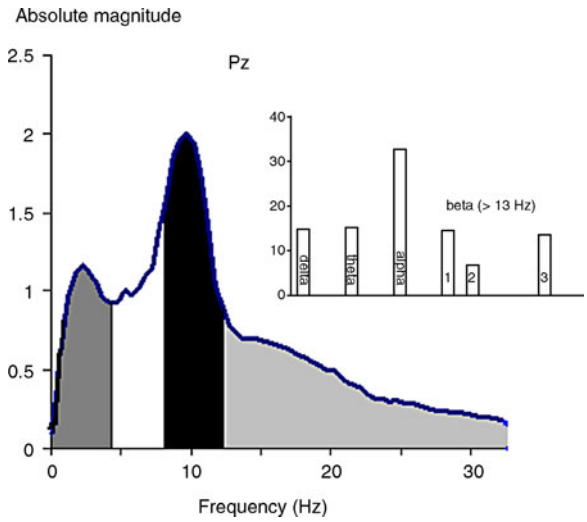
Electroencephalography. Fig. 3. EEG and (drug-induced) state changes. (**a**) epoch of scalp EEG simultaneously recorded from four midline electrodes according to the international 10–20 montage system showing a gradient of occipital alpha (spindle at Oz and Pz approximately 10 Hz) rhythm, "fading-out" in more anterior topography domains (**b**) dramatic EEG changes on clonazepam (1 mg i.v.); note the lack of alpha, and the slow wave activity in frontal leads. (**c**) drug-induced increased (fast) beta commonly occurs. Major tick 1 s, minor ticks 200 ms; calibration bar 100 μV. * *R-R interval from EKG.

man during waking states, but can be applied to sleep as well. For the hippocampal theta recordings (Fig. 2), power spectra have been used to perform statistical comparisons on extracted features under different behavioral conditions; dominant frequency associated with resting amounts values of 4 Hz which shift to about 5.5 Hz during walking. Rat EEG-recordings to relate beta-increases to midazolam plasma levels mentioned above are another good application of power spectral analysis. As pointed out, pharmacologist derive drug potency from dose (► ED50) or concentration-EEG effect relationship; for animals treated with ► flumazenil, a blocker of the benzodiazepine receptors, higher ► midazolam concentrations are necessary to induce the same EEG changes, which fits with a competitive agonist–antagonist interaction model. ► Benzodiazepines are widely studied because of known properties as anxiolytic, anticonvulsant, muscle relaxant, and sedative–hypnotic effects, but other mechanisms and therapeutic application can benefit from EEG. Straightforward examples of applied neuropharmacology in animal EEG are seen, for example, in natural or experimentally induced epileptiform, activity of great interest in the understanding and development of new ► anticonvulsants or novel compounds for the induction of ► general anesthesia. The translatability to humans is straightforward and is illustrated in the next section.

Clinical Applications

Shortly after computerized EEG analysis became available, the idea of using EEG as a diagnostic tool in patients suffering from neurological/psychiatric disorders began to be explored. EEG recording is harmless, easy to implement, and of low cost. Computational methods are available, but need group clusterization, hence are not very useful for individual subjects. EEG is commonly used in the diagnosis of epilepsy, sleep disorders, and as a research tool in a number of CNS-disorders. Cognitive decline is associated with EEG changes: a hallmark in Alzheimer's patients is the increase in slow waves and the decrease in alpha activity. Basic knowledge on the progression rate in EEG deteriorations needs follow-up tests over weeks or months. This can be assessed on different occasions in eyes-closed recordings which last for only a few minutes. An example of the magnitude (approaching EEG-amplitude, see Kiebel et al. 2005) as a function of frequency or spectrogram is shown in Fig. 4 for a healthy subject; the recording lasted 3 min.

Finally, the technique is widely applied for on-line monitoring of anesthesia. An illustration of benzodiazepine sedation can be found in Fig. 5a. It is important to stress the similarity in time course of both plasma levels

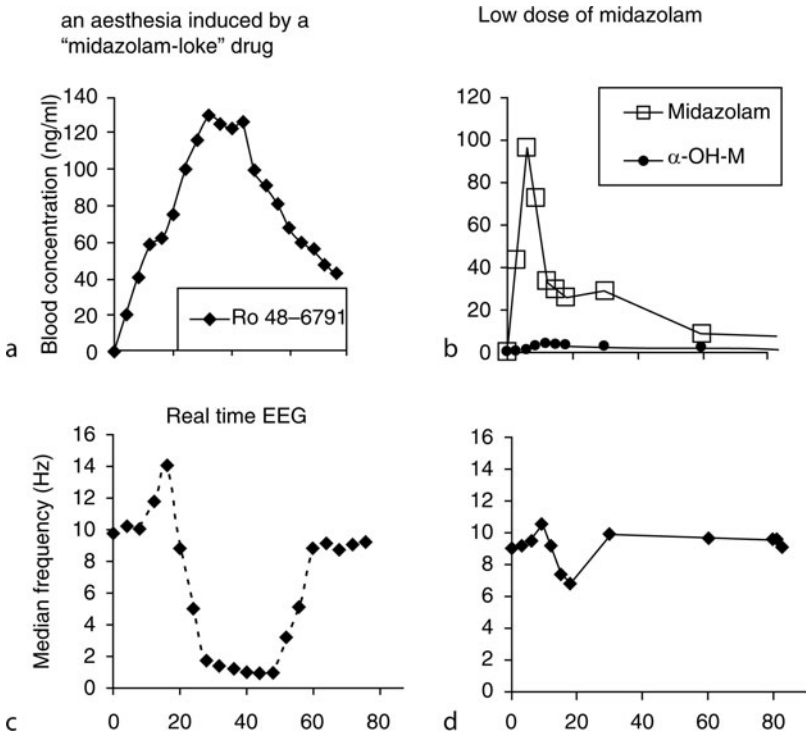


Electroencephalography. Fig. 4. Example of signal representation in the frequency domain as a spectrogram. The shaded areas give demarcations between classically defined bands; eyes-closed resting EEG can easily be repeated, has good test–retest reliability (not shown) and is recommended in drug studies. *y*-axis: square-root of power per spectral value yield a "magnitude," the center of gravity (=median frequency on *x*-axis) is normally around 9–10 Hz. Inset: Bargraph with labels of extracted features according to the names of the frequency bands. Drugs can almost independently modulate these, and this can even be different depending on the topographic location.

(plateau around 30 min) and the drop in EEG overall frequency (following a transient elevation in line with increased fast frequencies). Compartmental modelisation of PK-PD relationships fully validates the causality between input (drug i.v.) and output seen on the EEG. Sub-anesthetic doses of midazolam for the volunteer of Fig. 5b, for which EEG modifications are less pronounced than in the first case, rely on the same mechanistic principle and yield a good EEG pharmacodynamic response timing in relation to infusion onset. As for beta-EEG in animals shown previously, proper consensus on model characteristics is provided, e.g., ► triazolam (Greenblatt et al. 1994) for high frequency content in humans as is the case for midazolam (Fiset et al. 1995) but on the content of the whole spectrum.

Pharmaco-EEG in Humans

Signals as shown in left panel from Fig. 3a and "raw" spectrogram of Fig. 4 can be used to evidence a range of modulations/perturbations. Thus, the level of vigilance is reflected by the spectral composition of the brain signals.

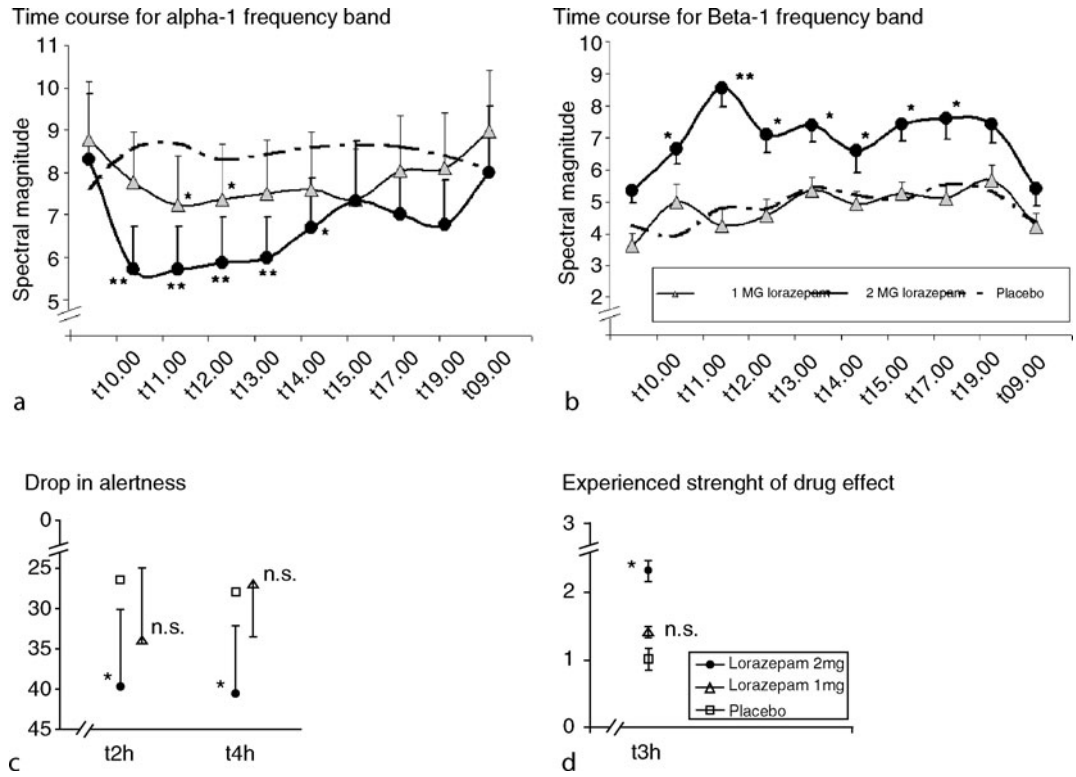


Electroencephalography. Fig. 5. (**a**) Pharmacokinetics for a single injection of the "midazolam-like" drug Ro 48-6791 at controlled infusion rate (3 ng/mL/min) in induction of anesthesia and conscious sedation. Curve peaks around 30 min when subject stopped responding. (**c**) changes in median frequency (qEEG) ; note the dramatic drop to 1–2 Hz center of gravity which remains stable around 30 min (adapted from Ihmsen H, Albrecht S, Hering W, Schüttler J, Schwilden H (2004) Modeling acute tolerance to the EEG effect of two benzodiazepines. Br J Clin Pharmacol 57(2):153–161). (**b**) Pharmacokinetic profile in a separate (own) experiment for a single i.v. injection for 15 min of a nonanaesthetic dose of midazolam (5 mg, 1/15th of dose for full sedation); note the rapid rise and fall in mother compound, and delay in (alpha-hydroxy) metabolite concentrations (concentration difference in the order of about one log-unit). (**d**) off-line analysis of the same parameter as in (**c**) but the lowering is less than one third of predrug values.

A simple experiment is to record the EEG during active waking with eyes closed: as the eyes open, dramatic changes in the EEG patterns occur (called "alpha-block"). More interactive recordings are beyond the scope of the present contribution, but can be found under ▶ event related potentials, which are the responses to specific stimuli, often sounds, recorded in the same manner as the EEG.

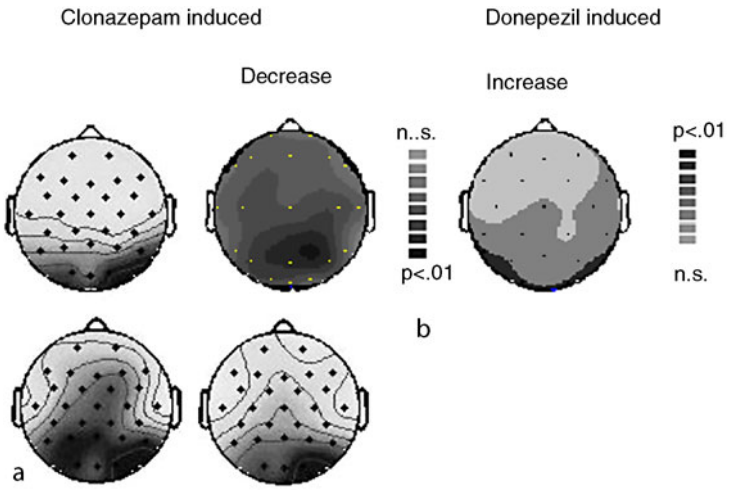
Life-style and habits also affect the EEG and must be taken into consideration. For example, long lasting changes are present in the EEG of cigarette smokers, particularly over parietal scalp regions (see Domino 2003 and ▶ Nicotine Dependence and its Treatment for relevant papers). Furthermore, consumption of ▶ caffeine and ▶ alcohol perturb the EEG (Gevins et al. 2002) and can bias study results. Gender, age, and mental health also affect the EEG and must be taken into consideration during the evaluation of drug effects in both healthy subjects and patient populations. When eliminating most of these confounding factors, the stability of spectrograms over time is satisfactory for the empirical detection of drug effects. EEG characteristics are strongly hereditary and as a consequence, intra-subject variability is low compared to inter-subject variability. Therefore, a cross-over design where the same individual receives both the drug and a placebo treatment is recommended whenever possible; this also controls better for systematic fluctuations unrelated to the actual drug (see ▶ Randomized Controlled Trials).

The top panels in Fig. 6 illustrate time course of EEG-effects induced by two doses of a benzodiazepine, ▶ lorazepam, and matching placebo. qEEG activity for beta-1 increased transiently followed by sustained elevations throughout the experimental day; alpha-1 was diminished

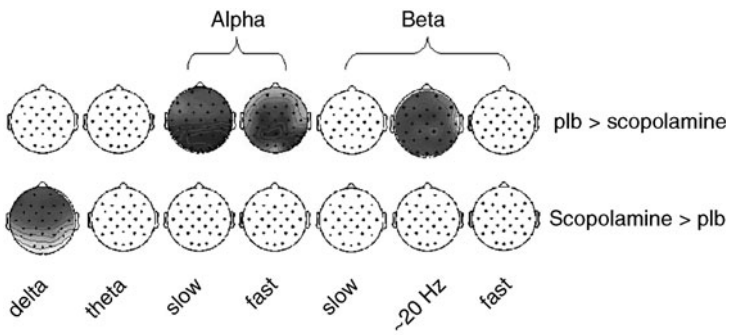


Electroencephalography. Fig. 6. Group data as part of a large project of qEEG for ten healthy volunteers, 1 or 2 mg doses. (**a**) Line-graphs (mean ± S.E.) for repeated measures of posterior alpha-1 EEG and the effects of two escalating (nontherapeutic) doses of lorazepam, a benzodiazepine drug having clearcut decreases for both treatments lasting about 4–5 h, with dose-dependency specially around 2 h postdose. Note the stability over time under placebo conditions. (**b**) same as in (**a**) but for frontal beta-1 EEG. (**c**) self rated alertness issued from VAS analog scales around the moment of significant EEG effects; only the 2 mg dose yielded a significance on the items interpreted as hypovigilance. (**d**) judgment of strength in drug effect (part of a separate project on metamemory) for the same two doses of lorazepam (adapted from Mintzer MZ, Griffiths RR (2005) Drugs, memory, and metamemory: a dose-effect study with lorazepam and scopolamine. Exp Clin Psychopharmacol 13:336–347).

for both doses from the first hour onwards, lasting >4 h, with a hint for dose dependency (see e.g., the 2 h). Comparative neuropharmacology of ► function of slow and fast alpha, issued from our unpublished multielectrode mapping of significant clonazepam modifications compared to placebo (Fig. 7 *middle column*, *top* p-values), or as single valued placebo-adjusted metric placebo (*middle column, bottom*). The decreased values cover almost the whole scalp. At the right, a similar statistical procedure shown increases for a single dose of donepezil which is more limited to the posterior scalp. Effects on other frequency bands are shown for the muscarinic acetylcholine receptor antagonist scopolamine (see ► Muscarinic Agonists and Antagonists). Scopolamine decreases slow and fast alpha (Fig. 8, *top row*) and has differential effects on e.g., the delta amplitude, which reaches enhanced levels in large precentral scalp regions (Fig. 8, *bottom row*). The decreasing alpha frequencies together with the increase in delta waves (► function of delta waves) show an increased sleep propensity, and are interpreted at the functional level as sedative "signature." Interestingly, ► benzodiazepine agonists (see also ► Benzodiazepines), anticholinergics, and first generation antihistamines (e.g., diphenhydramine, see ► Histaminic Agonists and Antagonists) yield similar EEG "signatures" and are all sedative. This suggests that their mechanisms of action converge onto similar vigilance-controlling substrates in the brain, despite the fact that their primary targets are different. A similar overlap has been found for drugs that cause increases in the beta frequency band: benzodiazepine anxiolytics, ► antidepressants, and ► barbiturates have similarities in their "signatures," most probably linked to $GABA_A$ receptor modulation. Such findings illustrate our increased understanding obtained by combining psychopharmacology and qEEG studies.



Electroencephalography. Fig. 7. *Left column*: descriptive qEEG topography for the alpha frequency band for a single subject without drug (*bottom image* with isocontours every 25 μV) and on clonazepam (*top row, left panel*). The crossover design allows subtraction (*bottom, middle image*) of EEG variables; finally inferential nonparametric testing of differences (mapping for groups) confirms drug-induced significant decreases. Topographic maps are constructed by interpolation for the values on 19 standard electrode positions+Oz and eight intermediate leads for active treatment. Example at the right mapping for a member of the class of acetylcholine esterase inhibitors, donepezil; a similar statistical procedure demonstrate that alpha frequency band increases in healthy volunteers (adapted from Boeijinga PH, Calvi-Gries F, Demazieres A, Luthringer R (2002) Planning of pharmacodynamic trials: specificities and possible solutions and interpretation of drug effects on EEG. Methods Find Exp Clin Pharmacol 24(suppl C):17–26).



Electroencephalography. Fig. 8. Pharmaco-EEG profile of scopolamine: inferential non-parametric testing ($N=12$) of differences has been carried out on an electrode-by-electrode basis with decreases in several bands at frequencies >8 Hz, and increases in delta, compared to placebo. Note that overall, a slowing in EEG can be deduced; the biomarker can be used to test reversal by (new) antidementia drugs and hence a single Phase I trial in a co-administration design, known as scopolamine model, predicts efficacy at an early stage.

EEG as Biomarker in Clinical Studies

In addition to being a diagnostic tool, EEG may be useful in assessing the effectiveness of particular therapies. EEG modifications in the diseased state are likely to reflect deficits in one or several neurotransmitter systems and conversely, pharmacotherapy should ideally normalize such deficits. For example, Acetylcholinesterase inhibitors as cognitive enhancers have been shown to reverse EEG abnormalities in patients with Alzheimer's disease, even after short-term treatment (rivastigmine; Brassen and Adler 2003). Similarly, EEG can be useful to assess directly and objectively the effectiveness of new hypnotics in sleep disorders and of anticonvulsants for epilepsy in patients. EEG

Electroencephalography. Table 1. Summary of EEG profiles for members of various classes of psychotropic drugs, separated in (**a**) increases in EEG variables, and (**b**) decreases in EEG variables compared to placebo (consensus from Mucci A, Volpe U, Merlotti E, Bucci P, Galderisi S (2006) Clin EEG Neurosci 37:81–98; Saletu B, Anderer P, Saletu-Zyhlarz, Arnold O, Pascual-Marqui RD (2002) Methods Find Exp Clin Pharmacol 24(suppl C):97–120 for the new generations of drugs like clozapine and citalopram, respectively, in the first two lines in (**a**) and (**b**), third and fourth line according to Boeijinga PH, Calvi-Gries F, Demazières A, Luthringer R (2002) Planning of pharmacodynamic trials: specificities and possible solutions and interpretation of drug effects on EEG. Methods Find Exp Clin Pharmacol 24(suppl C):17–26).

	Delta	Theta	Alpha	Beta		
			Slow/fast	Slow	~20	Fast
(**a**) Treatment > placebo						
Antipsychotics		▲	▲–			
Antidepressants						▲
Anxiolytics/tranquilizers	▲			▲	▲	▲
Anti-Alzheimer drugs		▲[a]	▲–			
(**b**) Placebo > treatment						
Antipsychotics	▼		–▼	▼	▼	
Antidepressants						
Anxiolytics/tranquilizers		▼	▼▼			
Anti-Alzheimer drugs	▼[a]					

[a]Only after uptitration for 7 days
Symbols ▲ and ▼ indicate increases/decreases with respect to placebo

recordings can be valuable as a biomarker in the development of drugs that perturb neurotransmitter systems and act in the central nervous system. Figure 1 schematically illustrates the theoretical interrelations between brain state, neurophysiology, and drugs that form the basis for using EEG to evaluate drug effects.

Whereas plasma levels of compounds are nearly always obtainable, measuring brain exposure of the same drugs in humans is not possible. Due to the very nature of compartmentalization, a delay with respect to plasma-T_{max} may occur for CNS-effects. Since eyes-closed resting EEG has good test–retest reliability and can easily be collected continuously or repeated at regular intervals, the technique can be used to determine the pharmacodynamics at an early stage of development in healthy volunteers (Phase I), that is the time of onset and duration of the drug effects in the target organ, the brain. The continuous metric of the EEG can vary in a dose-dependent manner; hence, measurements can assist in dose-finding. Comparing the pharmaco-EEG profile with that of substances for which the pharmacological mechanisms are known may help predict efficacy and action in patients from the results in healthy volunteers. This aspect must be seen in the light of the Classification of Psychoactive Drugs as summarized in Table 1.

Advantages of Using EEG/ERP Relative to other CNS Biomarkers

Electroencephalogram recording constitutes one of the most frequently explored physiological parameters during both waking and sleeping. Since the receptor composition in neuronal circuits has a large overlap across species, pharmaco-EEG is highly translational and can be used as a biomarker throughout preclinical and clinical development in both in vitro and in vivo animal and human studies. In all species this can range from EEG at wakefulness to sleep and sleep disorders or animal models. Using EEG as a biomarker does not require labeling of a radioactive ligand as is necessary for the ▶ PET imaging method. In addition, EEG is a readout of the functional activity of neural networks. The time resolution of EEG is highly superior to that of ▶ magnetic resonance imaging (functional). The sensitivity of EEG/ERP also compares favorably to that of symptom inventories or subjective evaluations of volunteers or patient's "feelings" as indicators of brain penetration and pharmacodynamic effects. As an addendum to sustained EEG effects (see above), subjective feeling (alertness, a nine item VAS factor) was significantly affected for only the highest dose from the second hour onwards (Fig. 6b). In another experiment, healthy subjects subjectively rated the strength of a drug

effect. The dose of 2 mg yielded clearcut effects, but the 1 mg dose was not different from placebo (Fig. 6c). Without EEG "monitoring," one would falsely conclude to the absence of bioavailability in the brain of the low dose. EEG perturbations may suggest potential effects on endogenous vigilance processes, memory, and cognitive functions, hence an interpretation of side effects such as attention deficits (e.g., sedation or pro-convulsant effects). Other successful EEG applications are the evaluation of limitations due to ▶ blood–brain barrier properties with respect to a comparator, or to prove the presence and disentangle the direction of effects for unknown active metabolites. Finally, one can infer the efficacy of enantiomers; for the racemic mixture of the dissociative anesthetic ▶ ketamine, in line with Fig. 5, median frequency of the EEG drops, but does so to a larger extent for S(+)−ketamine than for a similar dose of R(−)−ketamine.

One disadvantage of EEG is the high inter-subject variability, which makes comparisons between parallel groups problematic. In any case, age and gender must be matched. As pointed out, reproducible EEG results can be obtained when the volunteer is awake, with the eyes closed. Nevertheless, one aspect in data processing concerns artifact rejection, which is laborious and not devoid of subjectivity. Improved methods to automatically remove artifacts are available (e.g., independent component analysis (ICA) on the free access EEGLAB website (A Delorme and S Makeig) http://sccn.ucsd.edu/wiki/Chapter_01:_Rejecting_Artifacts. Even today, the evaluation of sleep-parameters is still carried out manually, and the quality of research relies heavily on inter-rater reliability; hence regular consensus meetings are very important. Professional organizations like the American Society of Electroneurodiagnostic Technologists (http://www.aset.org/) propose such events.

Cross-References

▶ Classification of Psychoactive Drugs
▶ Digital EEG Nomenclature
▶ ED50
▶ Event Related Potentials
▶ Extracellular Recording
▶ Function of Delta Waves
▶ Function of Slow and Fast Alpha
▶ Intracellular Recording
▶ Polysomnography
▶ Reference Electrode
▶ RSA
▶ Spectrograms
▶ Wakefulness

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Electroencephalography

Synonyms

EEG

Definition

Electroencephalography (EEG) is used to detect and record the electrical signals of the brain. The test is noninvasive and involves the placement of surface electrodes (flat metal discs) to the scalp of the test subject. This is particularly

useful in diagnosing a number of conditions that affect the brain such as certain types of epilepsy, where abnormal patterns of brain activity are observed even in the absence of a seizure. EEGs can also be used to assess brain function following a head injury or hemorrhage and serve as a useful tool to investigate sleep-related disorders.

2-D Electrophoresis

► Two-Dimensional Gel Electrophoresis

Electrospray Ionization

Synonyms

ES; ESI; Nanospray

Definition

A process in which ionized species in the gas phase are produced from a solution via highly charged fine droplets, by means of spraying the solution from a narrow-bore needle tip at atmospheric pressure in the presence of a high electric field (1,000–10,000 V potential).

Cross-References

► Mass Spectrometry (MS)
► Metabolomics
► Neuropeptidomics
► Post-Translational Modification
► Proteomics
► Two-Dimensional Gel Electrophoresis

Elevated Plus Maze

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Synonyms

Elevated X-maze; plus maze test

Definition

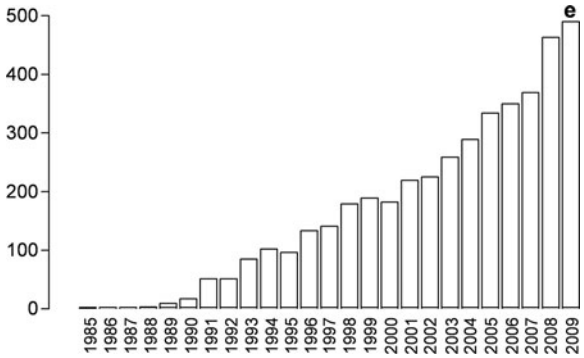
The elevated plus-maze (EPM) has been widely used (Fig. 1) as a reliable measurement tool to evaluate ► defensive behaviors related to ► anxiety in rodents, particularly mice and rats. Derived from Montgomery (1955) study concerning exploratory patterns, the EPM creates an approach–avoidance conflict where the environmental novelty is capable of simultaneously evokes fear and curiosity. This task was modified into an elevated maze with four arms arranged to form a plus shape (Fig. 2a) by Handley and Mithani (1984) as to detect either the anxiolytic- or the anxiogenic-like effect of drugs. An extensive pharmacological, physiological and behavioral validation of the EPM as an animal test of anxiety in rats was performed 1 year later by Pellow et al. (1985) and further extended to mice by Lister (1990).

Principles and Role in Psychopharmacology

The EPM stands as one of the most popular in vivo animal tests currently in use not only to drug discovery/development, but also to investigate the neurobiological mechanisms underlying ► anxiety. According to Fig. 3, over forty percent of EPM current use, estimates the emotionality of rodents submitted to previous genetical, biochemical and/or behavioral manipulations. Moreover, the EPM is an excellent example of task based on the study of unconditioned or spontaneous behavior. Its popularity, with around 4,300 published papers so far (Fig. 1), is likely due to its obvious and numerous advantages, namely: economy, rapidity, simplicity of design and bidirectional drug sensitivity, couple with the fact that it does not require lengthy training procedures or the use of food/water deprivation or electric shock (Pellow et al. 1985; Lister 1990; Rodgers et al. 1997; Carobrez and Bertoglio 2005).

The behavioral measures routinely scored during the 5-min EPM session are the frequency of open- and enclosed-arms entries and the amount of time spent on the open- and enclosed-arms. These data are used to calculate the percentage of open-arms entries {%OAE; [open entries/(open + enclosed entries)] × 100} and the percentage of time spent in open-arms {%OAT; [open time/(open + enclosed time)] × 100}. As illustrated in Fig. 2, there is a clear enclosed-arm preference. Under the influence of an anxiogenic-like drug, a further reduction in the open-arms exploration is observed. After being administered with anxiolytics, however, the animal displays significantly more open-arms exploration. In this context, it is worth mentioning that the efficacy of the EPM test in discriminating anxioselective compounds has been increased with the adoption of more ethologically-based analysis, i.e., the measurement of some acts and postures such as stretched-attend, head-dipping and grooming (Cruz et al. 1994). For instance, the frequency

of stretched-attend postures towards the open-arms (Fig. 2c,g) can be used as an index of ▶ risk assessment, a close behavioral dimension related to anxiety (Rodgers et al. 1997; Carobrez and Bertoglio 2005). The anxioselective discriminative property confers to the EPM test the predictive validity required to screen putative compounds and/or to identify alternative pharmacological interventions in anxiety field.

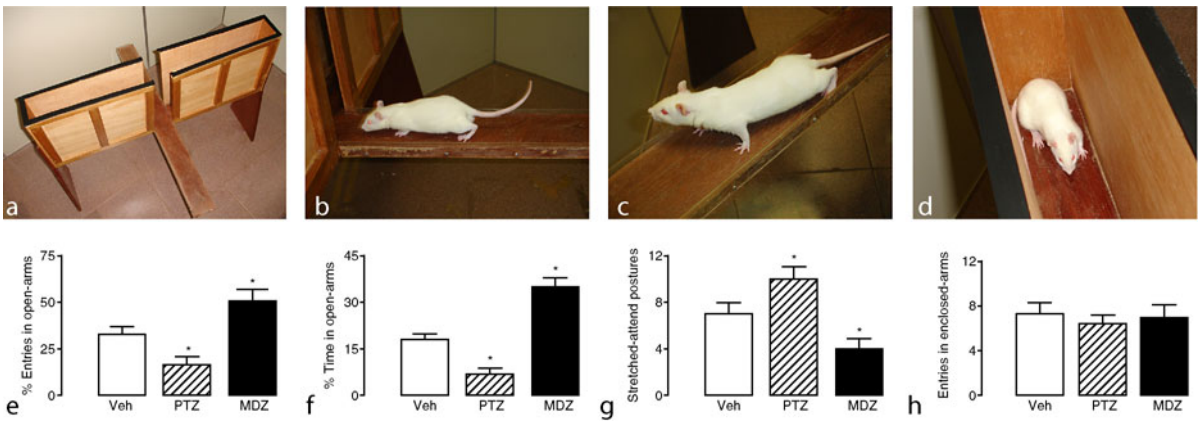


Elevated Plus Maze. Fig. 1. Published papers using the elevated-plus maze test in each year, according to the search performed on the PubMed site (http://www.ncbi.nlm.nih.gov/pubmed) in November 2009. e=estimated value based on the mean number of published paper per month in 2009.

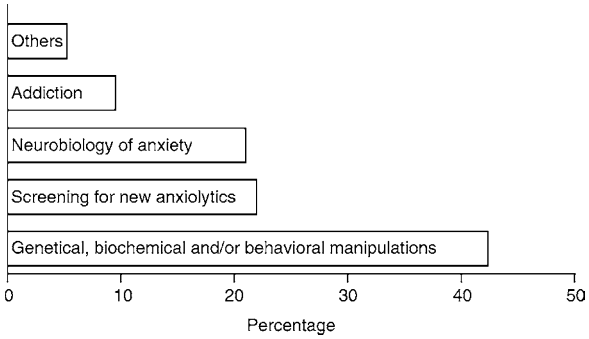
Methodological Variables

The main organismic variables of interest in the EPM test are species, strain, age, gender and estrus cycle/lactation, all of which have proven to interfere with its behavioral baseline level (Rodgers and Cole 1994). Furthermore, the different social role in the rodent group can be an important source of variation among dominant/subordinate males and females. As a consequence, either ▶ false-negative or ▶ false-positive results can occur if these important caveats are not taken into account. For instance, in spite of having similar defensive responses, mice and rats show a different level of general exploratory activity in the EPM test (mice been more active than rats). Anxiety scores also tend to change with age, apparently reflecting distinct brain development and/or the behavioral repertoire of the species.

Some procedural variables have also been shown to impact on the EPM baseline level. They include housing conditions, ▶ circadian rhythm, illumination level, time of testing, apparatus construction, definition of behavioral measures, prior handling/stress, and prior test experience. Together with organismic variables, these are the main sources of inter-laboratory variability in the use of the EPM (Carobrez and Bertoglio 2005). Based on the fact that behavioral responses and pharmacological effects observed in the EPM are under the influence of these



Elevated Plus Maze. Fig. 2. The (rat) elevated plus-maze consists of two opposite open-arms (surrounded by a small ledge), and two enclosed-arms, about 50-cm above the ground (**a**). Its use to measure anxiety is relatively simple: one may score the number of entries and the time spent on the open-arms (**b**). Besides these spatiotemporal measures, there are more subtle postures associated with anxiety such as the stretched-attend (**c**). They are collectively referred to as risk assessment behaviors. An ''anxious'' animal is one that displays risk assessment behavior very often, and rarely ventures out on the open-arms. In general, as can be seen in bottom panels, anxiolytics (e.g., midazolam, MDZ) increase open-arm exploration (**e**,**f**) and reduced stretched-attend postures (**g**) whereas anxiogenic drugs (e.g., pentylenetetrazole, PTZ) produce the opposite effect (**e**, **f** and **g**). One possible complication that an animal might not come out because it is inherently inactive, rather than anxious, can be dealt with by scoring the number of enclosed-arms entries, an index of general exploratory activity in this test (**d**, **h**).



Elevated Plus Maze. Fig. 3. The main focus of published papers using the elevated-plus maze test in 2008, according to the search performed on PubMed site (www.ncbi.nlm.nih.gov/pubmed).

variables (Hogg 1996), it would be imperative that laboratories using, or planning to use this test dedicate time and effort in order to define the optimal experimental conditions before starting their respective studies (Rodgers and Cole 1994).

Limitation of the EPM Task

Regarding possible apparatus limitations, it has been pointed out that within the rodent repertoire of defensive behaviors, the EPM is able to detect inhibitory avoidance and risk assessment. The expression of overt defensive behaviors such as ▶ freezing or flight, however, is not necessarily in the EPM range detection. Although both responses could be elicited by anxiogenic-like drugs, freezing could also be confounded with the enclosed reduced activity found in subjects treated with anxiolytics at sedative-like doses. Likewise, flight behavior induced by anxiogenics could also be confounded with the higher open-arms activity normally detected in animals treated with anxiolytic-like drugs. Overall, this limitation can also be applied as a note of caution when testing genetically modified organisms in the EPM. In fact, it might be extended to all organismic and procedural variables listed above.

A tendency towards automatic scoring of behavioral measures has been proposed to avoid subjective interpretation of the animals' behavior. Although these computer programs permit the analysis of spatiotemporal patterns of exploration in the EPM, some relevant (risk assessment) behaviors cannot be automatically recorded (Carobrez and Bertoglio 2005).

Furthermore, inconsistent results obtained in this test may indicate that the associated emotional state/reaction is critically dependent on stimulus parameters (Hogg 1996; Rodgers et al. 1997). Clearly, the behavioral expressions displayed in the EPM test represent a combination of exploratory and avoidance behaviors, as well as general activity, all of which are influenced by both genetic and environmental factors (Carobrez and Bertoglio 2005).

Cross-References

▶ Anxiety: Animal Models
▶ Anxiogenic-like Drugs
▶ Anxiolytic-like Drugs

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Elevated Prolactin (Luteotropic Hormone)

▶ Hyperprolactinemia

Elevated X-Maze

▶ Elevated Plus Maze

Elimination

▶ Excretion

Elimination Half-Life

Synonyms
Biological half-life; Terminal half-life

Definition
The plasma half-life of a drug ($t½$) is the time necessary to reduce the plasma concentration by half, for example, to decrease from 100 to 50 mg/L. The knowledge of the half-life is useful for the determination of the frequency of administration of a drug (the number of intakes per day) for obtaining the desired plasma concentration. Generally, the half-life of a particular drug is independent of the dose administered. In certain exceptional cases, it varies with the dose: it can increase or decrease according to, for example, the saturation of a mechanism (elimination, binding to plasma proteins, etc.).

Cross-References
- ▶ Area Under the Curve
- ▶ Bioavailability
- ▶ Distribution Phase
- ▶ First-Order Elimination
- ▶ Pharmacokinetics

Emetine

Definition
An alkaloid that inhibits protein synthesis by interfering with mRNA–ribosome interaction.

Emotion and Mood

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Synonyms
Affect; Feeling

Definition
At the broadest level, an emotion is a highly valenced experiential state. More precisely, emotions comprise coordinated neural, neuromuscular/expressive, and experiential responses to meaningful stimuli or events. In the affective sciences, the term emotion (or *basic* or *discrete* emotion) is used to specifically refer to strong transient states, such as anger, disgust, fear, sadness, surprise, and joy, which have a quick onset, a brief duration, possess clear behavioral tendencies, definable expressive and autonomic characteristics, and occur in response to species typical antecedents. These discrete emotions are distinguished from *moods*, which are valenced experiential states that occur over longer temporal spans, often lasting minutes or hours.

Principles and Role in Psychopharmacology
The modulation of mood and discrete emotional states are common targets of psychopharmacology. Additionally, agents designed to address neuropathological processes or improve cognitive functioning often have effects on mood, sometimes to enough of an extent as to influence patients' willingness to take the agent. Thus, accurate measurement of mood and emotion is critical to psychopharmacological research. Unfortunately, there is no accepted "gold standard" for assessing mood and emotion. However, the science of measuring mood and emotion has grown in sophistication in recent years, and attention to the details of assessment can substantially increase one's ability to detect pharmacological influences on emotional processing.

Assessing Basic Emotions
Basic emotion assessments are appropriate in situations where a pharmacological agent is intended to directly regulate or reduce the occurrence of a basic emotion such as fear or anger, as might occur during treatment of a phobia or borderline personality disorder. Basic emotions may also warrant assessment when administering pharmacological agents with extremely fast pharmokinetics, since such agents may directly induce a discrete emotion, such as fear or euphoria.

Because basic emotions are most frequently seen in response to characteristic situations or stimuli, it is essential to assess these emotions in relation to the occurrence of such triggering events. This can be accomplished either through retrospective self-report ratings or through laboratory-based exposure paradigms in which the individual is exposed to triggering stimuli or situations. Retrospective ratings have the advantage of potential aggregation over multiple time periods and triggering events in the person's everyday life, but provide limited, if any, ability to standardize the frequency, qualitative nature, or intensity of triggering events across conditions or individuals. Furthermore, the verification and coding of such events can be highly subjective and difficult to reliably

code. Additionally, unless the person is fitted with an ambulatory psychophysiological and videorecording system, it is not possible to collect any additional objective measures of the emotion.

In contrast, laboratory exposure techniques can be highly standardized, and allow the collection of data time-locked to the triggering event. By time-locking self-report ratings, an individual does not have to evaluate already long-past experiences to determine ratings. More importantly, time-locking allows the use of objective measures, which can compliment, or in some cases replace, self-report ratings. These objective measures consist of coding or direct measurement of facial muscle activity and psychophysiological measurements of correlates of sympathetic and para-sympathetic autonomic activity. Because basic emotions are accompanied by specific patterns of facial muscle movement (indeed, this is a common criteria for a basic emotion), the coding of facial expression are frequently used as markers of emotion. Detailed coding systems of facial expressions are well validated, and can be applied to video recordings of participants (Ekman et al. 2002). An alternative approach is to measure facial muscle activity with electromyography (EMG). EMG can detect weak activity of muscles even in cases in which a full expression is not completed. However, it is important in using this technique to record from a number of muscle groups simultaneously, as single muscle groups are often multidetermined. For instance, the corrugator supercilii muscles above the orbits are sensitive to anger, but also show increased activity during exposure to ambiguous or difficult stimuli (Pope and Smith 1994). ▶ Psychophysiological measures, such as electrodermal response, blood pressure, blood volume, heart rate, detailed analysis of electrocardiograms, respiration, and skin temperature are all useful as objective measures of the presence of an emotional experience. By combining psychophysiological measurements, it is possible to observe some degree of autonomic patterning specific to basic emotions. However, true discriminant validity is difficult to achieve with these measures, which often show properties characteristic of dimensional models of valence (or approach-avoidance) and arousal (Levenson 1988).

Although laboratory exposure techniques have a number of strengths for the assessment of basic emotions, they suffer from two major shortcomings. First, the laboratory events may be weak and somewhat unnatural approximations of real-life triggering events. Second, it is often difficult to aggregate over multiple exposures in the laboratory setting due to habituation. In such cases, the reliability of the assessment is often compromised.

Assessing Mood

In most psychopharmacological contexts, the assessment of more enduring mood states is more relevant than assessing basic emotions. For instance, the depressive disorders are diagnosed based on sustained enduring mood states, rather than individual discrete periods of emotion. Similarly, the goal of treatment for depression is to alter these enduring mood states as opposed to targetting discrete emotions. Such mood states may be less intense than the basic emotions, but they do not require assessments that are time-locked to triggering events.

Self-report remains the only viable option in most studies of mood, because there are few objective measures of mood. A first question arises regarding which mood terms a subject should rate. Factor analytic studies indicate that mood data are marked by two higher-order factors (Watson and Tellegen 1985), which are respectively labeled positive affect (PA) and negative affect (NA). (Note: The use of the term "affect" here refers to the subjective mood factor, rather than to an individual's observable expressed emotion, as the term "affect" is frequently used in psychiatric settings.) PA reflects a person's level of pleasurable engagement with the environment. High states of PA are characterized by terms such as interested, excited, and determined, which denote positive behavioral engagement. NA comprises a general factor of subjective distress, with high states of NA marked by descriptors such as distressed, nervous, and hostile. Taken together, PA and NA account for 50–75% of the common variance of mood.

An alternative dimensional schema for understanding mood states has been proposed by Russell (1980), who identifies a bipolar valence dimension (unpleasant–pleasant), and a second dimension of arousal. This schema has some advantages, particularly when examining immediate responses to stimuli, in which one often sees a clear inverse relationship between positive and negative experiences. However, when aggregating over multiple time points, or measuring longer retrospective periods, the inverse relationship between positive and negative experience weakens. This independence allows for the study of separable influences on PA and NA (which is not feasible with a single bipolar valence dimension in which pleasant and negative states are measured in opposition to each other). An important distinction can also be made between the Russell model and the PA/NA model of Watson and Tellegen in that the experience of pleasantness or unpleasantness may be seen as a consummatory response to stimuli or events. In contrast, PA and NA are more motivational in nature, with clear links to approach and avoidance. This consummatory vs. motivational

separation parallels Berridge's (1996) distinction between wanting and liking as applied to mesolimbic dopamine and opioid functions. This distinction between wanting and liking also appears useful in monitoring drug-induced mood changes. For instance, the Drug Effects Questionnaire (Fischman and Foltin 1991) asks subjects to separately rate drug wanting and drug liking, and these two ratings often show distinct patterns of correlations, and differential time courses following drug exposure.

PA and NA show different temporal patterns. Individuals typically show at least a moderate level of PA, with variability occurring around their own traitwise mean level. In contrast, NA is typically very low, with spikes occurring in response to specific negative or potentially negative events. This has implications for experimental designs, because the ability to observe a pharmacological agent's impact on NA may be limited in the laboratory environment if the person is not exposed to potentially unpleasant experiences.

The positive and negative affect schedule (PANAS), developed by Watson et al. (1988), provides a widely used measure of mood that taps the relatively pure factor structure of PA and NA. The scale includes 20 mood labels marking high (activated) PA and NA states, and has been repeatedly found to be sensitive to individual differences in both current and long-term mood. There are, however, a few important limitations of this type of scale. First, as originally designed, the PANAS does not measure mood states associated with reduced PA or NA. Specifically, terms such as fatigue (which appear to reflect an absence of PA) or calm (which appears to reflect an absence of NA) are not assessed. Subsequent measures, such as the expanded version of the PANAS (the PANAS-X), have attempted to capture these "low activation" markers. Yet, low activation markers do not possess as pure a factor structure as high activation markers of PA and NA. This occurs because terms such as boredom or tired not only reflect an absence of PA, but are also experienced as unpleasant, while states such as serenity or calm not only reflect an absence of NA, but are also experienced as pleasant. Because of this, low activation states require direct assessment, and should not be inferred by simply reverse scoring high NA or high PA terms. This issue takes on importance when we consider that many medications and street drugs are taken to alleviate feelings such as fatigue or to induce calm. Treatment studies provide further evidence of the need to directly assess low activation states, as antidepressants can produce differential effects on low activation vs. high activation PA states (Tomarken et al. 2004). Interestingly, alterations in low activation states figure prominently in the subjective effects of certain drugs. For instance, alcohol researchers frequently utilize the Biphasic Alcohol Effects Scales (Martin et al. 1993), which is a 14-item scale containing two factors: (1) a stimulant factor that corresponds to high PA, and increases during the rising limb of blood alcohol levels; and (2) a sedative factor that corresponds to an absence of PA (i.e., low activation), which increases during the descending limb of blood alcohol levels.

A second issue with the pure factor approach implemented by the PANAS arises because some important mood states reflect combinations of different levels of PA and NA. For instance, sadness can be viewed as a combination of reduced PA and heightened NA. Given the importance of sadness to the affective disorders, it is often essential to capture subjective states such as sadness, and the continued use of measures, such as the Profile of Mood States (McNair et al. 1981), which includes a Depression–Dejection scale, attest to this. In the NA domain, there is also sometimes utility in examining lower-order factors, such as anxiety or hostility. In doing so, it is important to determine to what extent observed associations are specific to the lower order factor vs. reflecting the higher order factor of NA more generally. For instance, even a scale such as the State Trait Anxiety Inventory (Spielberger et al. 1983), which is often treated as a specific measure of anxiety, captures elements of general distress, and thus cannot be used to draw conclusion about a specific subfactor of NA.

Drug-Specific Assessments

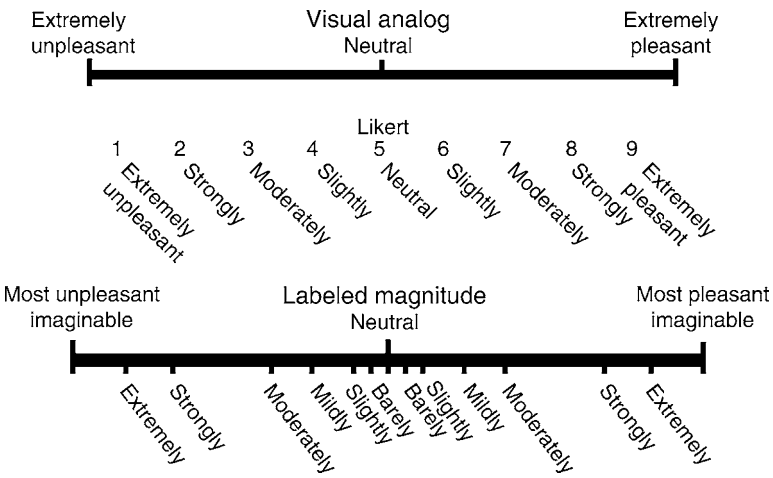
Studies examining the psychological effects of drugs of abuse require attention to the specific subjective effects of the agent. In particular, because of the intensity of basic emotion or mood states induced by drugs of abuse, typical mood scales may fail to appropriately capture such experiences, or may demonstrate ceiling effects (in which too many subjects give maximal ratings). For instance, ratings of joy may fail to capture the intensity of euphoric states. Several scales are in circulation that attempt to rectify this problem, by asking at least one question related to euphoria or related experiences. For instance, Van Kammen and Murphy (1975) developed the Amphetamine Interview Schedule to capture subjective responses to amphetamine, and include an item for euphoria, as well as related experiences of closeness to others, confidence, and overall feeling good. The Drug Effects Scale (Fischman and Foltin 1991) includes a rating of "feeling high," that may tap euphoric effects. However, the term "feeling high" is ambiguous, as it can also refer to a broad range of subjective experiences including perception of altered reality.

The most comprehensive scale for capturing the subjective effects of specific drugs is the ► Addiction Research Center Inventory (ARCI) developed by Haertzen et al. (1963), which measures subjective effects to a number of specific classes of drugs including ► morphine, ► LSD, and ► amphetamine, and among other symptoms tries to capture a euphoric–dysphoric continuum. With 550 true–false items, the inventory is problematically long for use as a real-time measure, so many investigators will restrict the questions to just those related to the specific drug of interest.

Types of Rating Scales

An important, and often overlooked, issue in studies of emotion and mood involves how to have participants rate their moods. Most studies have utilized either visual analog scales (VAS) or likert scales (LS). VAS consist of two verbal anchor descriptors that are placed on either end of a continuous line. Respondents provide ratings on VAS by indicating the point on the line that best represents the intensity of their current psychological experience. VAS may be considered to provide interval-like data in that they provide rank-order information about rating values and equal spacing exists between neighboring values along the entire scale continuum. Unfortunately, because the continuum lacks verbal descriptors, it is impossible to ascertain the qualitative intensity that corresponds to an intermediary rating. This means that intermediary ratings made by different individuals are not readily comparable. In contrast, to the VAS, LS consist of numeric points arranged along a discrete continuum, with intensity descriptor labels placed at both anchor points, and the intermediary numeric points. These labels have the advantage of leading individuals to use the intermediate ratings in a more qualitatively similar way. However, such scales are problematic, in that unless the intensity descriptors are truly equidistant, the applied numeric values do not represent the true quantitative (interval-like or ratio-like) differences in ratings. This is particularly problematic for bipolar scales (for instance, those running from unpleasant to pleasant), in that studies examining ratings of verbal descriptors have revealed that the magnitude differences of terms typically used to mark the low to moderate intensities cover a smaller distance than terms used to mark the moderate to the most intense anchors. This means a change in ratings between two descriptors in the lower intensity part of the scale cannot be considered equivalent to a change in two descriptors at the higher part of the scale (Fig. 1).

Recent research has led to the development of labeled magnitude scales (LMS), which attempt to address the weaknesses of the VAS and LS (Lishner et al. 2008). LMS utilize a visual analog scale framework, but includes descriptors that are placed along the scale at empirically determined intervals derived from rating studies of the intensity descriptors. Such scales also often use "most imaginable" instead of a term such as "extreme" as the highest intensity anchor in order to limit ceiling effects. To date, the LMS approach has not been widely used in psychopharmacological research, but this type of approach can be easily integrated into existing scales. However, it may be necessary to verify that the factor structure



Emotion and Mood. Fig. 1. Example of bipolar scales of pleasantness in a visual analog, likert, and labeled magnitude format.

of the existing measures is consistent when moving from an LS or VAS format to an LMS format.

Response Biases

A final consideration in self-report data relates to potential response artifacts that lead an individual to respond in a manner that is not representative of their true level of current mood. Response biases, including acquiescence biases, nay-saying biases, carelessness, and socially desirable response sets, all may contribute to error in the measurement of mood. However, such response artifacts do not invalidate mood ratings. They merely make it less accurate. Moreover, in some cases, it is possible to correct response artifacts or identify individuals with invalid data by specifically assessing for response biases. In summary, there continue to be challenges inherent to measures of emotion and mood, but through careful research design these measures can substantially contribute to psychopharmacological research.

Cross-References

- ► Arousal
- ► Liking
- ► Mesolimbic Dopamine
- ► Opioid
- ► Pharmokinetics
- ► Reward
- ► Wanting

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Emotional Learning

Definition

Learning paradigms that share one important characteristic, namely, that learning involves acquisition of an emotional state.

Emotional Learning and Memory

- ► Passive Avoidance

Emotional Numbing

Definition

Difficulties experiencing emotions, resulting in social distance, lack of interest in activities.

Emotional State

- ► Affective State
- ► Decision Making

Empathogen

- ► Entactogen

Empirically Based Treatments

Definition
Specific treatment interventions that have demonstrated effectiveness in clinical trials or interventions that are based on scientifically proven methods of change.

Cross-References
► Double-Blinded Study
► Randomized Controlled Trials

Emsam Patch

► Selegiline

Enantiomers

► Stereoisomers

Enantiomorphs

► Stereoisomers

Encoding

Definition
The acquisition of new information that leads to the establishment of at least a short-term memory.

Endo-3-(Diphenylmethoxy)-8-Methyl-8-Azabicyclo[3.2.1]Octane Methanesulfonate

► Benzatropine

Endocannabinoid Signaling

Definition
Alterations in synaptic plasticity that are produced by changes in endocannabinoid activation of CB1 cannabinoid receptors.

Endocannabinoids

Definition
Natural ligands for cannabinoid receptors, the receptors that mediate the pharmacological effects of the active compounds in the cannabis plant (marihuana). Among them is the appetite stimulating effects of this plant.

Endocytosis

Definition
A process by which a substance gains entry into the cell without passing through the plasma membrane; it involves invagination (the formation of a furrow) of the plasma membrane followed by membrane fusion by which an intracellular vesicle is formed. In this way, proteins that are incorporated in the plasma membrane can end up in the membrane of an intracellular vesicle.

Endogenous Factors

Definition
Internally generated influences on behavior.

Endogenous Opioid

Definition
The term endogenous opioid represents any substance produced by the body (to date these are all peptides) that interacts with MOR, DOR, or KOR receptors. Three genes encoding a range of endogenous opioid peptides have been identified: pro-opiomelanocortin, preproenkephalin, and prodynorphin.

Cross-References
► Endorphin
► Enkephalins

Endophenotype

Definition
An aspect of a phenotype that can in principle be related to underlying a genetic predisposition to a disorder and which provides a partial model or biomarker for a

recognized human disease state and related aspects of temperament. It is a marker for a heritable pathological condition and may also be present in non-affected relatives at a higher rate than in the general population.

Cross-References

► Animal Models of Psychiatric States
► Genetically Modified Animals

Endorphin

Definition

While this is popularly used as a term (endo-morphine) to refer to any endogenously produced and released opioid substance, it was originally defined (and still refers to) the small group of endogenous opioid peptides derived by peptidases from the proopiomelanocortin gene, which contains a single copy of the 31 amino acid peptide, β-endorphin, along with several other biologically active peptides. Other endorphins are shorter (active at opioid receptors) fragments of β-endorphin.

Cross-References

► Opioids

Enemas

Definition

Enema is the procedure of introducing liquids into the rectum and colon via the anus. Enemas are usually carried out as a treatment for constipation.

Energy Balance

Definition

The body maintains energy balance (EB) if energy intake (calories ingested and absorbed) matches energy expenditure (calories utilized by the body through basal metabolism, thermogenesis, and activity). If energy intake exceeds energy expenditure, a positive energy balance is achieved and excess calories are stored. Conversely, if energy expenditure exceeds energy intake, a negative energy balance is achieved and energy stores (in adipose tissue) are utilized. Sustained energy imbalance produces changes in body weight and composition.

Energy Intake

► Eating and Appetite

Energy Metabolism

Definition

Chemical energy has to be provided for brain function in the form of glucose and oxygen; glycolysis and mitochondrial respiratory chain activity are necessary to synthesize adenosine-tri-phosphate (ATP).

Engram

Definition

The material substrate or record of a particular item of memory. Also referred to as memory trace.

Enkephalinase

Definition

Enkephalinase is a neutral aminopeptidase enzyme (EC 3.4.24.11), initially thought to be responsible only for degradation of released enkephalins. It does, however, metabolize other peptides, and enkephalins are also subject to degradation by other peptidases. Nonetheless, direct application of enkephalinase inhibitors have been shown to produce opioid-like actions probably due to enhancement of endogenous opioid signaling.

Enkephalins

Definition

Two enkephalin ("in the head") pentapeptides were the first endogenous opioids discovered in 1975. They both contain the same amino acids in the first four amino terminal positions followed by either leucine ("leu-enkephalin") or methionine ("met-enkephalin") at the carboxy-terminal. Multiple copies of both peptides are contained in the large peptide precursor, preproenkephalin. Somewhat longer oligopeptide enkephalins have been

purified from various tissues, representing incomplete peptidase processing of the large precursore leu-enkephalin is also contained in the N-terminal sequence of dynorphins.

Cross-References
► Opioids

Entacapone

Synonyms
E-α-cyano-N,N-dietyl-3,4-dihydroxy-5-nitrocinnamamide

Definition
Entacapone (E-α-cyano-N,N-dietyl-3,4-dihydroxy-5-nitrocinnamamide) is a catechol-O-methyl transferase (► COMT) inhibitor, used for the treatment of Parkinson's disease in conjunction with L-DOPA. Entacapone prevents COMT from metabolizing L-DOPA, the dopamine precursor, in the periphery. Entacapone is always used in combination with ► L-DOPA for the treatment of Parkinson's disease, especially in those patients showing end-of-dose "wearing-off" signs. Entacapone is also available in a triple combination with L-DOPA and carbidopa, the DDC inhibitor, to further increase the half-life of L-DOPA.

Cross-References
► Anti-Parkinson Drugs

Entactogen

Synonyms
Empathogen

Definition
Entactogens are drugs, including MDMA (Ecstasy) and other MDxx structure compounds, that cause distinctive prosocial, emotional, and sensory effects in users. Most of them are substituted amphetamine compounds of the phenethylamine class.

Cross-References
► Ecstasy
► Methylenedioxymethamphetamine (MDMA)

Enterohepatic Cycling

Definition
Numerous drugs undergo elimination via the bile in the unchanged or conjugated form. Drugs eliminated in the bile are available for absorption in the gastrointestinal tract. This reentry into the body after "elimination" via the bile results in the "recycling" of drug and prolongs the time required for the drug to be irreversibly eliminated from the body.

Cross-References
► Area Under the Curve
► Bioavailability
► Distribution Phase
► Elimination Half-Life
► First-Order Elimination
► Pharmacokinetics

Entheogen

► Hallucinogen Abuse and Dependence

Entheogens

► Hallucinogens
► Ritual Uses of Psychoactive Drugs

Environmental Enrichment and Drug Action

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Synonyms
Drug effect; Stimulus enrichment

Definition
Environmental enrichment is a manipulation in which subjects are exposed to different environments that vary

in the amount of stimulus novelty. In the typical preclinical procedure, rodents are housed in either an enriched condition (EC) with novel objects and social cohorts or an isolated condition (IC) without objects or cohorts. In order to determine the relative contribution of novel objects and social cohorts, a separate group can also be housed in a social condition (SC) with social cohorts, but without novel objects. While enrichment is applied typically during the periadolescent period of development, it produces effects across the life span and it is reversible.

Current Concepts and State of Knowledge

Effects on Learning and Memory

The amount of stimulation received during childhood and adolescence has profound effects on behavioral and neurobiological development (Renner and Rosenzweig 1987). In rats, enriched environments produce numerous neuroanatomical changes, including increases in cortical weight, cortical thickness, size of neuronal cell bodies and nuclei, number of glial cells, number of dendritic spines, and number of synapses per neuron. Most likely as a result of these neurobiological changes, enrichment also improves performance on several measures of learning and memory. Differences are evident in some of the most basic behaviors, including activity in an inescapable novel environment and startle reactivity. In general, as task complexity increases, the difference in performance increases between EC and IC rats (Renner and Rosenzweig 1987). For example, while EC and IC rats do not differ in the acquisition of operant lever press behavior, EC rats perform better than IC rats in tests of spatial memory. EC rats process contextual conditioning cues more rapidly and display better discrimination between conditioned stimuli when compared to SC rats (Barbelivien et al. 2006).

Early research on environmental enrichment examined a variety of control conditions to determine if any one component of enrichment was most critical for producing the neurobiological effects related to learning and memory. Social stimulation alone is not sufficient to produce neurobiological changes similar to those observed with enrichment. Overall, this research suggests that cohorts, novel objects, and handling are all essential for robust enrichment. While neurobiological effects of enrichment are evident after just four days of enrichment, the effects are more consistent and reliable when rats are assigned to their respective environments after weaning and housed for 30 or more days.

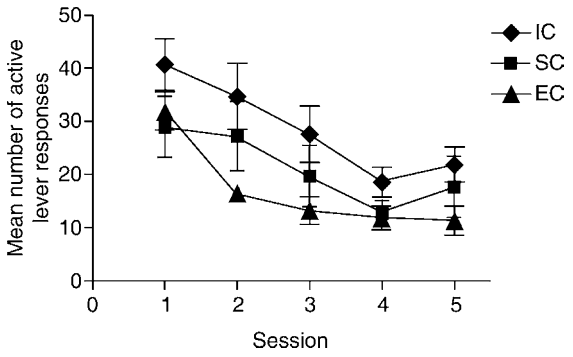
Effects on Drug Action

In addition to enrichment altering performance on a variety of measures of learning and memory, enrichment also alters the effects of a variety of drugs of abuse (Bardo and Dwoskin 2004). Several studies have examined the effects of enrichment on amphetamine-induced hyperactivity. EC rats display greater amphetamine-induced hyperactivity than IC rats following an acute injection of ▶ amphetamine. However, with repeated injections of amphetamine, IC rats display greater locomotor ▶ sensitization than EC rats. Similar results have been observed with cocaine and nicotine.

Interestingly, enrichment also appears to enhance conditioning to an amphetamine-paired context. Using the ▶ conditioned place preference (CPP) procedure, which is a measure of drug reward, EC rats display greater amphetamine CPP than IC rats. Similarly, using a low dose of amphetamine (0.3 mg/kg), context-dependent conditioned hyperactivity is obtained in EC rats, but not IC rats. Moreover, when the rate of ▶ extinction of conditioned hyperactivity is measured, EC rats extinguish at a faster rate than IC rats across a range of amphetamine doses. These results suggest that, in general, EC rats display a greater ability than IC rats to acquire and extinguish contextual conditioning of drug effects.

Numerous studies have examined the effects of enrichment on self-administration of stimulants, opiates, and sedatives. When drugs are available via the oral route, male EC rats increase their ▶ barbiturate consumption, but not their amphetamine consumption, when compared to male IC rats. Interestingly, female EC rats decrease their barbiturate consumption when compared to female IC rats, suggesting that sex can moderate the effects of enrichment. EC males also consume orally more ▶ cocaine and ▶ ethanol than male IC rats. The amount of oral ethanol consumption in male EC, SC, and IC rats also has been examined using a two-lever operant procedure in which one lever delivered 10% ethanol and the other lever had no programmed consequence. EC rats responded less than IC rats for oral 10% ethanol; SC rats were intermediate between EC and IC rats (Deehan et al. 2007, see Fig. 1), thus suggesting that enrichment may alter the reinforcing effects of oral ethanol itself.

Intravenous ▶ drug self-administration offers an advantage over the oral route because it eliminates the possibility that differences in taste reactivity may complicate interpretation of the results obtained. Several studies indicate that environmental enrichment decreases the self-administration of low unit doses of amphetamine and cocaine. In one initial study in which rats were trained to lever press for a low unit dose of amphetamine



Environmental Enrichment and Drug Action. Fig. 1. Mean number of active lever responses for oral 10% ethanol across five consecutive 30-min sessions in EC, SC and IC rats using a two-lever operant conditioning procedure. There was a main effect of group, with EC rats self-administering significantly less ethanol than IC rats; SC rats did not differ significantly from the two other groups. There was no difference between EC and IC rats in the number of responses on the inactive lever (which had no programmed consequence), although the number of inactive responses was negligible (~2 responses per session; results not shown). (From Deehan et al. 2007.)

(0.03 mg/kg/infusion) on a ► continuous reinforcement schedule, EC rats self-administered less amphetamine than IC rats; there were no differences between EC and IC rats at higher unit doses. A separate group of rats was trained to lever press for amphetamine on a ► progressive ratio schedule in which the number of lever presses required to earn a drug infusion increased until the rats stopped responding (i.e., breakpoint). As shown in Fig. 2, the ► breakpoint was significantly lower for EC than IC rats at the low unit dose, but not at the higher unit dose. These results suggest that enrichment decreases the reinforcing effect of amphetamine, but only at low unit doses.

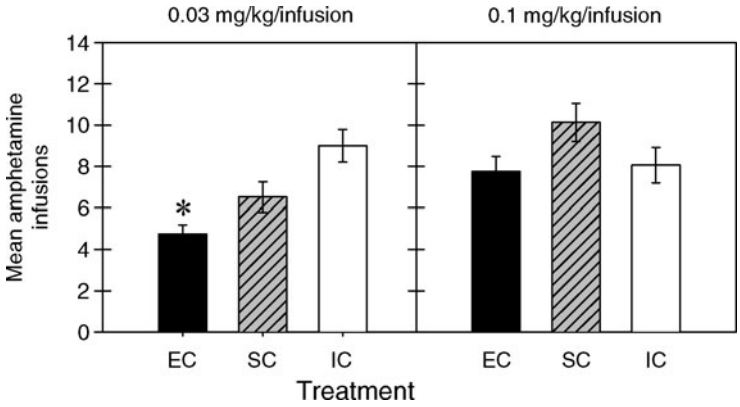
It is possible that the difference between EC and IC rats in amphetamine self-administration using low unit doses may reflect a difference in the rate of extinction or a difference in the ► reinstatement threshold. The rationale behind this possibility is that, at the beginning of each drug self-administration session, rats begin responding in a drug-free state. If a unit dose is too low, the responding may simply extinguish similar to what occurs when saline is substituted for drug. However, if several low dose infusions are earned in rapid succession, total drug intake may accumulate beyond some minimum threshold, thus engendering reliable responding within the session. Based on this notion, the decrease in amphetamine self-administration at a low unit dose in EC rats could represent either an accelerated rate of extinction within the session or an increase in the reinstatement threshold. A recent study using the reinstatement procedure found that EC rats extinguished responding faster than IC rats when amphetamine was replaced with saline (Stairs et al. 2006). When responding was reinstated following a noncontingent amphetamine priming injection, IC rats reinstated drug-seeking responses following a low dose prime, whereas EC rats only reinstated drug-seeking responses following a high dose prime. The higher reinstatement threshold in EC rats, taken together with a more rapid rate of extinction, may result in a loss of responding within the session, thus explaining the enrichment-induced reduction in drug intake.

Effects on Neurobiology Involved in Drug Action

Numerous studies have explored the neurobiological mechanisms that contribute to the ability of enrichment to decrease the reinforcing effect of drugs of abuse. Environmental enrichment increases thickness of the cortex, primarily by enlarging the size of neuronal cell bodies, increasing the density of dendritic spines and increasing the number of glial astrocytes. Metabolic activity is also enhanced, as revealed by an increase in the number of mitochondria and oxygenated capillary blood volume (Renner and Rosenzweig 1987). While these cellular changes also occur in subcortical regions such as the striatum, ► hippocampus, and ► nucleus accumbens, the ► prefrontal cortex appears to be especially sensitive to enrichment.

The ► medial prefrontal cortex (mPFC) has been implicated in the reinforcing effect of abused drugs, likely due to its inter-connections with limbic structures such as the anterior cingulate cortex and ► nucleus accumbens. Recent work has demonstrated that dopamine activity in mPFC is altered in EC rats compared to IC rats (Zhu et al. 2005). These investigators examined functional activity of the ► dopamine transporter (DAT). Compared to IC rats, EC rats have decreased DAT function as indexed by the velocity of uptake of [^{3}H] dopamine uptake into mPFC tissue slices. Measurements of DAT protein expression revealed that EC rats have less DAT than IC rats at the cell surface. Additionally, a recent study has shown that EC rats display a reduction in postsynaptic dopamine D1 receptors in mPFC (Del Arco et al. 2007). The enrichment-induced reduction in pre- and postsynaptic dopaminergic cellular processes in mPFC may reflect a compensatory decrease due to repeated stimulation of this cortical system by enriching stimulation.

Studies have shown that environmental enrichment also alters the neurochemical effects of various drugs of abuse. For example, when challenged with acute



Environmental Enrichment and Drug Action. Fig. 2. Mean number of amphetamine infusions earned by EC, SC and IC rats on a PR schedule of reinforcement using a unit dose of either 0.03 mg/kg/infusion (*left panel*) or 0.1 mg/kg/infusion (*right panel*). Asterisk (*) represents a significant difference from IC rats tested at the same unit dose, $p < 0.05$. (From Bardo and Dwoskin 2004.)

amphetamine, EC rats show a greater release of dopamine in the nucleus accumbens measured by in vivo ► microdialysis compared to IC rats. This enrichment-induced change is not specific to amphetamine, but appears to occur across various drugs of abuse. Alterations in reward-relevant brain regions likely play a role in the differential sensitivity of EC and IC rats to self-administer drugs of abuse.

In addition to dopamine, enrichment alters drug-induced glutamate release as measured by microdialysis (Rahman and Bardo 2008). ► Glutamate is an excitatory amino acid that has been implicated in drug reward. When challenged with amphetamine, EC rats show greater extracellular levels of glutamate in the nucleus accumbens compared to IC rats. Within the mPFC, EC rats also have increased glutamatergic tone compared to IC rats. This latter finding may be important from a drug abuse perspective because glutamatergic activity is not only important in drug reward, it may also be involved with behavioral inhibitory processes that become dysfunctional during the addiction cycle. While the effects of enrichment on the dopaminergic and glutamatergic systems contributes to the reinforcing effect of drugs of abuse, additional research is necessary to determine the interaction between these systems and the mechanism for the ability of environmental enrichment to decrease sensitivity to drugs of abuse.

Application to Humans

Teachers and educators are generally aware of the important role of enriching environments for promoting learning in children, adolescents, and young adults. In addition, there is considerable evidence that enriching stimulation, as provided by exercise and learning, protects against many neurodegenerative diseases that can occur later in life. While preclinical research indicates that enrichment also protects against drug abuse vulnerability, there is a paucity of information that addresses this issue specifically in humans. Nonetheless, genetic studies using twin concordance or familial assessment strategies indicate that the heritability of drug abuse is only around 40–60%, thus implicating a substantial role for environmental factors.

A recent study examined various summer programs implemented to promote healthy development among school-aged children and adolescents in order to determine the features that were important to demonstrate effectiveness (Bell and Carrillo, 2007). While a number of specific features were identified, a general conclusion was that the instructional techniques were most effective when academic learning was embedded in enriching activities. These results suggest that enrichment accelerates academic achievement and promotes positive development.

A more direct assessment of the effects of enrichment on human development and health-related risk was conducted by Raine et al. (2003). Children aged 3–5 years received enrichment or control treatment and were assessed subsequently in their young adulthood for personality disorders. Enrichment consisted of training in physical health, exercise, and multimodal enrichment provided by toys, art, handicrafts, drama, and music to improve verbal skills, visuospatial coordination, and memory. As young adults, enriched subjects had lower scores for schizotypal personality, antisocial behavior, and criminal

behavior (including drug-related charges) compared to control subjects. These results suggest that environmental enrichment during development protects against the emergence of drug abuse and associated personality disorders later in life. Further research is needed to determine what neurobiological alterations are associated with these long-term behavioral effects of enrichment.

Cross-References

- ▶ Conditioned Drug Effects
- ▶ Conditioned Place Preference and Aversion
- ▶ Operant Behavior in Animals
- ▶ Psychomotor Stimulant Abuse
- ▶ Psychomotor Stimulants
- ▶ Reinstatement of Drug Self-Administration
- ▶ Self-Administration of Drugs
- ▶ Sensitization to Drugs
- ▶ Sex Differences in Drug Effects

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Enzyme Induction

Definition

Process by which a molecule (e.g., a drug or a hormone) induces the expression of an enzyme, mostly by stimulation of protein synthesis.

Enzyme Inhibition

Definition

Inhibition of the catalytic activity of an enzyme by another molecule.

EOS

- ▶ Pediatric Schizophrenia

Epigenetics

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Synonyms

Chromatin remodeling; DNA-marking

Definition

The development of the idea and the first use of the term "epigenotype" occurred as far back as 1942 when Conrad H. Waddington suggested the existence of epigenetic mechanisms to explain the control of gene expression during cellular differentiation and maintenance of cellular identity. Implicit in the term epigenetics is that the mechanisms involved are labile (can be erased and reset), but also are heritable, in that they survive cell division. However, as the techniques required to directly analyze these epigenetic mechanisms have been developed and refined over the last two decades, it is now recognized that these same molecular processes can play an important information-coding role in post-mitotic tissues, such as occur in the brain. For the purposes of this review,

epigenetics can be loosely defined as the transmission and perpetuation of coding information that is not based on the alteration of the DNA sequence.

Principles and Role in Psychopharmacology

Mechanisms and Methods

The epigenetic code may be mediated via chemical marking of the DNA sequence itself (DNA methylation) and/or chemical tagging of ► histone proteins that bind DNA and are molecular tools by which gene expression levels are controlled. ► DNA methylation represents the simplest epigenetic process, and usually increased methylation levels at a gene loci equates to decreased expression of a gene. Most techniques to analyze DNA methylation rely on bisulfite treatment of the DNA. Here, bisulfite effectively deaminates methylated cytosines to uracils, providing a difference that can be detected by the direct assessment of the treated DNA sequence. Recently, methylated DNA immunoprecipitation (MeDIP) techniques, whereby an anti-5-methylcytosine monoclonal antibody is used to capture methylated genomic DNA fragments, have allowed a more global analysis of DNA-methylation.

Far more complex are the other epigenetic mechanisms related to ► chromatin modification. Differing histone protein modifications result in altered 3-D chromatin structures (open or closed), meaning the DNA sequences underneath are more or less accessible to transcription enzymes, which in turn leads to more or less gene expression. Applying ► chromatin immuno-precipitation (► ChIP) techniques, and utilizing recently developed antibodies that recognize specific histone modifications (acetylation, methylation, phosphorylation, etc.) to appropriately-processed tissue preparations, captures those stretches of DNA bound by these modified chromatin proteins. The relative abundance of a specific DNA sequence in a ChIP preparation allows the quantification of, for instance, Histone H3 acetylation at a given gene. However, unlike DNA methylation, the histone code is less easy to "read," due to the many different types of histone proteins and possible modifications.

The analysis of both DNA methylation and chromatin modification is likely to greatly benefit from the next-generation sequencing techniques (Mardis 2007). Previously, the final analysis of ChIP and MeDIP experiments was either target driven, using quantitative PCR measurements of specific genes, or coupled to microarray technologies (ChIP-on-chip) for a more global analysis of which genes were epigenetically modified. However, microarrays are limited by what is represented on the array itself. The next-generation sequencing technologies are capable of producing tens of millions of sequence reads during each instrument run, and identify *any* stretch of DNA that is marked by a given epigentic modification, effectively. Furthermore, ChIP-seq and MeDIP-seq offer other important advantages, including lower cost, minimal hands-on processing, and a requirement for fewer replicate experiments, which are of great importance in the analysis of epigenetic changes in discrete brain regions, and less input material.

Epigenetics and Neurodevelopment

As originally suggested, epigenetic mechanisms are crucial in determining cell programming and, consequently, development. Therefore, it is no surprise that epigenetic processes are implicated in a number of neurodevelopmental disorders. Some of these, such as Rett syndrome (altered DNA-methlyation and histone recruitment) and Rubinstein–Taybi syndrome (altered chromatin binding protein), are caused by a disruption of an epigenetic mechanism *per se* and consequently have greater effects on downstream genes thoughout development. Others are due to less global changes, but are caused by the disruption of the regulation of genes that are particularly sensitive to variations in epigenetic control. A good example of these are Angelman (AS) and Prader–Willi (PWS) syndromes, which are caused by mutations of a cluster of ► imprinted genes on Chr. 15q11-q13 that are particularly important for brain function (Wilkinson et al. 2007). The imprinted genes are subject to tight epigenetic regulation that results in expression of these genes from one parental allele (copy of gene) only; most genes are expressed from both the maternally and paternally inherited copies. The expression of imprinted genes is controlled by a combination of differential DNA methylation and histone recruitment to the parental chromosomes, and as a consequence any disruption of these epigenetic process leading to an inbalance in expression of these genes in turn results in abnormalities.

Many of these neurodevelopmental syndromes are quite severe, often resulting in mental retardation. However, there are also commonalities in terms of behavioral problems with other non-syndromic psychiatric illnesses, in particular autistic-like symptomology. These overlapping behavioral and cognitive problems may point to a common underlying mechanism (Wilkinson et al. 2007). This raises the possibility that more subtle alterations in the epigenome may contribute to the vulnerability to mental illness, particularly when in combination with an existing genetic predisposition (Isles and Wilkinson 2008).

Labile Epigenetic Mechanisms in the Brain

Although many epigenetic modifications are developmentally determined, there is also an inherent lability in some, and these provide a molecular mechanism by which environmental events may be integrated and translated into changes in the control of gene expression. A striking example of the epigenome's ability to alter has recently been shown by examining changes in DNA methylation and histone modification at the genome level over time. In monozygotic twins, where the DNA code is identical, the epigenome of twins diverged with age (Fraga et al. 2005), suggesting that this may be a molecular mechanism by which differing life experiences are encoded.

Although the idea of a role for epigenetic modifications in neural processes was posited many years ago (Crick 1984), it is only very recently that the tools and techniques have become available to investigators. One key area where the recently developed methods have been applied is in the study of molecular mechanisms underlying drug addiction. Work in animals models has examined the epigenetic processes involved in regulating the changes in control of expression of these genes by using behavioral neuroscience techniques combined with DNA-methylation and ChIP analysis on samples from key regions of the brain.

The expression of the Fos (*cFos, FosB*) family of transcription factors is correlated with the switch between acute and chronic ► cocaine exposure. Upon first exposure, these are highly expressed; however expression becomes desensitized upon repeated cocaine dosing. Conversely, chronic exposure results in the accumulation of *ΔFosB*, an alternative transcript from the *FosB* gene promoter. The control of this change in expresion is due, in part, to a subtle switch in chromatin modification at the *FosB* promoter (Kumar et al. 2005). Acute exposure results in increased acetylation of Histone H4, but upon repeated exposure (and indeed self-administration) there is increased acetylation of Histone H3. Interestingly, it seems that the accumulation of *ΔFosB* also mediates the desensitization and epigenetic silencing of another Fos transcription factor, *cFos*, following repeated simulant exposure (Pulipparacharuvil et al. 2008). Taken together, these data indicate that chromatin remodeling is an important mechanism underlying stimulant-induced neural and behavioral plasticity.

These techniques have now been applied to many other models of neuro- and psychopathology, and indicated that epigenetic factors such as DNA methlyation and chromatin remodeling may be important here too. These include the regulation of neural changes related to learning and memory (Miller and Sweatt 2007) and stress and depression (Tsankova et al. 2006).

Advantages and Limitations

The methods to examine DNA-methylation and chromatin modification that have been developed over the last decade or so allow us insight into the epigenetic control gene expression. Furthermore, these techniques have provided evidence for a biochemical system which can encode life events – environmental pressures and stressors being of particular importance to the vulnerability to psychiatric illness. However, in most cases, the existing techniques have been applied in animal models, as, in the majority of cases, the availability of suitable samples limits clinical studies of epigenetic changes to surrogate tissues such as blood and unlike sequence information (i.e., genetics), the extent to which surrogate tissues tell us anything about epigenetic changes occuring in brain is, at best, uncertain.

Additionally, although epigenetic mechanisms are clearly of potential clinical relevance, a key question is whether they are accessible to pharmacological intervention. There are a number of ► histone deacetylase (HDAC) inhibitors and ► DNA methyltransferase inhibitors that are currently being used and/or tested as anticancer drugs. However, how applicable these are in potentially treating neuropsychiatric disorders is not clear – although, ► valproate has HDAC inhibitor properties and may, in part, exert its action through epigenetic effects on the schizophrenia candidate gene *Reelin* (Guidotti et al. 2009). Currently, a major problem exists between the specificity of the epigenetic changes that may occur in response to a given environmental or developmental challenge in a specific population of brain cells, and the relative nonspecificity of the drug armory available to manipulate epigenetic mechanisms. Essentially, at present this is limited to HDAC and DNA methyltransferase inhibitors. Hence, experimentally, it can be difficult to prove causal significance between a change in behavior, or some other aspect of brain function, and a specific epigenetic change in a specific gene. Additionally, the current nonspecificity of the drugs available may limit therapeutic applications due to unwanted side effects. What is urgently needed are more selective drug agents able to interfere with particular epigenetic modifications that can be targeted somehow to particular genes. This would be a major step forward, not just for psychopharmacology, but for the use of such drugs across a wide range of other conditions, especially cancer. It is hoped that the ongoing epigenome project (http://www.epigenome.org/) and other

initiatives, focused on the structural and allied medicinal chemistry (for instance, see http://www.sgc.ox.ac.uk/chemicalprobes/) aspects of chromatin functioning will provide potential solutions to this limitation.

Cross-References

- ▶ Chromatin
- ▶ Chromatin immuno-precipitation
- ▶ DNA methylation
- ▶ DNA methyltransferase inhibitors
- ▶ Gene expression
- ▶ Gene transcription
- ▶ Histone
- ▶ Histone acetyltransferase
- ▶ Histone deacetlyase
- ▶ Histone deacetylase inhibitors
- ▶ Imprinted genes
- ▶ Learning & Memory: Molecular Mechanisms
- ▶ Trichostatin A
- ▶ Valproate

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Episodic Memory

Definition

The capacity to mentally travel back in time to reexperience personal events.

Epival

- ▶ Valproic Acid

EPS

- ▶ Extrapyramidal Motor Side Effects
- ▶ Movement Disorders Induced by Medications

EPSPs and IPSPs

Synonyms

Excitatory postsynaptic potentials; Inhibitory postsynaptic potentials

Definition

An excitatory postsynaptic potential (EPSP) is the change in membrane voltage of a postsynaptic cell following the influx of positively charged ions into a cell (typically Na+) as a result of the activation of ligand-sensitive channels. This results in a depolarization of the postsynaptic cell, thus increasing the likelihood of action potential propagation. These excitatory synapses serve to increase excitability in neurones. Conversely, inhibitory postsynaptic potentials (IPSPs) result from the influx of negative ions (e.g., Cl−) into, or the efflux of positive ions (e.g., K+), out of the postsynaptic cell. This results in cell hyperpolarization and thus decreases the likelihood of action potential propagation, and therefore represent inhibitory synapses. Both types of postsynaptic potential are graded and therefore sum together to have a cumulative excitatory or inhibitory effect.

Cross-References

- ▶ Action Potential

Equilibrium Dissociation Constant

Synonyms

K_D

Definition

Reciprocal of affinity. Equal to the ratio of the rate at which a ligand-receptor complex dissociates into the

separate reactants to the product of the reactants at equilibrium, $K_D = k_{off}/k_{on} = [L][R]/[LR]$.

Erectile Dysfunction

Definition

Erectile dysfunction is a sexual dysfunction characterized by the inability to develop or maintain an erection of the penis sufficient for satisfactory sexual performance. There are various and often multiple underlying causes. The most important physiological causes include cardiovascular disease, diabetes, and drug side effects. Often psychological or relational problems are implicated as well. Besides treating the underlying causes and psychological consequences, the first-line treatment of erectile dysfunction are PDE5 inhibitors, for example, sildenafil (Viagra), vardenafil (Levitra), or tadalafil (Cialis).

Cross-References

- ▶ PDE5 Inhibitors
- ▶ Sildenafil

Ergot

Definition

Ergot is the general name for the sclerotia from any of the species of the fungus *Claviceps* that infects grain crops. It produces the ergot alkaloids, which are very toxic, and in earlier times were responsible for outbreaks of ergotism, or St. Anthony's fire, where peripheral vasoconstriction could lead to gangrene and necrosis of the fingers or toes, and typically accompanied by hallucinations and bizarre behavior. Ergotism was caused by eating bread that had been made from ergot-contaminated flour. The ergot alkaloids have served as the starting materials for a number of valuable therapeutic agents such as ergonovine. Basic hydrolysis of ergot alkaloids leads to production of lysergic acid, the starting material for LSD.

Erotomania (Also Known as De Clerambault's Syndrome)

- ▶ Delusional Disorder

ERP

- ▶ Cognitive Behavioral Therapy
- ▶ QT Interval

ERP Components

- ▶ Event-Related Potentials Components

ERPs

- ▶ Event-Related Potentials

ES

- ▶ Electrospray Ionization

Escitalopram

Definition

Escitalopram is a selective serotonin reuptake inhibitor (SSRI). It is commonly used in the treatment of depression and anxiety disorders (e.g., obsessive–compulsive disorder, panic disorder, social anxiety disorder, generalized anxiety disorder). As with other SSRIs, the most troublesome side effect of escitalopram is sexual dysfunction (dysorgasmia and erectile dysfunction); mild side effects include drowsiness, headache, and nausea. Escitalopram is the *S*-enantiomer of racemic citalopram, which is also marketed as an antidepressant.

Cross-References

- ▶ Antidepressants
- ▶ Citalopram
- ▶ Selective Serotonin Reuptake Inhibitors

ESI

- ▶ Electrospray Ionization

Establishing Operation

Definition

Any operation that temporarily alters the effectiveness of a consequence as a reinforcer of behavior. The most commonly used establishing operation is deprivation. Establishing operations also temporarily increases the probability of behavior that has been reinforced previously by the event/stimulus whose reinforcing efficacy is increased.

Estazolam

Definition

Estazolam is a benzodiazepine derivative possesses anxiolytic, anticonvulsant, sedative, and skeletal muscle-relaxant properties. It is prescribed for the short-term treatment of certain sleep disorders. It is an effective hypnotic drug showing efficacy in increasing the time spent asleep as well as reducing awakenings during the night. Combination with non-pharmacological options for sleep management results in long-term improvements in sleep quality after discontinuation of short-term estazolam therapy. There are concerns that estazolam may have abuse potential when drug use is continued against medical advice.

Cross-References

► Anxiolytics
► Benzodiazepines

Estrogens

Definition

Estrogens are a class of hormones with 17β-estradiol being the most potent estrogen and the primary estrogen product of the ovary; other estrogens are metabolites of 17β-estradiol.

Eszopiclone

► Benzodiazepines

Ethanal

► Acetaldehyde

Ethanol

► Alcohol
► Alcohol Abuse and Dependence

Ethical Issues

Definition

Ethical issues are a set of moral principles, relating to or affirming a specified group, field, or form of conduct.

Ethical Issues in Animal Psychopharmacology

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Synonyms

Justifications; Morals; Philosophical basis

Definition

Justification for the care and use of animals in Psychopharmacology research is based on philosophical arguments, moral principles, and general consensus of reviewing boards and governing agencies.

Current Concepts and State of Knowledge

While the use of animals by humans for many purposes (e.g., food, labor, transportation) goes back to prehistoric times, and the use of animals for scientific research goes back several centuries; in the last several decades, the use of animals for research has generated controversy. Researchers have dedicated their lives to developing life-saving treatments through the use of animals, yet groups of activists believe that animals are not our property or subject to our control and experimentation. Thus, consideration of ► ethical issues is at the forefront of psychopharmacology research. This essay explores the ethical

use of animals in terms of whether animals should be used, how their use should be regulated, how their use has influenced psychopharmacological research, and what is the best animal to study. There are sources that have debated these ethical issues and provided examples of the ethical use of animals in psychopharmacological research to promote the health of humans and other animals (e.g., Carroll and Overmier 2001).

Ethical Considerations: Should Animals Be Used?

There have been several philosophers over the last few centuries who have addressed the issue of the use of animals in research. The use of animals for research can be traced back to the seventeenth century with René Descartes, a French philosopher/scientist (Descartes 1637). He established experimental methods for scientific investigation including his precepts never accept anything for true that is not clearly known to be such, divide difficulties into parts, analyze from simple to complex, and make complete descriptions of your experiments. His work became the basis of the Cartesian coordinate system and the histogram. He also dissected live animals and compared animals to machines without reason, soul, mind, or human intelligence. Descartes' dualistic beliefs divided the body and mind into separate entities.

In the eighteenth century, German philosopher, Immanuel Kant, addressed the issue of human rights and virtue (Kant 1785). He said that animals do not have rights or duties. Moral rights are given and received by humans, not among animals. Humans have obligations and can make moral claims with other humans, but nonhuman animals do not have moral obligations or rights. However, Kant recognized that animals have feelings and needs and that humans have a moral obligation to treat them well with human dignity.

Peter Singer is a utilitarian philosopher whose book entitled *Animal Liberation* (Singer 1975) ignited the animal liberation cause. ► Utilitarianism requires that a moral act should result in the greatest good (i.e., happiness) for the greatest number of people. Singer states that since humans and ► sentient animals can suffer, they are equally entitled to moral concern, and exclusion of animals from our moral concern is discriminatory (which he calls speciesism). Singer does allow for animal research only if its benefits greatly outweigh the harm done to animals. However, the question that remains is whether greater happiness is the only thing that matters when determining if something is morally correct?

Thomas Regan (1985) is another philosopher who is concerned with the moral status of nonhuman animals. He rejects the utilitarian claim on the basis of animals' ability to suffer, and states that nonhuman animals have rights simply because they have inherent value. He disagrees with Kant's idea that moral rights should only be ascribed to humans. However, he admits that when having to choose between a human and an animal's life, the human should take priority.

Carl Cohen is a philosopher who returned to Kant's ideas of moral rights for humans (Cohen 1986). He states that rights arise only among organisms (i.e., humans) who can make moral claims against one another. Animals cannot respond to moral claims and they cannot evaluate the conflict that may arise between their self-interest and what is just. He believes that we have obligations to animals to do no gratuitous harm (the principle of nonmaleficence) and to do good for animals within one's power (the principle of beneficence). He states that most people will agree that we should treat animals humanely, with decency and concern as sensitive human beings, but not as holders of human rights. In addition, morality is a basis for many of our laws, and when these laws are broken, a crime is committed. An animal cannot commit a crime because it does not understand morality or the concept of being guilty.

Adrian Morrison, a veterinarian and Professor Emeritus from the University of Pennsylvania, has thought and written extensively on the human–animal relationship. He has also endured attacks from animal activists for his defense of animal research. In a new book, Morrison (2009) points out the symbiotic nature of humans and nonhuman animals and the need for animal welfare laws that will maintain the health and well-being of both humans and nonhuman animals. He stresses that humans have a special obligation to provide excellent care for those animals under their control (e.g., pets, farm, zoo, research). He explains that animals used in research are supervised by veterinarians, protected by extensive legislation, and are housed and maintained by standards that far exceed any other form of animal husbandry.

How Should Animals Be Used?

The use of animals for research in the U.S.A. is highly regulated by the ► Animal Welfare Act (2006), the National Institutes of Health (NIH) regulations, Guide to Scientific Research, the National Research Council, and rules of the editorial boards of scientific journals. Before an animal can be used in research by a qualified and trained scientist, the care and use of the animals and the rationale for the research must be approved by a local ► Institutional Care and Use Committee (► IACUC) and the work is monitored by the US Department of Agriculture (USDA). There are frequent inspections, in some

cases unannounced (USDA), and follow-up visits if questions arise. IACUC applications must be resubmitted and reviewed every 3 years. Animal and research facilities must be maintained to extremely high standards and supervised by veterinarians who require strict compliance with the NIH and USDA rules for the care and use of the animals. In addition, the facilities that house animals are tested for temperature, humidity, and air quality and flow, and high standards are maintained. The NIH, major research centers (e.g., Sloan-Kettering Cancer Center, and St. Jude's Children's Research Hospital, the American Red Cross), and most large universities have accreditation from a review board, such as the American Association for the Assessment and Accreditation of Laboratory Animal Care (AAALAC), which reviews care, training, and physical plant issues regarding the care and use of animals in research. Animal research facilities have also become much more secure in recent years, due to the attacks and destruction of extremists. This prevents activists from releasing animals to a harmful environment and maintains the integrity of the research, but the downside is that the high level of security distances the research from the general public who funds most of the research and deserves to know about it.

The Use of Animals in Psychopharmacological Research

There are two main areas in which animal models are used for psychopharmacological research. The first is to study the etiology and neurobiology that underlies psychiatric disorders affecting humans. Research on these disorders is funded by the NIH institute, the National Institute on Mental Health (NIMH), and many other public and private organizations. Goals of these research institutes are to study brain disorders, some that develop early in life, such as ► attention deficit hyperactivity disorder, ► eating disorders, drug ► dependence, mood disorders such as ► anxiety and ► depression, personality disorders (e.g., antisocial), ► schizophrenia, and those occurring later in life such as Alzheimer's and other forms of ► dementia. Animal models that are reliable and have predictive validity have been developed to represent many of the DSM-IV (American Psychiatric Association 1994) diagnostic criteria for substance abuse, and animal studies have identified the underlying causes of these disorders and tested medications to treat them. Since many of these conditions involve a gene, environment, development, interaction, and ► neurobiological manipulations are necessary, they can only be conducted with animals, and those results have been most informative for advancing the treatment of mental illness. Animal research has been crucial to the development of many medications that allow mentally ill individuals to live normal, productive lives.

The second area is considered a subset of the first, but the problem (► drug abuse) is so immense that there are two other NIH institutes that represent it: the National Institute on Drug Abuse (NIDA) and The National Institute on Alcohol Abuse and Alcoholism (NIAAA). Deaths due to drug abuse, particularly tobacco use, approach nearly half a million a year; thus, understanding the etiology and neurobiology of drug abuse and developing effective treatment strategies is a national priority. Again, the abuse of drugs begins at an early age and involves factors (genetic, developmental, and environmental) that are difficult to prospectively study and experimentally control in humans; thus, animal models are essential to advance our knowledge. As is the case with the first area, there are critical scientific approaches that can only be done with animals, such as neurobiological assays, embryonic and developmental studies, and neuroimaging (PET), which cannot be done with children under 18.

It is also important to study factors that influence all phases of drug abuse, such as initiation, maintenance, escalation (binging), withdrawal, and relapse, as in humans drug abuse is a chronic relapsing disease. However, several of these phases are difficult to study prospectively in humans such as initiation and escalation or ► binge use of the drug, as it is unethical to introduce drugs to young teens or to encourage escalation of drug use in current users. Relapse is also difficult to control and study in humans, as it would be unethical to promote the reinstatement of drug use in abstinent individuals. While adult human drug users can be studied in the laboratory, it is difficult to interpret the data because their histories are varied and their self-report measures are unreliable. Furthermore, human subjects are not always compliant with instructions for medication use or nonuse of drugs of abuse prior to laboratory visits. They are often not available for extended periods of time that are required to study the variables related to the study, and absences are a problem for data collection.

The use of animals in drug abuse research has led to our recognition of the main transition phases associated with drug abuse (initiation, persistence, escalation, and relapse), and the efficacy of pharmacological and behavioral interventions may vary with phases of drug abuse (Carroll et al. 2009). Animal research has also informed us that individual factors such as age, sex, hormonal status, ► impulsivity, sweet preference, and a proclivity for exercise predict vulnerability to drug abuse. Recent studies with animals that have translated well to humans revealed the behavioral economics of drug abuse that describe the compulsive nature of this disorder. Emerging

evidence from animal research has also connected many common behavioral and neurobiological features of drug addiction with excessive eating in animals and humans, and principles resulting from these animal studies will be useful in understanding and treating the obesity epidemic. Rodent studies also identified environmental determinants such as stress and whether the individual is in an enriched versus impoverished environment are also critically important to the development of drug abuse and the chronically relapsing nature of it.

These vulnerability factors, which apply to drug abuse and other psychiatric disorders, were primarily identified through the use of animals in research. With rats, it was possible to discover that the sex differences in drug abuse and related disorders are accounted for by the ovarian hormones and to manipulate the hormonal milieu to compare behavior over phases of the estrous cycle in rodents or the menstrual cycle in nonhuman primates (NHP). Through ► selective breeding in rat or selection of high and low behavioral phenotypes in a large group of rats, it has been possible to relate sweet preference, impulsive behavior, or a proclivity for exercise for an avidity to self-administer drugs of abuse. Adolescence is a critical period when vulnerability to drug abuse is at its peak. We know that is true in humans, but is it cultural or developmental/physiological? Animal studies have indicated that in adolescence there is a confluence of hormonal surges, dietary influences, elevated impulsivity, risk taking, reactivity to stress, and aggression in adolescents, and these factors explain the vulnerability of adolescents to drug abuse, and other addictive behavior (e.g., food consumption), and their examination in animals will be important for developing prevention strategies for humans.

What Animals Should Be Used?

As animals are used in the evolution of research in psychopharmacology, more knowledge is gained about the species that provides the best representation of human behavior, both with respect to understanding the disorder and to the effectiveness of treatment. Mice, for example, have been invaluable for conducting gene knockout studies to elucidate the neurobiological bases of psychiatric disorders, and genetically altered mice have shown remarkable improvement in an animal model of Alzheimer's. Rat studies have been useful for developing animal models for depression, anxiety, drug abuse, and other disorders. Rat studies also allow for group comparisons including dose–response analyses and control conditions. Much of the behavioral pharmacology research that has been conducted in rodents has generalized well to results obtained in NHP and humans.

A disadvantage of rodent studies is that in some cases pharmacological agents that are efficacious in rodents are not always translatable to humans. For example, medications that prevent and reduce cocaine self-administration in rats (e.g., Prozac) have not always been successful to treat cocaine abuse in humans. It may be a species difference in metabolism or ► pharmacokinetics or the composition and distribution of receptors in rodent versus primate brains. NHP models offer access to the genetic, environment, early development, interaction that leads to the onset of mental illness in young adults. Psychopharmacology research in NHPs is closely translatable to humans, and there are several advantages of using NHP in this research; for example, NHPs have a similar, although condensed, developmental period, hormonal cycle, and life span compared to humans. Their long life span (up to 40 years) allows for examination of all ages and longitudinal studies. For drug abuse studies, NHPs are more amenable to being trained to drink or smoke drugs, modes of drug use that represent the most common forms of drug abuse in humans (Weerts et al. 2007). In contrast, rats are neophobic about drinking drugs; thus, self-administration studies are typically limited to the iv route.

It is important for researchers who use animals to recognize when an animal species is a good model for psychopharmacological research and when it is not, and the more animal models are used, more valuable feedback is provided about their validity in terms of what aspects of psychopharmacology can be successfully modeled in humans. For example, factors developed using rodent research on the relapse model have provided information about factors that trigger relapse and treatments that prevent it in humans (e.g., ► naltrexone for alcohol abuse). In contrast, mice may not be the best model for immunological research; thus, testing the newly developed ► vaccines for cocaine, methamphetamine, and nicotine may not be optimal in rodents. Thus, it is also important to recognize when we do not yet have a suitable animal model for the psychopharmacological research.

In conclusion, ethical issues in animal research have been discussed for centuries, and animal research is considered legal, and it is widely used but highly regulated. The US government sanctions and supports animal research, contingent upon adherence to strict guidelines and multiple forms of oversight from national and local boards. As a result, using animals over the last several decades, animal research in psychopharmacology has made important advancements in understanding underlying neurobiological mechanisms and in the development of psychotropic medications for psychiatric

disorders. Psychopharmacological research in the area of drug abuse has also gained important information from animal research regarding the genetic, neurobiological, and behavioral precursors of drug abuse. As a result, there are now successful treatments available for the most common forms of drug abuse (alcohol and tobacco use), and new treatments for psychostimulant drug abuse are on the horizon.

Cross-References

- ▶ Abuse Liability Evaluation
- ▶ Addictive Disorder: Animal Models
- ▶ Aggression
- ▶ Animal Models for Psychiatric States
- ▶ Anxiety: Animal Models
- ▶ Autism: Animal Models
- ▶ Behavioral Economics
- ▶ Cocaine Dependence
- ▶ Construct Validity
- ▶ Depression: Animal Models
- ▶ Eating Disorders: Animal Models
- ▶ Environmental Enrichment and Drug Action
- ▶ Face Validity
- ▶ Genetically Modified Animals
- ▶ Impulse Control Disorders
- ▶ Intracranial Self-Stimulation
- ▶ Open Field Test
- ▶ Operant Behavior in Animals
- ▶ Perinatal Exposure to Drugs
- ▶ Phenotyping of Behavioral Characteristics
- ▶ Predictive Validity
- ▶ Prepulse Inhibition
- ▶ Primate Models of Cognition
- ▶ Reinforcement Disorders
- ▶ Reinstatement of Drug Self-Administration
- ▶ Rodent Models of Cognition
- ▶ Schizophrenia: Animal Models
- ▶ Self-Administration of Drugs
- ▶ Sensitization to Drugs
- ▶ Sex Differences in Drug Effects
- ▶ Sex Hormones
- ▶ Social Stress
- ▶ Stress: Influence on Drug Action
- ▶ Translational Research
- ▶ Vaccines
- ▶ Withdrawal Syndromes

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Ethical Issues in Human Psychopharmacology

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Synonyms

Ethics of placebo prescription; Ethics of prescription

Definition

The application of ethical issues to the development, research, production, approval, marketing and prescription of psychotropic drugs to be used with human beings.

Ethics (from the Greek *ethos* "character") is that branch of philosophy systematically studying the nature of values relating to human conduct, with respect to the rightness and wrongness of actions and to the goodness and badness of the motives and ends of such actions. It seeks to address questions about morality, such as what nature of ethics or morality is (meta-ethics), how moral values should be established (normative ethics) and how morals be attained in specific situations (applied ethics).

The word ethics also refers to a system of moral principles (i.e., the ethics of a culture) or rules of behavior

assumed or mandatory in respect to a particular class of human actions or a particular group (i.e., bioethics, medical ethics).

Current Concepts and State of Knowledge

Psychopharmacology is an achievement of many players. The indispensable performers are the industry, which produces drugs, the researchers, who conceive new substances and test them, the Administration, which gives the final approval to medicaments, the doctors, who prescribe them and the patients, who take them. There are also other secondary players such as the shareholders who expect profits from their investment, those who are involved continuous medical education and policy makers at national and international levels. Although the final goal may be common, namely, to improve the condition of patients and to increase the overall health, their values may be different and therefore conflicting.

The ethics of medicine has three main sources that are often considered as stages in its development although all of them are present nowadays: (1) the ethics of welfare, which are the traditional medical ethics. From this perspective, the duties of doctors are the wellbeing of the patients and the harm to be avoided; (2) the ► ethics of autonomy, which considers that the patient is an autonomous human being, adult, free and, able to take his or her own decisions. Consequently, doctors have to inform patients about all possible diagnoses and treatments so that patients are able to decide and (3) the ethics of equity, also known as the ethics of management, which are the consequence of the impact of economic factors in medicine. From this perspective, the goal of health care is the equal access to health care resources for all patients and a larger level health care is only one among several needs and rights of citizens.

These three forms of ethics are present in different proportions in the performers mentioned above. As a result, the disagreement among them is often profound and therefore the number of guidelines, recommendations, rules, consensus documents, and regulations is overwhelming.

It is not easy to deal with the conflicts of values mentioned above, yet the perspective of ► Values-Based Medicine (Fulford) can be very useful when faced with conflicts of interests and values. Values-Based Medicine is the theory and practice of effective healthcare decision-making for situations in which legitimately different, and hence potentially conflicting, value perspectives are in play. Values-Based Medicine is a response to the growing complexity of the relevant values and it is a skills-based counterpart of the currently dominant quasi-legal form of clinical bioethics. Quasi-legal ethics prescribes "good outcomes" in the form of increasingly complex ethical rules and regulations. Values-Based Medicine emphasizes the importance of good process in the form particularly of improved clinical practice skills.

The Prescription of Psychotropic Drugs

Prescription of medicines is a basic aspect of clinical practice and it is responsibility of every clinician, which cannot be hangover to anybody. The prescription should follow full information from the doctor on the consequences, opportunities and dangers of taking it, or of not taking it, and of the available alternatives.

Yet, there have been discussion on several issues such as the obligation of informing the patient having in mind the goal of committing suicide, about the possible lethality psychotropic drugs that can help them to choose a ► tricyclic antidepressant instead of an SSRI because of the higher lethality of the older drug. In spite of these difficulties, it seems that patients should know that with some drugs the risk of death by poisoning is very elevated and to control the risk of suicide by other means. The issue for the clinician is not lethality, it is suicidality.

Confidentiality is an essential component of patient–doctor relationship and it includes the prescription of drugs.

Prescription is not an exclusive act in the framework of patient–doctor relationship, as all the partners mentioned above may interfere with it or may have the right of some input or control over it. Family members, the public and private health care administration, institutions, and even the legal system may claim a say on prescription. For that reason, it is the obligation of the doctor to maintain a level of professional formation and independent information, to allow him or her to make, at any moment, a rational, free and ethical decision in the best interest of the patient.

The fact that psychiatric classifications since 1980 rely on symptoms to make the diagnosis of a mental disorders has strong ethical implications which are absent when dealing with diagnoses based on any sort of pathology. A psychiatric diagnosis is based on the presence of a number of criteria selected from a set. If the number or the presence of some important criteria are absent, then the patient may suffer from a subsyndromal condition. Should it they be treated?

In most of the cases, psychiatric symptoms are also present in non-psychiatric populations. Consequently, other secondary criteria had to be added, such as suffering and disability. Both, suffering and disability are value-based concepts impossible to define scientifically. The levels of suffering and disability can be manipulated as

well as the criteria for diagnosis, leaving the door open for possible abuses.

Informed Consent in Severe Psychiatric Cases

There are differences in the legislation and practice in different countries concerning the requirement of consent on the part of psychiatric patients, depending on their level of mental capacity. Some countries like the United Kingdom have laws that authorize doctors to implement treatment in such cases: the doctor must exert his power justly and exclusively in the best interests of the patient. In Spain the fact that a patient is legally admitted does not automatically permits a prescription against the will of the patient, therefore an informed consent should be looked for; if this is not possible, the clinician has to follow the rules of good clinical practice and, above all, fulfill his duties as a clinician. Other countries such as Italy are very strict with long acting antipsychotics without the consent of the patient. The fact that compulsory ambulatory treatment is becoming possible in many countries is helping very much in difficult cases. A few decades ago, the impact of antipsychiatric propaganda and the stigma of mental disorders prevented such kind of forced prescriptions. Yet, the importance given in the media to tragic cases of homicides by untreated psychiatric patient or by those who interpreted treatment on their own has changed the public perception and attitudes. Clinicians should be aware that again, conflicting values are in conflict in these problem and that their duty is to try to establish an inspired doctor–patient relationship and as a consequence to safeguard the dignity of patients.

Several studies show that a substantial number of hospitalized chronic mental patients do not have the capacity to appreciate the risks and the benefits of the anti-psychotic medication[2].

The Ethics of Placebo Prescription

The term "drug" conveys a magical element, which is clearly manifested in the power of the ▶ placebo, and not only in psychiatric settings. Sometimes, this form of behavior is due to the lack of an effective treatment for a specific disease, but in others, it is simply to be freed of the pressure of the patient and their relatives. Independently of the cost of such behavior, placebo prescription outside of research protocols is a violation of the doctor–patient relationship. A doctor acting as such can only behave as a doctor. The Madrid Declaration is clear about it. If circumstances force him or her to take decisions that a clinician should not undertake, he or she could nevertheless proceed with them in order to prevent important harms, but with the clear knowledge that this may be the end of the doctor–patient relationship. This is the case of some court expert witness declarations. Placebo prescription fall with this perspective, with the added ethical unacceptable consequence of the sensation of superiority that is produced by having the authority to prescribe is recognized as one of the greater instruments of professional domination.

The Misuses of Psychotropic Drugs

In English language the word drug refers both to a medicine and to a poison, the same happens in ancient Greek with the word pharmakos. In other languages, the word drug is reserved for illicit substances, but still the cutting edge between both meanings is far from clear. For instance, there are restrictions on the prescriptions of ▶ benzodiazepines because of the potential risk of dependence, although the restriction criteria are not the consequence of scientific evidence. Why there is a 2 months limit and not a 2-week or a 6 months one? The case of white cell control with ▶ clozapine use is another example. The evidence is that the danger for a severe leucopenia becomes minimal after a few weeks of intake. Every Country has a huge database of patients on ▶ clozapine and weekly or monthly white cell counts, and nobody has have the courage to analyze them to produce clear guidelines on the controls needed to proceed with such a drug, or with other which may share the same risk.

▶ Cosmetic psychopharmacology refers to the use of psychotropic medication by people who are not ill but intend to enhance well being and functioning. A futile prescription is something different, because this is a medical intervention which has no value for the patient (who may be severely ill), although it will produce some effect.

Healthy persons that are unhappy with their own personality traits because they may not be socially acceptable may turn their eyes to cosmetic psychopharmacology to achieve a more satisfactory level of normality. The fact is that psychotropic drugs can produce such benefits: ▶ Fluoxetine allows feeling energetic, bright and accepted; ▶ beta-blockers and ▶ paroxetine can change the life of shy people and improve the performance of artists who suffer from stage fear. This last use has been considered as a form of doping. There is also an increasing use of ▶ cognitive enhancers to improve performance and endurance, commonly by students and people in intellectually very competitive jobs, although the evidence of their usefulness is very scarce.

As in the case of cosmetic surgery, the intervention needs a doctor and there is the risk that healthy people receive a psychiatric diagnostic in order to get a prescription or that diagnostic criteria become less restrictive.

The Development of New Medicines for the Health Care Market

The development of new medicines has generated ethical problems that have been dealt with legal norms and strict regulations.

In spite of the fact that modern pharmacology has contributed to a better quality of life for many patients all over the world, the issue of the advantages of new (and expensive) drugs versus older (and cheaper) ones is today a hot one. This is a typical case of conflict of values between doctors on one side and the health care authorities on the other. Doctors are guided by the ethical principles of welfare, and therefore any medicament that may bring a benefit to a patient classic, even a minor one, should be prescribed. The administration, working on tight budgets, which more often than not are short in time (very often yearly) and constrained (to the department of Health) follows the principles of the ethics of management. In the case of psychiatry, the stigma of mental disease and of psychiatry itself plays a major role in this context.

Pharmaco-economy studies cannot rely exclusively in the daily cost of the medication, but they must contemplate direct costs (hospitalization and use of the health care services, treatment of adverse effects and overdoses, home care, psychosocial interventions, etc.), indirect costs (absenteeism, social issues, etc.) and intangibles costs, such as, suffering, disability for the patient and the relatives and patient's quality of life, and cost in planning and management (suicide prevention programs, anti-stigma interventions, etc.).

Defensive medicine is not only a matter of doctors or hospitals; it also an issue of the health care administration, as the clozapine case shows.

The Ethics of the Marketing Psychotropic Drugs

The ethical problems of psychotropic drugs do not disappear when the drug is marketed. Even when a medicine has been approved and commercialized ethical problems in its prescription can appear. Commercialized medicines quality is assured by the proceedings and exigencies imposed by health care that guarantee the drug as a remedy (effectiveness) and in addition delimit the possible adverse effects (safety). The guarantees comprise the use in specified indications, based on the research presented for the approval. Yet, it should be clear that the goal of this process is to assure that the drug has potential effects on some disease or syndrome and the level of potential side effects is within acceptable limits. The rest, how the drug compares with others, what is its niche within the therapeutic armamentarium, what are the benefits in populations not previously exposed to the drug (children, elderly patients, patients with co-morbid conditions, and so on), the benefits in other disorders or in sub-threshold conditions is another story.

The pharmaceutical industry considers itself as an essential element of health care and probably more than other sector it has recognized ethical issues. In any case, it is a highly regulated industry, contrary to what happens with some other medical interventions.

Several ethical problems exist in the area of marketing of drugs to health care professionals: (1) gifts offered to health professionals, where the consensus that they must be of little value and be related to the practice of medicine or pharmacy; (2) hospitality in professional meetings, which should not include "congress tourism" activities; (3) the quality of all the advertising material, which should be prepared the scientific department pharmaceutical companies and duly supervised by health care authorities. David Healy has called attention to some of marketing campaigns and strategies deprived of sufficient scientific support. The World Psychiatric Association has included an item on the ethical implications of the relationship of psychiatrists with the industry as a part of the Madrid Declaration and most of the national and international organizations in the field of neuropsychopharmacology or psychiatry have produced ethical recommendations aiming to curb abuses in this field. The same aims are regulated in the European Union.

The fact that there is something wrong in this field was clearly exposed by Palmisano and Edelstein in the United States. They compared the expenses in medicine promotion by the pharmaceutical industry during the 1970s with the expenses on health care for young people by the health authorities. The results were overwhelming; $3000 per doctor per year in medicine promotion, as opposed to $212 per person per year in health care.

Research

Research, in general, and clinical research, in particular, plays a significant although indirect role in the act of the prescription, filtered by measures imposed by regulating authorities, information conveyed by the pharmaceutical industry and by continuous medical education activities, often promoted by the pharmaceutical industry. In addition, the publishing of clinical research in scientific publications is greater every day. Nevertheless, from an ethical perspective, the financial support of these means of diffusion on the part of the pharmaceutical companies, although societies or scientific committees of an independent nature guarantee their content.

Other biases that can change the prescription habits for psychotropic drugs is the influence exerted by the so called "opinion leaders," Another aspect is "ghost writing,"

which means that a scientific paper may have been written by pharmaceutical companies employees or by special firms engaged in the business of writing scientific papers and reports, and not by researchers involved in the actual investigation.

In a meeting of the Permanent Committee of Doctors of the European Community, they recognized the problems caused by the rapid increase of health care costs and acknowledged that this concerns not only governments and citizens, but also the medical profession. However, they concluded, unanimously, that it is "the duty of the doctor to oppose all measures that, destined to control expenses, violate medical ethics." In addition, they mentioned in the document that "the health sector not only is an expense, but also a benefit for the state and for public health, and, therefore, it is correct to consider it from an economically positive point of view and not only in terms of expenses." Yet, on the other hand, without health care services supported by the Administration, only wealthy patient could afford what a doctor prescribes, and for sure, the number of jobs for doctors would be very much reduced.

The use of placebo in clinical research raises major ethical problems. In a strict sense the use of placebo in clinical trials could be considered as being against the spirit of the Helsinki Declaration. But on the other hand treatment is not just the prescription of a drug. Treatment is the result of pharmacological effects and of the doctor–patient interaction. In psychotherapeutic research novel approaches are confronted with "treatment as usual" interventions. The challenge is to design studies where the more or less unspecific role of the doctor–patient relationship and the treatment as usual approach are as controlled as the effects of the drug being tested. The fact is that in the particular case of psychopharmacology there is a high response rate in many psychiatric disorders.

Patients as Research Subjects

Although already Claude Bernard declared in 1874 that "the principle of medical morality is to never perform an experiment on a human being that may be harmful to some extent, although it may be very beneficial to science, namely for the health of others," this principle was repeatedly violated and in an extreme form in Germany during the Third Reich. The fact is that doctors at least passively accepted laws put forward by the Nazi regime declaring that the regulation was designed to benefit the nation and not the patient, an example of conflict of values. Nowadays the Madrid Declaration of the World Psychiatric Association clearly affirms the independence of the psychiatrists and their right to practice their profession free from external pressures. The first international code of ethics for research on human beings is the Nuremberg Code that follows the Hippocratic principle *primum non nocere* and puts particular emphasis on obtaining the person's voluntary consent.

The ethical and scientific models for conducting biomedical research on humans have been developed through various international guidelines: the Declaration of Helsinki (1964) and its subsequent amendments (Tokyo 1975; Venice 1983; Hong Kong 1989, Somerset West 1996; Edinburgh 2000) of the World Medical Association (WMA); the International Ethical Guidelines of the Council for International Organizations of Medical Sciences (CIOMS) and the International Conference of Harmonization (ICH) guides for good clinical practice (GCP), which are at the core of most national and international legal standards on medical research involving human subjects.

The Nuremberg Code, the Declaration of Helsinki and the ICH Guides have led to GCP, an international standard of ethics and scientific quality for the design, implementation, records and reports on investigations involving humans.

Later on, the United Nations and World Psychiatric Association (1996) produced codes specifically oriented to psychiatry and the care of mental patients (Resolution 211, Hawaii Declaration 1977; Madrid Declaration 1996).

Publications and the Dissemination of the Results of Research

The publication and the dissemination of the results of research projects is a major ethical concern. The selective publication of clinical trials occurs and distorts the body of evidence available for clinical decision-making. Thus, researchers and editors are often more enthusiastic about the publication of studies that show a very significant effect of a new treatment (positive test) or an equivalence between two therapeutic approaches (non-inferiority trials). On the contrary, researchers and editors tend to show little interest in trials that show that a new treatment is less effective than the standardized treatment for a specific disease (negative trials), let alone those that are not clearly positive or negative, because inconclusive studies do not change routine clinical practice.

The editors of a several major medical journals have demanded greater transparency in the implementation and publication of clinical trials, requiring, as a prerequisite for dissemination, the registration of the trial in a public database.

Yet the publishing business is not free of unethical behavior and there is a risk that the danger may increase

in the future. Scientific journals with high impact factor are major players in research, as the investigator's career stands on his or hers published output. Therefore, the policies or even ideologies of a journal can have an indirect influence on grants accorded to investigators. This may even be present in editorials: the publication of a paper on comparison between typical and atypical antipsychotics, which showed favorable results for the latter based on retention rates, was accompanied by an editorial which only commented that there were not differences in the scores of the PANSS scale, withholding that this was a secondary outcome measure and the study was not powered to find differences in the clinical scales. The issue becomes more important as some journals are now considering themselves as major players in the health care sector, assuming the power to correct injustices around the world.

Cross-References

- ► Cognitive Enhancing Drugs: Neuroscience and Society
- ► Legal Aspects of Psychopharmacology
- ► Licensing and Regulation of Medicines
- ► Neuroethics

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Ethics of Autonomy

Definition

The ethics of autonomy considers that the patient is an autonomous human being: adult, free, and able to take his or her own decisions. Consequently, doctors have to inform patients about all possible diagnoses and treatments so that patients are able to decide.

Ethics of Placebo Prescription

► Ethical Issues in Human Psychopharmacology

Ethics of Prescription

► Ethical Issues in Human Psychopharmacology

Ethopharmacology

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Synonyms

Ethological pharmacology; Pharmaco-ethology

Definition

Ethopharmacology can be described as the study of drug effects on behavior, relying on observations and descriptions of species-specific elements (acts and postures). It is therefore strongly rooted in principles derived from ethology, the biological approach to the study of animal and human behavior. The roots of ethology lie in evolutionary biology as defined by Darwin and others and, more specifically, by the studies of Lorenz, Tinbergen and Von Frisch. Of central concern in ethology are the functional aspects of behavior and its adaptive value in evolutionary terms where it contributes along with genetic and environmental factors to natural selection.

Current Concepts and State of Knowledge

Ethologically based behavioral models, therefore, tend to focus upon a species' entire behavioral repertoire,

which is divided into clearly identifiable units of behavior (acts and postures, e.g., eating, grooming, walking, exploring, and fleeing). The repertoire is defined in naturalistic settings by comprehensive, systematic observation and recording of the species' behavior (including gender and age-related differences) without resort to a priori theories or hypotheses which putatively might bias the objectivity of the observation. Having exhaustively defined the behavioral repertoire and the environmental circumstances (antecedent, concurrent, and consequential) in which it is found, systemic alteration of environmental conditions, including the administration of a drug, can be undertaken.

Kršiak (1991) defined ethopharmacology as "the study of behavioral and other effects of drugs through the application of ethological concepts" in an article describing the historical contexts of the field. In his view, ethopharmacology is a subspecialty of the broader field of behavioral pharmacology, which reflects the behavioral effects of drugs on species by all kind of methods.

The first "ethopharmacological" studies were performed in the early 1960s of the last century (Chance and coworkers) by scientists coming from an ethological background. This group did most of their groundbreaking work on social behavior in rodents and they were the first to describe ethograms of isolated behaviors and social interactions (Grant and Mackintosh 1963). An ethogram is a list of all acts and postures of an animal in a certain environmental situation.

Ethopharmacology has particularly blossomed in the area of ► social interactions and ► aggression research probably due to the availability of ethologically trained scientists, the rich agonistic repertoire of rodents, and the translational aspects of such research into human biomedical (psychiatric) problems (Miczek et al. 1994).

The ethopharmacological approach is illustrated here in the area of aggression or ► agonistic behavior. Before the 1960s, the effects of drugs were assessed in very simple aggression tests often measuring only one parameter (e.g., the number of bites, Yen et al. 1959). Such parameters did not unravel whether a drug was selectively antiaggressive or just sedative. Therefore, ethological approaches were introduced to better describe and interpret the effects of drugs on behavior. Agonistic behavior, as found in a variety of animal models, includes a number of behavioral components with complex functions that have been organized in certain patterns and sequences. The species-specific behavioral patterns, taken together, can be considered the species' agonistic behavioral repertoire. The diversity of the repertoire, that is the number and subtlety of behavioral options available, is smaller in more primitive species and becomes apparently larger and more complex in the higher orders. Investigators try to use "models" of agonistic behavior and mostly this is done in rodents. Depending upon the model used, as defined by the specific environmental situation constructed, a particular frequent and temporal distribution of the species' behavioral repertoire can be elicited. In a territorial (resident–intruder paradigm) model of agonistic behavior in rats, the resident male ordinarily takes the offensive role and the intruder, a defensive role. Although both rats have available identical behavioral repertoires, the two rats show a completely different frequency, sequence, and temporal distribution of behavioral elements. On the basis of these different distributions, the overall behavior of each contributor can be classified as either offensive or defensive. The ethopharmacological approach has been used in developing specific antiaggressive drugs, serenics (Olivier et al. 1984, 1990a, b). These compounds have highly selective effects on offensive components of agonistic behavior while not influencing defense and flight. Using extensive ethograms (Olivier, 1981) and describing drug effects on frequency and time distributions on the sequential structure and the timing of behavioral elements enabled the very precise and sophisticated development of antiaggressive drugs, where effects on offensive behaviors could be distinguished from sedative, sensory, or motor deficits or interfering other behaviors (Miczek et al. 1989; Mos et al. 1987; Olivier and Van Daalen 1982). By testing an extensive battery of drugs from various classes (anxiolytics, antidepressants, antipsychotics, anticonvulsants) in different agonistic models, including maternal aggression in female rats, territorial aggression in male rats and mice, brain-stimulation-induced aggression and others (cf. Olivier et al. 1994) and using the ethological approach, an extensive and subtle profile of these psychotropics could be generated that appeared to be extremely helpful in describing the basal effects of these drugs on various aspects of agonistic behavior.

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Ethosuximide

Definition

Ethosuximide is an antiepileptic drug, used notably in treating absence seizures that are characterized by lapses of consciousness/staring that usually only lasts a few seconds.

Cross-References

► Anticonvulsants

Ethyl-Alcohol

► Alcohol

Ethyl Loflazepate

Definition

Ethyl loflazepate is a benzodiazepine that has anxiolytic, anticonvulsant, sedative, and skeletal muscle-relaxant properties. Its elimination half-life is 51–103 h. It also produces an active metabolite that is stronger than the parent compound. The symptoms of an overdose of ethyl loflazepate include sleepiness, agitation, and ataxia. Hypotonia may also occur in severe cases. These symptoms occur much more frequently and severely in children. High doses of the antidepressant fluvoxamine may potentiate the adverse effects of ethyl loflazepate. Like most similar compounds, it is subject to dependence and abuse.

Cross-References

► Abuse
► Benzodiazepines
► Dependence
► Fluvoxamine

Etizolam

Definition

Etizolam is a benzodiazepine that has anxiolytic, anticonvulsant, hypnotic, sedative, amnesic, and muscle-relaxant properties. It is used for short-term treatment of ► insomnia, ► anxiety, and ► panic attacks. Alpha-hydroxyetizolam is an active metabolite that is eliminated more slowly with an half-life of 8 h. Etizolam differs from other benzodiazepines in that the molecules possess a thiophene ring instead of a benzene ring. Cases of increased prolactin and ► neuroleptic malignant syndrome, which are typically reported for neuroleptics and not for benzodiazepines, have been reported with etizolam.

Cross-References

► Anxiolytic
► Benzodiazepines

EtOH

► Alcohol

EUFEST

Synonyms

Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder

Definition

An open, randomized clinical trial of a low-dose of haloperidol (1–4 mg) versus SGA in first-episode schizophrenia. This pragmatic trial found lower discontinuation rate

with SGA than with haloperidol. However, symptom reductions were virtually the same in all the groups, at around 60%.

Cross-References

► Haloperidol
► Second Generation Antipsychotics (SGA)
► Schizophrenia

Euonymaceae

► Celastraceae

Event-Related Potentials

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Synonyms

ERPs

Definition

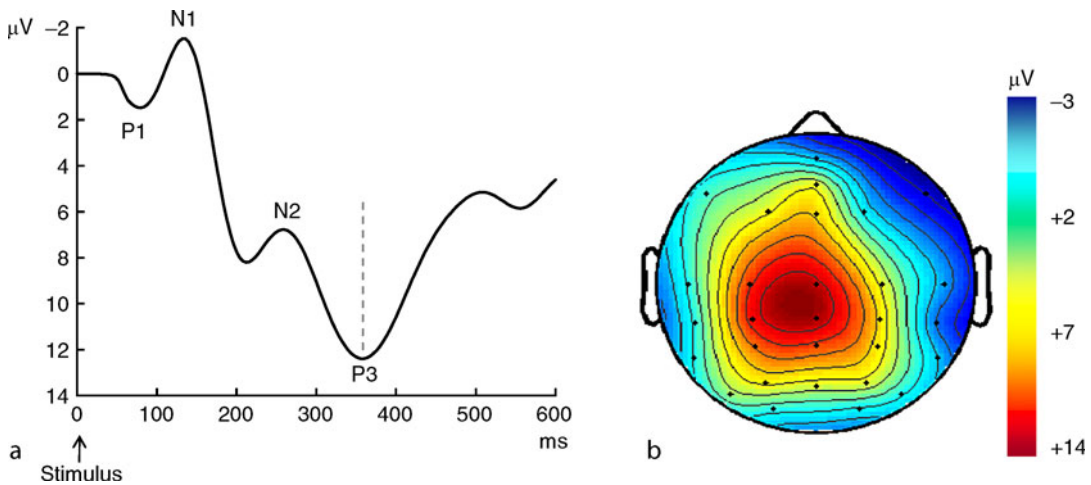
Event-related potentials are a general class of electrical brain potentials that are embedded in the ► electroencephalogram and that display a stable time relationship to a definable sensory, cognitive, or motor event.

Principles and Role in Psychopharmacology

► Electroencephalography is one of the most popular ► psychophysiological methods in clinical and preclinical research, and provides a recording that reflects the global electrical activity of the brain – the EEG. A limitation of the EEG is that it represents the summation of all the electrical activity at a given moment in time, making it difficult to isolate the activity associated with individual neurocognitive processes. A more powerful method for the study of isolated neurocognitive processes focuses on the specific EEG responses to particular sensory, cognitive, or motor events. Such specific responses are called event-related potentials (ERPs), to denote the fact that they are associated with specific events. The ERP is difficult to see in the EEG recorded for a single event. To isolate an ERP, one must collect the EEG of a large number of trials with the event-of-interest, time-lock the corresponding signals to the onset of this event, and then average the signals. The averaging process filters out all EEG activity that is not related to the event-of-interest, and isolates the ERP – the systematic response of the EEG to the event (Luck 2005).

Properties of ERP Components

ERPs consist of a series of peaks and troughs that are referred to as ► ERP components (Fig. 1a). The naming



Event-Related Potentials. Fig. 1. (**a**) Typical stimulus-evoked average ERP waveform. The abscissa indicates time from the onset of the stimulus, and the ordinate indicates the microvolt value for a specific electrode. Negative voltage is plotted upwards by convention. (**b**) Typical voltage distribution over the scalp, corresponding with the P3 peak latency.

of these components often reflects their polarity (P for positive, N for negative voltage) and their order of occurrence (e.g., P1 is usually the first negative component) or typical timing in milliseconds after the event (e.g., P300). Apart from their polarity and latency, ERP components can be characterized in terms of their general scalp distribution (Fig. 1b). The relationship between the voltage distribution observed over the scalp and the brain regions giving rise to this pattern is by no means transparent. This is because there is, in principle, an infinite number of cortical source configurations that can produce the same scalp distribution – a methodological problem known as the ► inverse problem. Nonetheless, the scalp distribution can be used to infer or test coarse hypotheses about a rather localized neuronal population or multiple, anatomically distributed populations that generate an ERP component. This can be achieved using ► source localization techniques, which limit the number of possible source configurations by making simplifying assumptions about the physics of the brain and head tissues, as well as the nature of the active neuronal populations (Handy 2005; Luck 2005).

One must exercise great caution when using ERP-component measures for drawing conclusions about underlying neural processes. One difficulty is that ERP components can reflect the combined activity of multiple, relatively independent, underlying or *latent* components that are overlapping in time and/or location. In that case, the neural process-of-interest typically corresponds with only one of those latent components. Furthermore, differences between experimental conditions or groups in the scalp distribution of a component need not necessarily represent the involvement of different neural sources, but may also reflect different relative contributions of the same sources. Techniques such as principal component analysis can sometimes be useful in identifying latent ERP components and their contributions to the observed ERP over the scalp. However, these techniques have significant limitations (Handy 2005; Luck 2005; Picton et al. 2000). Another potential pitfall concerns the variability in timing of some ERP components. Not only can there be large variability of the average component latency across individuals or groups, but also substantial variability in the timing of single-trial ERP components. Both cases may pose significant problems for the investigator, because an increase in latency variability results in a decrease in peak amplitude of the average (across individuals or trials). For example, two experimental conditions that differ in latency variability may appear to differ in component amplitude when examined in an average ERP, even when this is not the case in the single-trial waveforms. Investigators should take this possibility into account when examining and measuring ERP components (Picton et al. 2000). Indeed, sometimes it pays off to attempt to measure single-trial estimates of an ERP component and use the trial-to-trial variability in component latency or amplitude to address scientific questions.

In view of the above considerations, it is not useful to define a particular ERP component in terms of its polarity, latency, and scalp distribution. Peak latency and scalp distribution may differ between trials, conditions, and individuals, and even the polarity of a component may vary depending on the placement of the ► reference electrode. Modern definitions of ERP components acknowledge that a component may occur at different times under different conditions, and emphasize that two components are the same if they arise from the same neuroanatomical structure(s) and represent the same cognitive function (Luck 2005).

The Physiological Basis of ERP Components

Little is known about the physiological basis of ERP components. It is widely accepted that ERP components reflect the intracortical currents induced by excitatory and inhibitory postsynaptic potentials, which are triggered by the release of neurotransmitters. If many individual neighboring neurons with a similar orientation receive a similar excitatory or inhibitory input at approximately the same time, then the summation of the resulting postsynaptic potentials results in a measurable voltage at the scalp (Luck 2005). Thus, ERP components reflect the postsynaptic effects of neurotransmitters such as glutamate and GABA and indirect modulatory effects from neuromodulators such as norepinephrine, dopamine, and serotonin. Biophysical considerations suggest that the contribution of subcortical structures to the scalp-recorded EEG is small, and hence, most ERP components reflect primarily cortical activity. Whether an ERP component has a positive or negative polarity depends on many neurophysiological and nonphysiological factors and is little informative about the neural origin or functional significance of the component (Handy 2005).

With regard to the origin of ERP components, an important distinction can be made between traditional and synchronized oscillation theories of ERP generation (Klimesch et al. 2007). According to the traditional view, ERP components reflect phasic bursts of activity in one or more brain regions that are triggered by experimental events-of-interest. As explained above, this view treats the ongoing EEG as background noise that obscures the ERP signal-of-interest, and deals with that noise through data-averaging procedures. The synchronized oscillation

hypothesis challenges this approach and instead proposes that ERP components are generated when an event leads to the resetting of the phase of ongoing oscillations in the EEG, such that peaks and troughs in the oscillatory waveform become aligned to the resetting event. When aligned in this way, oscillatory peaks and troughs in the ongoing EEG are evident in the ERP waveform, even in the absence of transient bursts of neural activity. Empirically distinguishing between these two theories has proven difficult for a variety of methodological reasons.

ERP Components as Markers of Mental Processes

The study of ERPs has been of great importance for our understanding of mental processes, by augmenting traditional, behavioral measures such as reaction speed and accuracy (Rugg and Coles 1995). This approach is based on the assumption that changes in a certain cognitive process are selectively expressed in a particular component of the ERP. Then, if it has been established that ERP component X reflects cognitive process Y, one can investigate whether an experimental manipulation or mental state/trait (e.g., psychopathology) affects process Y by measuring its effect on component X. In particular, an effect on the component amplitude suggests a change in process Y or a change in the input to this process. For example, patients with obsessive–compulsive disorder exhibit an increased amplitude of the error-related negativity, an ERP marker of internal error detection. This finding confirms previous notions of a dysfunctional action-monitoring circuit in obsessive–compulsive disorder. Furthermore, an effect on the peak latency of component X suggests that the manipulation or mental state/trait has changed the duration of processes preceding and including process Y. In contrast, an effect on reaction speed in the absence of an effect on the peak latency of component X suggests a change in the duration of processes *following* process Y. For example, it is well known that the presentation of a warning signal can speed up the reaction to an imperative stimulus. ERP researchers have increased our understanding of this phenomenon by showing that the benefit in reaction speed is largely restricted to the time interval between an early ERP marker of spatial ▶ attention shifts and an ERP marker of hand-specific motor preparation, the lateralized readiness potential.

Of course, the logic outlined above depends on the validity of any given ERP component as a marker of a specific mental process. In the past decades, a large amount of research has focused on validating ERP components, and although there are many ongoing debates in the scientific literature, significant progress has been made in refining hypotheses about the functional significance and neural origin of ERP components (Key et al. 2005; Rugg and Coles 1995). This is particularly true for early ERP components such as the P1 and N1 (Fig. 1a). It is generally held that these components reflect aspects of stimulus encoding in modality-specific perceptual areas, such as visual or auditory cortex. Voluntary or involuntary changes in the amount of attention paid to a particular stimulus lead to amplitude modulations of the P1 and N1 components. Another prominent example of a "sensory" ERP component with a source in modality-specific perceptual areas is the mismatch negativity. This is a negative deflection with a typical latency of 100–250 ms that occurs in response to an odd stimulus in a sequence of stimuli, regardless of whether the subject is paying attention to the sequence.

Some other prominent ERP components are not sensory in nature, but reflect central cognitive processes. Important examples are the N2 and P3 components (Fig. 1a), both of which are sensitive to contextual variables, such as the relationship between the eliciting stimulus and the subject's goal of the task, and the subjective probability and novelty of the stimulus. The scalp distribution and latency of these components are highly variable across different task contexts. The N2 has been associated with various mental processes, including response inhibition and conflict detection. The P3 is thought to reflect updating of contextual memory representations or temporal filtering of motivationally significant stimuli and its latency is thought to index the end of stimulus-evaluation processes. Another cognitive ERP component is the error-related negativity, a negative deflection immediately following erroneous responses, that is clearly visible in the response-locked ERP. There is much evidence that the error-related negativity reflects the response of the dopamine system to unfavorable outcomes and events. Finally, there are a number of ERP components that are directly related to motor processes. The most important example is the Bereitschaftspotential or readiness potential, a measure of activity in the motor cortex that is leading to voluntary muscle movement. A derived measure, the lateralized readiness potential, reflects the relative activation of the left and right motor cortex and this has been very important for the study of covert aspects of motor preparation (Rugg and Coles 1995).

Investigating Drug Actions Using ERPs

One use of ERP methodology in psychopharmacology is to investigate the effects of a drug on specific neurocognitive processes (Carozzo et al. 2006; Pogarell et al. 2006). To that end, researchers examine whether and how the drug changes the corresponding ERP components. This

often allows for more detailed conclusions than examining behavioral measures alone. For example, ethanol, which has sedative effects, has been found to decrease P3 amplitude, whereas ► caffeine increases P3 amplitude, suggesting that these drugs affect high-level stimulus-encoding processes. Another example concerns the P50 wave, an ERP component that is used for the assessment of sensory gating – the habituation of responses to repeated stimuli. In healthy subjects there is an inhibition of responsiveness, that is, a diminished P50 to repetitive stimuli – an adaptive mechanism to prevent overstimulation. The NMDA receptor antagonist ► ketamine and the antipsychotic ► haloperidol disrupt P50 suppression, indicating that these drugs modulate sensory gating. Another ERP measure, the loudness dependence of the auditory evoked potential (LDAEP), has been proposed as a valid indicator of central serotonergic function in humans. This measure is assessed using the N1/P2-component of the auditory evoked potential and reflects the reactivity of the auditory cortex. Thus, this ERP measure is used as a marker of neuromodulatory function, rather than a cognitive function.

Investigating ERPs Using Drug Actions

Since ERPs reflect functional aspects of neurotransmitters and neuromodulators, drugs affecting particular neurotransmitter or neuromodulator systems are used to investigate the role of these systems in the generation of ERP components (Carozzo et al. 2006; Pogarell et al. 2006). A limitation of this approach is that most available drugs are not selective for a single system, which complicates the interpretation of the results. One exception is a class of drugs, ► serotonin reuptake inhibitors (SSRIs), which selectively increases the amount of serotonin in the brain. Accordingly, SSRIs have often been used to investigate the role of serotonin in the generation of different ERP components. Using this approach, it has been shown that serotonin affects the LDAEP strongly, but is not involved, for example, in the generation of the P3, which is modulated by cholinergic, dopaminergic, and noradrenergic drugs. The mismatch negativity is blocked by ► NMDA-receptor antagonists, indicating that the mismatch negativity critically depends on glutamatergic neurotransmission. These and many other findings have led to an increased understanding of the neural basis of ERP components. This, in turn, has informed theories of their functional significance. For example, the finding that the error-related negativity is modulated by dopaminergic drugs has strengthened existing views that link this ERP component to the literature on dopaminergic reward-prediction errors.

The Role of ERPs in Psychiatry: Sensitivity and Specificity

ERPs are not only important research instruments, but are also useful as clinical instruments in neuropsychiatry (Pogarell et al. 2007). ERPs can be used in the diagnostic workup of a wide range of neuropsychiatric disorders as well as in monitoring the course of the disorders and the prediction of treatment responses. To be useful in the diagnostic workup, an ERP component has to be sensitive enough to detect the disorder, but also sufficiently specific for the disorder to rule out alternative explanations.

► Alzheimer's disease is consistently related to smaller P3 amplitudes and prolonged P3 latencies. Using the P3 component, Alzheimer's patients can be diagnosed with high sensitivity and specificity (up to 88.5%). Furthermore, the P3 is effective in both monitoring and predicting the treatment response of Alzheimer's patients to cholinesterase inhibitors. Thus, the P3 may be an important instrument not only in the diagnostic workup, but also in the monitoring and prediction of the treatment response in Alzheimer's disease. This tool is still underutilized in the clinic, presumably because the P3 has not been generally accepted as a valid biomarker for Alzheimer's disease. Schizophrenic patients also show a decreased P3 amplitude. However, this is generally considered a trait marker rather than reflecting the neurological pathology causing ► schizophrenia, because the P3 amplitude reduction is not affected by neuroleptic medication and can also be found in remitted schizophrenics, relatives of schizophrenic patients, and other subjects at risk of developing schizophrenia. Thus, the P3 amplitude may be a sensitive marker, but is not a specific marker for schizophrenia and is therefore not used in the diagnostic workup. However, there are indications that in schizophrenic patients, the P3 may predict treatment response.

Advantages and Limitations of Event-Related Potentials

The major advantage of ERPs is their fine temporal resolution (on the order of milliseconds), indicating that ERPs reflect what is happening in the brain at the very same moment. Another advantage of ERPs is that electroencephalography is noninvasive and cheap compared with other brain-imaging methods. An additional convenience is that there are clear and widely agreed-upon guidelines for how ERP studies should be conducted, analyzed, and reported (Picton et al. 2000). The primary limitation of ERPs is that it is not possible to determine the neuroanatomical generator of an ERP component from the measured scalp potentials alone. Furthermore, the

geometrical orientation of neurons must be more or less parallel in order to detect the neural activity at the scalp. Signals from structures located deep within the brain are particularly hard to measure. Finally, during the averaging procedure for isolating the ERP from the EEG, all activity that is not time-locked to the event-of-interest is lost. In order to examine that information, other electrophysiological methods are needed.

Cross-References

- ▶ Attention
- ▶ Caffeine
- ▶ Electroencephalography
- ▶ Psychophysiological Methods

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Event-Related Potentials Components

Synonyms

ERP Components

Definition

Systematic response of the electroencephalogram to a particular sensory, cognitive, or motor event that is generated in a given neuroanatomical structure when a specific mental operation is performed. The naming of these components often reflects their polarity (P for positive, N for negative voltage) and their order of occurrence.

Cross-References

- ▶ Electroencephalogram
- ▶ Event-Related Potentials

Evidence-Based Guidelines

Definition

A series of statements, based on systematic searching of relevant scientific literature and critical appraisal of relevant sources, usually reached through consensus and designed to guide clinical practice. Greatest weight is given to evidence at the top of the "hierarchy" (meta-analyses and randomized controlled trials) with stronger recommendations than are possible when evidence is derived solely from less well-designed studies.

Evidence-Based Medicine

Synonyms

EBM

Definition

Evidence-based medicine aims to apply evidence gained from the scientific method to certain parts of medical practice. It seeks to assess the quality of evidence relevant to the risks and benefits of treatments (including lack of treatment).

Ex Vivo

Definition

The term originates from Latin and means "out of the living"; it refers to an experiment that is done in or on living tissue, and at least partially outside the organism. For example, for the measurement of ex vivo receptor binding, an animal can be treated with a test compound *in vivo*, followed by removal of the brain, exposure of brain slices with a radioligand specific for that binding site *in vitro*, and subsequent quantification of the amount of radioactivity in brain areas of interest. The degree to which radioactivity is reduced due to competitive binding of the test substance can be taken as a measure of receptor occupancy.

Excessive Sleepiness

Synonyms

Excessive daytime sleepiness; Narcolepsy

Definition

A subjective report of difficulty in maintaining the alert awake state, usually accompanied by a rapid entrance into sleep when the person is sedentary.

Cross-References

► Hypersomnias

Excitatory Amino Acid Transmitters

► Excitatory Amino Acids and their Antagonists
► Glutamate

Excitatory Amino Acids and their Antagonists

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Synonyms

Excitatory Amino acid Transmitters; Excitatory Neurotransmitters

Definition

There are more than 100 known *excitatory amino acids* (EAAs) and the large majority of them are non-protein-forming amino acids initially purified from algae or fungi (Lubec and Rosenthal 1990). The endogenous EAAs Glutamate (Glu) and Aspartate act in the nervous system as excitatory neurotransmitters; they are released from neurons and they induce neuronal excitation via ionotropic and metabotropic Glu receptors (iGluRs and mGluRs). Related endogenous molecules like N-acetylaspartylglutamate (NAAG) could also belong to the group of EAAs, but they have no demonstrated neurotransmitter properties. EAAs are usually grouped to distinguish them from AAs like GABA, Glycine, or Taurine exerting inhibitory effects on neuronal cells. Excitatory neurotransmission is present in central and peripheral nervous system, and in the periphery EAAs contribute to the regulation of gastrointestinal motility, pain sensation, as well as respiratory and cardiovascular functions. In non-neuronal cells, Glu receptors and transporters exert a role in the control of proliferation, immune response, and bone tissue dynamic (Gill and Pulido 2005).

Pharmacological Properties

History

Glu is the most abundant excitatory neurotransmitter in the brain. The first indications that Glu exerted excitatory actions on cerebral cortex were obtained by Hayashi in 1954, and later observations by Watkin and colleagues showed that Glu can depolarize and excite individual neurons in the cat spinal cord. However, it took the scientific community a long time to realize that Glu was functioning as a neurotransmitter, mainly due to its very high abundance in the brain and its involvement in important metabolic pathways. Full acceptance of the neurotransmitter role of Glu was achieved only with the characterization of selective agonists and antagonists for all Glu receptors (Roberts et al. 1981). The last decade has seen several attempts to exploit the therapeutic potential of Glu receptor ligands since molecular psychiatry and behavioral psychopharmacology have been instrumental in highlighting the possibilities of a pharmacological modulation of Glu in diseases like ► schizophrenia and ► treatment-resistant depression (► TRD).

EAA Receptors and Selective Agonists

Glu is a flexible chiral molecule that can adopt nine staggered conformations in physiological conditions by rotations around two of its carbon bonds. Because of the large flexibility of Glu, the characterization of the different subgroups of EAA receptors was only possible after the discovery of conformationally restricted Glu and Aspartate analogs. The observed selective binding properties of Glu analogs imply that Glu interacts with each receptor subtype in a distinct conformation (Krogsgaard-Larsen and Hansen 1992). Agents exerting a specific modulatory role on the effects of EAAs are also of therapeutic relevance in CNS disorders and are listed accordingly in Table 1.

EAA and iGluRs

iGluRs are ion channels which share a common genetic ancestor, and are divided into subclasses depending on their ability to interact with three different Glu analogues:

NMDA (N-methyl-D-aspartic-acid), AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid), and Kainic acid (KA, 2-Carboxy-3-carboxymethyl-4-isopropenyl-pyrrolidine). Each iGluR consists of four protein subunits, and each subunit in turn contains a large extracellular domain withholding the orthosteric binding site (the binding site for the endogenous ligand), four transmembrane (TM) domains, and an intracellular C-terminal domain responsible for anchoring and trafficking. The TM2 in each subunit forms a loop inside the cell

Excitatory Amino Acids and their Antagonists. Table 1. Ligands for the different excitatory amino acids (EAA) receptors described in the chapter.

Receptor	Agonist	Allosteric modulator	Competitive antagonist	Noncompetitive antagonist
AMPAR	AMPA	CX717	DNQX	GYKI-53784
	Kainate	CX614	CNQX	CP-456,022
	L-Quisqualate	CX929	Tezampanel	Perampanel
		CX1837	NGX426	Topiramate
KAR	Kainate		DNQX	AUBAs
	Domoate		CNQX	NS3763
	Acromelic acid		Tezampanel	Joro spider toxin (JSTX)
	L-Quisqualate		LY382884	Arachidonic acid
	AMPA		LY466195	Topiramate
	ATPA		UBP203	
	Willardiine		UBP316 (ACET)	
NMDAR	NMDA		D-α aminoadipate	MK-801-Dizocilpine
	Glycine		D-2-amino phosphonovalerate	PCP-Phencyclidine
	D-cycloserine	Spermine	AP-5	Memantine
	Homoquinolic acid	Spermidine	AP-7	Dextromethorphan
		Neurosteroids	LY274614	Dextrorphan
		Argiotoxin		Ketamine
				Ifenprodil (NR2B)
				Felbamate (NR2B)
				RO256981 (NR2B)
				CP-101,606 (NR2B)
				EVT101 (NR2B)
				Kynurenic acid
				Riluzole

	Agonist	Competitive antagonist	Positive allosteric modulators (PAM)	Negative allosteric modulators (NAM)
mGluRs	1S,3R-ACPD			
Group I	L-Quisqualate	MCPG		
	(S)-3,5-DHPG	LY367366		
mGlu1		LY367385	RO674853	CPCCCEt
				YM298198
				BAY36-7620
				EM-TBPC
				A-841720
				JNJ16259685

Excitatory Amino Acids and their Antagonists. Table 1. (continued)

	Agonist	Competitive antagonist	Positive allosteric modulators (PAM)	Negative allosteric modulators (NAM)
mGlu5	(S)-3,5-DHPG		DFB	SIB-1757
			CPPHA	SIB1893
			CDPPB	MPEP
			ADX47273	MTEP
			VU-29	Fenobam (NPL-2009)
			ADX63365	ADX10059
				AFQ-056
				ADX48621
				STX107
Group II	LY354740	L-CCG-I		MNI135
	LY404039	LY341495		RO676221
	LY2140023	MCPG		RO718216
		HYDIA		
		MGS0039		
mGlu2			LY487379	
			BINA	
			PTBE	
			AZ1007992	
			MRLSD-650	
			ADX71149	
Group III	(S)-AP4	MAP4		
	L-AP4	DCG-IV		
	(S)-SOP	LY341495		
	(1S,2R)APCPr			
mGlu4			PHCCC	
			SIB1893	
			MPEP	
			VU3423	
			VU155041	
mGlu7	AMN082 (allosteric)			MDIP
				MMPIP
mGlu8	(s)-3,4-DCPG		Thiomethylanilide A/B	

membrane to create the lining of the pore of the ion channel. The ion permeability properties of iGluRs are therefore determined by the amino acids residues contained in TM2 (Squire et al. 2008). ► *AMPA receptors* (AMPAR) are Na^+/K^+ ion channels, known as the principal transducers of fast excitatory transmission in the brain. The native AMPAR contains different combinations of the four subunits: GluR1-4. In the predominantly expressed GluR2 subunit an ► RNA-editing site is present in the center of the TM2 loop. Such editing results in an amino acid substitution (a neutral Glutamine is changed to a positively charged Arginine residue) which reduces the permeability of Ca^{2+} ions through the channel. The functional diversity of AMPAR subunits is further enhanced by additional RNA-editing as well as alternative splicing. Together this causes a large variation in the

extracellular region of GluR subunits, e.g., the presence of a splice region referred to as flip/flop, and results in receptor isomers exhibiting different kinetic and pharmacological properties (Squire et al. 2008). The trafficking of AMPAR to and from synapses is controlled by a complex sequence of interactions with several proteins. Briefly, the AMPAR M1 domain is tightly interacting with regulatory proteins (TARPS), which specifically controls the incorporation of the receptor into the synapses in association with ► long-term potentiation (LTP) or long-term depression (LTD) events affecting the synaptic plasticity.

The first generation of selective AMPAR agonists (and antagonists) was based on the AMPA structure (isoxazol derivatives), and they were useful to demonstrate the most relevant features of AMPAR: (1) rapid deactivation (channel closure upon Glu removal), (2) desensitization (channel closure during continuous exposure to Glu) due to a conformational change of the extracellular domain, (3) less pH sensitivity than NMDA receptor, (4) the presence of phosphorylation sites for kinases (PKC, PKA, and CAMKII). More recently, AMPA potentiators or ampakines have been identified which modulate the AMPAR by interacting at allosteric sites. ► Ampakines (e.g., CX717) have been shown to stabilize the receptor in the channel-open state prolonging ion flux and reducing desensitization. Generally, ampakines exhibit cognitive-enhancing properties while compounds (e.g., CX614, CX929, and CX1837) specifically interacting at the cyclothiazide-binding site of the AMPAR also induce the expression of neurotrophins (such as BDNF) and exhibit antidepressant properties.

The ► *NMDA receptor* (NMDAR) consists of a heterotetramer assembled from seven different subunits: NMDAR1 contains the glycine-binding site; NMDAR2 (A–D) contains Glu, polyamine, Zn^{2+}, and proton-binding sites; and NMDAR3 (A and B) with modulatory role (Gereau and Swanson 2008). Subunit R1 is required for channel formation while R2A–R2D play an important role in determining the affinity for both Glu and coagonists Glycine or D-cycloserine, and modulating the receptor activity. The restricted NMDA analogue Homoquinolinic acid which displays some selectivity against the NR2B-containing receptors can also be included among receptor agonists.

In neurons, NMDARs are likely heterooligomers of R1 and R2 subunits forming functional channels with different physiological and pharmacological properties. NMDAR-containing subunit NRA2B exhibit for instance the highest affinity for glycine and is inhibited only by micromolar concentrations of Zn^{2+}. During membrane-resting potential conditions Mg^{2+} ions are binding to and blocking the NMDAR channels and membrane depolarization (usually by activation of AMPAR) is required to release the Mg^{2+} blockade. Activation of the NMDAR allows Ca^{2+} influx to initiate numerous intracellular processes responsible for synaptic plasticity. Hyperactivation of the NMDAR, on the other hand, causes *excitotoxicity* and this is why the activation process is strictly controlled by binding of several endogenous ligands and interaction partners. Binding of polyamines (spermine and spermidine) and ► neurosteroids (e.g., dehydroepiandrosterone) to allosteric sites on the NMDAR positively modulates current amplitude; and for this reason, several polyamines are also ► excitotoxins (e.g., Argiotoxin 636) (Krogsgaard-Larsen and Hansen 1992). In spite of the high concentrations of Glycine present in extracellular fluids, the Glycine site of the NMDAR is possibly not always saturated because of the presence of efficient Glycine transporters (GlyT1 and GlyT2). Clinical evidence of NMDA hypofunction in schizophrenia has triggered attention for the pharmacological modulation of GlyT1, and inhibitors are currently under development as antipsychotics.

The *KA receptors* (KAR) form heteromeric cationic ion channels assembled from five different subunits, GluK1–5 (according to the new IUPHAR nomenclature, GluR5–7 are now named GluK1–3 and KA1 and KA2 are named GluK4 and 5). Glu activity at different KAR subunits is exerted in the low μM range and they are involved in NMDA-independent LTP. Similar to the AMPAR, RNA-editing occurs in KAR (e.g., at the Q/R site in TM2 on subunits GluK1 and GluK2) and the C-terminal domains of GluK1-3 are edited by alternative splicing (Gereau and Swanson 2008). The fully edited (modified by both RNA-editing and splice variation) variant of GluK2 is the most abundantly expressed subunit in the adult CNS. High expression of the KARs is seen in the synaptic connection between hippocampal mossy fibers and CA3 pyramidal cells. Neurotransmitter release modulated by KARs facilitates presynaptic forms of short- and long-term synaptic plasticity. When expressed at postsynaptic locations KARs also induce synaptic currents of small amplitude with slow kinetics. The cellular subunit localization of KAR is dynamic and AMPAR stimulation is known to increase GluK2 postsynaptic localization, while both GluK2- and GluK5 expression are decreased at the presynapse. The understanding of the function of KARs is lacking behind mainly because of the relative shortage of selective pharmacological tools. Selective agonists for the KARs are all natural products isolated from seeweed or poisoning mushrooms. Domoate and Acromelic acid are both more potent agonists than the prototypic agonist KA (Krogsgaard-Larsen and Hansen 1992). KA and related

compounds exhibit also nondesensitizing agonist activity at the AMPA receptor, while Domoate selectively activate KARs at low concentrations. Quisqualic acid activates several Glu receptors: KARs, AMPARs, and mGluRs. AMPA is acting as a partial agonist at recombinant GluK1 receptors, with no effect on GluK2; and the AMPA analogue ATPA shows selectivity towards GluK1 over AMPAR. Also Willardiine analogs show selectivity for GluK1 over AMPA subunits.

EEA and mGluRs

mGluRs are ► G-protein-coupled receptors (GPCRs) and they are responsible for slow excitatory/inhibitory transmission. Distinct from the majority of GPCRs, mGluRs exist as functional homodimers where a cystein-rich domain connects the two monomers of the receptor. mGluRs are characterized by a large extracellular domain and seven TM domains. The extracellular domain of each mGluR monomer contains the Glu-binding site located in a so-called bi-lobed structure (usually referred to as the venus flytrap domain). The Venus flytrap can have an open or closed configuration in the absence or presence of an agonist, respectively. The molecular mechanism of activation of mGluRs is not completely understood, but agonist binding is known to stabilize the closed form of the venus flytrap domain and result in specific conformational changes in the extracellular and TM domains which recruits and activates specific G-proteins. Eight subtypes have been identified in the family of mGluRs (mGlu1–8), classified into three major groups (I–III) based on their sequence homology, second messenger coupling, and pharmacology. Splice variants of mGluRs are mainly found in the intracellular carboxyterminals affecting the G-protein coupling efficiency and have to date been identified for mGlu1, mGlu3 and mGlu5 (Gereau and Swanson 2008). Glu shows varying affinity for the different mGluRs, spanning from the μM to the mM range.

EAAs interacting with the mGluR ► orthosteric site exhibit fast K_{on}/K_{off} rate and a limited capacity of discrimination between the three subgroups. Among them, L-AP4 helped the pharmacological definition of mGluRs long before the cloning of the receptors and is probably the most characterized mGluR agonist. The restricted Glu analogue 1S,3R-ACPD (highest affinity for Group I and II) was the first identified mGluR ligand that did not interact with iGluRs (Gereau and Swanson 2008). Allosteric binding sites, which are located in the TM region, have allowed the characterization of functionally more selective ligands. mGluR enhancers can increase potency and/or efficacy of an agonist and are generally identified as positive allosteric modulators (PAM). Noncompetitive antagonists can be referred to as negative ► allosteric modulators (NAM) and are reducing the effects of an agonist. Ligands which bind to the allosteric site without apparent changes in receptor pharmacology are named silent allosteric modulators (SAM) (Lutz and Kenakin 1999). The search for allosteric ligands of mGluRs has allowed the discovery of compounds that are able to discriminate between very similar mGluRs, e.g., within Group II and Group III mGluRs. In the near future, the same effort might also result in the discovery of new classes of compounds with multiple PAM/NAM activities on different mGluRs.

Group I mGluRs (mGlu1 and mGlu5) are predominantly expressed postsynaptically where they are positioned by scaffold proteins (acts as regulators of signaling pathways by binding to and localizing its components to specific areas) in close contact with the postsynaptic density. Activation of these receptors stimulates phospholipase C, potentiates L-type Ca^{2+} channels, and stimulates ► GIRK channels (G-protein-activated inwardly rectifying K) in recombinant systems. L-Quisqualate, also activating AMPAR, is the most potent Group I agonist while (S)-3,5-DHPG is a moderately selective agonist at the mGlu5 and to date, no selective agonist has been identified for mGlu1. The very first PAMs identified for mGluRs were a class of compounds (e.g., RO674853) potentiating the agonist-induced response at mGlu1. Enhancing the mGlu1 receptor activity has been shown, both from animal model and genetic studies, to be beneficial in cerebellar ataxia.

A complex interaction can be demonstrated between mGlu5 and NMDA receptors. Coexpression of NMDA and mGlu5 receptors in vitro and in vivo has revealed the presence of a tonic mGlu5-mediated potentiation of NMDAR activity. This observation is the reason for the current search for mGlu5 PAM with predicted antipsychotic properties. The benzaldazine DFB molecule was earlier identified as a PAM on mGlu5; and among its derivatives we can also find both NAM and neutral ligands, all showing partly overlapping binding sites in the TM domain. Compounds like CPPHA, CDPPB, ADX47273, and VU-29 enhance mGlu5 activity, facilitate hippocampal synaptic plasticity and have therefore a potential use as ► antipsychotics and ► cognitive enhancers. The ADX63365 mGlu5 PAM is presently in development for the treatment of schizophrenia.

Group II (mGlu2 and mGlu3) and III (mGlu4, 6, 7, and 8) mGluRs are predominantly expressed at the presynaptic terminal or in glial cells (mGlu3). They inhibit adenylate cyclase, activate GIRK channels, and inhibit presynaptic Ca^{2+} with an overall inhibitory effect on

neurotransmitter release. The first high affinity in vivo active agonist selective for Group II was the Glu analogue LY354740 (bicyclic structure). Several modifications have been made on this scaffold, changing both its receptor affinity and functional properties. An agonist derivative from this class LY404039 (with the prodrug LY2140023) was recently shown to have antipsychotic and ▶ anxiolytic effects in Phase-II clinical trials. Several mGlu2 PAMs have been characterized in preclinical models trying to obtain an antipsychotic profile similar to the mGlu2/3 agonists. Compounds like LY487379, BINA, PTBE, AZ1007992, MRLSD-650, and ADX71149 are the results of this search, while selective mGlu3 PAMs are still lacking.

For the Group III receptors (S)-AP4, (S)-SOP, and (1S,2R)APCPr are the most potent agonists, and the (S)-3,4-DCPG ligand show some selectivity for mGlu8. Because of the lack of selective ligands the pharmacology of the Group III receptors are still the least developed of the mGluRs. The first mGlu4 PAMs, such as PHCCC, SIB1893, and MPEP, were originally identified as NAMs at Group I mGluRs. More potent and selective mGlu4 PAMs are the VU3423 and VU155041 compounds which, in preclinical models, have shown to have a function in neurodegenerative disorders, particularly on reversal of motor deficits in Parkinson's disease. For the mGlu7 receptor there are no available PAMs to date, but AMN082 was recently identified as a mGlu7-selective allosteric agonist. Initial studies with this compound show activation of mGlu7 to be linked to anxiolytic-like effects in rodents. Two PAMs for mGlu8, Thiomethylanilide A and B, were recently introduced but in vivo data are still awaited.

EAA Receptor Antagonists

iGluR Antagonists

NMDAR antagonists: D-α aminoadipate and D-2-amino phosphonovalerate were among the first competitive antagonists that are selective for the NMDAR described in the literature. More potent orally active compounds with anticonvulsant and neuroprotective properties (like AP-5, AP-7, and LY274614) were prepared in the 1990s. These competitive antagonists however produced psychotic reactions and were soon dismissed in favor of noncompetitive ligands. The discovery of two use-dependent, high-affinity, noncompetitive antagonists (MK-801 – dizocilpine and PCP) binding in the ionic pore only in the open channel (commonly referred to as the PCP-binding site) created in fact a lot of interest. However, also these channel blockers had to be dismissed because of the euphoric and dissociative central effects responsible for their abuse potential and the induction of memory loss. Few NMDA antagonists have found applications in clinical practice. The open-channel blocker ▶ memantine (interacting at the Mg^{2+}-binding site) is well tolerated in chronic treatment and has shown mild but positive effects on cognition and agitation in clinical trials in Alzheimer disease dementia. Dextromethorphan (and its metabolite dextrorphan) is a commonly used cough depressant that inhibits the NMDAR by binding inside the ion channel and might have a potential use for children with ▶ Rett's syndrome. ▶ Ketamine, also an open-channel blocker for the NMDAR, is commonly used as dissociative anesthetic and at low doses against neuropathic pain. In ▶ treatment-resistant depression (TRD), the acute administration of ketamine is able to improve mood and anxiety while reducing suicidal thoughts in matter of hours and with a long-lasting effect. The possibility to discriminate, in a pharmacological manner, between the antidepressant properties and dissociative/euphoric effects mediated by NMDA antagonists is currently investigated using selective and high-affinity NMDA2B antagonist (e.g., Ifenprodil and Felbamate) (Kew et al. 1998). These compounds (also called polyamine site antagonists) cause a relative selective blockade of the NR2B-receptor subunit (100-fold over NR2A and NR2C). RO256981 and CP-101,606 are among the best-known antagonists of this kind and the orally active compound of this class, EVT101, is undergoing development for TRD.

Kynurenic acid, derived from tryptophan catabolism, is an endogenous antagonist at the NMDAR with selectivity for the glycine site at low concentrations while blocking also AMPAR and KAR at higher concentrations. A more potent antagonist for the glycine site is the 7-chloro-kynurenic acid. Riluzole is also a glutamatergic modulator with anticonvulsant, neuroprotective, and plasticity-enhancing properties which is presently approved for treatment of ALS and a promising candidate for treatment of mood disorders. It has several effects on the brain glutamatergic system: inhibiting Glu release via Na^{+}-channels, increasing ▶ Glu transporter (EAAT1) activity and expression, and increasing the surface expression of AMPA subunits GluR1 and GluR2. No direct interaction with NMDA or KARs is established although inhibition of NMDAR to prevent Ca^{2+} entry is a possible mechanism of action.

AMPA and KARs antagonists: Much progress has been made in developing selective AMPAR antagonists while it is only recently that selective KAR antagonists have been disclosed. The cross reactivity of AMPA and kainate on GluK1 and AMPAR resulted in the initial development of antagonists with effect on both receptors. The most

commonly used AMPAR antagonists are the quinoxalinediones (such as DNQX and CNQX), which are potent non-NMDA antagonists with selectivity for AMPAR (20-fold) over KARs. Tezampanel is a competitive AMPA/GluK1 antagonist with increased potency, and its orally active prodrug NGX426 is the first AMPA/KAR antagonist to be studied in clinical trials for chronic pain, including migraine and neurophatic pain. Some derivatives of tezampanel are functioning as selective KAR GluK1 antagonists (LY382884 and LY466195). Selectivity for AMPAR over GluK1 was only achieved when developing noncompetitive antagonists, e.g., GYKI-53784 and CP-456,022. These AMPAR antagonists do not function as open-channel blockers but are instead binding in the linker regions between the extracellular and TM domains, affecting the conformational changes induced by the agonist. Another potent and highly selective, noncompetitive, AMPAR antagonist Perampanel was initially developed as an add-on therapy to L-Dopa in Parkinson's disease, but is presently under investigation for neuropathic pain and epilepsy. UBP203 and UBP316 are potent competitive antagonists with enhanced KAR GluK1 selectivity achieved by SAR studies of the natural product willardiine. Selective competitive antagonists for the other KAR subtypes are not yet available. Noncompetitive antagonists have so far been identified for the GluK1 and GluK2 subtypes (e.g., the AUBA compounds) and for the GluK1 homomeric KAR (NS3763). These compounds are likely to be the starting point of further development of noncompetitive antagonists. Other modulators include the Joro spider toxin (JSTX) – blocking the unedited GluK2, Arachidonic acid, primarily blocking homomeric GluK2 and GluK1/GluK2 receptors and Topiramate which inhibits excitatory neurotransmission also through actions on KAR (GluK1) and AMPARs (Lutz and Kenakin 1999).

mGluR Antagonists

Competitive antagonists acting on mGluRs prevent the closure of the two lobes of the extracellular binding pocket (the venus flytrap). Potent competitive antagonists for the Group I receptors (e.g., LY367366) are derived from the (S)-MCPG structure, while LY367385 is a selective mGlu1 antagonist. Most potent Group II antagonists are derived from L-CCG-I (e.g., LY341495) while antagonists with better selectivity could be obtained by derivatization of agonist LY354740, e.g., HYDIA and MGS0039. Extensive preclinical studies have been performed with the Group II selective antagonists showing antidepressant and anxiolytic-like effects. The Group III mGluRs still lack competitive antagonists with high potency and selectivity while compounds like MAP4, DCG-IV, and LY341495 function as antagonists with moderate potency. Due to the high similarity of the orthosteric binding site of the different mGluRs, the most promising strategy to selectively antagonize this group of receptors is by targeting the allosteric binding site(s) using NAMs.

Group I NAM mGlu1: The most commonly used mGlu1 antagonist is the noncompetitive antagonist CPCCOEt which is structurally unrelated to Glu and is binding in the TM domain of the receptor. More potent NAMs are YM-298198, BAY36-7620, and EM-TBPC, interacting in the same region of the receptor. Blockade of mGlu1, by ► antisense oligonucleotides, antibodies, and NAMs, has shown its involvement in modulation of nociception and chronic pain. A-841720 NAM, structurally different to previous mGlu1 NAMs, has also shown to be effective in models of ► nociception and is presently under development for pain treatment. Antagonists of mGlu1 have been postulated to have a therapeutic effect in ► anxiety disorders which has been confirmed by the potent mGlu1 NAM JNJ16259685.

Group I NAM mGlu5: Brain areas expressing mGlu5 receptors (limbic cortex, hippocampus, amygdala, and basal ganglia) are known to play an important role in emotion and motor controls, and mGlu5 was early recognized as a potential target for ► mood disorders and neurodegenerative diseases involving motor dysfunctions. SIB-1757 and SIB-1893 were the first selective mGlu5 NAMs to be identified. They were further developed and optimized into the more potent and selective MPEP which is the most widely used mGlu5 antagonist (a prototype for mGlu5 NAMs). mGlu5 NAMs, such as MPEP and its more selective derivative MTEP, show a clear anxiolytic and antidepressant-like profile in a wide range of preclinical behavioral models. In the search for mGlu5 NAMs, the known anxiolytic compound fenobam was identified, binding to the receptor at the same site as MPEP. After this observation several pharmaceutical companies have filed numerous patents on compounds acting as mGlu5 NAMs (divided into two major classes: acetylene- and nonacetylene-containing compounds). The mGlu5 NAM ADX-10059 recently completed a ► Phase-II trial in migraine with successful outcome. The same compound was also the first in class to show positive results in a Phase-II trial for gastroesophageal acid-reflux disease. Supported by mGlu5 expression in cortical and basal ganglia structures, mGlu5 NAMs have been shown to treat L-Dopa-induced ► dyskinesia in rodent and primate models. MPEP has also been shown to protect the nigrostriatal system against toxicity, thus having a neuroprotective function and a possibility to prevent disease development. Based on these indications, the AFQ-056

and ADX48621 compounds are in development for reducing L-Dopa-induced dyskinesias in ► Parkinson's disease. It has been suggested that the loss of FMRP (► Fragile X Mental Retardation Protein) will result in an enhanced mGlu5 signaling, and attenuation of mGlu5 activity is therefore believed to provide not only symptomatic relief but also disease modification in Fragile X syndrome. NPL-2009 (Fenobam), STX107, and AFQ-056 are all in development as potential therapies for this autistic disorder (Jaeschke et al. 2008).

Group II NAM: Preclinical studies in rodents are supportive of a therapeutic potential for mGlu2/3 NAM in mood disorders and as cognitive enhancers. A class of ► benzodiazepines (e.g., MNI135, RO676221, and RO718216) has been disclosed as potent and in vivo active mGlu2/3 NAM. The discovery of antagonists with selectivity for the two subtypes, mGlu2 and mGlu3, would also help to clarify the specific role of these receptors under physiological and pathological conditions.

Group III NAM: The recent identification of selective allosteric agonists for mGlu4, 7 and 8 will greatly help to facilitate the pharmacological characterization of these receptors and the discovery of selective NAMs. Very recently a class of pyridine compounds (MDIP and MMPIP) was identified as mGlu7 NAM. They are likely to help the clarification of the physiological role of mGlu7 in anxiety since controversial results were seen in mGlu7 knockout mice and in studies using the allosteric agonist AMN082.

Conclusions and Perspectives

The effort placed during the past decades on the characterization of the molecular properties of EEAs and their antagonists has been rewarded with the development of some of these ligands for different therapeutic opportunities. The field is however still challenging. Further basic research is required to understand the function of the glutamatergic synaptic cleft in its entirety, as well as to clarify the peculiarities and the plasticity of the glutamatergic control on ► GABA neurons. Moreover, a number of Glu receptors and subunits are still missing selective ligands, and the definition of molecular determinants of receptor cross talk for mGluRs (e.g., mGlu2/5-HT2A) could bring new challenges for medicinal chemists and new tools for behavioral pharmacologists. The clinical development of several EAA receptor ligands (included in Table 1) has also increased the need for suitable PET ligands (positron emission tomography; an imaging technique using short-lived radioactive substances to show uptake and distribution of the substances in tissue) that could be used during the preparation of the different clinical trials and possibly could be of help both in diagnostic terms and to identify responders.

Proof of concept clinical studies for the different pharmacological targets brought forward by the glutamatergic hypothesis are certainly long awaited. They will help to understand if efficacy and tolerability of the pharmacotherapy of both schizophrenia and depression (McArthur and Borsini 2008) will be substantially improved in future years.

If there is, however, an achievement that already stands out because of the long-term impact it will hopefully have on the quality of life of the patients, this must be the observation of the effects of mGlu5 antagonists in ► Fragile X. The concrete hope of a cure has increased also the interest for the early diagnosis and for a better understanding of the disease progression during the first years of life. This is certainly one of the best examples of a successful molecular approach to the therapy of neurodevelopmental brain disorders.

Cross-References

► Allosteric Modulator(s)
► Allosteric Site
► Alternative Splicing
► Alzheimer Disease
► AMPA Receptor
► Ampakines
► Animal Model
► Antagonist
► Antidepressant
► Antipsychotics
► Antisense Oligonucleotides
► Anxiety
► Anxiolytic
► Autism
► Benzodiazepines
► Binding
► Cognition
► Cognitive Enhancers
► Cognitive Impairment(s)
► Dementia
► Depression
► Desensitization
► Dyskinesia
► G protein Coupled Receptor
► G-protein Coupled Inwardly Rectifying Potassium Channels (GIRK channels)
► GABA Receptors
► Glutamate
► Glutamate Receptors
► Glycine Transporter 1

- ▶ GPCR
- ▶ Group II Metabotropic Glutamate Receptor
- ▶ Hippocampus
- ▶ 5-HT_{2A} Receptor
- ▶ In vivo
- ▶ Ketamine
- ▶ Knockout
- ▶ L-Dopa
- ▶ Long Term Potentiation
- ▶ Memantine
- ▶ Membrane Potential
- ▶ Mood Disorders
- ▶ Neurodegeneration
- ▶ Neuroprotective Agent
- ▶ Neurotransmitter
- ▶ Nociception
- ▶ NMDA Receptor
- ▶ Partial Agonist
- ▶ Phase II Clinical Trial
- ▶ Receptor
- ▶ Receptor Antagonist
- ▶ Receptors: Ligand-Binding Assays
- ▶ Schizophrenia
- ▶ Second Messenger

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Excitatory Neurotransmitters

- ▶ Excitatory Amino Acids and their Antagonists

Excitatory Postsynaptic Potentials

- ▶ EPSPs and IPSPs

Excitotoxicity

Definition

This term was coined by Olney and colleagues in the 1970s to describe neuronal necrosis caused by the exposure of CNS tissue to EAAs. These neurotoxic lesions affect predominantly postsynaptic regions with swollen dendrites, dilated perykarial mitochondia, and endoplasmic reticulum while axons and presynaptic terminals are spared. In the late stage, nuclear pyknosis and vacuolations are apparent. EAA neurotoxic properties can be used in neurobiology to selectively lesion sensitive neuronal populations (eg., ibotenic acid).

Excitotoxins

Synonyms

Neurotoxin

Definition

Excitotoxins are agonists at the either of the glutamatergic receptor subtype (AMPA, NMDA or kainate) receptors and cause damage or cell death by permitting high levels of calcium ions to enter the cell. The calcium ions then activate a variety of enzymes including phospholipases, endonucleases, and proteases that can damage the internal structures of the cell, for example, DNA and cytoskeleton, potentially leading to cell death.

Excretion

Synonyms

Clearance; Elimination

Definition

Excretion is the elimination of the drug from the body.

Cross-References
► Distribution
► Excretion
► Liberation
► Metabolism
► Pharmacokinetics

Executive Functions

Synonyms
Cognitive control; Higher-order cognitive processing; Supervisory attentional system

Definition
Executive functions are mechanisms involved in the optimization of cognitive processing, monitoring, and coordinating the performance of lower-order cognitive processes during both the planning and the execution of behavioral output. Executive functions embrace, for example, cognitive flexibility, behavioral inhibition, and the regulation of attention. Preserved executive functioning depends primarily on intact frontal lobes and frontostriatal pathways in the brain.

Cross-References
► Cognitive Enhancers: Neuroscience and Society

Exocentric

► Allocentric

Exocytosis

Definition
A process by which the membrane of an intracellular vesicle fuses with the plasma membrane of the cell and by which the content of the vesicle is expelled in the extracellular space and membrane proteins (e.g., receptors) that are incorporated in the vesicular membrane become exposed on the plasma membrane.

Exogenous Factors

Definition
External influences on behavior.

Expectancies and Their Influence on Drug Effects

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Synonyms
Expectations

Definition
Substance-related expectancies are anticipatory cognitions that explain drug-seeking behavior by providing information about whether a substance will produce a desired effect (contributing to behavioral activation) or an undesirable outcome (resulting in behavioral avoidance). Expectancies need not be accurate or explicit to guide behavior.

Impact of Psychoactive Drugs
Expectancies help explain how individuals initiate and maintain psychoactive drug use. Prior to their own first use of a substance, individuals develop beliefs about the effects of drugs based on information gathered from parents, peers, advertising, and media. As individuals associate psychoactive drug use with subjectively positive outcomes, they are more likely to try the substance. If the expected effect is achieved, the expectancy is reinforced. Expectancies, however, can be reinforced by observing the behavior and communication of others, allowing individuals to maintain expectancies without trying the drug. It should be noted that most of the extant literature on substance abuse has focused on alcohol-related expectancies, although studies evaluating expectancies for other psychoactive substances have demonstrated similar findings.

Expectancies gained attention as an explanation for the placebo effect after it was observed that questionable medications were effective in some individuals. It was hypothesized that creating an expectation that the medication would be successful was the key in separating mental processes from chemical processes, which was supported by the fact that the absence or misattribution of this expectation led to the failure of the placebo effect. This concept of expectation was also used to explain the disinhibitory effects of alcohol use (MacAndrew and Edgerton 1969). It was argued that disinhibition was a psychological manifestation of the sociocultural *belief* that alcohol caused a lack of inhibition, rather than an actual pharmacological effect.

Experimental procedures were subsequently developed to test pharmacological versus psychological explanations for drug effects. Clinical drug trials using placebos were used successfully to test the efficacy of different psychoactive medications, such as ► imipramine, ► diazepam, and ► haloperidol. In contrast, Penick and Fisher (1965) conducted a study to test expectancies in which students were administered epinephrine or placebo while being told that they had received a drug that was either sedating or stimulating; they found that there were moderate expectancy effects such that some students reported feeling sedated on the epinephrine. Despite the promise of this area of study, there were methodological limitations that called for a more rigorous experimental design.

The ► balanced placebo design corrected for these limitations and allowed researchers to separate true pharmacological effects from the effects induced by ► expectancy set, or instructions that one has consumed a substance. Applied to the effects of ► alcohol, individuals received either an alcoholic beverage or non-alcoholic beverage and were given information about whether or not their beverage contained alcohol (Marlatt and Rohsenow 1980). As illustrated in Fig. 1, four distinct groups were created; two groups were given correct information about the alcoholic content of their drink (i.e., received alcohol/told alcohol; received no alcohol/told no alcohol), whereas the other two groups were told that they were given the opposite of what they actually received (i.e., received placebo/told alcohol, received anti-placebo/told no alcohol). The placebo was a non-alcoholic beverage designed to mimic an alcoholic drink, whereas the anti-placebo was an alcoholic beverage disguised as a non-alcoholic beverage. By comparing the behavior of those individuals who believed they received alcohol and actually did to the behavior of those who believed they received alcohol but did not, researchers were able to disaggregate the effects caused by alcohol from the effects of simply expecting alcohol.

		Participants actually receive…	
		Alcohol	No alcohol
Participants expect to receive…	Alcohol	Both pharmacological and expectancy effects	Expectancy effects only (given placebo)
	No alcohol	Pharmacological effects only (given anti-placebo)	No effects

Expectancies and Their Influence on Drug Effects. Fig. 1. Balanced placebo design depicting the four groups and measurable effects of the experimental manipulation.

Early alcohol research with the balanced placebo design demonstrated that both pharmacological and expectancy effects affected overall behavior, but that expectancy effects have greater effects on social behaviors (Hull and Bond 1986). Likewise, studies evaluating the effects of placebo versus marijuana found that previous experience with marijuana and the subject's expectancies were predictive of difficulties differentiating placebo from active drug. It was hypothesized that frequent users were responding to marijuana-related cues (e.g., smell, taste) rather than the true potency of the drug. In studying chronic pain management, it was found that placebo effects constituted a significant proportion of pain reduction attributed to analgesics, but placebo was not effective for those who held negative expectancies about the utility of the drug. The application of the balanced placebo design to nicotine studies yielded results that suggested that the expectation of ► nicotine in gum increased abstinence among smokers trying to quit. Mixed results were found in a study of ► cocaine versus placebo effects, with some studies supporting placebo effects and others finding pharmacological effects to outweigh placebo (Earleywine 2005). These and other findings led to the reasoning that placebo effects were based on people's beliefs about the effects of the drug; therefore, these beliefs could be studied outside of experimental designs, leading to the study of outcome expectancies as unique predictors of psychoactive drug use.

Substance-related outcome expectancies, or beliefs about the expected outcomes of the substance, have been differentiated into explicit and implicit types based on whether or not the individual is aware of the expectancy. Explicit expectancies are higher-order cognitive processes that can be deliberately recalled, reflected upon, and discussed. Implicit expectancies are automatic processes that do not rely on the individual's awareness to motivate behavior. Although evidence is limited, the current research on explicit and implicit expectancies has shown that each provides a unique contribution in predicting substance use (Goldman et al. 1999; Wiers and Stacy 2006). This is further supported by the existence of divergent explicit and implicit expectancies. Because the individual is aware of his own explicit expectancies, these

expectancies are subjected to cortical processing and cognitive filters such as social desirability. Researchers have yet to determine the association between implicit and explicit expectancies, but current hypotheses are that they are different facets of the same cognitive construct, discrete cognitive processes, or temporally-related constructs (i.e., explicit cognitions precede implicit cognitions such that learning becomes more automated over time, Wiers and Stacy 2006).

Explicit Expectancies

Explicit expectancies are measured using surveys that ask individuals to report their expectations about the behavioral and affective outcomes of using a psychoactive drug. Expectancy measures have been developed for alcohol, marijuana, tobacco, and cocaine (Patel and Fromme 2009). Many assessments evaluate both positive, or activating, and negative, or inhibiting, expectancies. As each person has multiple beliefs about using psychoactive substances, it is important to assess both positive and negative expectancies to determine how these beliefs act together to predict behavior. Studies have suggested that positive expectancies are more closely aligned with the initiation and maintenance of substance use, whereas negative expectancies are associated with past or decreased drug use (Jones et al. 2001).

Among studies evaluating expectancy effects on alcohol use, explicit expectancies have been shown to influence both the frequency and quantity of alcohol consumption, binge drinking, and alcohol-related consequences (Jones et al. 2001). The relation between these distinct measures of alcohol use and explicit expectancies suggests that expectancies shape decisions about alcohol consumption at many levels. The literature on tobacco use and expectancies demonstrates that stronger expected outcomes are found among smokers and more robust expectancies predict smoking after abstinence. Marijuana- and cocaine-related expectancies are similarly associated with more frequent use of each respective drug (Patel and Fromme 2009).

Implicit Expectancies

The influence of implicit expectancies on substance use has been shown to be as robust as that of explicit expectancies (Wiers and Stacy 2006). Alcohol use can be predicted by implicit expectancies among college students, at-risk youth, and community samples. Implicit expectancies are also associated with greater tobacco use, increased cravings for tobacco, and a higher likelihood of relapse after smoking cessation. Preliminary studies evaluating implicit expectancy effects on marijuana, opiates, and cocaine suggest that implicit expectancies are important factors in predicting drug use (Rooke et al. 2008).

Implicit expectancies are measured using experimental tasks that attempt to isolate different aspects of implicit cognition. Measurable areas of implicit cognition include attentional bias, arousal, and memory associations. ▶ Attentional bias refers to the identification of drug-related cues faster than cues not typically associated with drugs. Drug abusers demonstrate greater attentional bias toward drug-related cues. Implicit arousal assesses the level of physiological arousal and/or the level of arousal-related cognitions in response to the presentation of drug-related cues. Increased cognitive or physiological arousal in response to substance-related cues is associated with higher levels of drug use. Associative memory tasks present individuals with ambiguous words or sentences, which elicit a free association response that may be related to drug use. It is hypothesized that repeated experiences with psychoactive drug use leads to the development of specific memory associations between the drug of choice and ambiguous cues. Endorsing a greater number of drug-related associations predicts heavier drug use (Rooke et al. 2008; Wiers and Stacy 2006).

Harnessing Expectancies for Therapeutic Change

Expectancies have long been used for therapeutic change using placebos in medical settings. Placebos can include sugar pills, non-therapeutic doses of medications, therapies that are not empirically-supported, and medications that have not yet been proven effective for a specific disorder or population. In relation to psychotropic medication, the latter is a common occurrence because of the number of new drugs available and limited efficacy research, particularly among children and adolescents. Research in the past three decades has increasingly focused on finding treatments that surpass placebo effects; however, the utility of placebo effects continues to be a source for effecting change.

▶ Expectancy challenge interventions are designed to identify inaccurate expectancies and provide correct information about the effects of drug use. Findings for the efficacy of this intervention have been mixed, although there is evidence that expectancy challenges lead to transient reductions in drug use (Jones et al. 2001). Another promising area for reducing substance use is strengthening negative expectancies, which are related to decisions to reduce drug use (Jones et al. 2001). ▶ The attentional retraining intervention was designed to specifically target and reduce attentional bias for drug-related stimuli (Wiers and Stacy 2006).

Interventions that target both types of expectancies may be more effective in achieving sustained changes in substance use. This is supported by the evidence that heavy drinkers endorse positive explicit expectancies but hold negative implicit expectancies (Wiers and Stacy 2006). Conversely, addicted individuals who enter recovery may find that the opposite holds true; they endorse negative explicit expectancies but continue to experience physiological arousal and attentional bias, which undermines their efforts. This dissociation of explicit and implicit expectancies may be explained by cognitive dissonance or self-justification (e.g., "If I use the drug, I must enjoy it;" "If I have stopped using the drug, it must be bad") or may represent internal conflict over the decision to engage in substance use. Regardless of the mechanism, it appears important to address both types of expectancies in efforts to understand or to change substance use.

Conclusion

The decision to use psychoactive substances is influenced by numerous internal and external factors, including biological, genetic, and social phenomena. Cognitive determinants alone do not explain substance use; however, it is apparent that both explicit and implicit expectancies play a significant role in the etiology, maintenance, and cessation of substance use. Given their individual contributions, both types of expectancies are necessary in understanding substance use and creating effective interventions.

Cross-References

- ► Adolescence and Responses to Drugs
- ► Attentional Bias to Drug Cues
- ► Conditioned Drug Effects
- ► Placebo Effect
- ► Rodent Models of Cognition
- ► Social Recognition and Social Learning

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Expectancy Challenge

Definition

An expectancy challenge is an intervention designed to provide experiential demonstrations of expectancy effects through the use of placebo and active drug effects. Early expectancy challenges provided individuals with placebos but stated that they received an active drug. After administration, information about expectancies and their influence on behavior was provided. Recent expectancy challenges have used attentional bias to activate expectancies prior to administration of the substance or placebo. Other procedures provide either psychoactive drugs or placebos to individuals in the same group and ask group members to determine who has received the actual drug.

Cross-References

- ► Expectancies and Their Influence on Drug Effects

Expectancy Set

Definition

Expectancy set refers to the belief that a psychoactive substance has been consumed, regardless of whether or not it has been. During experiments designed to evaluate expectancy and pharmacological effects, instructions are given that either accurately or incorrectly inform individuals about whether they received a placebo or psychoactive substance to activate the expectancy set.

Cross-References

- ► Expectancies and Their Influence on Drug Effects

Expectations

- ► Expectancies and Their Influence on Drug Effects

Experimental Animal Models of Attention Deficit/Hyperactivity Disorder

▶ Attention Deficit Hyperactivity Disorders: Animal Models

Experimental Conflict

▶ Punishment Procedures

Experimental Drug Dependence

▶ Addictive Disorder: Animal Models

Experimental Medicine

▶ Translational Research

Experimental Models of Anxiety

▶ Anxiety: Animal Models

Explicit Expectancies

Definition

Explicit expectancies are conscious anticipatory cognitions about the effect of some phenomenon. Related to the use of psychoactive substances, expectancies describe an individual's beliefs about the expected outcomes of consuming the substance. Explicit expectancies are those that can be deliberately recalled, reflected upon, and discussed.

Cross-References

▶ Expectancies and Their Influence on Drug Effects

Explicitly and Implicitly Assessed Memory

▶ Declarative and Non-Declarative Memory

Exploding Head Syndrome

▶ Parasomnias

Exploratory Behavior

▶ Motor Activity and Stereotypy

Exposure and Response Prevention

▶ Cognitive Behavioral Therapy

Externalizing Disorders

Synonyms

Disruptive behavior disorders

Definition

Disorders characterized by disruptions in the ways that individuals interact with their environments. Examples include attention-deficit/hyperactivity disorder, substance use disorders, conduct disorder, pathological gambling, and kleptomania. Externalizing disorders are often diagnosed in late childhood and adolescence, at a time when impulsivity is high. Contrast to internalizing disorders, characterized by disruptions in the ways individuals deal with their emotions.

Cross-References

▶ Attention Deficit and Disruptive Behavior Disorders
▶ Impulse Control Disorders

Extinction

Synonyms

Habituation

Definition

A process that becomes active in certain situations and that leads to a reduction in the expression of a learned behavioral response. In operant conditioning, extinction typically refers to a procedure that reduces the rate at

which a previously acquired operant response is emitted. The subjects (laboratory animals or humans) are first trained to make an operant response (e.g., lever press) to earn a reinforcer. Once stable responding is obtained, the reinforcer is no longer presented when the operant response occurs. The number of responses decreases with repeated extinction sessions. Conversely, punished responses are strengthened after a punishing stimulus is withheld. In Pavlovian (classical) conditioning, extinction typically refers to the continued presentation of the conditioned stimulus with the unconditioned stimulus withheld; this results in a decrease in the magnitude of the conditioned response across repeated presentations of the conditioned stimulus. Extinction appears not to be the complete erasure or destruction of old learning, but the acquisition of new learning that competes with or inhibits the expression of the previously learned operant or Pavlovian conditioned response. Recent research on extinction learning has identified behavioral processes and distinct neurobiological mechanisms that are distinct from those responsible for the original conditioning, involving active processes of relearning about changed contingencies.

Cross-References

► Classical (Pavlovian) Conditioning
► Instrumental Conditioning
► Operant Behavior in Animals

Extracellular Recording

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Synonyms

Measurement of neuronal activity

Definition

Extracellular recordings are used to monitor neuronal activity from outside the cell. It provides a means to measure patterns of action potentials within many areas of the peripheral and central nervous systems. In addition, massed activity can also be recorded. The effects of pathology and drugs can be investigated over extended time-courses using this technique.

Principles and Role in Psychopharmacology

Principles of Extracellular Recording

Richard Caton (1842–1926), who performed ► electroencephalography (► EEG) from the surface of living brains in animals, first discovered the electrical nature of the brain (Caton 1875). These electrical impulses, in the form of ► action potentials, underlie the information processing capabilities of the central nervous system (CNS). The pattern, frequency, and coding of this activity allows messages to be transferred from one area to another of the CNS. Extracellular recordings represent a very powerful technique for investigating the function within CNS pathways, since it provides both high-resolution information from neural tissue in vivo and in vitro and information on the spiking (output) and synaptic activity (input) of neurons in a particular recorded area. Paired with our understanding of anatomy, recordings can reveal information on the input–output function in neuronal networks. In comparison, intracellular recordings and ► patch-clamp recordings, by their very nature, produce short lasting recordings of underlying events such as ► EPSPs (► excitatory postsynaptic potentials), ► IPSPs (► inhibitory postsynaptic potentials), and channel activity, whereas extracellular recordings can provide hours of recording, rendering the approach suitable for examining both detailed response characteristics and also pharmacological manipulations. The patterns of activity can be viewed and monitored in real time and so extracellular activity allows neuronal function to be studied in normal conditions and then be compared with pathological or dysfunctional states neuronal activity. Changes in neuronal activity in response to pharmacological manipulation can also be assessed. Importantly, neuronal activity provides an objective and unbiased way of observing changes in neuronal systems and these quantitative measures of firing of a neuron are less subjective than a behavioral response.

The general principle of extracellular recordings involves detecting the changes in the membrane potential of neurons, which occur during the firing of action potentials. Differences in the voltage fluctuations between the recording electrode (placed in the target tissue) and a reference wire (placed at a more distal site) are recorded. The firing of action potentials requires the transient opening of a sodium channel and since the concentration of sodium is greater outside of the neuron than inside, the sodium flows down its concentration gradient. This reduction of positive ions from the extracellular environment is observed as a negative voltage fluctuation with, respect to the reference electrode. Commonly, these

signals are small (<1 mV) and require signal amplification, and filtering with low- (<1 Hz) and high-pass (>3 kHz) filters, to produce a useful measurable output. Therefore, extracellular recording allows responses to be recorded and quantified as a result of controlled sensory or electrical stimulation, either as a means of activating neurons in one area to identify functional connections, or used as a conditioning stimulus or even simple ongoing activity. Once these responses have been measured, it is then possible to apply drugs by a wide range of routes, namely systemic, local (icv, by microinjection or spinal), or directly to the neuron.

Drugs can be used as agonists to activate either excitatory or inhibitory receptors, using their effects on action potentials as a measure of the existence of that receptor in the particular circuit. Antagonist studies, however, are likely to be the most powerful, since the physiological activation of a particular receptor, by release of the endogenous transmitter in the pathway under study, can be evidenced by the ability of a drug that blocks a receptor to alter activity in the neuron. This type of study can further be used to study the potential changes in transmitter systems in pathophysiological events by comparing responses between control and experimental groups. In this context, care is needed to ensure that similar populations of neurons are recorded in both groups to allow valid comparisons. In a similar way, the same measures can be made in wild-type and transgenic mice to allow functional roles of protein products to be ascertained in situations where pharmacological tools are lacking or insufficiently selective.

Technical Considerations

Extracellular activity is most often recorded in vivo under anesthesia throughout the study or, in the case of activity in unrestrained animals, have a recording device secured in place under surgical anesthesia. In the former case, volatile anesthetics such as isoflurane or halothane, often delivered in a gaseous mixture of N_2O:O_2, are used, with anesthesia maintained at a steady state throughout the recording period. Other approaches use urethane, pentobarbitone, etc. as anesthetics, but here fluctuations in levels with time may be issues. In most studies of this nature, the animals will be placed in a stereotaxic frame to maintain stability at the recording site during electrophysiological recordings and allow for defined brain areas to be located using coordinates found in a stereotaxic atlas; the placement of the electrode is confirmed histologically at the end of the experiment.

Electrodes of many types can be used, ranging from glass to parylene-coated tungsten. The ways in which action potentials or other forms of activity are monitored and measured are varied, but in general terms: a headstage will receive input from the recording electrode and often differential recordings are made where activity from the muscle, cardiovascular, and respiratory systems as well as an eventual electrical interference, from the surrounding environment, is subtracted from the main input. Efficient grounding of the recording system is necessary for high signal-to-noise recordings.

Equipment is needed to amplify and differentiate the input, to allow filtering between defined frequencies, and often the signal is monitored by both audible and then visible means on an oscilloscope. Neurones are differentiated according to their amplitude by use of a window discriminator with adjustable window height, to separate activity from the baseline background noise, or to discriminate a single neuron based on waveform and amplitude. The activity is then quantified and further analyzed, mostly online by use of an interface linked to a computer, where the captured data is quantified, analyzed, and displayed using software.

The ability to monitor action potentials in a dynamic fashion can be used in many ways. The recording of single unit activity allows an unequivocal measure of the integrated responses of a single neuron, but mass activity of neuronal populations can also be measured as ▶ field potentials or multiunit recordings and activity of more than one single unit in an area can be measured simultaneously using electrode arrays.

Single-unit Recordings

In vivo extracellular recordings can be performed with relatively little damage to the surrounding tissue. Single-unit recordings using an electrode with a small tip (<1 μm, microelectrode) can be used to monitor the electrical activity of a single cell. Neuronal activity is recorded once the microelectrode is positioned in proximity to a neuron. Current fields, generated by action potentials, are detected through the tip of a microelectrode and are displayed as small voltage deflections occurring in the millisecond range. Stimulation can be used to measure the postsynaptic effects of an afferent input to a neuron. Electrical pulses are applied to a stimulating electrode to activate neurons that project to where a target cell is recorded. For example, tungsten microelectrodes positioned in the dorsal horn of the spinal cord of rats, in an area receiving information from the hindpaw, can be used to measure the activity of second-order neurons receiving both afferent information from the periphery and descending modulation from the brain (Urch and Dickenson

2003). Neuronal activity is recorded in response to a wide range of stimuli applied at the periphery. Typically, post-stimulus time histograms (PSTHs) summating neuronal activity from a series of trials are compiled, allowing the measurement of even relatively weak responses. Together with pharmacology, this approach can be used to investigate the mechanisms involved in the transmission and processing of nociceptive information, for example (Suzuki et al. 2002).

Multi-unit Recordings

By increasing the diameter of the recording electrode, or by using multielectrode arrays, multi-unit recordings can be performed measuring the activity of several neurons simultaneously. Multi-unit recordings are often performed in conscious freely moving animals and can provide information on integrated systems facilitating the understanding of the transformation of sensory input to its functional behavioral output. Normally, the animals have been trained for a particular behavior and the aim is to look for a neuronal correlate to this behavior. This approach has proved particularly successful in the ▶ hippocampus where "place cells," which exhibit high-frequency firing in response to specific location, were first described (O'Keefe and Dostrovsky 1971). This technique can be used to observe both the synchronized activity of the neurons, within the locality of the recording electrode, and identify the number and type of cells responding to the stimulus in different brain areas. This process is known as spike sorting, where the time-course of a particular spike is defined by the size and shape of a neuron and its position relative to the recording electrode. Analysis based solely on changes in amplitude can be difficult to interpret as neurons are physiologically heterogeneous, such that the activity in one neuron may cancel out the activity in an opposing neuron. Thus, more sophisticated algorithms have been developed to separate and identify the activity produced by each individual neuron in the local vicinity.

In vivo recordings permit recordings from intact neuronal networks; however, it may be difficult to gain access to certain target structures. Recordings from in vitro studies, therefore, can be used to provide information from such areas and avoid any potential problems associated with anesthesia. In vitro electrophysiology can be performed on cell cultures, acute or cultured tissue slices, and isolated superfused structures (e.g., brainstem). Acutely isolated neurons, by mild enzymatic digestion of brain slices, and cultured neurons offer advantages over in vivo preparations, as they allow direct visualization using a microscope. The administration of ligands of defined concentrations can be applied rapidly and repeatedly, and molecular targets can be isolated by pharmacological manipulation using agents known to block undesired systems. However, these preparations lack the integrity of network interconnectivity and are devoid of the long-range targets that are present in in vivo recordings.

Similar to in vivo recordings, in vitro recordings can be performed extracellularly (as well as intracellularly). Because of the small signal, neuronal activity is often obtained using multi-unit recordings (field potentials) observing changes in the potentials of the neurons with respect to the recording electrode, visualized as a change in amplitude. The activity of individual neurons cannot be distinguished; rather the activity of a group of neurons is recorded as a field potential. This approach has been employed with great success in understanding the role of the hippocampus. For instance, the concept that learning and memory might be underpinned by persistent changes in the strength of synaptic contacts within the hippocampus, a structure with clearly defined pathways, laminae, and circuits, was borne out by the ability to activate a large number of synapses using an extracellular stimulator (e.g., perforant path) and record large responses of many cells simultaneously with an extracellular electrode placed in another area such as the granule cell layer or pyramidal layer (Bliss and Lømo 1973). This paved the way for the numerous studies of synaptic activity related to plasticity in the brain, with ▶ long-term potentiation (LTP) being the key proposed mechanism in this regard.

Carbon Fiber Amperometry

▶ Carbon fiber amperometry can be used to investigate exocytosis of neurotransmitters and hormones from presynaptic neurons and other secretory cells. Much of our current understanding of vesicular fusion and subsequent transmitter release has been gained by amperometric recordings (either alone or in combination with other techniques), such as the identification of the fusion pore (the initiating event of exocytosis), kiss-and-run fusion (fast vesicle recycling), and the understanding of the interplay between various parts of the synaptic machinery (e.g., Munc18-1/syntaxin) (Chow et al. 1992; Neher 1993).

The general principle involved relies on the measurement of amperometric spikes resulting from the electrochemical current elicited by the oxidation and reduction of certain molecules. This can be measured by placing a carbon fiber electrode held at a constant potential (amperometry) or cycling (voltammetry) close to the cell of interest. Certain neurotransmitters (namely monamines and catecholamines) lose (oxidation) or gain

(reduction) electrons at characteristic voltages, allowing the identification of particular brain chemicals. This approach provides information regarding the reuptake and metabolism of transmitters and vesicle release probability, but is limited to those cells that secrete a detectable substance. More recently, this technique has been developed by pairing it with other types of electrophysiology such as ► patch-clamping (patch amperometry) allowing the simultaneous determination of the fusion pore conductance, vesicle size, and the kinetics of transmitter release from the same vesicle. Fluorescence imaging is also employed, tagging proteins involved in the exocytotic machinery, thus allowing the investigation of the spatiotemporal dynamics of neurotransmission and secretion. Further advances have been made in the form of multielectrode arrays (MEAs) to study exocytotic events from multiple sites avoiding problems with micromanipulation, and this strategy has proved useful in the understanding of neuronal communication in brain slices, neuronal cultures, and has been used in drug discovery.

Cross-References

► Analgesics
► EEG
► Event-related Potentials
► Intracellular Recording
► Long-term Potentiation
► Synaptic Plasticity
► Voltammetry

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Extradimensional

Synonyms

ED

Definition

In the context of a ID/ED task, the extradimensional (ED) stage involves discriminating between two (generally novel) stimuli that differ from each other in at least two dimensions (e.g., color and shape), but for which the relevant discriminative dimension (e.g., shape) is unattended because the irrelevant dimension (e.g., color) has been primed by prior experience. In the ID/ED task, the critical comparison is between the ID and ED stages: although both are formally novel acquisitions, prior experience biases attention such that there is a benefit of ID over ED acquisition.

Cross-References

► Behavioral Flexibility: Attentional Shifting, Rule Switching and Response Reversal

Extrapyramidal Motor Side Effects

Synonyms

EPS

Definition

The extrapyramidal system is a neural network located in the central nervous system, which is involved in the coordination of movement. Extrapyramidal symptoms refers most commonly to the side effects of many antipsychotics that affect movements. They include neurologic syndromes such as dystonia, dyskinesia, Parkinson-like disturbances including tremor, rigidity, and bradykinesia as well as akathisia. These adverse events can occur both during acute and the chronic treatment with antipsychotics. They are sequelae of the dopamine antagonist properties of antipsychotics. In general, they are dose-dependent and more severe and frequent with first-generation antipsychotics than with the newer drugs.

Cross-References

► Antipsychotics
► First-Generation Antipsychotics
► Movement Disorders Induced by Medications
► Tardive Dyskinesia

Eye Movement Tasks

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Synonyms

Oculomotor tasks; Eye tracking; Saccaddes; Smooth pursuit

Definition

Eye movement tasks are a powerful tool with which researchers can study the effects of pharmacological compounds on brain function. Although there are several different classes of eye movements (see Leigh and Zee 2006), two types are particularly relevant to psychopharmacological research. Saccadic eye movements are rapid, conjugate movements of the eyes, which serve to orient the high acuity foveal region of the retina onto a specific region of visual space. ▶ Smooth pursuit involves slower eye movements that serve to keep an object foveated if it moves across our field of vision. Both saccades and smooth pursuit eye movements are influenced by ▶ endogenous factors, such as our goals and expectations, as well as ▶ exogenous factors, such as the size, shape and luminance of an object in the visual field, and as such can provide important insights into the effects of pharmacological compounds on cognitive function. In addition, eye movements made to more complex stimuli, such as faces or scenes can also reveal important information concerning cognitive function.

Principles and Role in Psychopharmacology

The use of eye movement tasks as a tool with which to investigate the effects of pharmacological interventions on brain function has a number of distinct advantages. Firstly, sophisticated eye tracking technology means that eye movements can now be measured with exceptional accuracy and reliability. Secondly, the neural systems involved in eye movement control have been well established by neurophysiological studies in non-human primates and lesion studies in humans – it has been argued that the oculomotor system provides researchers with a "microcosm of the brain" (Carpenter 1994). Thirdly the neural systems involved in eye movement control overlap considerably with those that mediate important cognitive processes such as those involved in ▶ attention and ▶ working memory, and the simplicity of eye movement tasks enables them to be manipulated in ways that allow specific cognitive processes to be isolated. Finally pharmacological compounds have been shown to have replicable effects on a range of eye movements.

Eye Movement Tasks

The majority of research into the effects of pharmacological compounds on eye movement function has used two very simple paradigms. In the ▶ prosaccade task participants typically fixate a central stimulus (such as a small cross) for a short period of time and then make a saccade towards a sudden onset target which appears in the left or right hemifield. Key metrics include the latency of the saccade (e.g., its reaction time with respect to the target onset), its amplitude, duration and peak velocity. In a standard ▶ smooth pursuit task participants are asked to follow a moving target (typically a small circle) with their eyes. The target moves backwards and forwards along the horizontal axis, with either a constant or sinusoidal velocity. Key metrics include pursuit velocity gain (the ratio of the eye velocity to target velocity) and the number of saccades made during pursuit. Reductions in pursuit velocity gain are typically compensated for by in an increase in the number of corrective "catch-up" saccades.

The prosaccade task seems, on the surface, to require very little in the way of cognitive processing, but the average prosaccade latency (~190 ms) is around 100 ms longer than would be required if the response was simply a reflex. It has been argued that this extra time reflects a "decision" process – our brain needs to determine not just where to look, but whether it is worth looking there at all. This decision reflects the influences of both ▶ exogenous (bottom up) and endogenous (top down) factors, and is clearly related to the processes that determine where we allocate our attention. The precise nature of the relationship between saccades and visual attention remains a topic of considerable debate, but there is agreement that the neural mechanisms underpinning them overlap considerably. Following a target as it moves horizontally also seems to require relatively little in terms of cognitive effort. Again, though, research has demonstrated that smooth pursuit eye movements involve a surprisingly complex set of information processing stages, including the generation of an internal model of the target's velocity.

Other eye movement tasks that have a more obvious "cognitive" involvement are increasingly being used in psychopharmacological research. These tasks typically place a greater role on higher cognitive functions than the prosaccade and smooth pursuit tasks described above. The ▶ antisaccade task is an important variant of the prosaccade task. The stimulus timings and properties

are identical in the two tasks, but in the antisaccade task participants are instructed to saccade to the mirror image location of the sudden onset target rather than towards it. The task thus requires participants to inhibit a highly prepotent response (to saccade towards the sudden onset target) and initiate an internally generated response (to saccade to the mirror image location). Many neuropsychological tasks sensitive to damage to the prefrontal cortex (e.g., Stroop) share this requirement to respond on basis of an internal goal as opposed to an external stimulus, and patients with lesions to this area, as well as patients with psychiatric disorders such as ► schizophrenia, in which prefrontal dysfunction is implicated, make a large number of antisaccade errors (prosaccades made towards the target). The key metric of the antisaccade task is the proportion of trials in which antisaccade errors occur. However, the latency, amplitude and velocity of correct antisaccades can also be informative.

There are other simple eye movement tasks that are routinely used in other research settings, but which have yet to be widely adopted in psychopharmacological studies. These include remembered and predictive saccades, and predictive pursuit. Eye movement tasks that use more complex stimuli are also potentially informative, and can also exploit the close relationship between eye movements and attention. For example, in visual search tasks, participants are required to identify one or more target items (e.g., the letter "L") presented in an array of distractors (e.g., the letter "T"). Standard visual search tasks provide a single measure – reaction time. When combined with eye tracking, however, metrics such as the number of refixations on previously identified targets or the average angle between saccades can provide important information concerning the functionality of working memory and attentional processes, and the high level strategies participants are using to perform the task. Eye tracking can also be used to provide important insights into performance on other standard tasks of cognitive function. In the dot-probe task, for example, two images are presented simultaneously for a short period of time, and participants' reaction time to a dot that appears subsequently behind one or the other is measured. The task is typically used to measure ► attentional biases (e.g., towards drug related stimuli in a drug addict) but can also be used to index potentially subtle effects of psychopharmacological compounds on specific types of information processing – for example, whether ► alcohol biases attention towards negative or positive facial expressions. Recording eye movements during dot probe performance allows variables such as the time to first fixation, first fixation duration and total dwell time for each of the images to be measured. These measures can potentially reveal subtle effects of pharmacological compounds that a simple reaction time measure may be insensitive to.

Eye Tracking Techniques

Eye movements can be recorded using a variety of techniques (see Duchowski 2007 for a comprehensive discussion). Early research mainly used electro-oculography, in which pairs of electrodes placed near the eye record small changes in voltage that occur as it moves. Most current eye trackers are video based, and use high speed cameras and sophisticated image analysis systems to establish the location of the pupil and the corneal reflection of an infrared light source. After a simple calibration procedure the vector between these two points can be used to determine the location of gaze. In some eye tracking systems the camera recording the eye movement is mounted on a lightweight head-set, but increasingly remote optics are being used, with fixed cameras placed beneath the monitor on which stimuli are displayed.

Eye Movement Tasks in Psychopharmacological Research

There are two broad areas of psychopharmacological research in which eye movement tasks have been widely used. (1) investigations into the acute effects of pharmacological compounds on psychological functioning in healthy participants, and (2) investigations into the more chronic effects of pharmacological treatments in clinical (typically psychiatric) populations. Evidence from these two fields of research will be considered separately. A very thorough treatment of both literatures is provided by Reilly et al. (2008).

Acute Effects in Healthy Participants

The majority of studies into the acute effects of pharmacological compounds on eye movements have been done in the context of tolerability studies. A number of different psychopharmacological compounds have been shown to have replicable effects on eye movements. Early research established clear dose dependent relationships between serum concentrations of ► benzodiazepines such as ► diazepam and ► temazepam and saccade peak velocity – saccade velocity decreases as serum concentration of benzodiazepines increases. These effects are presumably mediated via GABA-ergic connections between the caudate nucleus and the substantia nigra pars reticular, and between the nigra and the superior colliculus – both regions that lesion studies have confirmed are critical for the generation of saccades. The clear relationship between saccade velocity and benzodiazepine dose led to the use of eye movement tasks as an index of the sedative effects of

psychopharmacological compounds. Recent studies have confirmed that saccade velocity is more sensitive to the sedative effects of benzodiazepines than other common measures of altertness such as rating scales or measures of psychomotor speed. Benzodiazepines also have consistent effects on smooth pursuit velocity. Again studies have demonstrated a dose dependent relationship such that increases in serum concentration of benzodiazepine are associated with a reduction in smooth pursuit velocity gain, and consequent increase in the number of corrective "catch-up" saccades.

Other pharmacological compounds, in particular ▶ first generation antipsychotics, whose primary action is the blockade of dopamine receptors and anticonvulsant/mood stabilizing compounds such as ▶ lithium have also been found to decrease prosaccade peak velocity, and disrupt smooth pursuit performance. In both cases, the effects likely reflect the sedative properties of these compounds on CNS function. The effects of ▶ second generation antipsychotics on eye movement tasks have not been well established, although reductions in prosaccade velocity have again been observed.

Stimulants, such as ▶ amphetamines and cholinergic agonists like ▶ nicotine, do not appear to improve performance on standard prosaccade or smooth pursuit tasks, possibly because performance on these simple tasks is typically already optimal. Interestingly, SSRIs and 5HT agonists have been found to impact on some eye movement metrics –most notably resulting in increases in saccade peak velocity and pursuit velocity gain. The underlying mechanism by which these improvements are mediated is not clear (they do not appear to reflect an increase in alertness), but there are known serotonergic pathways in brain-stem regions involved in saccade generation.

Despite the well established effects of benzodiazepines and antipsychotics on prosaccade and smooth pursuit function, comparatively few studies have explored the effects of these compounds on antisaccade performance, or other eye movement tasks requiring greater attentional and cognitive control. In one study ▶ lorazepam, but not ▶ chlorpromazine was found to increase antisaccade error rate (although not, surprisingly, antisaccade velocity). A larger number of studies have explored the effects of nicotine on antisaccade performance in healthy participants. Several studies have found that nicotine can increase correct antisaccade latencies and reduces the number of antisaccade errors. Nicotine has also been found to improve performance on visual search tasks in smokers, resulting in a reduction in the number of fixations on non-target items.

Treatment Effects in Patient Populations

As Reilly et al. (2008) note, given the potential advantages outlined earlier, it is perhaps surprising that the literature examining the effects of medication on eye movement function in patients with clinical disorders is comparatively limited. Whilst medication is often included as a factor in studies that have measured eye movement function in clinical populations, longitudinal randomized designs (which would allow direct inferences concerning the effects of different medications on oculomotor function) are rare. In addition, methodological differences between studies with respect to the eye movement tasks used make comparisons difficult. The effects of psychiatric and neurological disorders themselves (as opposed to medication effects) are reviewed comprehensively elsewhere (e.g., Leigh and Kennard 2004).

The effects of first and second generation antispsychotics on eye movement performance in patients with schizophrenia are perhaps the best characterized. In accordance with the findings of single dose studies in healthy participants, first and second generation antipsychotics have been found to reduce prosaccade velocity in patients with schizophrenia. Antipsychotic medications also result in a reduction in prosaccade amplitude – ▶ hypometria. This hypometria is particularly pronounced for endogenously generated saccades, such as occur in the remembered saccade task (in which participants initiate a saccade to a location based on their memory for where the target stimulus appeared) and the predictive saccade task (in which participants saccade to a target moving backwards and forwards between two locations at a predictable frequency). Interestingly saccade hypometria is a feature of patients with ▶ parkinson's disease, and thus may reflect decreased striatal dopamine availability. Performance on the antisaccade task does not appear to be effected by antipsychotic treatment, despite improvement in neuropsychological indices of cognitive function that can occur with treatment. Another important finding is that studies investigating changes in psychotic symptoms and eye movements as a result of treatment initiation in previously antipsychotic free patients have found that changes in both over time are unrelated.

Interestingly, mirroring their beneficial effects in healthy participants, nicotinic compounds have been shown to slightly ameliorate impairments in smooth pursuit and antisaccade performance in patients with schizophrenia. In contrast, anticholinergic compounds such as ▶ procyclidine have been found to impair performance on these tasks in this population.

The evidence concerning the effects of medication on eye movements in other disorders is sparse and often

contradictory. There is no consensus as to the effects of stimulants such as ► methylphenidate on eye movement task performance in patients with ► attention deficit hyperactivity disorder (ADHD). Some, but not all studies have found that treatment with dopamine agonists improves performance on some eye movement tasks in patients with parkinson's disease.

Limitations

Whilst one of the potential advantages of basic eye movement tasks such as prosaccades and smooth pursuit are their simplicity, there are a myriad of methodological variations in the ways in which these tasks are presented. It is becoming increasingly clear that small differences in apparently minor details such as the size of the target, its distance from the central fixation point or its temporal relationship with the offset of the central fixation stimulus, can all have a significant impact on metrics such as saccade latency and amplitude. These differences considerably complicate cross study comparisons. The situation is perhaps even more serious for more "cognitive" eye movement tasks such as antisaccades, in which differences in the way instructions are given has been shown to have an impact on the number of errors made (see Hutton 2008).

Future Directions

There have been comparatively few investigations into the effects of pharmacological compounds on variations on the standard eye movement tasks, such as the antisaccade task and predictive smooth pursuit. Even fewer studies have attempted to use eye tracking to explore the effects of pharmacological interventions on eye movements made to more complex stimuli (such as scenes or faces) or more complex tasks (such as visual search or matching familiar figures tests). Future research using these more complicated tasks, and related tasks that exploit the link between gaze and endogenous attentional processes, may provide important insights into the effects of pharmacological compounds on brain function.

Another important use of eye movement tasks in the future will be in pharmacogenetic studies. Researchers have already employed eye movements as intermediate phenotypic markers of schizophrenia in family genetic studies. In addition, several studies have established relationships between genotype and oculomotor function in patients with schizophrenia – for example, male patients with the Met/Met allele of the catechol-o-methyltransferase (COMT) Val/Met polymorphism had significantly better smooth pursuit performance compared to patients with other genotypes. Other research has found that the sensitivity of smooth pursuit velocity gain to benzodiazepines is moderated by genotype – carriers of the Ser385 allele, associated with alcoholism, demonstrated a smaller benzodiazepine induced reduction in pursuit velocity gain than non carriers. Such finding suggest that basic eye movement tasks such as prosaccade and smooth pursuit, as well as more complex eye movement tasks, will continue to provide researchers with important insights into the mechanisms through which pharmacological compounds impact on cognitive function.

Cross-References

► Antidepressants
► Antipsychotic Drugs
► Benzodiazepines
► Decision Making
► Executive Functions
► First-Generation Antipsychotics
► Nicotine
► Pharmacogenetics
► Psychomotor Performance in Humans
► Schizophrenia

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Eye Tracking

► Eye Movement Tasks

Eyes Closed Occipital Waves

► Function of Slow and Fast Alpha

E-α-Cyano-N,N-Dietyl-3,4-Dihydroxy-5-Nitrocinnamamide

► Entacapone

F

FAA

Definition
Federal Aviation Administration (USA).

FAAH

► Fatty Acid Amide Hydrolase

Face Validity

Definition
The phenomenological similarity between the behavior or other signs exhibited in an animal model and the specific symptoms of the human condition. This is an intuitively appealing and important criterion, but it can also be misleading because of its subjective nature; similar signs and symptoms may be engendered by different underlying mechanisms.

Cross-References
► Animal Models of Psychiatric States
► Construct Validity
► Predictive Validity

Facial Dysmorphology

Definition
Anomalies in the shape and contour of the face and skull.

False Memory

Definition
A retrieved memory item that does not correspond to veridical experience but believed to be so by the subject.

False Negative

Definition
In animal modeling, a false negative is a drug that shows similar clinical effects to the reference drug, but shows different effects in the animal model.

False Positive

Definition
In animal modeling, a false positive is a drug that shows similar effects to the reference drug in the animal model, but is clinically inactive in humans.

FAS

► Foetal Alcohol Spectrum Disorders

FASDs

► Foetal Alcohol Spectrum Disorders

Fast Fourier Transformation

Synonyms
FFT

Definition
A fast Fourier transform (FFT) is an algorithm to compute the discrete Fourier transform that decomposes a sequence of values in the time domain into components of different frequencies. It is applied to EEG analysis to calculate the power in various frequency bands such as theta (4–7 Hz), alpha (8–12 Hz), and beta (12–30 Hz) thought to represent discrete physiological processes.

Cross-References
► Electroencephalography

Ian P. Stolerman (ed.), *Encyclopedia of Psychopharmacology,* DOI 10.1007/978-3-540-68706-1,

Fast-Scan Cyclic Voltammetry

► Electrochemical Techniques and Advances in Psychopharmacology

Fat Soluble

► Lipophilic

Fatigue

Definition

This word describes a weariness caused by exertion. In some neurological diseases as multiple sclerosis and ► Parkinson's disease, fatigue as a rapidly developing or abnormally long-lasting weariness may be a major symptom. Fatigue is a subjective feeling and may include physical fatigue (muscle weakness) or mental fatigue (loss of concentration, attention, and transient deterioration of cognitive functions) or both.

Fatty Acid Amide Hydrolase

Synonyms

FAAH

Definition

The enzyme that metabolizes the endocannabinoid, *N*-arachidonylethanolamine, to arachidonic acid and ethanolamine.

FCE21336

► Cabergoline

FDA Pregnancy Category

Definition

Category *A*: *Controlled studies show no risk*: adequate, well-controlled studies in pregnant women have failed to demonstrate risk to the fetus. *B*: *No evidence of risk in humans*: either animal studies show risk, but human findings do not; or, if no adequate human studies have been performed, animal findings are negative. *C*: *Risk cannot be ruled out*: human studies are lacking and animal studies are either positive for fetal risk or lacking as well. However, potential benefits may outweigh risks. *D*: *Positive evidence of risk*: investigational or postmarketing data show risk to the fetus. Nevertheless, potential benefits may outweigh risks. *X*: *Contraindicated in pregnancy*: studies in animals or humans, or investigational or postmarketing reports, have shown fetal risks that clearly outweigh any possible benefit to the patient.

Fear

Definition

An aversive emotional state elicited by an explicit threat. In animal studies, it refers to an inferred psychological state that serves to organize and coordinate various species-specific defensive responses necessary for survival.

Fear Conditioning

Synonyms

Conditioned fear

Definition

A type of learning in which an aversive stimulus to produce fear is associated with a neutral stimulus (e.g., a tone).

Fear of Being Alone

► Agoraphobia

Fear of Crowded Areas

► Agoraphobia

Fear of Public Places

► Agoraphobia

Fear-Potentiated Startle

► Pavlovian Fear Conditioning

Fear Reaction to Somatic Anxiety Symptoms

► Agoraphobia

Federal Medical Center, Lexington

► Narcotics Prison Farm

Feeling

► Emotion and Mood

Fenfluramine

Definition

Fenfluramine is chemically an amphetamine derivative that has been used as an antiobesity agent. It lacks the typical psychomotor stimulant properties of ► amphetamine and its mechanism of action is different, predominantly involving the serotonergic system rather than catecholamines such as dopamine. It has been withdrawn from the market because of the risk of heart valve disease.

Cross-References

► Appetite Suppressants
► Eating and Appetite

Fentanyl

Definition

Fentanyl is an extremely potent, synthetic opioid agonist that acts selectively on μ-opioid receptors. It is mainly used to treat chronic pain and also commonly used for anesthesia, including veterinary anesthesia. It is approximately 100 times more potent than morphine but has a very short duration of action. Intravenous fentanyl is extensively used for anesthesia and analgesia, most often administered in combination with a benzodiazepine, such as ► midazolam, to produce procedural sedation for endoscopy, cardiac catheterization, oral surgery, etc. In addition, due to its potent analgesic effects, it is often used in cancer therapy and other chronic pain management where its short duration of action facilitates self-regulation of dosing. It has also been much used in experimental psychopharmacology as a prototypic μ-opioid agonist.

Cross-References

► Analgesics
► Morphine
► Opioids
► Opioid Analgesics

FFT

► Fast Fourier Transformation

Field Potentials

Synonyms

Local field potentials

Definition

Field potentials are the electric potentials produced by excitable cells (e.g., nerve or muscle cells), recorded from outside the cell. Recordings such as EEGs typically represent the massed behavior of many cells from a certain target area.

Cross-References

► Electroencephalography

Final Ratio

► Breakpoint

Financial Incentives

► Contingency Management in Drug Dependence

Firing Pattern

Definition
The distribution of action potentials over time; usually expressed as number of bursts, percent of bursts, percent of spikes in burst.

Cross-References
► Extracellular Recording

Firing Rate

Definition
The number of action potentials (spikes) over time; usually expressed as number of spikes per second (Hz).

First-Generation Anticonvulsants

Synonyms
Classical anticonvulsants; Older anticonvulsants; Traditional anticonvulsants

Definition
This category includes all medications developed before 1990.

Cross-References
► Carbamazepine
► Ethosuximide
► Phenobarbital
► Phenytoin
► Valproate

First-Generation Antipsychotics

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Synonyms
Classical antipsychotics; Classical neuroleptics; Conventional antipsychotics; Conventional neuroleptics; Major tranquilizers; Old antipsychotics; Old neuroleptics; Traditional antipsychotics; Traditional neuroleptics; Typical antipsychotics; Typical neuroleptics

Definition
Antipsychotics introduced to the market in USA before ► Clozapine (before 1989).

Pharmacological Properties
► First-generation antipsychotics (FGA) is a heterogeneous group of ► dopamine D_2 receptor antagonists with different chemical, pharmacological and clinical profile. Main clinical characteristic of the FGA is more ► Extrapyramidal Motor Side-Effects (► EPSE), more frequent ► hyperprolactinaemia and less clinical efficacy if compared with the ► second-generation antipsychotics (SGA). There are, however, some exceptions from and inconsistencies in the definition above. For example ► amisulpride and ► risperidone, two SGA significantly increase prolactin levels and so some authors do not acknowledge hyperprolactinaemia as a good group differentiating factor. Moreover, clinical comparison of FGA and SGA gives ambiguous results. Today it is clearer that there are not sharp boundaries between FGA and SGA and maybe in the near feature more pertinent classification will be adopted.

Chemical Profile
Using chemical profiles FGA can be classified as ► butyrophenones (e.g., ► haloperidol, ► bromperidol, ► benperidol, droperidol, pipamperone, spiperone, trifluperidol).

Dibenzoxazepines: loxapine. Diphenylbuthylpiperidines: fluspirilene, penfluridol, ► pimozide. ► Phenothiazines (e.g., ► chlorpromazine, clopenthixole, ► fluphenazine, metophenazate, metotrimeprazine, periciazine, ► perphenazine, ► prochlorperazine, ► promazine, ► promethazine, prothipendyle, ► thioridazine, ► trifluoperazine, triflupromazine. Substituted benzamides: ► sulpiride. *Other tricyclic antipsychotics*: ► carpipramine, clorotepine, oxyprothepine. ► Thioxanthenes (e.g., chlorprothixene, cisclopenthixole, ► flupenthixole, ► thiothixene, ► zuclopenthixole).

Many of these compounds are no more on the market.

Low and High Potency Antipsychotics
From clinical as well as pharmacological point of view FGA can be classified as *high-potency* and *low-potency* antipsychotics. Potency refers to their affinity to dopamine D2 receptors and the average therapeutic dose, compared with a 100 mg of chlorpromazine (so called

chlorpromazine equivalent) (Baldessarini et al. 1988). The example of low-potency antipsychotics in light of ▶ evidence based medicine is chlorpromazine (Leucht et al. 2003). Low potency antipsychotics have been suggested to be more sedative than high potency antipsychotics but on the other hand induce less EPSE than high-potency antipsychotics. In sufficiently high doses, low potency antipsychotics are not, in principle, less effective than high potency antipsychotics such as haloperidol (Leucht et al. 2003). Low-potency antipsychotics induce more EPSE than ▶ clozapine, ▶ olanzapine and risperidone but not more than other SGA (Leucht et al. 2009). Low-potency antipsychotic are less sedative than ▶ clozapine, ▶ NNH (Number Need to Harm) 13 [7–220], but do not differ in this respect from other SGA (Leucht et al. 2009). Weight gain is similar to that after SGA and higher than after ▶ aripiprazole and ▶ ziprasidone (Leucht et al. 2009).

High-potency antipsychotics induce more EPSE than low-potency antipsychotics and SGA. The typical representative of this group is haloperidol. NNH for haloperidol to induce EPSE was between 2 for clozapine and 5 for ▶ zotepine (Leucht et al. 2009). On the other hand haloperidol was associated with less weight gain than most of SGA and was not different from aripiprazole and ziprasidone in this respect (Leucht et al. 2009). Haloperidol was significantly less sedating than clozapine (NNH 5 [3–14]), ▶ quetiapine (NNH 13 [8–20]), and zotepine (NNH not significant) but significantly more sedating than aripiprazole (NNH 33 [20–1,001]; (Leucht et al. 2009).

Efficacy of the FGA

The recent ▶ meta-analyzes concluded that the FGA as a group were less efficacious than some but not all antipsychotics from SGA (Leucht et al. 2009). In Leucht et al. (2009) meta-analysis 95 studies were included with haloperidol, 28 studies with chlorpromazine, five studies with perphenazine and less than five with other FGA. So results from this meta-analysis are more related to haloperidol or chlorpromazine than to other FGA. In the concrete, FGA was less effective in overall change of symptoms than ▶ amisulpride, ▶ clozapine, ▶ olanzapine, and ▶ risperidone; in the management of positive symptoms FGA were less effective than amisulpride, clozapine, olanzapine, quetiapine, and risperidone; in the management of negative symptoms FGA were less effective than amisulpride, clozapine, olanzapine and risperidone, and in alleviation of depression FGA were less effective than amisulpride, aripiprazole, clozapine, olanzapine and quetiapine (Leucht et al. 2009). FGA are less effective in long term treatment of schizophrenia than olanzapine (NNT 17 [8–100]), risperidone (NNT 11 [7–33]), and ▶ sertindole (NNT 14 [8–50]). FGA improve ▶ quality of life less than amisulpride, clozapine and sertindole (Leucht et al. 2009).

Naturalistic (Effectiveness) Studies

Results from real world effectiveness studies such as ▶ CATIE (Rosenheck et al. 2006), and ▶ CUtLASS (Jones et al. 2006) suggest that mid-potency FGA compounds would have been more appropriate, because they are less likely to cause EPSE and they are not associated with sedation and weight gain. The representatives of this group are ▶ perphenazine and ▶ sulpiride. Efficacy of SGA was not better than perphenazine on ▶ PANNS total score (Rosenheck et al. 2006), cognition (Keefe et al. 2007), cost (Rosenheck et al. 2006), quality of life, and psychosocial functioning (Swartz et al. 2007).

Another pragmatic trial (EUFEST) compared the effectiveness of SGA with that of a low dose of haloperidol (1–4 mg), in the first-episode schizophrenia (Kahn et al. 2008). This pragmatic trial found lower discontinuation rate with SGA than with haloperidol. However, symptom reductions were virtually the same (about 60%) in all groups. Despite the fact that the difference in discontinuation rates was the primary outcome variable one cannot definitively conclude that SGA are more efficacious than is the low dose haloperidol in first-episode schizophrenia, since discontinuation rates are not necessarily consistent with symptomatic improvement.

Other Side Effects of the FGA

There are other typical side effects of the FGA than only EPSE and hyperprolactinaemia. These side effects are observed mainly in low-potency antipsychotics and are related to anticholinergic, antiadrenergic and antihistaminic activity. Anticholinergic activity of low-potency antipsychotics leads to dry mouth, blurred vision, difficulty passing urine, urinary retention, constipation, glaucoma and rarely ileus. Antiadrenergic activity can induce postural hypotension, reflex tachycardia, and sexual dysfunction (particularly erectile dysfunction). Antihistaminic activity is responsible for sedative effect and weight gain. Idiosyncratic side effects are: leucopenia or agranulocytosis, cholestatic jaundice, altered glucose tolerance, skin photosensitivity (sun block is important in sunny weather), pigmentation to skin or to eye, ▶ neuroleptic malignant syndrome. Some FGA can lower seizure threshold (i.e., chlorpromazine) or could prolong ▶ QT interval (chlorpromazine, droperidol, pimozide, thioridazine).

Cross-References

▶ Amisulpride
▶ Antipsychotics

- ▶ Aripiprazole
- ▶ Benperidol
- ▶ Bromperidol
- ▶ Butyrophenones
- ▶ Carpipramine
- ▶ CATIE
- ▶ Chlorpromazine
- ▶ Clozapine
- ▶ CUtLASS
- ▶ EUFEST
- ▶ Extrapyramidal Motor Side-effects
- ▶ Flupenthixole
- ▶ Fluphenazine
- ▶ Floropipamide
- ▶ Haloperidol
- ▶ Hyperprolactinaemia
- ▶ Olanzapine
- ▶ Pericyazine
- ▶ Perphenazine
- ▶ Perphenzine
- ▶ Phenothiazines
- ▶ Pimozide
- ▶ Prochlorperazine
- ▶ Promazine
- ▶ Promethazine
- ▶ Quality of life
- ▶ Quetiapine
- ▶ Risperidone
- ▶ Second-Generation Antipsychotics
- ▶ Sulpiride
- ▶ Thioridazine
- ▶ Thiothixene
- ▶ Thioxanthenes
- ▶ Trifluoperazine
- ▶ Ziprasidone
- ▶ Zotepine
- ▶ Zuclopenthixol

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First-Order Elimination Kinetics

Synonyms

Kel

Definition

First-order elimination kinetics depends on the concentration of only one reactant (drug) and a constant fraction of the drug in the body is eliminated per unit time. The rate of elimination is proportional to the amount of drug in the body. The majority of drugs are eliminated in this way.

Cross-References

- ▶ Bioavailability
- ▶ Elimination Half-Life or Biological Half-Life
- ▶ Pharmacokinetics

First-Rank Schizophrenic Symptoms

Definition

Psychopathological symptoms like delusional perceptions, commenting auditory hallucinations, thought withdrawal,

thought broadcasting, etc., which are strongly associated with schizophrenia, if a somatic cause is not present.

Fischer (F344)/Lewis (LEW) Rat Strains

Definition

The Fischer and Lewis rat strains are inbred rat strains independently developed as models of cancer susceptibility and tissue transplantation, respectively. Many differences between the F344 and LEW rats have been identified, leading to direct comparisons in studies of genetic contributions to disease-relevant differences in physiology and behavior, for example, drug susceptibility.

Cross-References

► Inbred Strains

Five-Choice Serial Reaction Time Task

Synonyms

5-CSRT; 5-CSRTT

Definition

A cognitive task initially developed for use in the rat, capable of examining the effects of neural, pharmacological, and behavioral manipulations on aspects of impulse control, accuracy of discrimination, response times, and perseveration. Animals are trained to detect flashes of light presented at one of five holes and to make nose-pokes at the appropriate location to receive a food reward. The task necessitates withholding of responding until stimulus onset. Measures include premature responses (a measure of impulse control) and accuracy of stimulus discrimination (attentional capacity). The translational version of this task for humans is the CANTAB five-choice serial reaction time test.

Cross-References

► Rodent Models of Cognition

Fixed Ratio

Definition

A fixed ratio (FR) is a schedule of reinforcement that sets the contingency for the delivery of a reinforcing stimulus (i.e., a drug injection in the case of a self-administration experiment) according to a predetermined number of responses. Under an FR1 (or continuous reinforcement) schedule, a reinforcer would be delivered immediately following a single response.

Cross-References

► Operant Conditioning

Flashback

Definition

Recollection of a past experience, usually vivid.

Cross-References

► Hallucinogen Abuse and Dependence

Flexibility

► Elasticity

Flicker Fusion Rate

► Critical Flicker Fusion Frequency

Flicker Fusion Threshold

► Critical Flicker Fusion Frequency

Floropipamide

Definition

Floropipamide is a first-generation (typical) antipsychotic drug that belongs to the butyrophenone type indicated for the treatment of schizophrenia. However, it possesses more potent antagonist properties at 5-HT_{2A} than D_2 receptors. It can induce extrapyramidal motor side effects, hypotension, and fatigue, but it displays generally low toxicity. Extrapyramidal side effects with floropipamide appear to be less common than with other butyrophenones.

Cross-References
► Butyrophenone
► Extrapyramidal Motor Side Effects
► First-Generation Antipsychotics
► Schizophrenia

Fludiazepam

Definition
Fludiazepam is an anxiolytic benzodiazepine medication used in the treatment of anxiety disorders. Unwanted effects include sedation, headaches, paradoxical excitement, confusion, cognitive and psychomotor impairment, and confusion in the elderly. Long-term use may induce dependence with withdrawal reactions. Recreational use and abuse can occur.

Cross-References
► Benzodiazepines
► Minor Tranquilizers

Fluid

► Liquid Diet for Administering Alcohol

Flumazenil

Synonyms
Flumazepil; Ro-15-1788

Definition
Flumazenil was the first substance found to act as an antagonist at the benzodiazepine site of the $GABA_A$ receptor. It competitively inhibits the effects of benzodiazepines and is used clinically to reverse benzodiazepine-induced sedation, and to diagnose and treat benzodiazepine overdose. It may also be used with imaging techniques to visualize $GABA_A$ receptors in the brain and has been invaluable as a research tool in experimental psychopharmacology for determining whether drug effects involve benzodiazepine receptors. It is a weak ► partial agonist, although its action is very much weaker as an agonist than as an antagonist.

Cross-References
► Benzodiazepines
► Sedative, Hypnotic, and Anxiolytic Dependence

Flumazepil

► Flumazenil

Fluoxetine

Synonyms
Prozac

Definition
Fluoxetine is a selective serotonin reuptake inhibitor (SSRI). One of the earliest of these drugs to be developed, it is widely perceived in the popular culture to be paradigmatic of the class. It is commonly used in the treatment of depression and the more severe anxiety disorders (e.g., obsessive–compulsive disorder, panic disorder). Fluoxetine is also approved for the treatment of bulimia nervosa, anorexia nervosa, and premenstrual dysphoric disorder. A distinguishing pharmacokinetic feature of the drug is its long elimination half-life (up to 4–6 days during long-term use and up to 2 weeks for the major active metabolite norfluoxetine). As with other SSRIs, the most common troublesome side effect of fluoxetine is sexual dysfunction (dysorgasmia and erectile dysfunction); mild side effects include drowsiness, headache, and nausea. Some patients develop a syndrome of psychomotor activation upon starting the drug, which has been characterized as similar to akathisia.

Cross-References
► Antidepressants
► Selective Serotonin Reuptake Inhibitors

Flupenthixol

Definition
Flupenthixol is a typical thioxanthene antipsychotic, sharing similar profile to phenothiazines. It acts as an antagonist at D1 and D2 dopamine receptors, as well as α-adrenergic receptors. Its antipsychotic effects are

thought to result from postsynaptic D2 receptor blockade. Due to its long-acting nature (elimination half-life ranging from 5 to 113 days after depot injection), flupenthixol is often used for maintenance treatment of schizophrenia. As with other typical antipsychotics, flupenthixol is associated with a high incidence of extrapyramidal symptoms, but it has less anticholinergic effects. Like many other antipsychotic agonists, it has also been used in experimental psychopharmacology to test the importance of dopamine receptors in various physiological and psychological phenomena; the different selectivity of the (+)- and (−)-isomers has to be taken into account.

Cross-References
► Antipsychotics
► First-Generation Antipsychotics

Fluphenazine

Definition
Fluphenazine is a first-generation antipsychotic in the phenothiazine class, which is also available in a long-acting intramuscular preparation. It exerts its action mainly via dopamine D2 receptors blockade. It has a fairly long half-life (up to 60 h) and is metabolized mainly by 1A2 and 2D6 CYP450 isoenzymes.

Cross-References
► First-Generation Antipsychotics
► Phenothiazines

Flurazepam

Definition
Flurazepam is a benzodiazepine that has anxiolytic, sedative, and anticonvulsant properties. It has a very long duration of action, mainly due to a long elimination half-life (24–100 h), and conversion to the active benzodiazepine metabolites hydroxyethyl- and desalkyl-flurazepam. Flurazepam has been used to treat insomnia and is subject to tolerance, dependence, and abuse.

Cross-References
► Anxiolytics
► Benzodiazepines
► Hypnotics

Flutazolam

Definition
Flutazolam is a benzodiazepine derivative that has anxiolytic, anticonvulsant, hypnotic, sedative, amnesic, and muscle-relaxant properties.

Cross-References
► Anxiolytics
► Benzodiazepines

Flutoprazepam

Definition
Flutoprazepam is a benzodiazepine derivative that has anxiolytic, anticonvulsant, hypnotic, sedative, amnesic, and muscle-relaxant properties. It is used mostly in Japan and Asia and can be abused. It is four times more potent than diazepam.

Cross-References
► Anxiolytic
► Benzodiazepine

Fluvoxamine

Definition
Fluvoxamine is a selective serotonin reuptake inhibitor (SSRI). It was one of the earliest of these drugs to be developed and widely marketed. Although originally released as an antidepressant, it is now commonly used in the treatment of obsessive–compulsive disorder. Fluvoxamine is also used to treat other anxiety disorders (e.g., ► panic disorder, ► social anxiety disorder). As with other SSRIs, the most common troublesome side effect of fluvoxamine is sexual dysfunction (dysorgasmia and erectile dysfunction). Milder side effects include drowsiness and headache. Fluvoxamine may be somewhat more likely to cause nausea and vomiting than other SSRIs.

Cross-References
► Antidepressants
► Obsessive–Compulsive Disorder
► Selective Serotonin Reuptake Inhibitors

fMRI

► Magnetic Resonance Imaging (Functional)

Foetal Alcohol Spectrum Disorders

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Synonyms

Alcohol-related neurodevelopmental disorder; FAS; FASDs; Foetal alcohol syndrome

Definition

Foetal Alcohol Spectrum Disorder(s) are umbrella terms used to describe conditions arising in the infant, child and, later, adult, resulting from a *confirmed* range of prenatal alcohol exposure be it acute or chronic or low, high, or binge dose variety.

There are two diagnostic categories:

1. ► *Foetal Alcohol Syndrome (the ► Facial Dysmorphology Disorder)*
   (a) Evidence of a characteristic pattern of facial anomalies that includes features such as short palpebral fissures and abnormalities in the premaxillary zone (i.e., flat upper lip, flattened philtrum, and flat midface)
   (b) Evidence of growth retardations in at least one of the following forms:
   - Low birth weight
   - Decelerating weight over time not due to nutrition
   - Disproportional low weight to height (Ht and Wt below tenth percentile)

   (c) Evidence of CNS neurodevelopmental abnormalities, such as:
   - Structural brain abnormalities, i.e., decreased cranial size at birth, microcephaly (head circumference under third percentile), partial or complete agenesis of the corpus callosum, and cerebellar hypoplasia
   - Neurophysiological abnormalities, complex partial seizure disorder, absence seizure, and other seizures
   - Neurological hard or soft signs (age-appropriate):
     - Motor: gross motor function; poor tandem gait, positive Romberg test, balance problems with fine motor function, fine motor problems with evidence of constructional apraxia, poor hand–eye coordination, motorically disorganized in the under 5 years age group
     - Sensory: abnormal sensation in upper or lower limbs, neurosensory hearing loss, abnormal visual, auditory, gustatory, olfactory, or tactile sensations, including hallucinations, regulatory disorder in the under 5 years age group

   (d) Attentional, cognitive, and language problems can also be found as in ARND.

2. ► *Alcohol-Related Neurodevelopmental Disorder (the Non-Facial ► Dysmorphology Disorder)*
   (a) No characteristic pattern of facial anomalies
   (b) No or little growth retardation
   (c) CNS deficits as for FAS
   (d) Also deficits shown in:
   - **Behavior**, with visual or auditory attentional problems, distractibility, poor impulse control, poor organizational skills, and poor adaptive functioning
   - **Cognition** with complex learning disorders, which are often a mixture of verbal and nonverbal inabilities, inability to link cause and effect, mathematics disorder with dyscalculia, poor insight, and impaired judgment.
   - **Language** with deficits in higher level receptive and expressive language i.e., the patient does not understand the "gist" of a social situation, has an impairment in social communication and interaction, and has problems in understanding and expressing emotional feeling i.e., ► alexithymia.
   - **Gross and Fine Motor problems** may also be found, as in FAS.

(Sources: Hagerman 1999; Koren et al. 2003; O'Malley 2008; Stratton et al. 1996; Streissguth and Connor 2001; Streissguth and O'Malley 2000).

Epidemiology

Foetal Alcohol Spectrum Disorders (FASDs) are more common than have been initially thought and it was the

University of Washington group who first estimated a figure of 9.1 per 1,000 live births. Although some populations namely Aboriginal or Native American have been deemed more susceptible to the effects of prenatal alcohol exposure, international research continues to show that FASD is prevalent in all ethnic populations in which the mother drinks alcohol during pregnancy.

Pathophysiology of Foetal Alcohol Spectrum Disorders

Streissguth and Connor (2001) reviewed animal studies of over 25 years that have demonstrated that heavy doses of alcohol administered to a wide range of laboratory animals produced a spectrum of CNS effects starting with the cell death **seen in nerve cells**. Also, prenatal alcohol has been demonstrated in many animal studies to interfere with the embryological development of most of the **neurotransmitters**. This has been reported by Manteueffel (1996), Stratton et al. (1996), O'Malley and Hagerman (1998), and Hagerman (1999).Deficits have been found in the dopaminergic, noradrenergic, serotonergic, GABAergic, cholinergic, glutaminergic, and histaminergic systems.

The deficits in dopaminergic and noradrenergic systems most likely are connected with the ► attentional deficit hyperactivity disorder (ADHD presentation of patients with FAS or ARND. Previous animal research on rats has demonstrated that the D1 receptors of the mesolimbic dopamine system are affected by prenatal alcohol more than the nigrostriatal or tegmental dopamine D1 receptor system.

Ongoing neurological research is analyzing the clinical effect of the prenatal alcohol disruption of the balance between ► GABA the inhibitory and ► Glutamate the excitatory neurotransmitter in the brain. Scientists in the USA have shown the kindling of seizures due to the effect of prenatal alcohol on the GABAergic cells in the hippocampus which leads to a lower seizure threshold.

Recently, a research has studied the effect of alcohol on inhibiting L1, an immunoglobulin cell adhesion molecule that promotes cell–cell adhesion, neurite outgrowth, cell migration, and synaptic plasticity.

Role of Psychopharmacology

Although this is used quite extensively with children, adolescents, or adults with FASD, it is important to remember that there are no US Food and Drug Administration (FDA) or UK National Institute for Health and Clinical Excellence (NICE) approved medications for these conditions. Thus, the use of medication in FAS or ARND has not been properly evaluated, and as O'Malley and Hagerman (1998) have commented, the brain of a prenatally brain-damaged infant, young child, or adolescent is especially vulnerable to an atypical medication response or side effects.

The role of medication is one of symptom control in order to facilitate other modalities of treatment. There is extensive literature on the psychopharmacotherapy of patients with mental retardation and also with brain injury, both of which are relevant to this patient population. Only a small number of studies have been performed on children or adolescents with mental retardation and comorbid psychiatric disorder. They have been reviewed by O'Malley and Hagerman (1998), Hagerman (1999), Byrne (2008), and O'Malley (2008).

If medication is being considered, it is essential to have a recent complete medical examination by a family physician or pediatrician to rule out any alcohol-related birth defects (ARBD) such as kidney or cardiac problems, to name a few (Stratton et al. 1996).

ADHD Symptomatology

The animal research, coupled with the evidence from Hagerman (1999) and O'Malley (2008), has indicated that prenatal alcohol affects the developing ► mesolimbic and not the fronto-nigral dopamine neurotransmitter system.

In mental retardation/intellectual disability studies on children, ► Methylphenidate relieves ADHD symptoms, but is less effective if the IQ is under 50. The previous research on animals and humans, as reviewed by O'Malley and Hagerman (1998), Byrne (2008), and O'Malley (2008), has indicated that dextroamphetamine (short or long acting) may be a better first-line psychostimulant than methylphenidate (short or long acting) for FAS or ARND patients with ADHD symptoms, as it modulates the mesolimbic dopamine system, whereas methylphenidate modulates the fronto-nigral dopamine system. A dose of 1 mg/kg/day is a good ceiling dosage, and 2 mg/kg would be likely to cause side effects such as aggression, irritability, schizoid demeanor.

Methylphenidate still remains a reliable medication and is probably a good second-line choice.

The biphasic newer preparations such as Concerta and Equasym appear to be useful after initial stimulant response is established. Studies need to be done to clarify the ► pharmacokinetics in these preparations, as patients with FAS or ARND often metabolize psychotropic drugs at a faster rate than patients without this developmental neuropsychiatric disorder. It is worth remembering that prenatal alcohol can affect the developing heart, kidney, and even liver, so side effects are more unpredictable. Blood pressure, ECG, blood sugar, and thyroid function should be tested.

FAS is a growth retardation condition, and long-term stimulants run the risk of lowering the growth hormone. A number of patients have shown decreased bone age or decreased linear growth due to long-term high dose psychostimulants (usually, methylphenidate).

A clinically significant but also potentially negative side effect of psychostimulants in FAS or ARND is their ability to increase arousal and help the patient focus, but at the same time contribute to an increased level of ► perseveration especially in patients with pre-existing autistic or obsessive features.

► Atomoxetine (Strattera) seems to be more helpful in older children or teenagers with ADHD symptoms and has less risk of dependency. Liver function and ECG need to be tested if atomoxetine is given.

Impulse Control with ADHD

Impulsivity is a pervasive problem and is not always associated with physical hyperactivity. Sometime the inattention subtype of patients with ADHD can be pervasively impulsive.

► Fluoxetine is helpful as a treatment. It is better to start with the liquid preparation so that low initial dose can be given. This medication has also been shown to have positive effect in mental retardation of child population with the same symptoms.

► Valproic acid and ► carbamazepine are also useful especially if there is a mood instability associated with the impulsivity. The mood or affective instability frequently presents with a rapid cycling bipolar disorder picture.

Anxiety with ADHD

Guanfacine and clonidine are both useful and can be added to a psychostimulant. It is important to check BP and pulse while lying and sitting and do a pretreatment ECG. These patients frequently have a history of PTSD or developmental trauma disorder.

Conduct Disorder and/or Disruptive Behavioral Disorder and ADHD

There are no specific medications, but SSRIs are useful and atypical antipsychotics such as risperidone and olanzepine are both helpful with aggressive/disruptive behaviors. These medications can be used successfully if ADHD is present.

Intermittent explosiveness alone can respond to carbamazepine or valproic acid or GABA agents, such as ► gabapentin. This can be related to a complex partial seizure disorder or it can sometimes be seen in patients with "hyperactive" symptomatology who do not respond to dextroamphetamine, or methylphenidate, or may be precipitated by too long a treatment with an SSRI.

Depressive disorders are best treated with SSRI such as ► fluoxetine, ► sertraline, ► citalopram, or ► bupropion (as second-line agent). It is important to be aware that SSRIs may unmask a ► bipolar disorder or may precipitate ► extrapyramidal side effects in patients over 20 years of age, as this is a more neurologically sensitive brain-damaged population. Impulsive suicide risk may be increased by excessive activation or excitation in the first week as a response to SSRI; so this early period should be carefully monitored.

Psychotic features (such as auditory or visual hallucinations) respond to neuleptil oral drops alone or to ► anticonvulsants such as carbamazepine or valproic acid if the patient has an epileptic focus in the temporal lobe and clinical presentation of complex partial seizures.

The newer atypical antipsychotics (e.g., risperidone, olanzapine, seroquel, or clozaril) may have a use here (only after failed treatments with other antipsyhotics or in very ill hospitalized patients). Recent work on the atypical antipsychotics has shown that they can double the risk of abnormal glucose metabolism including diabetes, hyperprolactinaemia, and pancreatitis. The population of patients with FAS or ARND is also more likely to need benztropine as they develop extrapyramidal symptoms (EPS) easier. Parenteral medication such as fluanxol has proven effective in once a month regime, useful in noncompliant older patients with ► schizoaffective symptomatology.

Panic attacks and generalized anxiety disorder respond to ► lorazepam (short acting), ► buspirone (longer onset of action and less risk of drug dependency) or bupropion if mood symptoms are present. GABAergic agents such as gabapentin should be used if mood instability like bipolar disorder is present.

Bipolar disorders or more correctly affective/mood instability may be precipitated/ unmasked by too long administration or too high dose of SSRI agents. Often the symptoms decrease with change of dosage of SSRI or discontinuation of the drug. The symptoms can include rather disarming pathological laughing or crying akin to **emotional incontinence** seen in brain-injured patients.

The affective/mood instability unrelated to medication can respond to carbamazepine, valproic acid, or GABA agents (e.g., gabapentin).

Sleep disorders respond to ► melatonin (liquid or tablet form), ► trazodone, or l-tryptophan (safe if the patient is pregnant).

Alcohol dependence is still a poorly understood phenomenon in adolescents and young adults with

FAS or ARND. Research with animals and humans have shown that ► prenatal alcohol exposure increases the risk for alcohol craving probably via its effects on the developing brain, specifically the nucleus accumbens. Narcotic antagonists, such as ► naltrexone, have proven useful in curbing this alcohol craving and subsequent dependence (O'Malley 2008.)

► **Autistic spectrum disorder** or ► **Asperger's disorder** can be the primary clinical presentation of FAS or ARND, and explosiveness with or without ADHD symptomatology is the key clinical feature.

There are a number of **medications that should be used with caution** in children and adolescents with FAS or ARND

- ► Lithium carbonate causes cardiac, renal, and thyroid problems.
- ► Tricyclic antidepessants (amitriptyline, imipramine, desipramine, clomipramine) cause cardiac toxicity, sudden death, and lower seizure threshold and are lethal in overdose.
- New antidepressants affecting serotonergic and noradrenergic systems. (Effexor) may cause cardiotoxicity due to noradrenergic activity.
- ► First generation antipsychotics (chlorpromazine,* stelazine, nozinan, and haldol) cause excess sedation, increased risk of EPS and possible liver toxicity, and sun sensitivity*.
- ► Second generation atypical antipsychotics can affect weight and glucose metabolism.
- Paroxetine (SSRI) has now been recommended by FDA not to be used in under 18 year old patients. It causes increased interaction with other psychotropics because of its inhibition of **cytochrome P450 2D6 isoenzyme** liver pathway.

Future Considerations for Psychopharmacology

Increasingly, researchers and clinicians show that patients exposed to prenatal alcohol are frequently exposed to stress at many different levels i.e., domestic violence, abandonment by partner, and physical or sexual abuse which predates pregnancy. The role of the ► hypothalamic–pituitary axis is being reconsidered in the population of patients with FAS or ARND who have been born into environments of high stress (Meewisse et al. 2007).

Excess cortisol has been shown to stop many metabolic, neuronal, and immune systems, including potential nerve growth factor. It remains to be seen if psychopharmacological agents affecting the balance of the HPA axis have an ameliorating or neuroprotective role in FAS or ARND.

Some neuroprotective agents have already been used to counterbalance the effect of prenatal alcohol on the developing fetus. They include folate, vitamin B12, thiamin, Vitamin B6, and choline (reviewed in O'Malley 2008).

Cross-References

► Addictive Disorder: Animal Models
► Attention Deficit Hyperactivity Disorders: Animal Models
► Alcohol
► Alcohol Abuse and Dependence
► Attention Deficit and Disruptive Behavior Disorders
► Autistic Spectrum Disorders and Mental Retardation
► Impulse Control Disorders
► Impulsivity
► Personality: Neurobehavioural Foundation and Pharmacological Protocols
► Traumatic Stress (Anxiety) Disorder
► Verbal and Non-Verbal Learning in Humans

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Foetal Alcohol Syndrome

Definition
A developmental neuropsychiatric disorder with characteristic facial dysmorphology resulting from prenatal exposure to alcohol.

Cross-References
► Foetal Alcohol Spectrum Disorders

Folate

Definition
Folate is one of the 13 essential vitamins. Dihydrofolate is the form of folate obtained from dietary intake, while folic acid is the synthetic form of folate contained in over-the-counter and prescription vitamin supplements. Dihydrofolate and folic acid are ultimately converted by the body to L-5-methyl-tetrahydrofolate (MTHF); the only form of folate that passes into the brain and is utilized by trimonoamine neurons to facilitate neurotransmitter synthesis.

Force Platform

► Force-Plate Actometer

Forced Swimming Test

► Behavioral Despair

Force-Plate Actometer

Synonyms
Force platform

Definition
A force-plate actometer consists of a rigid, low mass floor supported by force sensors whose force-proportional electronic signals are processed by a computer to allow the computation of a subject's x–y location in the horizontal plane, and, at the same time, to record the time series of reactive forces as the subject moves on the plate. It is especially useful for quantifying the rhythms of rodent movements concurrent with the recording of distance traveled, rotations, wall rears, and other features of behavior.

Cross-References
► Motor Activity and Stereotypy

Forgetting

Definition
The inability to retrieve one or a number of memory items. Is usually understood as the time-dependent erosion or loss of memory traces.

Formal Thought Disorder

Definition
Disorder of the mechanisms of thinking as characterized descriptively.

Forward Genetics – Random Mutagenesis

► Forward Genetics/Reverse Genetics

Forward Genetics/Reverse Genetics

Synonyms
Forward genetics – random mutagenesis; Reverse genetics – targeted mutagenesis

Definition
Forward genetics is the examination of the genetic cause of an altered or abnormal phenotype introduced by a chemical mutagenesis or mutation by irradiation (e.g., phenotype → genotype). In reverse genetics, a particular gene is altered and the phenotype is investigated (e.g., genotype → phenotype).

Cross-References
► Genetically Modified Animals
► Phenotyping of Behavioral Characteristics

Fostering

Synonyms
Cross fostering

Definition
A procedure used in animal studies to control for potential residual effects of drug exposure during pregnancy on subsequent maternal behavior that involves placement of prenatally drug-exposed offspring with nondrug-exposed foster mothers.

Fourier Analysis of Time Series

► Power Spectral Analysis

Fourier Spectrum

► Spectrograms

Fourier Transform

► Power Spectral Analysis

Fovea

Definition
The small portion of the retina (subtending 2–3° of visual angle) that contains the highest density of cone cells, and thus is responsible for the clearest, most acute vision.

Fragile X

Definition
Fragile X is the most common cause of inherited mental impairment and the most known genetic cause of autism. Elongated face and large and protruding ears are characteristics physical features for the disease. Males are more severely and more often affected (1:4000) than females (1:8000). The disease is caused by an expansion of CGG repeats upstream of the FMR1 gene leading to hypermethylation of the promoter region, reducing the transcription of the FMR1 gene and consequently the expression of the FMRP (fragile X metal retardation protein).

Free Radicals

Synonyms
Reactive oxygen species

Definition
Free radicals are chemical compounds that contain one, or more, unpaired electrons in the outer orbits. This has the effect of making the atom or molecule more reactive than its non-radical relation. Such compounds can capture electrons from other molecules thereby oxidizing such molecules.

Cross-References
► Oxygen and Nitrogen Reactive Species

Freebase

Definition
Freebase cocaine or amphetamine is the active drug without the chemical component that makes these drugs soluble in water (e.g., hydrochloride or HCl). This "base" or "freebase" form of the drug is prepared by dissolving the hydrochloride form of the stimulant with a strong alkali, and drawing out the cocaine from its impurities. The preparation of freebase cocaine involves the use of highly explosive solvents such as ether.

Cross-References
► Amphetamine
► Cocaine

Free-Floating Anxiety

► Generalized Anxiety Disorder

Freezing

Definition
A defensive response typically seen in rodents, defined as the absence of all movement except that required for respiration.

Frequency Estimation

► Power Spectral Analysis

Frequency of Oscillation

► Rhythmicity

Frequency Spectrum

► Spectrograms

Function of Delta Waves

Synonyms
Delta activity; Slow waves

Definition
Signals in the human EEG in the frequency range from near-DC to ~4 Hz are considered as part delta activity. Consensus on the functional correlate exists; it reflects the amount of sleep pressure. Indeed, its amplitude fluctuates dramatically comparing waking state and, for example, stage N3, deep or slow-wave sleep.

Cross-References
► Electroencephalography
► Polysomnography

Function of Slow and Fast Alpha Waves

Synonyms
Alpha waves; Eyes closed occipital waves; Spindles; Thalamocortical 10 Hz rhythm

Definition
Signals in the human EEG in the frequency range from 8 to 13 Hz are considered to be part of the alpha activity. As simplest functional correlate, one can describe it as an "idling" wave, which much like a screensaver keeps neurons at a minimum alertness. Indeed, the amplitude fluctuates with attention and arousal and, for example, stimulants can switch the balance from slow to fast alpha or increase both, interpreted as an altered vigilance state.

Cross-References
► Electroencephalography

Functional Magnetic Resonance Imaging

Synonyms
Magnetic resonance imaging (functional)

Definition
Functional magnetic resonance imaging (fMRI) is a method for measuring hemodynamic (brain blood flow/oxygenation) responses related to neural activity in the brain. This technique has been used in conjunction with neurocognitive tasks to measure brain activation during discrete cognitive processes and effects of pharmacological agents on such processes. It is a recently developed form of neuroimaging. The advantages of fMRI include its low invasiveness, lack of radiation exposure, and relatively wide availability.

Functional Outcome

Definition
Functional outcome distinguishes itself from clinical outcome, focused instead of an individual's recovery in areas such as vocational and social functioning rather than symptom resolution. Its measurement speaks to the impact of severe and chronic illnesses, such as ► schizophrenia, and a growing awareness that functional and clinical recovery do not necessarily parallel each other.

With schizophrenia, it was held for many years that the positive symptoms (e.g., delusions, hallucinations) were central to the gradual decline in functioning commonly seen over the course of the illness. However, more recent evidence suggests that other features of this illness, for example, deficit (negative) symptoms and

neurocognitive changes, may play a more critical role in compromising functional recovery. This has diminished focus on positive symptoms and the implicit assumption that their resolution ensures a return to premorbid level of functioning and, in so doing, has forced a reconceptualization of schizophrenia and expanded current treatment/research strategies.

Cross-References

► Antipsychotics
► Second- and Third-Generation Antipsychotics

Functional Selectivity

Synonyms

Biased agonism; Ligand-directed trafficking; Stimulus trafficking

Definition

According to the classical receptor-occupancy theory of receptor, activation receptors are in equilibrium between one active and one inactive state. In correspondence with this model, the ability of a given ligand to modulate either one of the receptor's signaling pathways should be similar. Experimental observations have provided an important lesson though: a receptor is not just either on or off, and ligands can display distinct efficacies toward different effector systems. The ability of a ligand to preferentially stabilize specific GPCR conformations, each associated with its own repertoire of signaling behavior, is called functional selectivity.

Cross-References

► Agonist
► Allosteric Modulator
► Antagonist
► Inverse Agonists
► Partial Agonist
► Recombinant Cell Line

Functional Somatic Syndromes

► Somatoform and Body Dysmorphic Disorders

G

G protein-Coupled Receptors

Definition

A family of metabotropic receptors (formed by seven transmembrane hydrophobic domains linked by hydrophilic groups) coupled with a heterotrimeric protein named G-protein (consisting of α, β, and γ subunits), that, upon binding guanosine phosphates (GTP or GDP) in response to extracellular signals (e.g., neurotransmission), activate or inactivate specific intracellular effectors systems.

GABA

Definition

An abbreviation for gamma-aminobutyric acid, the principal inhibitory neurotransmitter, ubiquitous throughout the mammalian brain. GABA-bearing neurons constitute inhibitory interneuronal populations in the cortex and projection neurons in subcortical (e.g., striatal) regions. GABA released from axonal presynaptic terminals typically dampens electrical excitation and suppresses axon potential generation in postsynaptic neurons. GABA-ergic neurotransmission is thought to tightly regulate excitatory neurotransmission, information processing, and neuroplastic events via polysynaptic connectivity with glutamatergic neurons.

$GABA_A$ Receptor

Definition

The GABA receptors are a class of receptors that respond to the neurotransmitter gamma-aminobutyric acid (GABA), the most common inhibitory neurotransmitter in the central nervous system. $GABA_A$ and $GABA_C$ receptors are ligand-gated ion channels, whereas $GABA_B$ receptors are G protein-coupled (metabotropic) metabotropic receptors. Each receptor comprises five subunits arranged around a central pore. Binding of GABA molecules to extracellular binding sites triggers a conformational change that opens the pore to allow chloride ions to pass down an electrochemical gradient into the cell, resulting in hyperpolarization of the postsynaptic membrane. In addition to the GABA binding site, $GABA_A$ receptors appears to have distinct binding sites for ▶ benzodiazepines and many anesthetic agents such as ▶ barbiturates, inhaled anesthetics, and propofol.

Cross-References

▶ Alcohol or Alcohol Abuse and Dependence
▶ Anticonvulsants
▶ Antidepressants
▶ Antipsychotic Drugs
▶ Premenstrual Dysphoric Mood Disorder

GABAergic Transmission

Definition

GABAergic transmission refers to activation of GABA receptors and release of GABA by endogenous or pharmacological modulators. g-Aminobutyric acid (GABA) is the most prevalent inhibitory neurotransmitter in the mammalian central nervous system.

Cross-References

▶ Alcohol or Alcohol Abuse and Dependence
▶ Anticonvulsant
▶ Antidepressant
▶ Antipsychotic Drugs
▶ Premenstrual Dysphoric Mood Disorder

Gabapentin

Definition

Gabapentin acts on GABA receptors to produce anticonvulsant effects and is also used in the management of neuropathic pain. Its half-life is 5–7 h; it is not metabolized in the liver but is eliminated by renal excretion.

Ian P. Stolerman (ed.), *Encyclopedia of Psychopharmacology,* DOI 10.1007/978-3-540-68706-1,

GAD

► Generalized Anxiety Disorder

Galantamine

Definition

Galantamine is a drug marketed for treating the cognitive impairments (learning, memory, and attention) in Alzheimer's disease. It has mainly been used in patients in the mild to moderate stages of the disease and like the drug ► donepezil works by enhancing brain levels of ► acetylcholine, a chemical that is reduced in Alzheimer's disease and is known to be relevant to cognition. It has been suggested that galantamine also acts as a positive ► allosteric modulator of neuronal nicotinic receptors, which are also the target of nicotine found in tobacco. Since nicotine has been shown to have some cognitive benefits, and various drugs being developed are targeting nicotinic receptors in the brain, it has been proposed that this additional mechanism is relevant to the use of galantamine in Alzheimer's disease.

Cross-References

► Cognitive Enhancers: Neuroscience and Society
► Dementias and Other Amnestic Disorders

Gambling

Definition

Placing something of value (usually money) at risk in hopes of gaining something of greater value.

Gambling Addiction

► Pathological Gambling

Gamma Camera

► Gamma Camera System

Gamma Camera System

Synonyms

Gamma camera

Definition

A gamma camera system consists of the hardware and software necessary to localize and detect photons emitted by SPECT radionuclides. Many SPECT imaging systems use more than one gamma camera to detect photons from different points of reference. The overall design of the camera system affects the sensitivity and resolution of the method.

Cross-References

► SPECT Imaging

Gamma-Hydroxybutyrate

► Oxybate

Gangliosides

Definition

Sygen, a GM1 monosialoganglioside (H3-α-acetylneuraminosyl-gangliotetraglycosylceramide) is one of about 60 plasma membrane glycosphingolipids thought to modulate cell signal transduction. It was developed for Parkinson's disease but was withdrawn due to an association with Guillain–Barre syndrome and a lack of benefit in Parkinson's disease. It was not available in the USA, except for compassionate use in spinal cord injury.

Cross-References

► Anti-Parkinson Drugs
► Neuroprotectants

Gat

► Khat

Gel Electrophoresis

► Two-Dimensional Gel Electrophoresis

Gender Differences

► Sex Differences in Drug Effects

Gene Expression

Definition

The process controlling the types and amounts of individual genes expressed (transcribed into mRNA and protein) in a tissue.

Gene Transcription

Definition

Process by which a messenger RNA molecule is synthesized according to instructions encoded in DNA.

Cross-References

► Learning and Memory: Molecular Mechanisms

General Anesthesia

Synonyms

Anesthesia

Definition

General anesthesia is a temporary, drug-induced state in which a patient is rendered unconscious and insensible to noxious stimuli such as surgery. Anesthesia is considered adequate if the patient shows no sign of consciousness, exhibits no cardiovascular stress responses to surgery (such as rising heart rate and blood pressure), and on recovery from anesthesia has no recall of intraoperative events.

Generalized Anxiety Disorder

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Synonyms

Anxiety neurosis; Free-floating anxiety; GAD

Definition

Generalized anxiety disorder (GAD) is characterized by an excessive and inappropriate worrying that is persistent and not restricted to particular circumstances. Patients have physical anxiety symptoms (such as tachycardia and tremor) and key psychological symptoms, including restlessness, fatigue, difficulty in concentrating, irritability, and disturbed sleep. The disorder is common and disabling: a recent review of epidemiological studies in Europe suggests a lifetime prevalence of approximately 5%, and the associated functional impairment is similar to that with major depression. However, many of those who might benefit from treatment are not recognized or treated, which is disappointing, as a range of evidence-based treatments are available.

Role of Pharmacotherapy

Efficacy in Acute Treatment

Current ► Evidence-Based Guidelines for the pharmacological management of patients with GAD recommend initial treatment with either a ► selective serotonin reuptake inhibitor (SSRI) or a serotonin–norepinephrine reuptake inhibitor (► SNRI), on the basis of proven efficacy and reasonable tolerability in randomized placebo-controlled trials (Baldwin et al. 2005; Bandelow et al. 2008). Approximately, 40–60% of patients will "respond" to placebo and 60–75% to the SSRIs ► escitalopram, ► paroxetine, or ► sertraline, when using global measures of improvement, and similar findings are seen for the SNRIs ► duloxetine or ► venlafaxine and for the novel anxiolytic drug ► pregabalin (Baldwin and Ajel 2007). Symptom severity on the primary outcome measure, traditionally the ► Hamilton Rating Scale for Anxiety, HAMA, can be reduced markedly, but many patients remain troubled by distressing anxiety symptoms at study end-point, despite seemingly making a good overall "response" to treatment.

Benzodiazepines are also efficacious (and can provide a rapid reduction in symptoms) in many patients and have similar overall efficacy to the psychological treatment cognitive therapy. However, they are usually ineffective in relieving comorbid depressive symptoms, and unwanted effects include sedation, disturbance of memory, and psychomotor function; other potential problems include development of ► tolerance, abuse and dependence, and distressing withdrawal symptoms. Because of these, it is advisable to use benzodiazepines only for short-term treatment (up to 4 weeks) or in patients who have not

responded to at least two previous treatments and who remain troubled by severe and impairing anxiety symptoms (Baldwin et al. 2005; Tyrer and Baldwin 2006).

Only few randomized controlled trials (RCTs) have allowed the assessment of the relative efficacy of different drugs, when compared with placebo. A recent analysis of RCT findings found an overall mean effect size of 0.39, with pregabalin having the highest effect (0.50) and the azapirone anxiolytic ▶ buspirone the lowest effect (0.17) (Hidalgo et al. 2007). However, this represents a *post hoc* analysis of pooled data, derived from RCTs that differ in design and which were not powered for this comparison. Nevertheless, there is much scope for improvement in developing pharmacological treatments with greater overall efficacy (Baldwin 2008).

Prediction of Response to Treatment

It is hard to predict reliably which patients will make a good response to treatment. Greater severity but shorter duration of symptoms, more pronounced impairment, and the presence of comorbid depressive disorders may predict a greater likelihood of response to antidepressant medications. Lower symptom severity, a history of benzodiazepine treatment, and the presence of comorbid personality disorders may be associated with a lesser chance of responding. Similar difficulties are seen when deciding how long the initial drug treatment in GAD should continue, before it is reasonable to conclude that the chance of responding is too low to justify proceeding with the current approach, although recent analyses shows that an onset of efficacy (defined as a reduction in HAMA score by 20% or more) after 2 weeks of treatment is strongly predictive of response at the study endpoint for duloxetine (Pollack et al. 2008; Baldwin et al. 2009).

Prevention of Relapse

GAD is usually regarded as a chronic disorder, waxing and waning in severity, over many years, although many patients have a more episodic course, with periods of anxiety symptoms and intervening better health. Unlike the situation in recurrent unipolar depression, where continuation of antidepressant treatment beyond initial response substantially reduces the risk of early relapse and later recurrence of depressive symptoms, the value of long-term treatment in GAD is less well established due to the limited number of ▶ Relapse Prevention Studies. Four studies with this design demonstrate the value of continuing pharmacological treatment, with escitalopram, paroxetine, pregabalin, or duloxetine. A formal relapse prevention study with venlafaxine did not reveal efficacy, but significantly fewer patients relapsed during venlafaxine treatment in a separate prolonged randomized double-blind placebo-controlled trial. A currently (November 2009) unpublished relapse prevention study with the second-generation antipsychotic drug quetiapine suggests that it has some efficacy in relapse prevention.

Further Management After Nonresponse to Initial Treatment

There is much uncertainty about subsequent stages in patient management after a poor response to first-line treatment. Commonly employed interventions include an increase in dosage, a switch to another evidence-based drug treatment, augmentation with an additional psychotropic agent, and the combination of medication with a psychological treatment. There is no published dosage escalation study in GAD, in which patients either continue with the initial low dose or switched to a subsequent higher dose, and the findings of fixed-dose randomized placebo-controlled studies do not provide consistent evidence that higher doses are more efficacious. Most guidelines recommend an SSRI for first-line pharmacological treatment; so, common second-line approaches include an SNRI, buspirone, the tricyclic antidepressant imipramine, pregabalin, or a benzodiazepine. Buspirone is more efficacious when GAD patients have not previously been treated with a benzodiazepine; so, it makes sense to consider the use of buspirone before prescribing benzodiazepine anxiolytic (Chessick et al. 2006).

Some doctors recommend an antipsychotic drug after nonresponse to SSRI or SNRI treatment, perhaps fearing the development of tolerance or dependence with the use of benzodiazepines. The conventional neuroleptic drug ▶ trifluoperazine has proven efficacy in acute treatment, and more recently, the second-generation antipsychotic drug ▶ quetiapine has also been found efficacious in placebo- and comparator-controlled studies. However, the adverse effect profile and potential long-term risks of antipsychotics should usually lead them to be reserved for patients who have not responded to earlier SSRI treatment, perhaps followed by an SNRI treatment. Both ▶ risperidone and ▶ olanzapine can enhance the efficacy of SSRI treatment, on at least some measures, and other potential alternative augmentation approaches include the use of ▶ pregabalin, or the novel antidepressant drug ▶ agomelatine, which has recently been found efficacious (Stein et al. 2008). Combining pharmacological interventions with psychological interventions is often advocated for patients with anxiety disorders, but in GAD, it is uncertain whether the combination treatment is superior to psychological or drug treatment given alone (Bandelow et al. 2007).

Tolerability of Current Treatments

The acceptability to patients of prescribed medication is an important consideration, particularly when recommending long-term treatment. The adverse effects of SSRIs and SNRIs including headache, nausea, and increased nervousness and the drowsiness associated with benzodiazepines and pregabalin, usually diminish after a few weeks, though other side effects can become more important over subsequent months. Common concerns during longer-term treatment with SSRIs or SNRIs include the development of sexual dysfunction, weight gain, persistent disturbed sleep, and the potential for experiencing ► Discontinuation Symptoms on stopping the treatment.

The latter are common with many classes of psychotropic drugs, including SSRIs, SNRIs, and benzodiazepines. Symptoms are typically mild and only transient, but many patients report severe and distressing symptoms, despite gradual discontinuation by tapering the prescribed dose of medication. Compounds differ in their propensity to cause discontinuation symptoms (Baldwin et al. 2007), but it is hard to predict which patients will be the most affected. Gradual withdrawal ("tapering") is often advised in the hope of minimizing symptoms, but this is not fully established and there is a need for withdrawal studies with a randomized double-blind staggered design, in which patients and doctors are unsure of whether treatment ends slowly or swiftly, or when the dosage reduction has occurred.

Cross-References

► Anticonvulsants
► Antidepressants
► Antipsychotics
► Benzodiazepines
► Randomized Controlled Trials
► SSRIs and Related Compounds
► Withdrawal Syndromes

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Genetic Polymorphism

Synonyms

Allotropy; Pleomorphism

Definition

The regular and simultaneous occurrence in a single interbreeding population of two or more alleles of a gene – each responsible for a different characteristic or phenotype – where the frequency of the rarer alleles is greater than can be explained by recurrent mutation alone (typically greater than 1%). The concept includes chromosome polymorphism.

Cross-References

► Gene Expression and Transcription
► Pharmacogenetics
► Pharmacogenomics

Genetically Engineered Animal

► Genetically Modified Animals

Genetically Modified Animals

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Synonyms

Genetically engineered animal; Genetically modified organism; GMO; Transgenic animal

Definition

A genetically modified animal is one whose genetic material has been altered by the use of genetic engineering or recombinant DNA technology. In biomedical sciences, genetically modified animals are typically generated for the purpose of studying the function of a particular gene.

Principles and Role in Psychopharmacology

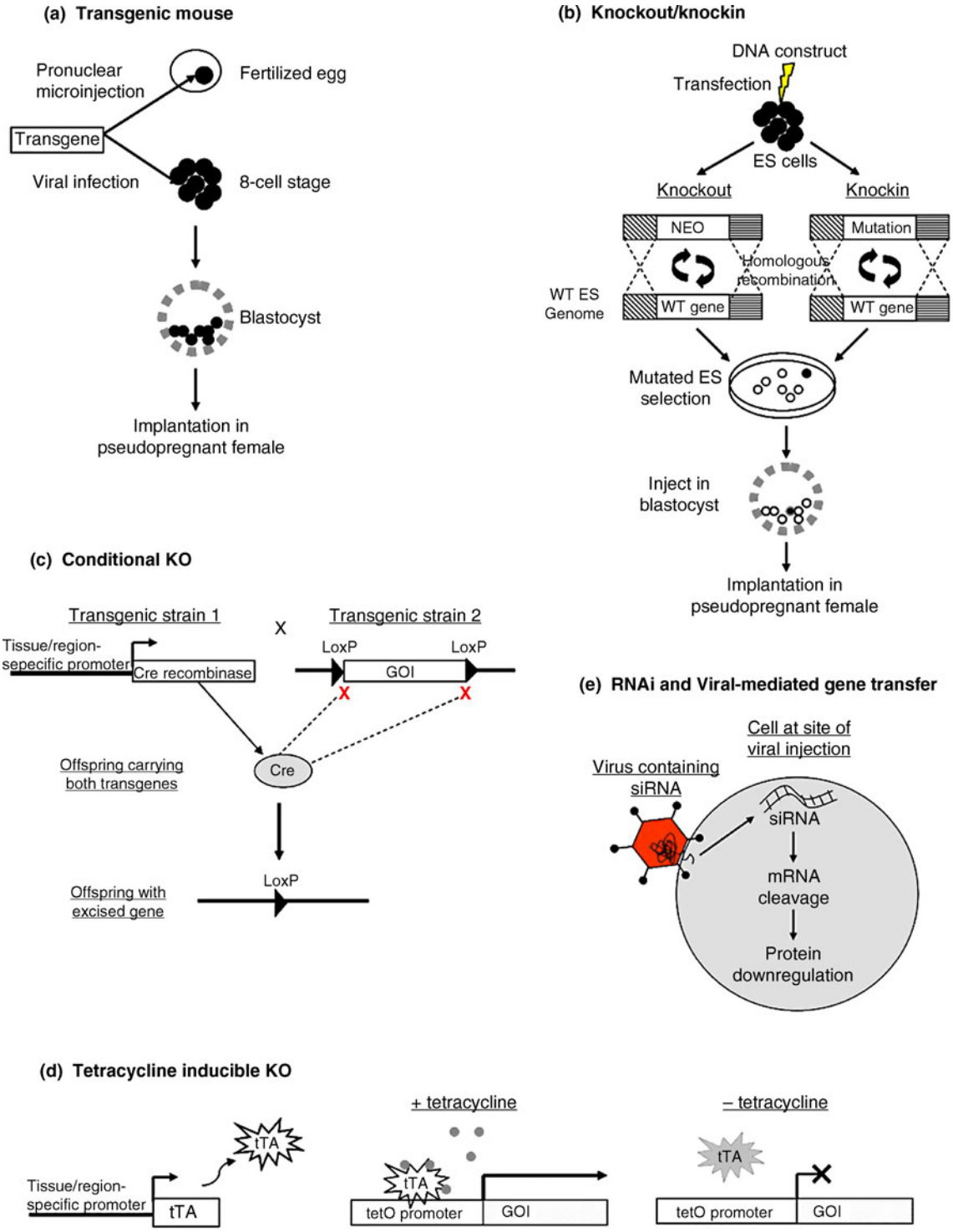
One of the main goals of the field of genetics is to classify and functionally characterize individual genes. The investigative approach to studying genes in living organisms has principally been divided into three strategies: (1) analysis of natural variation, (2) random mutagenesis, and (3) targeted mutagenesis and transgenesis (Rudolph and Mohler 1999). Analysis of natural variation (e.g., spontaneous mutations) and random mutagenesis (e.g., chemical or irradiation) are the primary approaches of ▶ forward genetics in which the genetic cause (▶ genotype) of an altered or abnormal ▶ phenotype is investigated. However, with random mutagenesis, many chromosomal loci are often targeted and it is difficult to trace any phenotype back to a specific genetic origin. The development of ▶ reverse genetic approaches, in which a particular gene is altered and the phenotype is investigated, provided tools to investigate specific gene function in a more targeted manner (Brusa 1999). Since the development of these tools in the 1980s and 1990s, their use in the field of biomedical research and pharmacology has been substantial owing to the ability to develop suitable animal models of specific diseases, to genetically dissect the underlying mechanisms of disease, and to identify and verify molecular targets of pharmacological agents.

In the past two decades, a variety of techniques have been developed to introduce genetic modifications in various species for specific research purposes. Among the most targeted species are *Drosophila melanogaster*, *Caenorhabditis elegans*, and mice, which have each played integral roles in identifying genes involved in development, aging, cell differentiation, and other major biological functions. Other genetically modified animals that have been developed include xenopus, zebrafish, rabbits, pigs, and cows. More recently, transgenic and ▶ knockout rats have been developed, which will allow more extensive research in the neurosciences because of their extensive use in behavioral paradigms (Abbott 2004). In addition, the first transgenic primate disease model (for Huntington's disease) was recently created (Yang et al. 2008). While a wide variety of genetically modified organisms have been created to date for numerous research purposes, techniques for genetically modifying mice are the most advanced and the most applicable to the field of psychopharmacology, which represent the main focus of the remainder of this article.

Transgenic Technology

While the term "transgenic" has grown to include any type of genetically modified animal, the traditional definition of a ▶ transgenic organism is one containing foreign DNA, whether from the same species or a different one. The expression of foreign DNA in a mouse is a valuable technique, since it allows for the investigation of the functional role of this gene in a living organism. For instance, transgenic mice overexpressing a particular gene are often generated to analyze exaggerated phenotypes. The expression of a human gene or a mutated gene in mice is also often used to explore gene function, particularly in the context of a specific disease.

There are several ways to create a transgenic mouse; however, all methods consist of first designing a DNA fragment, or "genetic construct," which contains the gene of interest (GOI) and other features necessary for the expression of this gene in a mammalian system (e.g., gene promoter, enhancer, polyA signal, etc.). The traditional transgenic method consists of physically injecting the transgenic construct into the nucleus of a fertilized egg (pronuclear microinjection), allowing it to develop in vitro to the blastocyst stage, and then implanting the egg into a ▶ pseudopregnant female (Fig 1a). The embryos must then be screened for the presence of the transgene and unlike the production of knockouts, the transgene typically occurs in an all or none fashion, with the embryo either containing the transgene in every cell or in no cells at all. Alternatively, transgenic animals can be produced by viral infection of the fertilized embryo (see below) or transfection of embryonic stem cells (ES) with the gene of interest (Dale and von Schantz 2002). While the transgenic approach is fast and efficient, limitations of the technology include: (1) The GOI may randomly integrate into the genome, which can result in expression in ectopic sites, interference with the endogenous gene, or severe



Genetically Modified Animals. Fig. 1. Diagrams of methods for producing genetically modified animals.

disruption of the homeostasis of the cells and organism; (2) The level of ► gene expression is unable to be controlled and is dependent upon where the gene inserts into the host genome and on the number of copies inserted. Overexpression of the gene could have unexpected detrimental effects, including lethality; (3) Mosaic or chimeric animals are sometimes produced, particularly when the transgenic animal is generated with the viral method, owing to infection of only a subset of cells within the blastocyst; (4) The genetic background of mice can considerably influence the ability of the manipulated egg to survive microinjection, implant in the uterus, and develop to term (Brusa 1999; Dale and von Schantz 2002).

Gene Knockout Technology

The creation of a traditional knockout (i.e., removal of a gene) mouse consists of disrupting all or part of the coding sequence of the GOI, with the purpose of exploring the phenotype in the absence of the gene. The exact locus of the GOI can be targeted by creating a genetic construct that is homologous to the region of the GOI on a particular chromosome. The genetic construct is injected into embryonic stem cells where rare homologous recombination events can occur with the endogenous GOI at the intended chromosomal locus. In the knockout approach, the GOI is often replaced with neomycin (Neo) or another selectable marker, which allows for in vitro selection and identification of the stem cell colonies that have undergone appropriate recombination (Fig. 1b). Selection against random integration into the genome is often attained by using a second selectable marker outside the inserted region. Once the mutated stem cells are identified and verified, they are microinjected into a blastocyst and implanted into a pseudopregnant female as in a transgenic mouse. Most of the offspring produced using this technique are ► chimeras (or mosaics),which is the result of the presence of both mutated and nonmutated stem cells within the blastocyst. Embryonic stem cells from a different color strain of mice than the fertilized egg are often used because the chimeric mice are then easily identifiable due to bi-colored fur. The next step consists of breeding chimeric mice to identify individuals with germ cells that have undergone homologous recombination. These founder mice will then be bred to produce homozygous mutant animals (Dale and von Schantz 2002) (except when homozygous are lethal, in which case heterozygous breeding may be the preferred approach). Similar to knockout mice, ► knockin technology, where one or more exons of a certain gene are replaced with an altered version (Fig. 1b), is often used to study specific polymorphisms, or the human equivalent of the GOI.

While knockout organisms have been paramount in the goal to elucidate the function of specific genes, problems associated with knockout technology include that removal of a gene is often lethal or that the absence of the gene product during development leads to compensatory events that can obscure the analysis of the function of the missing gene. Specifically, these compensatory developments likely differ from the disease mechanisms that the knockout animal is intended to model, as disease processes rarely include full loss of gene function.

Conditional Knockout Technology

The desire for greater specificity and the need to bypass potential developmental compensations and occasional lethality has led to the development of ► conditional or inducible knockouts, where the experimenter has either temporal or regional control over expression of the GOI. Several systems have been developed for this purpose including the Cre-LoxP system, Flp-FRT system, and the tetracycline-inducible system. The Cre-LoxP system of bacterial origin employs Cre recombinase, which mediates site-specific recombination by targeting a DNA sequence called LoxP (Houdebine 2007). To implement this system, one strain of mice is engineered to express Cre under a tissue- or developmental stage-specific promoter and these mice are bred to a second strain of mice in which the GOI has been flanked with LoxP sites. The resulting offspring then have the GOI removed only in the tissues (or at the developmental time point) where/when Cre is expressed (Fig. 1c). The Flp-FRT system originated in yeast and is used in the same manner as the Cre-LoxP system with Flp recombinase excising the GOI flanked by FRT DNA sequences (Houdebine 2007). Importantly, these two systems can be used together to allow for a range of additional approaches.

The tetracycline-inducible system is based on the tetracycline-resistant gene from bacteria and has been modified for use in mammals to essentially act as a switch to initiate or terminate gene expression. In bacteria, the tetracycline-resistance gene is typically kept in the off position by a repressor bound to a specialized DNA sequence in the promoter of the gene, the tetracycline operator (*tetO*) sequence. For use in mammalian transgenics, the repressor protein was modified into a transactivator (tTA), which allows constitutive expression of genes bound to *tetO*. Thus, in the presence of tetracycline, gene expression is terminated when the drug binds to tTA, removing it or preventing its binding to *tet*O. A modified version of tTA (rtTA) requires the presence of tetracycline to bind to *tetO*, thereby allowing activation of a gene in the presence of tetracycline. For these systems

to work, two transgenes in a single animal are needed; one expressing tTA under the control of a site- or temporal-specific promoter and the GOI under control of the *tetO* (Fig. 1d) (Brusa 1999).

RNAi and Gene Transfer In Vivo

The recent discovery and exploitation of the endogenous ► RNA interference (► RNAi) mechanism has aided in the development of loss of function models. The endogenous mechanism consists of short sequences of double-stranded RNA, which bind and cleave complementary mRNA sequences, thereby silencing or inducing downregulation of the specific gene (Dunn et al. 2005). Short sequences of double-stranded RNA (~22 nucleotides), termed small interfering RNA (siRNA), are easily synthesized and can be delivered in vivo using a variety of gene transfer techniques (see below and Fig. 1e). Interestingly, in vivo manipulations using siRNA result in rather limited downregulation of the GOI (when compared with the global KO); yet, they seem to produce marked functional effects (Thakker et al. 2005). Similar to RNAi, antisense technology is the expression of the reverse complement of mRNA, which interferes with normal translation, thereby reducing protein synthesis (Dale and von Schantz 2002).

While conditional and inducible knockouts provide certain level of site and temporal specificity, they are dependent on the availability of promoters that provide the desired specificity. The development of viral-mediated gene transfer has allowed more flexibility in producing the desired manipulations. In addition to an alternative method of producing transgenic animals (discussed above), viral vectors can be used to transfer genetic material in a temporal and site-specific manner in both neonatal and adult mice. Modified virons such as herpes, lenti-, adeno-, and adeno-associated viruses can be engineered to carry a transgene, siRNA, or other genetic material. These viral vectors are then able to infect cells and transmit the desired genetic material. Viral-mediated gene transfer has the additional advantage over conditional mutants that the genetic manipulation occurs only at the site of infection and cell-type-specific promoters can be used for additional specificity. Depending on the type of virus used, the genetic material may be integrated into the genome or may remain epichromosomal. The type of virus also influences the infection rate, type of cells infected, and the size of DNA insert (Dunn et al. 2005). While viral-mediated gene transfer technology is widespread, nonviral gene transfer to the central nervous system has also been achieved using in vivo electroporation and both intracerebroventricular and intrathecal infusion (Gilmore et al. 2006).

Roles of Genetically Modified Animals in Psychopharmacology

The creation of the first knockout mouse in 1989 led to a Nobel prize for Sir Martin Evans (Cardiff University in Wales), Oliver Smithies (University of North Carolina at Chapel Hill), and Mario Capecchi (University of Utah in Salt Lake City) in 2007. Since the development of the technology, using knockout mice along with other types of mutants to investigate critical questions in psychopharmacology has become a standard practice. In particular, genetically modified mice have been essential in psychopharmacology for (1) elucidating both the function of a gene and the molecular elements associated with a gene; (2) creating animal models of human disease; (3) identifying and validating drug targets and drug specificity, and (4) examining temporal aspects of gene function.

One of the first major breakthroughs in the field of neuroscience using targeted mutagenesis came from Eric Kandel's group at Columbia University. In a series experiments using the tetracycline-inducible system, they were able to express a calcium-independent form of the forebrain-specific calcium-dependent kinase, calcium-calmodulin kinase II (CaMKII), and found deficits in ► spatial memory and hippocampal ► long-term potentiation (LTP) (Mayford et al. 1996). These groundbreaking experiments provide a classic example of the power of how spatial and temporal control over molecular elements can aid in elucidating the function of specific genes and their role in higher brain function. The CaMKII promoter still remains one of the most popular promoters to express numerous genetic constructs in the mouse forebrain.

Another critical role for transgenic animals is the development of animal models for human disease, by either the introduction of a mutated gene or the elimination of a gene putatively involved in the illness. In the field of neuroscience, this has been particularly useful in modeling a wide variety of disorders, including ► Alzheimer's disease (AD), Huntington's disease, neuropsychiatric disorders, and cerebral ischemia. In particular, AD is characterized by the formation of ► neurofibrillary tangles of hyper-phosphorylated tau protein and by ► amyloid β-peptide (Aβ) plaques. Mutations in the amyloid precursor protein (APP), presenilin 1 and 2 (PS1, PS2), and apolipoprotein E (APOE) are all implicated in the disease. Studies now show that mice overexpressing APP and PS1 form Aβ plaques and display memory deficits, both characteristic symptoms of AD (Brusa 1999), consequently highlighting the important role of genetically modified animals in testing potentially causal mechanisms involved in human disease. In some cases, it is

necessary to replace the murine gene with the human gene because of distinct structural differences between the human gene and mouse homolog at the molecular level (Rudolph and Mohler 1999), or simply to replicate the human pharmacological signature (e.g., 5-HT_{1B}, NK_1...).

The development of genetic animal models for human diseases has provided a solid foundation for drug discovery and for the identification of drug targets. The specificity of the genetic manipulation (i.e., removing a gene coding for a particular receptor subtype) ensures virtually absolute selectivity, thereby offering a great advantage over classical pharmacological approaches. For instance, the function of receptor subtypes can be examined using both knockin and knockout approaches. A particularly relevant example is that of the utilization of transgenic mice in determining the role of specific ► $GABA_A$ receptor subunits in distinct actions of the benzodiazepine, ► diazepam. Diazepam is known to act on $GABA_A$ receptors containing the α1-, α2-, α3-, or α5- subunits. By examining mice carrying point mutations in the benzodiazepine binding sites of each subunit, investigators were able to genetically dissect the different functions of diazepam (e.g., sedative vs. anxiolytic) acting at otherwise similar $GABA_A$ receptors (Rudolph and Mohler 1999).

Other critical uses of genetically modified animals are the dissection of second messenger signaling pathways and the determination of critical developmental time-windows for gene function. The latter was elegantly demonstrated by the use of a tetracycline-inducible knockout of the serotonin 1A (5-HT_{1A}) receptor. Gross et al. (2002) showed that when the 5-HT_{1A} receptor was knocked out during development, it resulted in behavior similar to the knockout mouse (increased anxiety). However, when the receptor was knocked out in adults, the phenotype was absent (anxiety levels were normal), thereby implicating the 5-HT_{1A} receptor as a critical developmental factor for normal emotional behavior (Gross et al. 2002).

In summary, the primary goal of reverse genetics is to create a targeted mutation and then investigate the resulting phenotype. We briefly discussed several methods of targeted mutagenesis, including the development of transgenic animals and the techniques for developing global, conditional, and inducible knockouts. The values of this technology have been far-reaching and have played a considerable role in psychopharmacology. We have highlighted some of the most common uses for genetically modified animals in this field, including the dissection of molecular mechanisms, modeling human disease, drug discovery and validation, and the investigation of critical time windows in gene function. While several other approaches for creating genetically modified animals exist (e.g., the use of modified male gametes) along with other applications for these animals (e.g., pharming), we focused on the role of genetically modified mice in psychopharmacology, as their impact on this field has been substantial. New approaches to developing and using genetically modified organisms are quickly evolving, including modifications and combinations of the discussed systems, which will likely further impact psychopharmacology.

Cross-References

► Epigenetics
► Ecogenetics
► Gene Expression and Transcription
► Pharmacogenetics
► Phenotyping of Behavioral Characteristics
► Translational Research

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Genetically Modified Organism

► Genetically Modified Animals

Genomic Imprinting

► Imprinted Genes

Geocentric

► Allocentric

GHB

► Oxybate

GIRK Channels

Definition

GIRK channels are G-protein coupled inwardly rectifying K^+ channel (also known as $K_{ir}3$ channels) causing membrane hyperpolarization and plays a very important role in reducing neuronal excitability in most brain regions and in the heart. Four subunits have been identified in mammals, and neuronal GIRK channels are predominantly heteromultimers of GIRK1 and GIRK2. The channels are activated through the G-protein βγ dimer, derived mainly from $G_{i/o}$ heterotrimers.

Cross-References

► G-Protein-Coupled Inwardly Rectifying Potassium Channels

Global Knockout

► Knockout/Knockin

Glucocorticoid Hormones

Definition

Steroid hormones synthesized and secreted from the zona fasciculata of the adrenal gland in response to ACTH after exposure to a stressor or during the diurnal peak. The main endogenous glucocorticoids are corticosterone in rodents and cortisol in humans.

Glucocorticoid Receptor

Definition

A transcription factor regulating the CRF gene. Glucocorticoid receptors (GR) are stabilized in the cytosol by various chaperones before homodimerizing and translocating into the nucleus. Childhood abuse and polymorphisms in FKBP5, a chaperone for GR, are associated with posttraumatic stress disorder.

Cross-References

► Gene Expression and Transcription

Glutamate

Definition

The principal excitatory neurotransmitter in the central nervous system, ubiquitous throughout the cortex and subcortical regions of the mammalian brain. Glutamate released from axonal presynaptic terminals generates electrical excitation and action potentials in postsynaptic neurons. It is a key molecule in learning, memory, and cellular metabolism. Different glutamate receptor systems play differential roles in information transfer, neuroplasticity, and maintenance of synaptic strength. There are four distinct glutamate receptors: ► NMDA, ► AMPA, and kainate, all ion channel receptors, and a ► metabotropic receptor. The NMDA receptor, in particular, has been linked to a long-term potentiation of neuronal activity, which may be a basis for synaptic plasticity and learning.

Glutamate and EAA Transporters

Synonyms

EAAT

Definition

Glutamate (Glu) and EAA transporters (EAAT) are membrane transport proteins responsible for removing Glu from the synapse into glial cells (EAAT1-3) or neurons (EAAT4). They belong to the larger family of neurotransmitter transporters including GABA transporters, glycine transporters, and the different monoamine transporters. Glu transporters play a crucial role in regulating the amount of synaptic Glu and are therefore responsible for terminating synaptic transmission. By reducing the

exposure to Glu, they further serve to protect the cell from excitotoxicity. Known EAAT inhibitors are WAY213613 and dihydrokainic acid.

Glutamate Microelectrode Arrays

Definition

To measure glutamate, a selective and highly active glutamate oxidase from *Streptomyces* sp. X-119-6 is applied to two microelectrode recording sites (Hascup et al., 2007). Reference or "sentinel" microelectrode sites are created by applying a chemically inactive protein (bovine serum albumin) to other recording sites. All recordings are performed using amperometry at +0.7 V versus an Ag/AgCl reference with a FAST16mkII electrochemical recording system (Quanteon LLC, Nicholasville, Kentucky). Drugs are locally applied from micropipettes or cannulae between the recording sites using pressure ejection or volume displacement, respectively. Subtraction algorithms are used to remove the background and interfering signals by using the responses from the sentinel or self-referencing recording sites.

Cross-References

► Microelectrode Arrays

Glutamate Receptors

Definition

Glutamate receptors are transmembrane receptors located on neuronal membranes. There are several receptor subtypes including the ► NMDA (*N*-methyl-*d*-aspartate glutamate receptor), kainate, ► AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate acid glutamate receptor) and mGluR receptors. Glutamate is one of the major excitatory transmitter systems in the central nervous system and many of these systems have been implicated in learning and memory processes. ► Alcohol acts as a weak antagonist of glutamate receptors during initial exposure to alcohol. However, chronic exposure to alcohol can result in an increase in the number of glutamate receptors (upregulation); such an effect has been reported with NMDA receptors. An increase in glutamate receptors may lead to a neuronal circuit that is hyper-excitable. This hyper-excitability is more pronounced in the absence of alcohol and may be a critical component in the underlying neurobiology of alcohol withdrawal.

Glycine Transporter 1

Definition

Glycine transporter 1 is widely expressed in astroglial cells throughout the mammalian central nervous system and has been implicated in the regulation of N-methyl-D-aspartate (NMDA) receptor activity. Glycine transporter 1 plays a pivotal role in maintaining the glycine level at the glutamatergic synapse.

Cross-References

► Glycine
► N-Methyl-D-Aspartate Receptor

Glycolysis

Definition

Characterizes the metabolism of glucose in the cell cytoplasma; an important example of such a metabolite is acetyl-coenzyme A, which is, for example, important for the synthesis of acetylcholine (lost in AD) and adenosine-triphosphate (ATP), which are necessary for cell functioning.

GMO

► Genetically Modified Animals

GnRH

► Gonadotropin-Releasing Hormone

Go/No-Go Task

Synonyms

Response conflict task

Definition

Behavioral tests in which subjects respond in the presence of a *Go* signal or cue and inhibit responding in the presence of a *No-Go* signal or cue. For example, in a rodent version, responding in the presence of the *Go* stimulus is reinforced but in the presence of the *No-Go* stimulus it is not (although in some "symmetrically reinforced"

versions withholding the response in the presence of the *No-Go* stimulus is also reinforced). Response accuracy can be examined using ► signal detection theory, which uses a 2 × 2 matrix of signal (*Go* or *No-Go*) and response (occurred or omitted). Responses occurring during the *Go* signal are called hits. Responses occurring during the *No-Go* signal are false alarms. Trials on which there are no responses during the *Go* signal are misses. Trials on which there are no responses during the *No-Go* signal are correct rejections.

Goal Tracking

Synonyms
Anticipatory food seeking; Anticipatory goal seeking

Definition
Goal tracking refers to orientation and approach behavior to the source or location of a rewarding (appetitive) stimulus such as food, water, sex, etc. In rats, this may be operationalized as head-entries into the receptacle where sucrose is delivered. For nonhuman primates, this could be measured as hand entries in a recessed container where food or treats are provided. Goal tracking is a widely used behavioral measure of associative learning.

Cross-References
► Classical (Pavlovian) Conditioning
► Occasion Setting With Drugs

Gonadal Hormones

Definition
Gonadal hormones are hormones produced by the gonads (i.e., the testes in males and the ovaries in females).

Cross-References
► Sex hormones

Gonadotropin-Releasing Hormone

Synonyms
GnRH

Definition
Gonadotropin-releasing hormone (GnRH) is a hormone released from the female ► hypothalamus that stimulates anterior pituitary release of follicular-stimulating hormone (FSH) and luteinizing hormone (LH). When a woman takes a GnRH agonist, she will experience a decrease in GnRH secretion, a reduction in FSH and LH, and thus a reduction in ovarian production of estradiol and progesterone.

Gonads

Synonyms
Ovary or testis

Definition
A gamete-producing reproductive gland that secretes sex-specific steroid hormones.

Cross-References
► Sex Differences in Drug Effects
► Sex Hormones

GPCR

Definition
G-protein-coupled receptor. This is the largest group of transmembrane receptors, including all opioid receptors, that predominantly transducer intracellular signals via G-proteins or trimeric GTP binding proteins. A large number of psychoactive drugs act on GPCRs.

G-Protein-Coupled Inwardly Rectifying Potassium Channels

Synonyms
GIRK channel

Definition
A group (Kir 3.1 – 3.4) of inwardly rectifying (so-named because they have a higher conductance for potassium entering than leaving the cell) potassium channels that are activated by G-protein βγ-subunits. When activated, they hyperpolarize membranes to reduce excitability.

Gradient-Echo EPI

► Echo-Planar Imaging

Gradient-Echo Images

Synonyms

Gradient-echo MRI; Gradient-recalled-echo (GRE) planar images

Definition

Gradient-echo imaging is one of the two most frequently used pulse sequences in modern day MRI as distinct from spin-echo (SE) MRI. There are many variations of the basic gradient-echo (GE) sequence. It is the most common form of fMRI pulse sequence, typically with echo-planar imaging (EPI) or more recently, spiral imaging.

Cross-References

► Magnetic Resonance Imaging (Functional)
► Magnetic Resonance Imaging (Structural)

Gradient-Echo MRI

► Gradient-Echo Images

Gradient-Recalled-Echo (GRE) Planar Images

► Gradient-Echo Images

Group II Metabotropic Glutamate Receptor

Synonyms

Metabotropic glutamate receptors 2 and 3

Definition

Group II metabotropic glutamate receptors (mGluRs) are a type of glutamate receptors that are active through an indirect metabotropic process. They are members of the group C family of G-protein-coupled receptors. Like all glutamate receptors, Group II mGluRs bind to glutamate.

Cross-References

► Glutamate

Guard Column

Definition

In ► high-pressure liquid chromatography, this guard column is a short column (typically 1–5 cm), normally packed with the same stationary phase as the analytical column, and placed immediately before the analytical column. It serves two main purposes: first as a filter to remove any fine particulate material from the mobile phase before it reaches the analytical column and second to pre-saturate the mobile phase before it reaches the analytical column, thus protecting the analytical column from dissolving.

H

Habit Reversal Therapy

Synonyms

CBIT; Cognitive behavioral therapy for trichotillomania; Comprehensive behavioral intervention for tics or trichotillomania; HRT

Definition

Habit reversal therapy (HRT) is an evidence-based behavioral therapy used in the treatment of tics, trichotillomania, and other body-focused impulse control disorder. HRT involves several different components – self-monitoring, awareness training, stimulus control, and competing response training.

Habit Reversal Training

Synonyms

HRT

Definition

A behavioral intervention that attempts to replace a tic with a voluntary movement or sound that can then be discarded. The premonitory urge that subsides following the performance of the tic suggests that the relief of the premonitory sensation reinforces the performance of the tic. In HRT, subjects are taught to initiate an alternative movement (or sound) upon detection of the premonitory urge and to continue the voluntary movement until the urge subsides.

Habituation

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Synonyms

Extinction

Definition

Habituation is a decrement in responding that results from repeated presentations of an initially novel stimulus in the absence of sensory adaptation and motor fatigue. Experimentally, habituation can be distinguished from sensory adaptation or motor fatigue by the demonstration of ▶ dishabituation or by demonstrating stimulus specificity (i.e., the response still occurs to other stimuli). Habituation is considered to be the simplest form of learning. More specifically, habituation refers to a nonassociative form of learning insofar as it occurs in the absence of any contingency associated with the stimulus. Habituation is a prerequisite to selective attention; in the absence of habituation, an organism would continue to respond to all stimuli depending upon its inherent characteristics.

Characteristics of Habituation

As detailed elsewhere (Thompson and Spencer 1966; Rankin et al. 2009), habituation is a general phenomenon that can be observed across species, stimulus modalities, and response systems. Although habituation typically refers to behaviors, some use the term to refer to decrements in responses, such as neuronal firing, ▶ event-related potentials, or even biochemical responses. In theory, the process of habituation is expected to exhibit a progressive exponential decay to an asymptotic level of the frequency and/or magnitude of the given response. In practice, the decrement is commonly linear or may exhibit facilitation prior to decrementing because of the simultaneous process of ▶ sensitization. Sensitization, in the Pavlovian sense of the term, is an incremental change in the response to a stimulus in the absence of any associated contingency. Dual-process theory suggests that the observed response in an experimental study of habituation reflects the summed effects of the two independent underlying processes of habituation and sensitization, with sensitization typically being most evident in response to the first several stimulus presentations, and habituation becoming the dominant process as the presentations continue (Groves and Thompson 1970). Sensitization is expected to be directly proportional to stimulus strength. In contrast, the less intense the stimulus, the more rapid and more pronounced the behavioral response decrement, i.e., the habituation.

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Presentation of a different stimulus in the same or different modality may lead to an increase of the habituated response to the original stimulus, a phenomenon called "dishabituation." The experimental test required to demonstrate dishabituation is to show an increase in response to the original stimulus, not the response to the dishabituating stimulus, which may not even elicit an observable response on its own. Spontaneous recovery is a related phenomenon in which the habituated response recovers at least partially if the stimulus is withheld and then presented again.

Habituation typically refers to relatively short-term changes within a series of repeated stimuli, but can also refer to longer-term reductions in response frequency and/or magnitude that may last for hours, days, or weeks. This distinction is sometimes described as within- versus between-session habituation. In analogy with short- and long-term memory, short- and long-term habituation phenomena appear to be subserved by somewhat different underlying mechanisms, the latter presumably involving changes in protein synthesis (Rankin et al. 2009). Furthermore, pharmacological effects on short-term habituation are not reliably predictive of parallel changes in long-term habituation. A related consequence of exposure to a within-session habituation protocol is the phenomenon of latent inhibition, in which it becomes more difficult to learn an association to a previously habituated stimulus than to a novel (i.e., nonpreexposed) stimulus. As with ▶ extinction learning, latent inhibition can be shown to differ from simple long-term habituation, but only when an intervention can be interposed between the original habituation protocol and the acquisition training of the new association. Thus, in studies of genetically modified animals or psychiatric populations, the effects on habituation versus latent inhibition are fundamentally confounded.

Impact of Psychoactive Drugs

As noted, habituation affects many, if not all, stimulus-response systems. In human psychophysiology, the most common stimuli are visual, auditory, or tactile, and the most common measures are motor reflexes or skin conductance orienting responses (Bernstein 1987; Groves and Thompson 1970). In the field of psychopharmacology, however, the most common measures are based on motoric ▶ startle responses, in part, because skin conductance responses are variable, quite transient, and highly sensitive to peripheral autonomic changes. When mammals are exposed to a sudden stimulus, typically a rapid-onset acoustic noise or tactile (e.g., airpuff or shock) stimulus, a startle response is elicited (Davis 1980). In both rodents and humans, habituation can be quantified by measuring the magnitude of the startle response to repeated presentations of startling stimuli. Using startle habituation measures is advantageous in psychopharmacologic research for a number of reasons (Geyer and Braff 1987). First, startle habituation in rodents has some face, predictive, and construct validity for startle habituation in humans. Second, startle habituation exhibits some stability across repeated testing sessions, enabling one to use longitudinal designs to explore developmental and environmental perturbations on habituation over time and across experience. Third, startle habituation involves fairly rapid tests that do not involve complex stimuli, increasing their ease of use and their reliability. Since startle relies on a simple reflex measure, its reliability and reproducibility are greater than more complex behavioral measures that are modulated by competing behaviors or motivations (e.g., approach/avoidance behavior), and increases the chances of translation of these effects to humans.

Startle habituation has been found to be reduced in ▶ schizophrenia and schizotypal patients, and also in patients with panic disorder (Geyer and Braff 1987; Ludewig et al. 2003). Attentional and information processing dysfunctions have long been considered important in understanding schizophrenia and other psychiatric disorders. The deficit in habituation seen in schizophrenia is thought to reflect an inability to filter or "gate" sensory (and, theoretically, cognitive) information. Theoretically, impairments in basic information processing functions such as habituation contribute to difficulties in maintaining selective attention, which, in turn, leads to disordered thought and cognitive fragmentation observed in psychotic disorders such as schizophrenia. Given the cross-species comparability of startle habituation protocols, identification of genetic contributions to startle habituation in humans can be extended to parallel studies, using genetically engineered mice or other relevant strains of rats or mice (Geyer and Braff 1987; Halberstadt and Geyer 2009).

The psychopharmacology literature is not rich in definitive studies of habituation. Many studies have reported putative changes in the habituation of the exploratory response of rodents to novel environments. Nevertheless, the fundamental difficulties in quantifying the initial response to the stimulus, and in even defining the discrete stimulus itself, have complicated the interpretation of drug effects as being related to the process of habituation *per se*. As noted above, measures of startle habituation have proven more tractable to study in rodents as well as humans. It should be noted, however, that typical habituation protocols in

rodents involve tests of 30–60 min in duration. Hence, it is critical to consider potential confounding of the time after drug administration with changes in the process of habituation. Furthermore, despite the long-standing acceptance of the dual-process theory, empirical approaches to separating effects on sensitization versus habituation remain weakly based upon the premise that sensitization effects are short-lived, relative to habituation effects (Meincke et al. 2004; Halberstadt and Geyer 2009). These complications have contributed to the lack of clarity in the literature on the psychopharmacology of habituation. Among the most robust observations is that deficits in startle habituation can be induced in rodents and, apparently, in humans, by treatment with serotonergic agonists, including ► hallucinogenic drugs such as mescaline or LSD (Geyer and Braff 1987; Dulawa and Geyer 2000). Evidence suggests that these deficits in habituation are attributable to the agonist actions of these drugs at 5-HT_{2A} receptors. Conversely, 5-HT_{2A} antagonists can accelerate habituation in a manner that is not due to the time-course of the drug action. Similarly, psychotomimetic glutamate antagonists such as ► phencyclidine or ► ketamine have been reported to attenuate startle habituation, although some of these effects may be complicated by effects of the drugs on the initial level of responding, prior to any influence of habituation. There is also evidence of phenotypic differences in sensitization and habituation of startle in mutant mice, in which specific subtypes of serotonin or dopamine receptors have been deleted (Dulawa and Geyer 2000; Halberstadt and Geyer 2009).

Cross-References

► Extinction
► Latent Inhibition
► Prepulse Inhibition
► Schizophrenia
► Startle

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Halazepam

► Benzodiazepines

Half-Life

Synonyms

Biological half-life; Elimination half-life

Definition

Half-life is defined as the time interval required for a quantity undergoing exponential decay to reach half of its initial value. In the context of a drug injection, half-life refers to the interval required for drug levels from a single drug administration to decline to half of the peak value. Half-life is governed by ► pharmacokinetic variables such as drug degradation and clearance from the body.

Hallucinations

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Definition

Hallucinations are perceptions without objective reality; that is, in the waking state, sensory events are experienced,

which are unfounded but appear to emanate from external space. Hallucinations can develop in any sensory modality but most commonly are visual or auditory in nature. They can be simple, for example patterns or noises, or complex, for example images of people, objects and scenes, voices of people speaking in coherent sentences, or musical recitals.

Hallucinations normally develop in association with other mental state abnormalities, when there is a medical condition adversely affecting brain function. However, they can also occur as isolated phenomena in people who are otherwise normal. For example, it is not uncommon to experience the physical presence or voice of a deceased loved one in the early stages of bereavement. Auditory or visual hallucinations can also be experienced when waking-up or falling asleep and are known as hypnopompic and hypnagogic hallucinations, respectively. Even a small percentage of the general public report hearing voices on a fairly regular basis when going about their daily routine. In these circumstances, hallucinatory experiences are usually transient or mild and do not give rise to significant distress. When people who experience hallucinations come to medical attention, it is usually because they are vivid, frequent and intrusive, and when insight into their veracity is lost.

Hallucinations can arise during the course of an organic disorder, usually in the context of diffuse cerebral cortical dysfunction, as in states of delirium where consciousness is impaired due to a metabolic derangement or a toxic influence. Notable examples are the alcohol withdrawal states of ► delirium tremens, when vivid visual hallucinations of animals are commonly experienced ("pink elephants") as well as tactile hallucinations of insects burrowing into the skin (formication), and alcoholic hallucinosis, when intense persecutory voices are heard. Hallucinations also commonly develop in organic disorders where consciousness is not impaired but when there is a widespread neurodegeneration of the cerebral cortex, as in ► Lewy body dementia or ► Alzheimer's disease. However, it is the study of hallucinations occurring in more rare circumstances, when there is specific focal pathology, which has provided important information concerning their neural basis. This has shown that hallucinations can arise when there is an abnormality in the sensory pathway corresponding to the modality of the hallucination itself which can be located anywhere from the primary sensory organ to the secondary sensory association cortex. Hence, the Charles Bonnet syndrome, in which vivid visual hallucinations of people, animals, or scenery are experienced, is most often associated with acquired damage to the retina or optic nerve. An auditory equivalent, musical hallucinosis, has been described in acquired deafness. Subcortical lesions of the thalamus, cerebral peduncles, and brainstem, due to tumor or infarction, can also give rise to complex visual or auditory hallucinations, presumably due to the transection of modality-specific ascending sensory nerve fibers (Braun et al. 2003). A common finding in functional neuroimaging studies of these disorders is that, even when the pathological locus is "downstream," there is increased activity in the corresponding modality-specific secondary association cortex (Allen et al. 2008). Secondary sensory association cortex is the area in which sensory stimuli are organized into coherent percepts, having been processed in fragmented form in primary sensory cortex. Thus, one explanation is that secondary association cortex spontaneously generates images or false perceptions using "top down" input from memory circuitry in an attempt to make sense of reduced or aberrant sensory input (Allen et al. 2008; Braun et al. 2003; Frith and Dolan 1997).

In the lesion cases described above, insight into the hallucinatory nature of experiences is often retained. When insight is disturbed and hallucinations are regarded as real, a disturbance of supra-modal association cortex is implicated, especially that of the frontal lobe. This has largely been demonstrated by the study of hallucinations in mental illnesses (Allen et al. 2008) known as "functional psychoses" because there is no obvious associated organic pathology. Schizophrenia is the most prominent example of such a disorder in which hallucinations of voices discussing the person in a derogatory fashion or commenting on their actions are core symptoms. One view is that neural processing in circuitry, critically involving dorsolateral prefrontal and anterior cingulate cortexes, is weakened as part of the neurobiology of the disorder. This circuitry is considered to be involved in monitoring and assigning significance to information being processed elsewhere and instigating actions accordingly. Central to this function is distinguishing whether events or actions, e.g., images or thoughts, are generated by the self or not. This is consistent with an influential psychological explanation of hallucinations by Frith (1995) as being the product of a failure of ► self-monitoring. That is, the failure to recognize that actions such as inner speech are initiated by the self results in them being misattributed to external agencies.

► Delusions are false beliefs that are held with complete conviction, unaffected by clear evidence to the contrary and implausible or bizarre. For a belief to be considered a delusion, it should additionally not be shared by other members of the culture from which the individual who holds it originates.

Delusions commonly occur alongside hallucinations as part of the spectrum of psychotic phenomena. Like hallucinations, they can arise in the context of organic disorders affecting cerebral function or mental illness. Again, like hallucinations, there are different forms of delusions typified by their content and sometimes associated with specific disorders.

The most frequent type of delusion is self-referential in nature. Paranoid delusions are the most common, witnessed in many organic or functional ▶ psychoses, and characteristically are imbued with fear and anxiety. Thus, persecutory delusions include beliefs about being threatened, deceived, or conspired against, and delusions of reference are beliefs that every day events, such as those reported on the TV or in newspapers, are about them. Delusions associated with an abnormally elevated or depressed mood are seen in the affective psychoses. Hence, grandiose delusions are typical of the manic state in ▶ bipolar disorder and concern an inflated sense of self-importance such as having special powers or being chosen by God for a special purpose. In psychotic depression, delusions of guilt, that one has committed a heinous crime or is responsible for some disaster; hypochondriasis, that body parts are failing or rotting; and nihilistic delusions, that the self or other people do not exist, are characteristic.

Another set of delusions known as "first rank symptoms" (Sims 1991) are more characteristic of ▶ schizophrenia. These cannot be understood to arise from ordinary life experience and, so long as there is accompanying social or occupational dysfunction, are alone sufficient for the diagnosis. These concern the belief that thoughts, feelings, or actions are under the control of outside forces. For example, thoughts may be inserted, withdrawn, or broadcast to the outside world and actions may be "made" or externally directed (also known as somatic passivity).

Current Concepts and State of Knowledge

The Neurochemistry of Hallucinations and Delusions

Insight into the neurochemical basis of hallucinations comes from the study of ▶ Parkinson's disease (PD) in which the primary pathology is degeneration of the ascending midbrain ▶ dopamine projections to basal ganglia and cortex. Hallucinations develop in up to 40% of patients and are mainly visual. In most cases, these are directly attributable to the dose of ▶ antiparkinsonian medication as they recede when this is reduced. Studies have shown that the direct dopamine D_2 receptor agonists are most likely to induce hallucinations in susceptible individuals but hallucinations have also been reported with other antiparkinsonian drugs, including 3,4-dihydroxy-L-phenylalanine ▶ L-DOPA, anticholinergic compounds, ▶ amantadine, monoamine oxidase-B inhibitors, and catechol-methyltransferase inhibitors, all of which have the common action of enhancing dopamine neurotransmission. One explanation is that in some cases, doses that are effective in treating the PD movement disorder, which is due to nigrostriatal dopamine depletion, may cause overstimulation of the mesolimbic/mesocortical dopamine system and that this mediates the emergence of hallucinations.

Other evidence supports a central role of abnormal dopamine neurotransmission not only in the development of hallucinations but also delusions. Indirect dopamine agonists, such as ▶ amphetamine and ▶ methylphenidate, administered at doses that are ineffective in healthy subjects, have been found to worsen both of these psychotic phenomena in schizophrenia (Lieberman et al. 1990). In addition, it has been known for several decades that drugs that block dopamine D_2 receptors, for example the typical or ▶ first-generation antipsychotics, such as ▶ haloperidol, are efficacious in the treatment of hallucinations and delusions, regardless of the context in which they occur. The atypical or ▶ second-generation antipsychotics are also efficacious in this respect. Although these have heterogeneous pharmacological profiles including the blockade of serotonin receptors or other dopamine receptors, they share the common mechanism of D_2 receptor blockade.

Other neurotransmitters have also been implicated as mediators of psychotic symptoms but less strongly than dopamine. This is based on self-reports of individuals under the influence of psychoactive drugs. Specifically, the so-called ▶ hallucinogens, lysergic acid diethylamide (LSD), psilocybin, and mescaline, are all 5-hydroxytryptamine 2A ($5\text{-}HT_{2A}$) receptor agonists suggesting a role for serotonin; the anesthetic drugs ▶ ketamine and ▶ phencyclidine are both ▶ *N*-methyl D-aspartate (NMDA) antagonists suggesting glutamate neurotransmission also plays a part. These compounds most often produce dissociated states and altered perceptions in the form of visual illusions or simple hallucinations rather than the more complex hallucinations and delusions experienced in organic and mental illness. Nevertheless, the known interactions between ▶ dopamine, ▶ serotonin, and ▶ glutamate in the modulation of neural processing in circuitry involving frontal cortex, thought to be abnormal in patients experiencing psychotic symptoms, substantiates the involvement of neurotransmitters other than dopamine in psychosis.

The Dopamine Hypothesis of Psychosis

Two variants of the dopamine hypothesis have been proposed: the postsynaptic variant proposes that abnormal dopamine transmission is related to hypersensitive D_2 receptors; the presynaptic variant holds that abnormal dopamine transmission is related to elevated dopamine synthesis or release.

While initial molecular imaging studies using [^{123}I] IBZM-SPECT (single-photon emission computed tomography, ► SPECT) were suggestive of abnormally elevated D_2 receptor binding in schizophrenia, later studies that included unmedicated patients produced negative findings, suggesting that antipsychotic medication may have been an important confound in early work. However, several positron emission tomography (► PET) studies, for example using [^{18}F]-DOPA, have provided evidence for elevations in presynaptic dopamine availability, even in antipsychotic-naïve patients and patients in the prodrome for psychosis (Howes et al. 2007). Furthermore, studies that measured stimulant-induced dopamine release in antipsychotic-naïve patients with schizophrenia have reported not only that dopamine release is elevated in these patients, but that the extent of dopamine release is strongly related to the increase in psychotic symptoms following stimulant administration. Together, these findings reinforce the importance of dopamine in the generation of psychotic symptoms, particularly delusions. However, there remains a gap in understanding the mechanism by which increased dopamine release might cause an individual to develop such persistent and irrational false beliefs.

In order to fill this gap, a number of theorists have sought to explain the link between dopamine and delusions by appealing to the function of dopamine in the healthy brain. Many studies have suggested that while dopamine is not necessarily released when rewards (e.g., food) are actually delivered, it is released when rewards are expected. Others have suggested that dopamine may act as a teaching signal during reward learning. In particular, it has been suggested that dopamine release mediates motivational salience in the brain, i.e., the ability of stimuli associated with reward to drive goal-directed behavior. Salient stimuli are those that stand out from their surroundings and automatically capture attention due to some distinguishing characteristics, be it perceptual contrast, novelty, surprise, or emotional association. Recent evidence suggests that novelty salience may also trigger dopamine neuron firing, raising the possibility that dopamine may play a more general role in encoding salience in the brain.

Appealing to this notion of dopamine as a general signal for salience, a recent hypothesis suggested that psychosis and, in particular, delusions might be related to a state of "aberrant salience," driven by poorly regulated dopamine release (Kapur 2003). In this framework, the release of dopamine out-of-context with the environmental surroundings leads to the tagging of irrelevant stimuli as salient, leading individuals to attribute to them some importance or relevance. In this framework, a delusion is conceptualized as the post-hoc rationalization of accumulated aberrant salience experiences. One of the strengths of this hypothesis is that it explains why delusions take some time to resolve following the onset of antipsychotic medication. It suggests that ► antipsychotics do not treat delusions directly, but instead limit the aberrant salience experiences that cultivate them, allowing delusions to extinguish gradually. It also explains why patients dislike taking antipsychotic medication, since both aberrant and normal motivational salience processes will be affected by D_2 blockade, resulting in a state in which individuals experience a lack of motivation or energy. However, further work is required to test the numerous predictions made by this influential hypothesis.

Cross-References

► Alcohol Abuse and Dependence
► Alzheimer's Disease
► Delirium Tremens
► L-DOPA
► Lewy Body Dementia
► Parkinson's Disease

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Hallucinogen

► Hallucinogen Abuse and Dependence

Hallucinogen Abuse

Definition

Describes a rare maladaptive pattern of hallucinogen use despite evidence and knowledge of harm as a result of this substance use.

Hallucinogen Abuse and Dependence

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Definition

► Hallucinogen abuse and dependence are known complications resulting from the illicit use of drugs in this category, such as LSD and psilocybin. Users do not experience withdrawal symptoms, but the general criteria for ► substance abuse and ► dependence otherwise apply. Dependence is estimated in approximately 2% of recent-onset users in the United States. Acute hallucinogen intoxication may induce a plethora of physical and psychological effects that can become so overwhelming to the user as to result in seeking emergency psychiatric care. Providing supportive psychotherapy usually proves effective, though sometimes the use of a sedative hypnotic for anxiety is indicated in addition. No randomized controlled trials have examined treatments of hallucinogen abuse or dependence, but standard treatments (motivational interviewing, relapse prevention, outpatient counseling, participation in self-help groups, family therapy) should still be offered.

Role of Pharmacotherapy

Both hallucinogen abuse and ► hallucinogen dependence are characterized by patterns of compulsive and repeated drug use despite the knowledge of significant harm caused by the activity. However, it is important to point out that hallucinogen use very rarely leads to the development of classic dependence syndromes, such as those seen with opiates or alcohol. As a class, the ► hallucinogens lack significant direct effect on the dopamine-mediated reward system, and studies to date have failed to train animals to ► self-administer these compounds as is typical for dependence-inducing drugs (Nichols 2004). In contrast to the users of other substances of abuse, hallucinogen users do not experience withdrawal symptoms and, therefore, this trait is not a criterion for diagnosing hallucinogen dependence. It should also be noted that, in general, ► tolerance rapidly increases when hallucinogens are used frequently, and exponentially so with daily use.

Overall rates of abuse and dependence are thought to be low when compared with other substances (Wright et al. 2007). In the USA, hallucinogen dependence has been estimated in 2% of recent-onset users (first use within 24 months of survey) and 5% of past-onset users (first use 24+ months, last use within 12 months), with a relative risk of dependence apparently greater in users with very early age of onset of hallucinogen use (10–11 years old) (Stone et al. 2007). These figures are likely to be an overestimate, as the survey included the non-hallucinogenic structured amphetamine ► methylenedioxymethamphetamine (► MDMA) (that does have entactogenic properties) and the ► dissociative anesthetic PCP within their definition of hallucinogen.

Similar to other substances of abuse, hallucinogens may induce specific, related disorders. These include hallucinogen intoxication, hallucinogen-induced psychotic, mood, anxiety, delirium, or not otherwise specified (NOS) disorder, and the very rare ► hallucinogen persisting perceptual disorder (HPPD). These disorders arise in the context of substance use and may manifest during intoxication, after the acute effects have subsided, or in the days that follow (APA 2000). The diagnosis of a hallucinogen-induced psychotic, mood, anxiety, or delirium disorder is made only if the symptoms are in excess of what is expected from intoxication (APA 2000).

Symptoms, Diagnosis, and Treatment

Hallucinogen ingestion is the central component of hallucinogen abuse and hallucinogen dependence. It is therefore necessary to first discuss the effects, evaluation, and treatment of patients suffering from acute pathological cases of hallucinogen intoxication.

Physical and Psychological Effects of Acute Hallucinogen Intoxication

The typical syndrome of psychological alterations associated with the ingestion of hallucinogens, commonly referred to as "tripping," may induce a wide variety of emotional, cognitive, and behavioral effects (Table 1) (Hollister 1984). The visual components are typically not true hallucinations but illusions, such as the perception of geometric patterns or scenic dream-like visions appearing before closed eyes, perception of movement in stationary objects, and ► synesthesias. Content of visual and most emotional phenomena typically reflect the psychodynamics of the user (Leuner 1962). Colors may appear intensified, and altered human and animal forms may appear in the visual field. Hallucinogens activate affectivity and may cause significant changes in mood, where users may change from euphoria to depression or anxiety or vice versa. In some cases, psychotic-like reactions may also be experienced. In short, the psychological effects of hallucinogens are highly variable and strongly influenced by both the individual's mind-set (► expectancies and their influence on drug effects), and their physical surroundings and social setting. Toxicity of LSD, psilocybin, and other classical hallucinogens is very low (see Passie et al. 2008). Overdosing is possible with respect to psychological reactions, but no case of lethal overdose is known, and there is no evidence of long-term neurocognitive toxicity (► neurotoxicity) (Halpern and Pope 1999).

Diagnosis of Acute Hallucinogen Intoxication

Patients present for treatment most often because they experience a panic or depressive reaction, commonly referred to as a "bad trip." Such reactions can begin any time

Hallucinogen Abuse and Dependence. Table 1. Hallucinogen[a] intoxication may include a cluster of the following.

Physical effects[b]	Psychological effects
Typical (mild to very mild): Tachycardia Cardiac palpitation Hypertension or hypotension Diaphoresis Hyperthermia Motor incoordination Tremor Hyperreflexia Altered neuroendocrine functioning	Typical: Intensification and lability of affect with euphoria, anxiety, depression and/or cathartic expressions Dream-like state Sensory activation with illusion, ► pseudo-hallucination, hallucination, and/or synesthesia Altered experience of time and space Altered body image Increased suggestibility Lassitude/indifference/detachment Acute cognitive alterations with loosening of association, inability for goal-directed thinking, and memory disturbance
Typical (mild to strong): Mydriasis Arousal Insomnia	"Positive": Sense of perceiving deeper layers of the world, oneself, and others ("consciousness expansion") Mystical experience Sense of profound discovery/healing (See ► ritual uses of psychoactive drugs)
Occasional: Nausea Vomiting Diarrhea Blurred vision Nystagmus Piloerection Salivation	"Negative": Psychosomatic complaint Impaired judgment Derealization Depersonalization Megalomania Impulsivity Odd behavior Paranoid ideation Suicidal ideation

[a]Indolealkylamine and phenylalkylamine hallucinogens only

[b]Some effects are reactionary to psychological content (e.g., increased heart rate and nausea due to anxiety), and complaints can be dependent on factors such as mindset, setting, dose, and supervision. Intoxicated individuals may also deny physical impairment or claim increased energy, sharpened mental acuity, and improved sensory perception

after the onset of effects and may include fears of "going insane" (Strassman 1984). There may also be paranoid ideation, feelings of being manipulated, or being in a situation without any escape. The acute syndrome of hallucinogen intoxication should be suspected when a patient (or companion) reports recent ingestion of a hallucinogen, and presents with a characteristic constellation of sympathomimetic findings with a clear sensorium (unlike NMDA antagonist dissociative anesthetics like PCP that induce a clouding of consciousness). Since laboratory testing is generally not available in most acute settings, obtaining an accurate history and clinical examination is critical in establishing the diagnosis. Street drugs often contain various adulterants; therefore, the actual identity of the ingested substance may not be known. However, the hallucinogens typically produce similar effects, which should be carefully assessed. Signs and symptoms of hallucinogen intoxication are reviewed in the previous section (see Table 1). Physical examination will also provide important clues that can support the diagnosis of hallucinogen intoxication (in particular, widely dilated pupils that do not rapidly/tightly constrict to accommodate bright light). Hallucinogens have varying duration of action; nevertheless, the acute reaction typically lasts less than 10 h (maximum 12–24 h), and reactions lasting longer will require further investigation to rule out other etiologies.

Treatment of Acute Hallucinogen Intoxication

The "talk down" (more accurately the "talk through") is usually the primary effective intervention indicated in these situations (Taylor et al. 1970). This consists of keeping the patient in a low-stimulus environment (i.e., a quiet space with dimmed lights and minimal distractions) and providing emotional support. Arranging for a reliable sitter (a non-intoxicated companion) to look after the patient is recommended. The sitter can help in keeping the patient calm and oriented by providing a sympathetic presence. In addition, the sitter can also provide reassurance to the patient that the experience is generally non-hazardous, drug-induced, and time-limited, which will resolve with full recovery. The patient should not be left alone until the effects of the drug wear off.

If severe agitation does not respond to redirection and concerns for safety of the patient or others remain, ▶ benzodiazepines are quite effective in reducing anxiety and panic. Many authorities recommend oral ▶ diazepam or ▶ lorazepam, although intramuscular and intravenous routes are more immediately effective. Avoid physical restraints if possible and limit the use of ▶ antipsychotics since paradoxical effects have been reported (Strassman 1984). While no controlled trials have examined the efficacy of antipsychotic drugs for hallucinogen-induced agitation, rare cases may require such an intervention after benzodiazepines have not proven sufficient. However, great caution must be exercised, since ▶ first generation antipsychotics lower the seizure threshold and may also induce hypotension.

Once the acute symptoms subside, patients are usually able to go home accompanied by a companion (Strassman 1984). It is important to advise patients that subsequent ingestion of hallucinogens may precipitate similar reactions. If symptoms persist for longer than 24 h or there are accompanying severe mood or psychotic symptoms that warrant independent clinical attention, hospitalization may be considered.

Gastric lavage should be avoided as it is not effective in removing substances that were usually ingested several hours prior to hospital presentation. Moreover, gastric lavage will invariably worsen the patient's mental state.

Diagnosis of Hallucinogen Abuse and Dependence

Multiple drug use is common; the differential must always contain other substance use or substance-induced disorders. ▶ Alcohol abuse and dependence frequently occurs comorbid to hallucinogen abuse and should therefore also be assessed carefully in this population. ▶ Schizophrenia, schizophreniform, ▶ bipolar, and ▶ schizoaffective disorders must also be ruled out in these patients by assessing the longitudinal course of the symptom constellation and their temporal relation to hallucinogen ingestion.

Treatment of Hallucinogen Abuse and Dependence

There are no ▶ randomized controlled trials that have examined the treatment of hallucinogen abuse or dependence. However, general principles that apply to other substances of abuse should be employed in treating these patients. Motivational interviewing, detoxification, relapse prevention, intensive outpatient counseling, involvement with self-help groups, and family therapies are examples of interventions that need to be individualized for each particular patient.

Since polysubstance abuse and dependence is common, treatment should also target other substance abuse and dependence that are thought to be contributing to the disturbances. Furthermore, treatment should be provided with a dual diagnosis approach, and any underlying psychiatric disorder should be treated concurrently. No controlled trials have been conducted to evaluate the efficacy of pharmacotherapies.

Cross-References

- ▶ Alcohol Abuse and Dependence
- ▶ Antipsychotic Drugs
- ▶ Benzodiazepines
- ▶ Bipolar Disorder
- ▶ Dissociative Anesthetics
- ▶ Expectancies and Their Influence on Drug Effects
- ▶ First-Generation Antipsychotic Drugs
- ▶ Hallucinogens
- ▶ Methylenedioxymethamphetamine (MDMA)
- ▶ Neurotoxicity
- ▶ Randomized Controlled Trial
- ▶ Ritual Uses of Psychoactive Drugs
- ▶ Schizoaffective Disorder
- ▶ Schizophrenia
- ▶ Self-Administration of Drugs

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Hallucinogen Dependence

Definition

Dependence should be considered when a chronic pattern of abuse appears to be out of control, such as using larger amounts than was intended or the inability to cut down the use, and continues despite awareness of social, psychological, or physical harms related to hallucinogen use.

Hallucinogen Intoxication

- ▶ Hallucinogen Abuse and Dependence

Hallucinogen Persisting Perception Disorder

Synonyms

HPPD

Definition

A rare condition in which some sensory element of hallucinogen intoxication is evocatively reexperienced in the days to weeks to months (and rarely years) after intoxication has ceased. Sometimes referred to as "flashbacks," HPPD is diagnosed when clinically significant impairments occur related to the symptoms.

Cross-References

- ▶ Hallucinogen Abuse and Dependence

Hallucinogens

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Synonyms

Entheogens; Psychedelics; Psychotomimetics

Definition

Hallucinogens are drugs that are characterized principally by their ability to produce alterations in perceptual processes. They can effect profound changes in consciousness that involve all of the sensory modalities. At lower doses they produce alterations and distortions in sensory processing, often including ▶ synesthesias, or mixing of the senses, where, as an example, music may be perceived as colorful kaleidoscopic patterns. They produce changes in mood and affect, and can alter perception of time, space, and self in ways that ordinarily occur only during dreaming, or at times of religious exaltation. They increase the intensity and lability of affective responses, and engender a feeling of portentousness, e.g., a sense that the

experience is highly meaningful and momentous. Alterations in consciousness can range from feelings of bliss and a sense of oneness with the universe, to fear, paranoia, and psychotic reactions. Hallucinogens also produce ► cognitive impairments, such as deficits in ► working memory and associative learning, yet leave executive functions largely intact. They also impair high-level motion perception and reduce binocular rivalry rate and rhythmicity. The user's expectations (mind-set) and the environment (setting) fundamentally alter the nature of the experience.

Pharmacological Properties

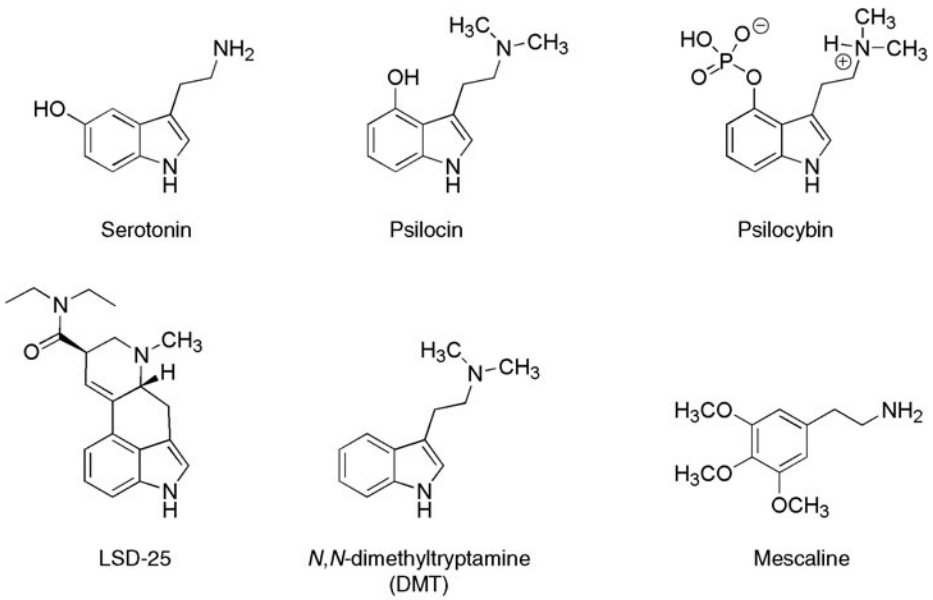
History

For the purposes of this discussion we shall consider hallucinogens to be those compounds, primarily natural or semi-synthetic, that share a common pharmacological mechanism of action and similar human psychopharmacology. This discussion will not cover substances like anticholinergic atropine-like compounds, or glutamate antagonists, which also can produce profound disruptions of consciousness, but have different mechanisms of action and are not generally accepted to have psychopharmacology similar to the classic hallucinogens.

The use of hallucinogens, in the form of natural plant substances and plant decoctions, stretches back into antiquity, with written records indicating the use of these materials in ancient India (e.g., *Soma*), Greece (*kykeon*), and by indigenous Mesoamerican peoples (*peyotl*, *teonanacatl*) (Schultes and Hofmann 1992). As powerful modifiers of consciousness, they were often tools of the shaman, or tribal healer, but also found a place in certain religious rituals and social events. Largely unknown to Western man until the end of the nineteenth century, they were dramatically "rediscovered" in the late twentieth century, becoming popular with college students, artists, and musicians in the 1960s, a phenomenon that ultimately led to strict legal control and proscriptions on their use.

The first "modern" study of a hallucinogen occurred in the late 1890s, when Arthur Heffter, a highly respected German pharmacologist, physician, and chemist, isolated and identified mescaline as the active principle in *peyotl*, the "peyote" cactus (*lophophora williamsii*), used by the Aztecs. A number of books and essays were written in the twentieth century describing the effects of mescaline, and as an outstanding example one might cite Aldous Huxley's 1954 book *The Doors of Perception*.

Chemically, mescaline is the simplest of the hallucinogens (Fig. 1). As noted above, it was originally isolated from the peyote cactus, and is the prototype of the phenethylamine class of hallucinogens, i.e., a substituted



Hallucinogens. Fig. 1. The structures of the natural neurotransmitter serotonin, and the hallucinogens, psilocin, psilocybin, LSD-25, DMT, and mescaline. The chemical similarity between serotonin, psilocin, and LSD is the underlying basis for the interaction between tryptamines and serotonin receptors.

phenyl ring separated by two carbon atoms from a basic amino group.

The second major class of hallucinogens is comprised of the ► tryptamines, represented by DMT and psilocybin, also shown in Fig. 1. The natural neurotransmitter ► serotonin is a tryptamine, and is shown for comparison. Although structurally more complex, close examination reveals that LSD (LSD-25) also contains a tryptamine fragment within its structure; thus it can be considered to be a special case of a tryptamine.

Popularity of these substances began to increase dramatically in the early 1960s, when LSD became easily available and inexpensive. This story began in 1943, when Swiss natural product chemist Albert Hofmann, working at the Sandoz laboratories in Basel, Switzerland, accidentally discovered the very powerful hallucinogenic effects of a semi-synthetic ► ergot derivative he had first prepared in 1938. This substance, lysergic acid-*N*, *N*-diethylamide, became known as LSD (or LSD-25), or simply "acid." The extremely potent effects of LSD were manifest following oral doses as low as 25–50 μg. Sandoz initially made LSD available to psychologists and clinical investigators in the belief that it produced a model psychosis, so that psychiatrists might gain insight into the nature of mental illness, although it is now recognized that the effects of LSD have distinct differences from the symptoms of ► schizophrenia.

It should be noted that the discovery of LSD preceded only by a few years the isolation and identification of the neurotransmitter ► serotonin from gut tissue, and its subsequent detection in mammalian brain. It was quickly observed that LSD incorporated a tryptamine moiety in its structure, which also was the essential core template of serotonin itself. The relative temporal conjunction of these two events catalyzed an intense research focus on the role of serotonin in the brain and its involvement in brain functioning. That interest by the neuroscience community continues to the present time and has led to several new types of therapeutics, including the SSRI class of ► antidepressants, and treatments for migraine headache, among others. It is rarely appreciated that the discovery of LSD had such a direct and profound effect on the neurosciences.

Following his discovery of LSD, Dr. Albert Hofmann then studied a number of natural plant materials that were employed in religious rituals by South American Indians. The first of these was the mushroom *Psilocybe Mexicana* ("teonanacatl," or flesh of the gods), which had been used by the Aztecs. He was able to isolate and characterize the active principle, a substituted tryptamine derivative that he named psilocybin. A minor product in this mushroom is the non-phosphorylated molecule, known as psilocin. It is now known that psilocybin is hydrolyzed by phosphatases after ingestion, and that psilocin is the active hallucinogenic substance.

Dr. Hofmann then proceeded to isolate and identify the active principle in *Ololuiqui*, obtained from the seeds of a species of morning glory also employed by the Aztecs. In that case the active substance surprisingly proved to be lysergic acid amide, a molecule chemically very closely related to LSD.

These substances largely remained academic curiosities until the 1960s, when Harvard psychology professor Timothy Leary began to promote and encourage the widespread use of LSD, particularly among the college age population with his mantra, "turn on, tune in, drop out." A strong governmental and law enforcement response resulted, and interest in these substances among scientists and clinicians fell off for many decades as a result of increased restrictions on their availability and use, as well as a sort of widespread social taboo that discouraged their further exploration. In addition, government funding agencies were no longer interested in supporting work on these substances unless it was related to understanding their abuse properties. These factors all came into a confluence that stifled research on hallucinogens for nearly four decades. Fortunately, that situation has slowly begun to improve, and there are now several clinical studies underway in the USA and elsewhere that are assessing the medical value of hallucinogens in carefully controlled settings.

Mechanisms of Action

Very early animal studies of LSD demonstrated that it markedly affected brain serotonin systems. Indeed, the fact that LSD incorporated a tryptamine fragment within its structure reinforced early experimental results indicating an effect on brain serotonin systems. There was much initial debate as to whether LSD "blocked" serotonin systems, or enhanced the activity of serotonin systems, and it took about 30 years before a consensus emerged that LSD, and other hallucinogens, acted as agonists or partial agonists at serotonin receptors. At the present time there is a scientific consensus that hallucinogens have, as their primary site of action, agonist activity at cortical serotonin receptors of the 5-HT_{2A} subtype (Nichols 2004). Although numerous animal behavioral studies had strongly supported that conclusion, the definitive study was carried out by Franz Vollenweider, where pre-administration of the serotonin ► 5-HT2A receptor

antagonist ketanserin was able to block the hallucinogenic effects of psilocybin in man (Vollenweider et al. 1998). ► PET studies also have demonstrated that hallucinogens produce a global increase in rate of cerebral glucose metabolism with significant and most marked increases in the frontomedial and frontolateral cortex, temporomedial and anterior cingulate cortex, and a somewhat lesser response in the basal ganglia.

Although the 5-HT_{2A} receptor appears to be the essential target for hallucinogens, it may not provide the entire explanation for their pharmacology. That is, activation of this receptor may be a necessary, but not sufficient action to understand all of their effects. For example, the phenethylamine-type of hallucinogens have nearly comparable affinity and efficacy at both the 5-HT_{2A} and 5-HT_{2C} receptor types, and there has been no drug available that is a specific agonist only for the 5-HT_{2A} receptor. The tryptamines and LSD present a similar pharmacological profile with respect to these two receptor subtypes, but in addition also have high affinity and efficacy at the serotonin 5-HT_{1A} receptor subtype. Activation of this receptor in the brainstem raphe nuclei suppresses their firing, which would have profound consequences for serotonin tone throughout the brain. These receptors also are expressed at high density in regions of the limbic system, and one would expect activation of the receptors in these brain areas also to have behavioral consequences. Nevertheless, a contribution of the 5-HT_{1A} receptor to the psychopharmacology of tryptamine hallucinogens has not been elucidated.

LSD presents the most complex pharmacology of all of the known hallucinogens, and its effects may not be simply explained by a serotonergic mechanism. In addition to its high affinity and efficacy at the 5-HT_{2A}, 5-HT_{2C}, and 5-HT_{1A} receptors, it acts at a variety of additional serotonin receptors. It also has activity at alpha-2 adrenergic receptors, as well as dopamine receptors, particularly the D_2-like family of dopamine receptors. It is presently unclear, how, or if, any of these other interactions might account for the unique psychopharmacology and potency of LSD.

Interestingly, the pioneer LSD researcher Dr. Daniel X. Freedman described the psychopharmacological effects of LSD in man as occurring in two temporal phases. The initial phase was considered psychedelic and euphoric, whereas after this initial phase, the effects of LSD in many subjects resembled paranoid psychosis, with ideas of reference and paranoid ideation. Temporally dependent pharmacology has not been reported for any of the other hallucinogens. Recent studies in rats have shown that the effects of LSD in rats also occur in two temporal phases. Nevertheless, there is good evidence that LSD does activate brain dopamine systems, and this action of LSD may be relevant to its human psychopharmacology (Marona-Lewicka et al. 2008). In particular, there is some evidence that the dopamine D4 receptor may play a role in the action of LSD, at least in rat behavior models (Marona-Lewicka et al. 2008).

Recent studies also have pointed to a role of ► glutamate in the action of hallucinogens. Administration of hallucinogens to rats or mice leads to increased extracellular levels of glutamate (Benneyworth et al. 2007).

Animal Models

The most useful and widely employed animal model for studying hallucinogens is the ► drug discrimination paradigm, an operant procedure that has been used in rats, mice, monkeys and pigeons. This method is very sensitive, so that doses of drugs can be used that do not produce overt behavioral effects. Typically, rats (or mice) are trained in a two-lever operant chamber using positive reinforcement, to discriminate between injections of saline and a particular drug, such as LSD. Animals are taught to associate one lever with the saline injection, and the other with the injection of the "training drug," e.g., LSD. Emitting a response on the appropriate lever results in reinforcement. Over a period of 2–3 months rats reliably learn this discrimination task so that administration of either saline or the drug results in a preponderance of lever pressing responses only on the lever associated with that treatment condition. Various treatments can then be employed in attempts to antagonize the response, or drugs can be administered that are thought to have a similar pharmacology, so that conclusions can be drawn about the mechanism of action. In the absence of human clinical trials, this method has been used to predict whether a novel molecule may have hallucinogenic effects in man.

Hallucinogens do not produce many other behavioral responses in animal models that are particularly useful. They generally do not affect locomotor activity per se, except at high doses, although they may alter patterns of locomotor and exploratory activity in rodents. They are not self-administered, and are not considered to be reinforcing. Hallucinogens do disrupt ► prepulse inhibition (PPI), which is based on the finding that a weak prepulse reduces the startle reflex to a given, usually acoustic, stimulus.

Pharmacokinetics

Most of the hallucinogens are well absorbed. LSD, mescaline, and psilocybin are all active after oral

administration, with effects lasting about 8–10 h for the first two, and 4–6 h for the latter. A number of substituted tryptamines also are orally active. Very few studies of the ► pharmacokinetics of hallucinogens have been reported. Early studies studied the formation and identification of major metabolites, but the work in this area is sparse. The best pharmacokinetic study for a hallucinogen was reported for psilocybin (Hasler et al. 1997).

Efficacy

Up until the early 1960s, LSD was hailed as a powerful new type of technology that had the potential to revolutionize psychiatry. More than 40,000 subjects were administered LSD in studies described in more than a thousand published clinical studies. Sadly, poor clinical designs, poor controls, and inadequate follow-up resulted in data that are, for the most part, useless in assessing the true medical value of hallucinogens. There are certainly hints from case reports, and trends in several studies suggesting possible utility in treating difficult to treat conditions such as alcoholism.

By contrast, the use of LSD to reduce anxiety and improve mood in dying patients is an indication that has been relatively well documented in studies carried out at the Baltimore State Hospital in the late 1960s. Inclusion of LSD in a program that only had a modest amount of counseling gave some degree of benefit in 60–70% of patients, seen as improved mood and a reduced need for pain medication.

More recently, in 2006 it was reported by a team led by Roland Griffiths at Johns Hopkins University that administration of psilocybin to normal volunteers engendered mystical experiences in a large percentage of subjects, with a majority reporting the experience as one of the five most meaningful experiences of their lives (Griffiths et al. 2006). Significant positive personality improvements induced by the experience were maintained at the 14-month follow-up (Griffiths et al. 2008). Another study of the efficacy of psilocybin in treating depression and anxiety in a small number of end-stage cancer patients has just been completed at UCLA Harbor Medical Center, with promising trends obtained.

Safety/Tolerability

From a physiological standpoint, hallucinogens are very safe. Their safety can be understood by the fact that 5-HT_{2A} receptors are not involved in essential vegetative functions. The only deaths associated with the direct actions of these drugs have occurred in a few individuals who had access to relatively large amounts of pure crystalline LSD tartrate. The author argues that it is not possible to become dependent on hallucinogens due to a process called ► tachyphylaxis, or rapid development of ► tolerance. In contrast to drugs that produce dependence and addiction, the repeated use of hallucinogens leads to a loss of their effect within 3 or 4 days, even with increasing dosages.

Conclusion

In summary, hallucinogens are a very old class of psychoactive substance that have profound effects on consciousness. They were important in a variety of social and religious contexts in older cultures. Their targets in the brain are 5-HT_{2A} receptors, which modulate function of cortical cells. They are presently being reinvestigated for potential medical value after a research hiatus of some four decades. In addition, they would seem to be very powerful tools to study consciousness.

Cross-References

► Drug Discrimination
► Emotion and Mood
► Hallucinogen Abuse and Dependence
► Methylenedioxymethamphetamine (MDMA)
► Ritual Uses of Psychoactive Drugs

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Haloperidol

Definition
Antipsychotic drug of the older, first generation category (mainly dopamine D2 receptor blocker/antagonist).

Haloxazepam

► Benzodiazepines

Haloxazolam

Definition
Haloxazolam is a benzodiazepine derivative with hypnotic properties similar to those of the benzodiazepines triazolam and flunitrazepam.

Cross-References
► Anxiolytic
► Benzodiazepines
► Hypnotic

Hamilton Rating Scale for Anxiety, HAMA

Definition
A 14-item observer-rated scale designed to assess the severity of psychological and somatic symptoms in patients with anxiety disorders. Some items are rather insensitive to change, and this has encouraged the development of shorter and more sensitive scales, but the HAMA is still regarded by many as the "gold standard" for assessing efficacy of treatment in randomized placebo-controlled studies.

Haploid Genotype

► Haplotype

Haplotype

Synonyms
Haploid genotype

Definition
Haplotype is a set of single-nucleotide polymorphisms (SNPs) on a single chromatid that are statistically associated on one chromosome or a part of a chromosome (i.e., one set of alleles of linked genes).

Cross-References
► Gene Expression and Transcription
► Pharmacogenetics
► Pharmacogenomics
► Single-Nucleotide Polymorphism

HATs

► Histone Acetyltransferases

HD

► Huntington's Disease

HDACs

► Histone Deacetylase

HDACs Inhibitors

► Histone Deacetylase Inhibitors

Health Anxiety

► Somatoform and Body Dysmorphic Disorders

Hedonic Reactions

► Taste Reactivity Test

Heightened Illness Concern

► Somatoform and Body Dysmorphic Disorders

Hematoencephalic Barrier

► Blood–Brain Barrier

Hemostasis

Definition

Hemostasis is a complex process that causes bleeding to stop. Usually, this includes the changing of blood from a fluid to a solid state, by the formation of a blood clot (thrombus). Intact blood vessels and platelets are central to modulate blood's tendency to clot; the disruption of the correct balance between the involved regulators may result in different diseases. In physiology, the process of thrombus formation starts when damage to the endothelium of blood vessels occurs.

Hepatotoxicity

Synonyms

Liver toxicity

Definition

Hepatotoxicity in pharmacology refers to chemically driven liver damage.

Herbal

► Herbal Medicinal Product

Herbal Ecstasy

Definition

Herbal ecstasy tablets, legally sold in many countries, usually contain the sympathomimetic herb Ephedra (*Ma Huang*) rather than the drug Ecstasy (MDMA).

Cross-References

► Entactogen
► Methylenedioxymethamphetamine (MDMA)

Herbal Medicinal Product

Synonyms

Herbal; Herbal medicine; Herbal remedy

Definition

Any medicinal product, exclusively containing as active ingredients one or more herbal substances or one or more herbal preparations, or one or more such herbal substances in combination with one or more such herbal preparations.

Herbal Medicine

► Herbal Medicinal Product

Herbal Remedies

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Synonyms

Medical herbalism; Phytotherapy

Definition

Herbal medicines are increasingly popular. It is therefore relevant to evaluate their efficacy, safety, quality, and cost. Numerous clinical trials have tested the efficacy of herbal medicines, and several systematic reviews of these data are now available. They demonstrate that, for a relatively small minority of herbal medicines, efficacy is well established; for others, it is likely, but the vast majority has not yet been adequately tested. Herbal medicines are associated with complex safety issues. They are related to adverse effects of herbal ingredients, interactions with conventional drugs, contamination and adulteration of herbal preparations, and misidentification of herbs within herbal mixtures. In most countries, herbal medicines are marketed as (largely unregulated) dietary supplements, and the quality of some has been shown to be suboptimal.

Economic analyses of herbal medicines would be desirable, but are currently scarce. Thus, it is uncertain whether their use saves or costs extra money. It is concluded that each herbal medicine should be judged on its own merits on the basis of the evidence from rigorous investigations. Where such data are currently not available, we cannot make assumptions but should initiate research to fill the sizable gaps in our present knowledge.

Pharmacological Properties

Introduction

Many of today's synthetic drugs originated from the plant kingdom, and only 200 years ago, our pharmacopeia was dominated by herbal medicines. Medical herbalism (i.e., the medicinal use of preparations that contain exclusively plant material) went into rapid decline when pharmacology established itself as a leading branch of therapeutics. In much of the English-speaking world, herbalism virtually vanished from the therapeutic map during the last part of the 19th century and early part of the 20th century. In contrast, many developing countries never abandoned medical herbalism (e.g., Ayurvedic medicine in India, Kampo medicine in Japan, and Chinese herbalism in China), and in other countries (e.g., Germany and France), medical herbalism continued to co-exist with modern pharmacology, albeit on an increasingly lower key.

In recent years, this situation has started to change again. Herbal medicine is most commonly employed for allergies, insomnia, respiratory problems, and digestive problems. The total out-of-pocket expenditure amounted to $5.1 billion in 1997, and the total number of herbal medicines currently available in the USA has been estimated to exceed 20,000.

Herbal medicines usually contain a range of pharmacologically active compounds; in some cases, we do not even know which constituents are (the most) important for the therapeutic effect. This situation can render efficacy testing more complex than with synthetic drugs. One approach is to view the entire herbal extract as the active principle. To optimize the reproducibility of such studies, extracts need to be sufficiently characterized. This is often achieved through standardization based on a key constituent of the extract (e.g., a pharmacologically active ingredient or, if such an ingredient is not known, a marker substance). Adequate product characterization and quality control are essential for the reproducibility of scientific tests of herbal remedies.

If these rules are observed, clinical trials of herbal medicines are feasible much in the same way as for other drugs. Numerous randomized clinical trials of herbal medicines have been published and systematic reviews/meta-analyses of these studies have become available (Barnes et al. 1998). Table 1 provides examples of such papers. Their conclusions are often limited by the varied methodological quality of the primary studies. High-quality trials are, of course, expensive and research funds in this area are generally scarce, not least because plants are not patentable.

Generalizations about the efficacy of herbal medicines are not possible. Each herbal medicine has to be judged on its own merits; some have been demonstrated to be efficacious for certain indications, others may not be efficacious and by far, most of them have not been submitted to extensive clinical testing (Barnes et al. 1998).

Efficacy of Traditional Herbalism

The use of an extract of a single plant to treat one conditions (e.g., St. John's wort for ▶ depression) is dramatically different from what actually happens when patients consult herbal practitioners. These clinicians, regardless of which tradition they may subscribe to (e.g., traditional Chinese herbalist or herbalist in the European tradition) would investigate their patients according to the criteria of their tradition and subsequently prescribe a mixture of herbs that is "tailor-made" for their constitution and individual set of symptoms. Thus, 10 patients with depression might receive 10 different herbal mixtures, which may or may not contain St. John's wort.

This individualized form of prescribing is more difficult to submit to rigorous scientific testing, but such investigations are undoubtedly possible. To date, only very few randomized clinical trials of this type of herbalism have been published. Those that are available have recently been reviewed. The results demonstrated that there is currently no good evidence to suggest that individualized herbalism is efficacious (Canter et al. 2005).

Safety

Consumers are attracted to herbal medicines not least because they equate "natural" with "safe" (Barnes et al. 1998). Yet some herbal medicines are associated with serious risks (Carlo et al. 2001). These risks relate to a range of circumstances.

First, the active principles in herbal medicines can, of course, cause desirable as well as undesirable effects. Table 2 lists examples of commonly used herbal medicines that have been associated with serious adverse effects (Barnes et al. 1998). Traditional use does not guarantee for safety and is not an acceptable substitute for data. A poignant example is kava (*Piper methysticum*), a herbal remedy that has been used for centuries apparently without problems. During the last decades, it was shown to be a powerful

Herbal Remedies. Table 1. Examples of systematic reviews and meta-analysis of herbal remedies.

Common (Latin) name	Pharmacologically active ingredients [1]	Indications	Number of trials included(total sample size)	Average methodological quality of primary studies	Efficacy	Main result	Reference
Feverfew (*Tanacetum parthenium*)[2]	Parthenolide	Migraine prevention	5	Good	Likely	3 trials were positive, 2 were negative	Vogler (1998)
Garlic (*Allium sativum*)[3]	Alliin	Hypercholesterolemia	13	Good(some excellent)	certain but effect small	Overall effect is significant but of debatable clinical relevance	Stevinson (2000)
Ginkgo (*Ginkgo biloba*)[3]	Ginkgolides, bilobalide	Intermittent claudication	8	Good to excellent	certain	Overall positive result	Pittler (2000)
Horse chestnut seed extract(*Aesculus hippocastanum*)[2]	Triterpene saponins	Chronic venous insufficiency	8 trials vs placebo; 5 trials vs reference treatments	Good	Likely	Active treatment more effective than placebo and equally effective as reference treatments	Pittler (1998a)
Peppermint oil (Menta x piperial)[3]	Menthol	Symptoms of irritable bowel syndrome	8	Good	Likely	Positive effect of peppermint oil compared with placebo	Pittler (1998b)

[1]examples
[2]narrative systematic review without statistical polling of results
[3]meta-analysis

Herbal Remedies. Table 2. Examples of herbal medicines associated with serious risks.

Common (Latin) name	Indication	Adverse effects (examples)
Aloe vera (*Aloe barbadensis*)	Various	Juice may cause intestinal pain and electrolyte loss
Feverfew (*Tanacetum parthenium*)	Migraine prevention	"Post-fever syndrome" after discontinuation (migraine, anxiety, insomnia, muscle stiffness)
Hawthorn (*Crataegus*)	Congestive heart failure	Additive effects with other cardiac glycosides
Kava (*Piper methysticum*)	Anxiety	Toxic liver damage
St. John's wort (*Hypericum perforatum*)	Depression	Increased clearance of a range of prescribed drugs
Tea tree oil (*Malaleuca alternifolia*)	Skin problems (external)	Allergic reactions
Valerian (*Valeriana officinalis*)	Insomnia	Morning hangover

► anxiolytic medicine in rigorous clinical trials (Barnes et al. 1998). Recently, it has been associated with several cases of serious liver damage. Hence, it has been withdrawn from the markets of several European countries.

Second, the active principles in herbal medicines might interact with prescription drugs. A classic example of this scenario is provided by St. John's wort (*Hypericum perforatum*). One or several constituents of St. John's wort (most likely hypericin) act as an enzyme inducer on the ► cytochrome P450 system and increase the activity of the P-glycoprotein transmembrane transporter mechanism. Both mechanisms lead to a reduction of the plasma level of several conventional drugs (De Smet PAGM 2002). This can lead to a range of serious adverse effects.

Third, some herbal medicines (particularly Asian herbal mixtures) have been demonstrated repeatedly to be contaminated with heavy metals or adulterated, e.g., with prescription drugs. Because, in many countries (e.g., the USA and UK), most herbal medicines continue to be marketed as dietary supplements, their quality is not adequately controlled and suboptimal quality may put consumers at risk.

Finally, substitutions of one (innocent) herb from a herbal mixture with a toxic herb may occur either inadvertently or fraudulently. A famous example of such a scenario was the introduction of *Aristolochia* into a Chinese herbal mixture used for body weight reduction. This caused serious kidney damage and subsequent malignancies in many Belgian consumers (Ernst 2002).

Because positive safety data are usually not available, herbal remedies should be viewed as contra-indicated during pregnancy and lactation (Barnes et al. 1998). Our present post-marketing surveillance systems are likely to register only a minute proportion of all the adverse effects of herbal medicines. Consumers are less prone to report adverse effects of herbal medicines than those of other OTC medications (Ernst et al. 2006). As herbal medicines become more and more popular, we should find better ways of minimizing the risks that may be associated with them.

Quality

Commercially available herbal products have repeatedly been found to be of varying and at times suboptimal quality (Guo et al. 2007). As pointed out earlier, poor quality can cause harm, for instance, in the case of contamination with toxic substances. Any clinical trial of insufficient herbal product would generate a negative result, even if the herb tested is *per se* efficacious.

In most countries, herbal medicines are marketed as dietary supplements with no need to demonstrate efficacy, safety, or quality in the way of licensed medicines. Thus, many products available to patients may be of inadequate quality, for example, they may be underdosed. For consumers, it is notoriously difficult to identify products of high quality. Table 3 lists some manufacturers known for their experience, quality, and investment into research.

Cost

Very few economic analyses of complementary/alternative medicines exist. The few that have been published are methodologically weak and, therefore, far from convincing.

Herbal Remedies. Table 3. Examples of manufacturers who market high-quality standardized products and invest in research.

Name of the company	Country	Main herbal medicine
Bionorica	Germany	Sinupret[1]
Lichtwer	Germany	Garlic
Madaus	Germany	Echinacea
Pharmaton	Switzerland	Ginseng
Schwabe	Germany	Ginkgo biloba

[1]herbal mixture

Interestingly, retrospective analyses tend to suggest that complementary/alternative medicine can reduce costs, whereas (the more rigorous) prospective analyses tend to imply that the use of complementary/alternative medicine is associated with an increase in cost (Nortier and Muniz Martinez 2000). The situation with herbal medicines is much the same as with other complementary/alternative medicines.

Comment

Investigations of the efficacy, safety, quality, and cost of herbal medicines are feasible and, vis-à-vis, the popularity of such preparations is highly desirable. For some, but by no means all herbal medicines, efficacy data are now emerging (Barnes et al. 1998). They show that some herbal medicines are efficacious for certain indications. All herbal medicines are associated with safety issues which, in some instances, can be complex. Economic evaluations of herbal medicines are still extremely scarce.

Research into herbal medicines is much less active than research into conventional drugs. Lack of commercial impetus, owing to lack of patent protection, is one obvious reason. The legal status of herbal medicines might be another: as for dietary supplements, there is no formal obligation to prove efficacy. If we want to find the answers for many open questions in herbal medicine, we should consider other means of finding adequate funds for research in this area.

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Herbal Remedy

► Herbal Medicinal Product

Heritability

Definition

The proportion of variance in a particular phenotype that is attributable to genetic, as opposed to environmental, factors.

Heroin

► Diamorphine

Heroin Addiction

► Opioid Dependence and Its Treatment

Hetero-Oligomers

Definition

Functional protein complexes formed by oligomerization of similar subunits. Functional opioid receptors and many other GPCRs are almost certainly formed from multiple identical (hom-oligomers) or closely related (e.g., MOR and DOR subunits can form a single functional receptor) receptor proteins. Hetero-oligomeric receptors may have pharmacological properties that are distinct from either of the subunits that make them up.

Heterosynaptic

Definition

When neural activity involving one of a neuron's synapse or synapses causes the strength of another neuron's synapse or synapses to change.

High Performance Liquid Chromatography

► High Pressure Liquid Chromatography

High Pressure Liquid Chromatography

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Synonyms

High performance liquid chromatography; HPLC

Definition

High pressure liquid chromatography (HPLC) is a means of separating constituent chemical compounds in a mixed solution in a chromatographic column. They can then be purified (preparative HPLC) or identified and quantified (analytical HPLC).

Principles and Role in Psychopharmacology

In the context of psychopharmacology the most common application of HPLC is analytical: that is for identifying and quantifying endogenous chemicals in brain perfusates in vivo (e.g., from ► microdialysis), in vitro (e.g., from brain slices) and in post mortem tissue. Compounds normally measured include endogenous neurotransmitters, synthesis and metabolic products, and exogenously applied chemicals, such as drugs. It can also be used to measure these compounds in blood, as indirect indicators of brain levels, and to measure the pharmacokinetic and pharmacodynamic profile of drug action.

Principles

There are two principle stages in HPLC analysis: separation, in which the sample is resolved into its constituent compounds; and detection, where these compounds are identified and quantified.

The sample to be analyzed is introduced into the mobile phase, which is continuously pumped through the ► analytical column under high pressure, without disrupting the flow or changing the pressure. This is achieved using a high pressure switching valve which may be a manual valve, where the experimenter "injects" each individual sample into the fluid stream, or it may be an autoinjector, where the valve is incorporated in an autosampler, such that batches of samples can be injected without the need for the experimenter to be present. The latter approach has advantages where large numbers of samples are to be analysed, but can have disadvantages in the amount of sample required to make an injection. If using an autoinjector, it is wise to include a chilled sample tray, to reduce degradation of the sample while waiting to be injected.

Chromatographic Separation

Separation is achieved in the analytical column and is dependent on the interaction of the constituent components in the sample with the mobile and stationary phases, which can be manipulated using different choices of solvents and column packing. These interactions are dependent on the size, the ionization, the polarity and the sterioisometry of the molecule (see Table 1).

Of these methods, reverse phase partition HPLC (RP-HPLC) is the most common HPLC method used in psychopharmacology, primarily due to its versatility and its relative ease of use. In RP-HPLC, separation is achieved by a partition of the compounds in the sample between the hydrophobic (non-polar) stationary phase and the hydrophilic (polar) mobile phase, and is dependant on a compound's relative affinity for each: this in turn is dependent on the hydrophobic/hydrophilic nature of the compound itself. Generally, compounds that are more hydrophilic, and so more similar to the mobile phase,

High Pressure Liquid Chromatography. Table 1. The main categories of separation types used for preparative or analytical HPLC.

Type	Mechanism	Uses
Adsorption	Separation based on differences between adsorption affinities of the sample components for the surface of the stationary phase (often alumina).	Mainly used for preparative or purification HPLC.
Partition	Separation based on the differences between the solubility of components in the mobile and stationary phases. There are two distinct types of partition. chromatography:	Reverse phase chromatography widely used for separating many different classes of chemical compounds. It is the most versatile and widely used analytical HPLC technique.
	Normal phase – partition between a polar stationary phase and a non-polar mobile phase	
	Reverse phase – partition between a non-polar stationary phase and a polar mobile phase	
Ion exchange	Separation based on differences between ionic charge of sample components. A charged stationary phase attracts molecules of opposite charge, which are retained on the column. These are then eluted off the column by introducing another ion of similar charge. Either anion or cation exchange columns can be used depending on the charge of the compound to be separated.	Mainly used for preparative and purification HPLC. Principles of ion-pair chromatography can be incorporated into reverse phase chromatography, by the use of ion-pairing agents.
Molecular exclusion	Separation based on the hydrodynamic volume of the molecule to be separated, relative to the pores in the non-adsorbing stationary phase.	Mainly used for purification.
Affinity	Separation based on the unique and highly specific biological interaction between the analyte and a ligand (e.g. enzyme-substrate interaction; antigen-antibody interaction).	Mainly used for purification: for example nucleic acid purification, protein purification, antibody purification.
Chiral	Stereoisomers separated by using chiral phases.	Separation of stereoisomers of a compound.

will pass through the column more quickly that those which are more hydrophobic, and so more like the stationary phase.

The mobile phase in PR-HPLC is based on an aqueous (polar) solution, typically also containing a proportion of an organic solvent (e.g., methanol or acetonitrile). The organic content of the mobile phase is an important determinant of retention in the column. Retention will be greater (i.e., longer retention times) when mobile phases of low organic content are used, while higher organic content will result in less retention in the column, and shorter retention times.

In RP-HPLC, a major factor in determining the retention of a compound in the column, is the ionization of the compound, since the more polar a compound is, the less it will be retained in the column, and so the more quickly it will pass through. Therefore, the degree of ionization of analytes will have a major impact on the speed they pass through the column, and thus the pH at which the chromatography is carried out is a crucial factor in determining the separation. At low pH, acidic molecules will be essentially unionized, and so will be retained, while basic molecules will essentially be ionized and will pass through the column quickly. At high pH, the opposite will be true: unionized basic molecules will be retained, and charged acidic molecules will not.

Ion-pair HPLC may be seen as a hybrid of RP-HPLC and ion-exchange HPLC. An ion pairing agent, a molecule with one non-polar terminal, which binds to the stationary phase, and a polar (ionized) terminal which is in contact with the mobile phase, is used. The principle effect of the ion pairing agent is to increase the retention in the column of compounds in the sample with an ionic charge opposite to that of the ion pair (since opposite charges attract): it may also have a small effect of decreasing the retention of similarly charges molecules, although the effect is minimal, and is of little use in changing separation characteristics.

From this it can be seen that adjusting the pH, and the use of ion-pairing agents have differential effects on the retention times (that is they have different effects on different compounds), whereas changing the organic content of the mobile phase, affects the retention of all compounds in an indiscriminate manner.

For many separations, it is adequate to use an isocratic buffer system: that is continuous perfusion with a single buffer. One drawback with this approach is that, in order to achieve good separation of compounds which elute more quickly from the column, those which elute more slowly are often retained for an unacceptably long time. This has two adverse effects: first, it can make the run time excessively long and therefore reduce the throughput of samples to an unacceptably low level; and second, the longer the peak is retained on the column, the wider and lower the peak appears, such that small peaks with long retention times may become impossible to measure.

To overcome this problem, gradient elution is often used. For this type of elution the content of the mobile phase changes steadily over the duration of a chromatographic run, such that the strongly retained components of the sample elute more quickly, whilst the separation of the least retained compounds is maintained. The two most common gradient elutions used are a pH gradient (i.e., the pH changes over the duration of the run) or an organic gradient (i.e., the organic content of the buffer changes over the duration of the run). Thus, for example, with an organic gradient, the run starts with a low content of organic component (e.g., methanol) in the mobile phase, allowing good separation of the least retained compounds, while the strongly retained compounds move very slowly through the column. As the organic content of the mobile phase increases in the gradient, these retained compounds move through the column faster, thus giving a more rapid elution than under isocratic conditions. In order to implement a gradient elution, two buffers of different organic content are used, and are mixed automatically in appropriate proportions to create a gradient. With a pH gradient, the same principles hold, but the change in retention is brought about by changing the pH, and thus the degree of ionization of the strongly retained compounds.

In order to achieve stable and reproducible measurements, it is essential to use a high purity mobile phase which has been filtered and degassed, as particulate material in the buffer will block the analytical column. It should be noted that even after filtration, some very fine particulate material may remain in the buffer, and so it is still beneficial to include a ▶ guard column. This is a shorter column, packed with similar stationary phase to the analytical column, which is installed immediately before the analytical column. Its purpose is to protect the analytical column, thus maintaining optimal separation and prolonging its usable life.

Detection

Once separated, the components of the sample must be measured and quantified. There are three main types of detection used in psychopharmacology; ultraviolet (UV) absorption, fluorometric and electrochemical detection. Of these, UV absorption is applicable to the widest variety of compounds, since most organic molecules show at least some degree of absorption of UV radiation. However, since different molecules absorb optimally at different wavelengths, optimizing the wavelength for one compound will mean suboptimal or even zero absorption for other compounds. The use of diode array UV detectors enables simultaneous measurement of UV absorption at different wavelengths, allowing several compounds to be measured simultaneously. Although UV detection is the most versatile, in terms of the number of compounds which can be detected, it has the disadvantage that the signals measured are not always very large, and so it has limited sensitivity. In psychopharmacology, this UV detection is primarily used for measuring drug concentrations, which are typically relatively high, although it can also be used for measuring endogenous neurochemicals under some circumstances.

Some organic molecules have natural luminescence (e.g., tryptophan, serotonin), which can be detected fluorometrically. Absorption of light at specific wavelengths, causes excitation of the molecule and subsequent emission of light at a longer wavelength: this emission is measured in fluorescence spectroscopy. For compounds which exhibit fluorescence, fluorometric detection is 10–1000-fold more sensitive than UV detection. However, individual chemicals have optimal excitation and emission wavelengths, so although measurement at one excitation/emission wavelength combination may be optimized for one molecule, it may completely fail to detect other molecules. While this is appropriate in some applications (see below), for other applications, it is beneficial to use ▶ detectors which switch rapidly between different excitation and emission wavelengths.

Many molecules do not themselves exhibit fluorescence, but can be conjugated to a fluorescent molecule, to create a fluorescent derivative (e.g., amino acids). Although some amino acids do exhibit a degree of innate fluorescence, all amino acids can be conjugated with a fluorescent "tag," for example orthophthalaldehyde (OPA), to produce a fluorescent derivative, which can

then be measured by fluorescence spectroscopy. In this situation, since one is essentially measuring the same fluorescent molecule, albeit "tagging" different amino acids, a single optimal excitation and emission combination is appropriate, and so a fixed wavelength detector is adequate.

Electrochemical detection depends on the redox equilibrium reaction of molecules (e.g., $A \leftrightarrow A^+ + e^-$). Application of a positive potential drives the oxidation reaction, and application of a negative current drives the reduction reaction. In electrochemical detection, a positive potential is applied and the current produced by the oxidation is measured at the working electrode. Although many compounds will oxidize if a high enough potential is applied, only a few oxidize at usable potentials. Notable among these are amine transmitters, such as dopamine, serotonin, and noradrenalin, and many of their metabolites. Most amino acids are not electrochemically active within a useful potential range, but their OPA derivatives (see above) do show electrochemical activity. Therefore it is also possible to use electrochemical detection for amino acids. While this has not been widely used for most amino acids, it is useful for GABA, which has often proved difficult to measure fluorometrically.

Enzymatic Modification

Some neuroactive compounds, notably ► acetylcholine, are difficult to detect using any of these methods. However, enzymatic treatment yields an electrochemically active product, which can be detected. Thus for acetylcholine, an additional column is placed after the analytical column, which has the enzymes acetylcholine esterase and choline oxidase immobilized onto the stationary phase. These enzymes break acetylcholine down, and produce hydrogen peroxide as a bi-product: hydrogen peroxide can be measured with an electrochemical detector. Any choline in the sample will also produce hydrogen peroxide, but can be distinguished from acetylcholine because the two have first been separated chromatographically on the analytical column.

The output from the detector feeds to a recording device, such as a chart recorder, or more commonly, an integrator: changes in current, representing the presence of a detectable entity, are displayed as peaks on a current versus time plot (the chromatogram). The area under the curve of these peaks is proportional to the concentration of the compound, and can be quantified by reference to standards of known concentration, run under identical conditions. Similarly, for a given ► mobile phase and ► stationary phase combination, individual compounds will have a constant retention time, and thus component compounds in a mixture can be identified by comparison with standards.

Thus, HPLC is an extremely versatile technique, and methods can be devised for separation, identification and quantification of a wide variety of chemical compounds. It is widely used in psychopharmacology to measure endogenous compounds, such as neurotransmitters, and metabolites, and exogenous compounds such as drugs, in post mortem brain tissue, in vitro, and in vivo procedures. It can also be used to measure these compounds in CSF and blood, as indicators of brain levels, and to measure the pharmacokinetic and pharmacodynamic profile of drug action.

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Cross-References

► Excitatory Amino Acids and Their Antagonists
► Microdialysis
► Pharmacokinetics
► Trace Amines

High-Speed Chronoamperometry

► Electrochemical Techniques and Advances in Psychopharmacology

Higher-Order Cognitive Processing

► Executive Functions

Hippocampal EEG Domain

► RSA

Hippocampus

Definition

A region of cerebral cortex, lying within the medial temporal lobe adjacent to lateral ventricles and olfactory cortex.

Hippocrateaceae

► Celastraceae

Histamine Receptor Agonists and Antagonists

► Histaminic Agonists and Antagonists

Histaminic Agonists and Antagonists

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Synonyms

Antihistamines; Histamine receptor agonists and antagonists

Definition

Histaminic agonists and antagonists are drugs that mimic or antagonize the actions of histamine at one of its four ► G protein-coupled receptors (H_1–H_4).

Pharmacological Properties

Histamine is a biogenic amine that is widely distributed in the body and is involved in a number of physiological and pathophysiological functions (Hill et al. 1997; Parsons and Ganellin 2006). These include allergic inflammation, cardiovascular regulation, gastric acid secretion, and neuromodulatory functions within the central nervous system (CNS). Histamine is produced by decarboxylation of the amino acid L-histidine and is metabolized by histamine N^{τ}-methyltransferase (HMT) and diaminoxidases. In the case of its neurotransmitter role within the CNS, histamine-containing neurons are characterized by a high level of histidine decarboxylase activity and removal of synaptic histamine is mainly via metabolism (as a consequence of HMT activity). The actions of histamine are mediated by four different G-protein-coupled receptors (Thurmond et al. 2008). These G-protein-coupled receptors have all been cloned and interact with specific heterotrimeric G-proteins to trigger a variety of intracellular processes by altering the levels of intracellular messengers (e.g., cyclic AMP and Ca^{2+} ions) or by influencing the opening of cell surface ion channels.

Histamine H_1-Receptor

The human histamine H_1-receptor was the first of the histamine receptors that was identified and successfully targeted with therapeutically active drugs (i.e., by antihistamines for the treatment of allergic inflammation). It is a 487 amino acid receptor that has the characteristic seven transmembrane spanning domains of a G-protein-coupled receptor. It is characterized by a very large third intracellular loop (208 amino acids; through which it mediates interactions with G-proteins) and a short (17 amino acids) intracellular C terminal tail. The H_1-receptor couples to $G_{q/11}$-G-proteins and mediates responses primarily via the activation of phospholipase Cβ, which hydrolyzes phosphatidylinositol-4,5-bisphosphate into the intracellular second messengers inositol 1,4,5-trisphosphate (IP_3) and diacylglycerol. The water soluble IP_3 then acts on its own ligand-gated ion channel in the endoplasmic reticulum to release intracellular free Ca^{2+} ions, while diacylglycerol is retained in the plasma membrane and can activate various isoforms of protein kinase C. Activation of this receptor has also been shown to affect other signaling pathways including stimulation of phospholipase A2 and stimulation of p42/44 MAP kinase (Hill et al. 1997; Bakker et al. 2004).

Histamine H_1-receptors are found throughout the body. Histamine acting via this receptor is a potent smooth muscle spasmogen (particularly in vascular, airway, and gastrointestinal smooth muscle). In the endothelial cells lining blood vessels, H_1-receptor-stimulation also leads to increased vascular permeability (which generates the classic "weal" response observed in the skin in response to intradermal injection of histamine) and increased synthesis of mediators (prostacyclin and nitric oxide) that can relax vascular smooth muscle. Intradermal injection of histamine also activated H_1-receptors on peripheral sensory nerve endings leading to itching and a surrounding vasodilatation due to an axonal reflex involving release of peptide neurotransmitters from collateral nerve endings. In the brain, H_1-receptors are present in the cerebral cortex, hippocampus, nucleus accumbens, thalamus, and posterior hypothalamus where they predominantly excite neuronal activity (Hill et al. 1997).

H_1-Agonists

Several derivatives of histamine have now been identified, which are more potent as agonists than histamine and are relatively selective for the H_1-receptor. These include 2-(3-(trifluoromethyl)phenyl)-histamine, 2-(3-bromophenyl)-histamine, histaprodifen, and N-methylhistaprodifen. The role of these compounds is, however, restricted to a use as pharmacological tools. Compounds originally developed as drugs for completely different classes of receptors have also been identified as H_1-receptor agonists. For example, the dopamine/serotonin receptor agonist 8R-lisuride is probably the most potent and stereospecific partial agonist for the H_1-receptor yet reported (Bakker et al. 2004).

H_1-Antagonists

Antagonists of the histamine H_1-receptor include mepyramine, chlorpheniramine, ▶ promethazine, triprolidine, diphenhydramine, cyclizine, loratidine, and cetirizine (Hill et al. 1997). All of them have proved useful in the treatment of hay fever, allergic rhinitis, insect bites, and anaphylactic reactions (Thurmond et al. 2008). However, at therapeutic doses, many of the older generations of H_1-antagonists (particularly promethazine, diphenhydramine, mepyramine, etc.) give rise to sedation as a consequence of H_1-receptor antagonism in the brain. More recently, a second generation of nonsedating H_1-antihistamines have been developed, which are much less able to cross the ▶ blood brain barrier. These include temelastine, terfenadine, acrivastine, astemizole, cetirizine, fexofenadine, and loratidine. Cetirizine is one of the antihistamines that exists as stereoisomers and the active levo-isomer is now available for clinical use. Many H_1-receptor antagonists also possess marked muscarinic receptor antagonist properties (e.g., promethazine, diphenhydramine, cyclizine) and this "side-effect" is exploited for the treatment of nausea and motion sickness. Several other classes of drugs, such as the ▶ antidepressants ▶ doxepin and ▶ amitriptyline, are also potent H_1-antihistamines. Interestingly, all of the H_1-antihistamines in current clinical practice are ▶ inverse agonists i.e., they are able to reduce agonist-independent constitutive receptor activity in cells where H_1-receptor-overexpression allows spontaneous receptor-G-protein coupling and functional activity.

Histamine H_2-Receptor

The human histamine H_2-receptor is best known for its ability to stimulate gastric acid secretion and this physiological action underpins the use of H_2-receptor antagonists in the treatment of duodenal and gastric ulcers (Parsons and Ganellin 2006). It is a Gs-coupled receptor that has a short third intracellular loop (30 amino acids) and a much longer C-terminal tail (70 amino acids) than the H_1-receptor. The H_2-receptor stimulates adenylyl cyclase and stimulates intracellular responses via the formation of the second messenger cyclic AMP. In the heart, H_2-receptor-mediated activation of adenylyl cyclase leads to positive chronotropic and inotropic effects while in smooth muscle (e.g., airway and vascular) H_2-receptors produce relaxation via cyclic AMP-dependent mechanisms. H_2-receptors in the brain generally mediate inhibitory effects on neuronal activity, although in hippocampal neurons they produce a block of the long-lasting after-hyperpolarization and accommodation of firing, which results in potentiation of excitatory stimuli.

H_2-Agonists

A number of potent and selective agonists are available for the histamine H_2-receptor. These include impromidine, arpromidine, dimaprit, and amthamine. In the case of impromidine and apromidine, the compounds are 48 and 100 times more potent, respectively, than histamine itself. However, while acting as agonists at the H_2-receptor, some of these compounds act as antagonists at other histamine receptors, e.g., arpromidine is an H_1-receptor antagonist, and impromidine and dimaprit are H_3-receptor antagonists (Lim et al. 2005).

H_2-Antagonists

Burimamide was the first compound to be described as an H_2-antagoinst that demonstrated selectivity for H_2- over H_1-receptors. However, with the discovery of the H_3- and H_4-receptors (see below), this compound was subsequently found to be a more potent H_3-receptor antagonist and to have H_4-agonist activity (Lim et al. 2005). Cimetidine was developed directly from burimamide and proved to be an effective agent in the treatment of gastric and duodenal ulceration because of its ability to inhibit basal and gastrin-stimulated gastric acid secretion via antagonism of the actions of endogenous histamine. A wide range of highly selective H_2-receptor antagonists are now available and are in regular clinical use including ranitidine, titotidine, famotidine, and mifentidine. Studies in transfected cells overexpressing the H_2-receptor have shown that cimetidine and ranitidine are both inverse agonists at the H_2-receptors, while burimamide behaves as a neutral H_2-antagonist. It remains to be established, however, whether inverse agonism is a property that contributes to the therapeutic effect of these compounds.

Histamine H_3-Receptor

The human histamine H_3-receptor (445 amino acids) couples to the Gi/o family of G-proteins that can inhibit adenylyl cyclase activity and inhibit neurotransmitter release (Bongers et al. 2007). It has a long third intracellular loop (142 amino acids) and a short C-terminal tail (29 amino acids). It was first identified as a presynaptic autoreceptor, inhibiting the synthesis and release of histamine from histaminergic nerves in the CNS. Histaminergic nerves originate in a small number of cell bodies in the posterior hypothalamus that innervate most areas of the forebrain. However, H_3-receptors have also been identified on the terminals of nerves containing other neurotransmitters in both the peripheral and central nervous systems. For example, in the brain H_3-receptors are present on nerve terminals that use acetylcholine, 5-HT, dopamine, and noradrenaline as neurotransmitters. In the periphery, H_3-receptors inhibit the release of sympathetic neurotransmitters in human saphenous vein, heart, bronchi, and trachea.

Unlike the genes for human H_1- and H_2-receptors, the H_3-receptor-gene contains introns and as a consequence, at least 20 splice variants have been identified for the human receptor and additional isoforms have been described for rodent and guinea-pig H_3-receptors (Bongers et al. 2007; Sander et al. 2008).

H_3-Agonist

Agonists with good selectivity for H_3-receptors (relative to H_1- and H_2-receptors) have been developed and these include R-α-methylhistamine, imetit, and immepip. However, a number of them also affect the histamine H_4-receptor (see below).

H_3-Antagonists

The initial compounds developed as selective H_3-receptor antagonists (relative to the H_1- and H_2-receptors) included thioperamide, clobenpropit, iodoproxyfan, ciproxifan, and impentamine and these all have substantially lower affinity for H_1- and H_2-receptors. However, the discovery of the histamine H_4-receptor subsequently revealed that there is considerable overlap in the pharmacology of some of these compounds for the H_3- and H_4-receptors. The existence of species H_3-receptor heterogeneity also revealed unexpected but significant variability in the affinity of certain of the prototypical H_3-receptor ligands (particularly thioperamide and ciproxifan). For example, thioperamide revealed similar affinity for the human H_3 (pKi 7.4) and H_4 (pKi 7.4) receptors, but a much higher affinity for the rat H_3-receptor (pKi 8.4). Clobenpropit turned out to be a high affinity H_4-agonist but also a high affinity inverse H_3-agonist, while ciproxifan does possess some preference for the human H_3-receptor over the H_4-receptor (Sander et al. 2008; Thurmond et al. 2008).

The H_3-receptor appears to be naturally expressed in a constitutively active form in the CNS providing a means for pharmacological interference by inverse agonists as well as agonists and neutral antagonists (Arrang et al. 2007). This natural constitutive H_3-receptor activity appears to be due to the sequence similarity of the C-terminal end of the third intracellular loop of the receptor and the mutations required in other G-protein coupled receptors to produce constitutively active mutant receptors. Many of the compounds developed as H_3-receptor antagonists have been shown to behave as inverse agonists in cell lines expressing recombinant H_3-receptors. These include thioperamide, clobenpropit, and iodophenpropit. Proxyfan was originally described as a neutral antagonist, but it has since been reclassified as a protean agonist that can act as an agonist or inverse agonist depending on the signal transduction pathway measured and the degree of constitutive receptor activity present (Arrang et al. 2007).

More recent emphasis has been placed on the development of nonimidazole-based antagonists and inverse agonists as clinical candidates. Some of the first lead compounds came from the natural ligands aplysamine-1 (extracted from the marine sponge Aplysina sp. (verongidae)) and conessine (a nonaromatic steroid-related alkaloid), which have pKi values of 7.5 and 7.2 for the human H_3-receptor, respectively. Nonimidazole and selective H_3-receptor antagonists have now been developed that have high affinity for the H_3-receptor and these include ABT-239 (pKi 9.4), GSK 189354 (pKi 9.9), JNJ 10181457 (pKi 8.9), and tiprolisant (pKi 8.6) (Sander et al. 2008).

Potential Therapeutic Indications for H_3-Antagonists

A number of H_3-receptor antagonists are currently in clinical trials (Phases I and II) for a range of potential CNS disorders including ▶ cognitive impairment and ▶ narcolepsy (Sander et al. 2008). Histamine has been long thought to have a role in maintaining the waking state because of its diffuse innervation of much of the forebrain from discrete nuclei within the tuberomammillary nucleus of the ▶ hypothalamus, and the well-known sedative side effects that have been associated with the classical H_1-receptor antihistamines. In keeping with this wake-enhancing role for histamine, the first preclinical and clinical data with nonimidazole H_3-antagonists

(which act by antagonizing presynaptic H_3-receptors leading to increased levels of postsynaptic histamine in distinct brain regions) has shown that they have marked wake-promoting actions accompanied with enhanced cortical EEG rhythm. The histamine-mediated increase in ► attention and vigilance associated with postsynaptic H_1- and H_2-receptor stimulation in the CNS that would follow H_3-receptor antagonism has also led to an evaluation of these compounds in conditions of impaired cognition (e.g. ► attention deficit/hyperactivity disorder).

Histamine H_4-Receptor

The H_4-receptor (390 amino acids) is the most recently identified histamine receptor and unlike the H_3-receptor appears to be exclusively expressed in the periphery. It is encoded by an intron-containing gene on chromosome 18. Like the H_3-receptor, it couples to the Gi/o family of G-proteins and can inhibit adenylyl cyclase activity. The H_4-receptor has been identified in a number of inflammatory cells including mast cells, eosinophils, dendritic cells, T lympohcytes, monocytes, and macrophages (Zhang et al. 2007; Thurmond et al. 2008). This distribution of the H_4-receptor has suggested that it may be an important target for drugs in inflammation, allergy, and autoimmune disease (Thurmond et al. 2008). There is also some overlap with H_1-receptor function in certain allergic conditions, which suggests that a combined H_1- and H_4-receptor antagonist may provide added benefit over the existing H_1-antagonist monotherapy.

H_4-Agonists

A wide range of ligands that act on $H_{1\text{-}3}$ receptors have been evaluated as agonists of the histamine H_4-receptor. The H_4-receptor shares the highest sequence homology with the H_3-receptor and it is therefore not surprising that a number of H_3-ligands have been identified as high-affinity H_4-agonists. These include R-α-methylhistamine (full), N-α-methylhistamine (full), immepip (partial), clobenprobit (partial), proxyfan (partial), and imetit (partial) (Lim et al. 2005). However, it is notable the H_3-agonist R-α-methylhistamine is several hundred-fold less effective as an H_4-receptor agonist than it is as a H_3-receptor agonist. Other potent H_4-agonists include burimamide (partial), the atypical antipsychotic drug clozapine (full) and 4-methylhistamine (full). In the case of 4-methylhistamine, this is probably the most selective and potent H_4-agonist available at present (Lim et al. 2005).

H_4-Antagonists

The H_3-receptor antagonists thioperamide, iodophenpropit, and clobenpropit all bind with high affinity to H_4-receptors, but clobenpropit also possesses weak H_4-agonist activity. Two compounds have emerged from high throughput screening programs as selective H_4-antagonists with very low affinity at H_3-receptors. These are JNJ 7777120 and VUF 6002 and these should prove useful in evaluating the potential anti-inflammatory actions of H_4-antagonists (Thurmond et al. 2004).

Conclusions

Histamine appears to play a key role in many physiological processes and the first two receptors (H_1 and H_2) discovered to respond to this biogenic amine have proved to be major and successful targets for drug development in the fields of allergic and gastrointestinal disease. The more recent discovery of the histamine H_3- and H_4-receptors and their differential distribution in the CNS and inflammatory cells has provided the potential for these two histamine receptors to also become the target for highly selective blockbuster drug candidates.

Cross References

► Antidepressants
► Cognitive Enhancers
► Inverse Agonist

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Histone

Definition
Histones are the main protein components of chromatin. They act as spools around which DNA winds, and they play a role in gene regulation. There are a total of six classes of histones (H1, H2A, H2B, H3, H4, and H5). Covalent modification of histones (e.g., their acetylation, methylation, phosphorylation, etc.) controls the degree to which chromatin is active or inactive.

Cross-References
► Chromatin
► Gene Expression and Transcription
► Histone Deacetylase Inhibitors

Histone Acetyltransferases

Synonyms
HATs

Definition
Histone acetyltransferases are a class of enzymes that add acetyl groups to the N-terminal tails of histones. The action of HATs causes the relaxation of the chromatin structure.

Cross-References
► Epigenetics

Histone Deacetylase

Synonyms
HDACs

Definition
Histone deacetylases are enzymes that remove the acetyl groups from N-terminal tails of histones, causing the condensation of the chromatin structure and thereby generally inhibit ► gene expression.

Cross-References
► Epigenetics

Histone Deacetylase Inhibitors

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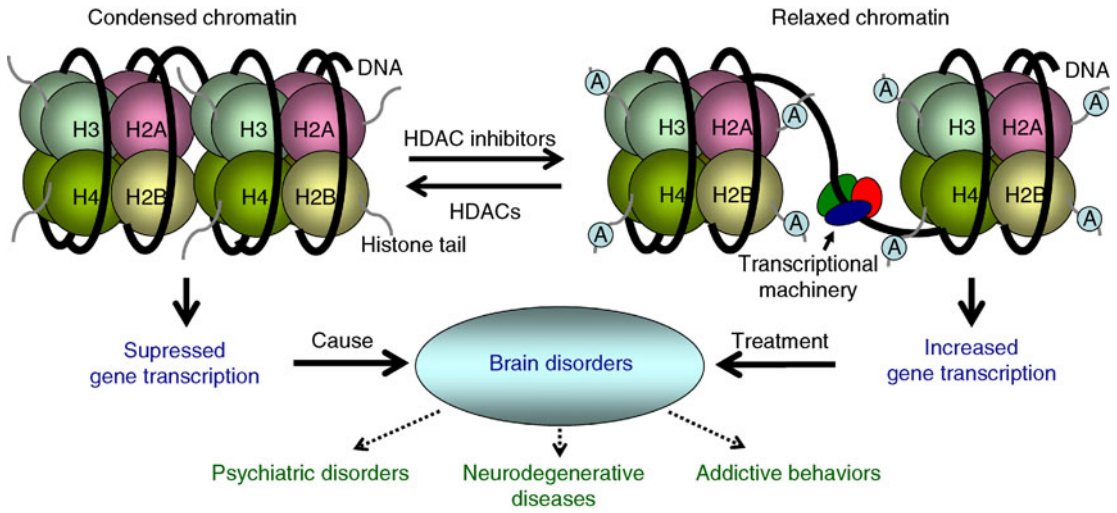
Synonyms
HDACs inhibitors

Definition
► Histone deacetylase (HDAC) inhibitors are compounds that have the ability to prevent the deacetylation of lysine residues found within the N-terminal tails of histone proteins (Nuclear proteins that DNA wraps around to form the chromatin structure which organizes into the nucleosome; see Fig. 1). These compounds were initially developed to treat cancers (Lee et al. 2008), but have recently been used to treat various brain disorders in animal models, suggesting that HDAC inhibitors may potentially develop into novel therapeutic agents (Abel and Zukin 2008; Kazantsev and Thompson 2008).

Pharmacological Properties

Role in Chromatin Remodeling
Chromatin architecture consists of DNA, histones, and nonhistone proteins. The nucleosome represents the basic repeating unit of chromatin and consists of DNA wrapped around a histone octamer that contains H2A, H2B, H3, and H4 histones. ► Chromatin remodeling occurs due to covalent histone modifications (acetylation, methylation, phosphorylation, ubiquitination, and sumoylation) and ► DNA methylation (Tsankova et al. 2007). Two major enzymes, ► histone acetyltransferases (HATs) and HDACs, regulate histone acetylation and deacetylation, respectively. The acetylation of histones leads to a relaxed chromatin state, which allows the DNA to interact more easily with various components of transcriptional machinery, such as transcription factors, transcriptional regulatory protein complexes, and RNA polymerases, resulting in increased gene transcription (Renthal and Nestler 2008). The removal of acetyl groups from histones (deacetylation) by the activation of HDACs condenses the chromatin structure, causing a decrease in gene transcription. HDAC inhibitors can increase overall gene expression by inhibiting HDAC activity, thus preventing the condensation of the chromatin structure (see Fig. 1). Therefore, HDAC-induced chromatin remodeling plays



Histone Deacetylase Inhibitors. Fig. 1. Hypothetical model of histone deacetylases (HDACs)-induced chromatin remodeling via histone deacetylation (condensed chromatin). HDAC inhibitors cause the opening of the chromatin structure (relaxed chromatin) due to its ability to increase histone acetylation (A). HDAC inhibition may serve as a potential therapeutic remedy for the treatment of brain disorders.

a fundamental role in regulating gene expression (► Epigenetics; ► Gene expression and transcription).

HDAC Inhibitors and Therapeutic Implications

Mammalian HDACs have been classified into four classes based on their homology to yeast HDACs and subcellular localization (Xu et al. 2007; Kazantsev and Thompson 2008). Class I HDACs are mostly nuclear and include HDAC 1, 2, 3, and 8. Class II HDACs can be either cytosolic and/or nuclear and include HDAC 4, 5, 6, 7, 9, and 10. Class IV HDACs include only HDAC 11, which display properties that are closely related to class I HDACs and are mainly localized in the nucleus. Class I, II, and IV HDACs require Zn^{2+} for activation and are therefore referred to as Zn^{2+}-dependent HDACs. On the other hand, class III HDACs are NAD^{+} -dependent enzymes that are collectively called sirtuins. Sirtuins are not structurally related to either class I, II, or IV HDACs. HDAC inhibitors that are specific to the Zn^{2+}-dependent class I and II HDACs and their clinical implications are described below.

A number of HDAC inhibitors belonging to different classes (hydroxamates, aliphatic acids, benzamides, and cyclic peptides) have been developed during the last decade and are currently in phase I and II clinical trials for the treatment of various cancers. Recently, the HDAC inhibitor Vorinostat (*SAHA* suberoylanilide hydroxamic acid), has been approved by the US Food and Drug Administration to be used for the treatment of cutaneous T-cell lymphoma (Xu et al. 2007; Lee et al. 2008). Despite the tremendous amount of progress regarding the clinical use of HDAC inhibitors to treat cancers, these compounds can display some forms of toxicity. These include fatigue, nausea, vomiting, thrombocytopenia, neutropenia, and cardiac irregularities (Balasubramanian et al. 2009). Drug development efforts have been diverted to synthesize HDAC isoform-specific inhibitory compounds with some success in the cancer field (Lee et al. 2008) and this approach may overcome the problems associated with drug toxicity (Balasubramanian et al. 2009). The HDAC inhibitors: ► Trichostatin A (TSA), sodium butyrate, SAHA, and ► valproic acid have been used in animal models to treat neurodegenerative (► Neurodegeneration and its prevention; ► Learning & Memory: Molecular Mechanisms) and psychiatric disorders (► Schizophrenia; ► Generalized Anxiety Disorder; ► Anxiety: animal models; ► Depression: animal models) (Tsankova et al. 2007; Kazantsev and Thompson 2008; Abel and Zukin 2008; Guidotti et al. 2009). Using an animal model for depression, it has been suggested that hippocampal chromatin remodeling may play a role in the pathophysiology of depression (► Animal models for psychiatric states; ► Antidepressants), and HDAC inhibitors may be beneficial in treating depression (Tsankova et al. 2006). Genetic and pharmacological manipulations of HDACs in the ► nucleus accumbens (NAc) brain region have been

shown to modify the behavioral sensitivity to ► cocaine, and TSA treatment can decrease cocaine self-administration (► Cocaine; ► Cocaine dependence) in rats (Renthal and Nestler 2008; Romieu et al. 2008). Acute ethanol has been shown to inhibit HDAC activity, and ethanol withdrawal after chronic ethanol exposure has been shown to increase HDAC activity in the ► amygdala of rats. Blocking HDAC activity by TSA treatment during ethanol withdrawal has prevented the development of anxiety-like behaviors (► Alcohol; ► Alcohol abuse and dependence) and has also corrected deficits in histone acetylation in amygdaloid brain regions of rats (Pandey et al. 2008). Collectively, these results suggest that HDAC inhibitors may represent potential therapeutic agents for the treatment of various brain disorders. Given that several HDAC isoforms exist and previous studies have used pan-HDAC inhibitors, it is important to investigate the role of specific HDAC isoforms in different brain disorders using both pharmacological and genetic approaches to block the action of specific HDACs that may lead to development of HDAC isoform-specific pharmacotherapy of brain diseases.

Cross-References

► Alcohol
► Alcohol Abuse and Dependence
► Alcohol Withdrawal-Related Anxiety
► Animal Models for Psychiatric States
► Antidepressants
► Anxiety: Animal Models
► Cocaine
► Cocaine Dependence
► Depression: Animal Models
► Epigenetics
► Gene Expression and Transcription
► Generalized Anxiety Disorder
► Learning & Memory: Molecular Mechanisms
► Neurodegeneration and Its Prevention
► Schizophrenia

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History of Psychopharmacology

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The field of psychopharmacology may be regarded as the point of confluence of theories, lines of inquiry, and methodologies pertaining to pharmacology, psychology, and psychiatry. Other disciplines, including ethology, genetics, and anthropology also contributed to the growth of psychopharmacology. The diversity of the roots of psychopharmacology goes a long way toward explaining the different definitions given to this term and why it means different things to different practitioners in the field. The goal of this essay is to briefly review the family tree of psychopharmacology and with it the development of the discipline.

The Origins of the Term Psychopharmacology

There is little doubt that psychopharmacology came of age in the 1950s with the ascent of behavioral pharmacology and the appearance of the first ► antidepressants and ► antipsychotic drugs. The first textbook of psychopharmacology (Wolfgang de Boor's *Pharmakopsycologie und Psychopathologie*) was published in 1956. Experimentation with psychotropic drugs, however, had been going on for many years before. The term "psychopharmacology" was used for the first time by David I. Macht in a paper titled "Contributions to Psychopharmacology," published in 1920 in the Bulletin of the Johns Hopkins Hospital. In the following year, Macht would write: "The effect of drugs on psychological functions and animal

behavior has been the subject of remarkably little investigation on the part of either psychologists or pharmacologists. With the exception of two substances – alcohol and caffeine – the contributions to this subject have until very recently been few and meager, so that the field of what may be termed 'psychopharmacology' is virgin soil, full of possibilities." The "little" that had been done until then was largely the work of Emil Kraepelin who had introduced the term *Pharmakopsychologie* in an 1892 monograph (*Über the Beeinflussung einfacher psychischer Vorgänge durch einige Arzneimittel* 1892). Even before the terms psychopharmacology and pharmacopsychology were coined, however, there had been sparse scholarly studies on opium, hashish, coca, and other natural substances. Furthermore, attempts at finding medications for mental disorders had began well before the pharmacotherapeutic revolution of the 1950s. A study on the early history of psychopharmacology should therefore be articulated in various phases.

Psychopharmacology Before Experimental Psychology

Although it is customary to start any history of psychopharmacology by mentioning the use of drugs in ancient times, the truth is that the ancients had very little understanding of the psychological effects of drugs except for the fact that some of these effects could be exploited for recreational or ritual purposes. It was only with the advent of evidence-based medicine in the nineteenth century that the scientific exploration of the psychoactive effects of drugs would begin, owing to the isolated efforts of physicians based in France, Germany, Great Britain, and Italy. The work of some of these scientists was quite innovative. The French physician Pierre-Alexandre Charvet was the first to conduct studies of comparative psychopharmacology by administering opium to a variety of species (*De l'action comparée de l'opium et de ses principes constituans sur l'economie animale* 1826). Another French physician, Jacques-Joseph Moreau (also known as Moreau de Tours) was the first to suggest a drug model of psychosis by comparing the mental status induced by hashish to that of mentally ill patients (*Du haschich e de l'aliénation mentale* 1845). Paolo Mantegazza, professor of *Materia Medica* (loosely corresponding to present day pharmacology) at the University of Pavia, was the first to report on the euphoriant effect of coca and to propose a comprehensive classification of psychoactive plants and plant extracts (*Sulle virtù igieniche e medicinali della coca e sugli alimenti nervosi in generale* 1859). The scope of these pioneering efforts was, however, hampered by the lack of quantitative methodologies as well as by inadequate conceptual frameworks of mental functions. Both of these obstacles began to be overcome in the second half of the nineteenth century with the acquisitions of sensory physiology and the rise of experimental psychology.

Psychology and Psychopharmacology

Experimental Psychology and the Scientific Study of Psychological Drug Effects

The role of experimental psychology in the development of early psychopharmacology is often forgotten or belittled. Yet it was in the Leipzig laboratory of Wilhelm Wundt, the founder of experimental psychology, that Emil Kraepelin began his investigation of the psychological effects of drugs (including ▶ alcohol, ▶ caffeine, tea, amyl nitrite, ▶ chloral hydrate, chloroform, ethyl ether, ▶ morphine, and paraldehyde) using "strict" methodologies and with the support of a working theory of the mind. The methodologies employed in Wundt's laboratory were largely based on self-experimentation and in particular, on the procedure of *selbst-beobachtung*, which unfortunately has been rendered in English mainly as "introspection" instead of "self-observation," the literal and more accurate translation of the term. Self-observation allowed the experimenters to turn themselves into experimental subjects. It has been calculated that 50% of studies conducted in Wundt's laboratory were concerned with sensation and perception. Not surprisingly, among the tasks used by Kraepelin were: simple reaction time (67 experiments), choice reaction time (58 experiments), differentiation reaction time (31 experiments), word reaction time (6 experiments), time estimation (12 experiments), associations (14 experiments), serial addition (10 experiments), and reading (7 experiments). Psychometric testing after drug administration was not an absolute novelty in itself, the effects of caffeine, alcohol, and opium on reaction times having been previously investigated by Sigmund Exner (1873), and by Michael J. Dietl and Maximilian von Vintschgau (1877). However, Kraepelin was the first to include in the experimental design healthy volunteers and controls, to employ high precision chronographs (in the millisecond range), to investigate dose-response relationships, and to conduct rudimentary statistical analyses. Although Kraepelin's goals were ambitious ("to recognize the true nature of certain psychological processes from the special effects of an already accurately known drug") the data he collected were plagued by exceedingly high variability and could be regarded, by today's standards, as having more to do with physiology than with psychology.

In the following years, psychometric studies continued to be conducted in European and American universities.

The most important advances were due to William H. R. Rivers at Cambridge University, who introduced ► placebo pills, and to Harry L. Hollingworth at Barnard College, who abandoned the technique of self-observation, adopting group averages calculated on a number of experimental subjects. Hollingworth's name is linked to the Chattanooga Trial of 1911 against the Coca Cola Company. Hired as an expert witness by the defense, on the condition that he would be allowed to publish the results of his research regardless of the outcome, Hollingworth adopted an extremely sophisticated design (the first ► double-blind clinical trial in the history of psychopharmacology), demonstrating that the caffeine content of Coca Cola was not harmful.

Another line of inquiry based on introspection was represented by the studies carried out at the turn of the century by Edmund B. Delabarre (1899), Edward W. Scripture (1893), and others on the effects of ► cannabis on consciousness and will, which somewhat echoed the work done half a century earlier by Moreau de Tours.

Comparative Psychology, Pavlov's Conditioned Responses, and the Ascent of Behavioral Psychology

Before, during, and after the emergence of experimental psychology other, more fundamental currents were developing in the field of psychology, which would have great importance for the shaping of modern psychopharmacology. In the first place, Charles Darwin's *The Descent of Man* (1871) and *Expression of Emotions in Man and Animals* (1872) provided the theoretical basis for comparative psychology. By breaking the separation between human and animal mental processes ("mental continuity doctrine") it became possible to turn the latter into bona fide subjects of psychological investigation. In the following years, Douglas A. Spalding began the scientific study of imprint and instinct and Conwy Lloyd Morgan developed, on the basis of experiments conducted in both humans and animals, a learning theory centered on the association between behavior and its pleasant or unpleasant consequences. These developments would coalesce in the departments of philosophy of North American universities, where functionalism and then behaviorism became the dominant paradigms in psychology.

In 1896–1897, Edward Lee Thorndike, at Columbia University, probably inspired by early research of Lloyd Morgan and John Lubbock, conducted a classical series of experiments with cats and chickens using puzzle boxes. Thorndike's theory of learning, based on the "law of effect" (whereby "satisfiers" would "stamp-in" whereas "annoyers" would "stamp-out" certain stimulus-response connections), would dominate the field of learning theory for over 30 years. The late 1890s also saw Pavlov's discovery of conditioned responses, which would be at the core of the behaviorist revolution promoted by John B. Watson. As a PhD student in Henry Donaldson's laboratory at the University of Chicago, Watson, had at his disposal the experimental subjects (albino rats) and the apparatuses (including the mazes, invented, in 1899, by Willard Small at Clark University) necessary for a rigorous investigation of animal learning. Building on Thorndike's learning theory and Pavlov's work, Watson developed a manifesto (*Psychology as the Behaviorist Views it*, 1913) in which psychology was reduced to the study of behavior "in terms of stimulus and response, in terms of habit formation, habit integrations and the like." Psychology's theoretical aim was defined as "the prediction and control of behavior" whereas the investigation of hypothetical psychological constructs and the study of the central nervous system's "mystery box" were placed outside its boundaries. Within 10 years, Watson's approach would come to dominate American psychology and in the 1930s various brands of behaviorism would emerge, including Edward C. Tolman's cognitive behaviorism, Edwin R. Guthrie's contiguity theory of learning, Clark L. Hull's drive-reduction theory of learning, and, most influential of all, Burrhus F. Skinner's behaviorism. Skinner not only pushed Watson's theoretical approach to its most radical formulation but also developed a procedure, based on Thorndike's "law of effect" and on ► Pavlovian conditioning, which would become central to psychopharmacological research in the following decades. In his "► operant conditioning apparatus" (Skinner box), reminiscent of Thorndike's puzzle box, the behavior of the experimental subject could be "shaped" into performing a given action so as to obtain a "reinforcing" stimulus. In the 1940s, Skinner and his associates embarked on a massive investigation of the effect of the ► schedule of reinforcement on responding, which, according to Skinner's own appraisal, represented his most important contribution to psychology.

Surprisingly, the developments outlined above had a relatively minor impact on the growth of psychopharmacology, at least in the short term. In Pavlov's laboratory, Igor Zavdaskii investigated the effect of ► morphine, ► cocaine, ► alcohol, and ► caffeine on the conditioned salivary reflex of the dog (1917). Among the behaviorists, Watson (who in his 1913 manifesto had mentioned the "psychology of drugs" as a field in "vigorous growth") studied the effect of strychnine and caffeine on rat learning and Skinner the effects of caffeine, ► amphetamine, and ► phenobarbital on conditioning and extinction (1937). More remarkable was a series of studies

concerning the effects of morphine and other ▶ opioids on rat behavior conducted, in the mid-1930s, by, Nathan B. Eddy of the University of Michigan Medical School. While Macht in his 1921 study had used a circular maze, Eddy and colleagues (Report of Committee on Drug ▶ Addiction, National Research Council, 1929–1941) used an elevated maze previously developed by Walter R. Morris to study "Drug effects measured by acquired patterns of response" (1929). Overall, however, it is fair to say that between the 1920s and the 1950s, psychopharmacology had entered a phase of relative quiescence.

Behavioral Pharmacology

Behavioral pharmacology originated in the 1950s in the department of pharmacology of Harvard University, where the freshly hired Peter B. Dews was introduced to behavioral psychology by Skinner. ▶ Operant conditioning procedures were promptly grafted onto pharmacology by Dews and his Harvard colleagues, Roger T. Kelleher and Will H. Morse. Behaviorism's preoccupation with the practical aspects of psychology found an ideal application in the systematic study of the revolutionary ▶ antidepressant and ▶ antipsychotic drugs that had just entered the market. In the following decades, the methodologies developed at Harvard would be extended to the study of the discriminative and ▶ reinforcing stimulus effects of drugs. ▶ Drug-discrimination procedures were pioneered by J. Conger, Don Overton, and Jane Stewart, but the earliest studies employing a two-lever operant conditioning chamber were published in the late 1960s. In 1962, James R. Weeks described a new technique allowing for the first time the study of intravenous morphine ▶ self-administration in the rat. More than two decades earlier, Sidney D.S. Spragg had shown that chimpanzee would work to obtain a shot of morphine but until Weeks's report the notion that a non-primate could become addicted was highly contentious. Drug-discrimination and drug self-administration procedures became standard paradigms for investigating the ▶ abuse potential of drugs.

In retrospect, it is not easy to evaluate the contribution of Dews, Kelleher, and Morse to psychopharmacology. On the one hand, they contributed to this discipline a wealth of methodologies based on conditioned ▶ operant behavior in animals that are still at the core of psychopharmacological research, especially of addiction research. On the other hand, it can be argued that the lack of interest (to put it mildly) of these most orthodox behavioral pharmacologists in the psychological phenomena and the neurobiological mechanisms underlying the behavioral effects of drugs somewhat hampered the growth of psychopharmacology.

Biological Psychology and Psychopharmacology

While behavioral pharmacology was establishing a cultural hegemony in North American departments of pharmacology, a different brand of psychopharmacology was brewing in the departments of psychology. In spite of the edicts by Watson and Skinner, the majority of animal psychologists remained interested in the neurobiological basis of fundamental psychological processes such as reward and motivation, learning and memory, aggression, emotions, and the like. Biological psychology brought to psychopharmacology an impressive range of techniques developed from within (e.g., chemical and electrolytic lesions, ▶ brain stimulation reward, in vivo ▶ microdialysis, in vivo ▶ voltammetry) or imported from related disciplines (e.g., operant conditioning procedures, ▶ conditioned preference/aversion procedures, ethological methods, ▶ spatial learning, social learning, electrophysiological techniques, ▶ fMRI, functional neuroanatomy, genetic manipulations, etc.) as well as powerful theoretical constructs. On the other hand, drugs provided biological psychologists with new tools for manipulating brain activity in a relatively selective manner. Drugs could even be microinjected into discrete brain regions, thus activating or blocking specific neural pathways. Drugs also provided biological psychologists with new areas of investigation, concerning in particular, the phenomenon of drug addiction. This line of research has been steadily growing in the last two decades and more than 50% of all papers published in the last volumes of the journal *Psychopharmacology* are concerned with addictive drugs. From a certain point of view, a large majority of biological psychologists can be considered as psychopharmacologists.

Psychiatry and Psychopharmacology

Early Pharmacotherapy of Psychiatric Disorders (1860s–1930s)

Beginning with the 1860s, and completely independently from the developments summarized above, a number of drugs were introduced for the treatment of mentally ill patients (see Table 1). In this early phase of psychiatric pharmacotherapy, drugs were used to achieve three main effects: sedation, deep sleep, and convulsions. Morphine, potassium bromide, ▶ chloral hydrate, atropine, hyoscyamine, and ▶ scopolamine were used, alone or in combination, for the control of agitated, aggressive patients, thereby reducing the need for physical restraint. Morphine was isolated from opium (which had been used for centuries to control "frenzy") by Friedrich Wilhelm Adam Sertürner in 1804 but its widespread use in

History of Psychopharmacology. Table 1. Milestones in psychopharmacotherapy.

Drug	Isolation or synthesis	Introduction in therapy	Therapeutic use
Morphine	1804	1850s	Sedation
Potassium bromide	1826	1850s	Sedation
		1900s	Sleep therapy
Atropine/hyoscyamine	1931	1860s	Drowsiness
Chloral hydrate	1832	1860s	Hypnosis
Scopolamine	1881	1880s	Drowsiness
Barbital	1903	1910s	Hypnosis
		1910s	Sleep therapy
Insulin	1921	1920s	Sedation
		1930s	Coma therapy
		1930s	Convulsive therapy
Amphetamine	1887/1929	1930s	Antidepressant effect
		1930s	Therapy of narcolepsia
		1930s	Therapy of ADHD
		1930s	Appetite suppression
Camphor	1903[a]	1930s	Convulsive therapy
Penthylenetetrazol	1925	1930s	Convulsive therapy
Lithium	1817	1949[b]	Antimanic effect
Iproniazide	1951	1951	Antidepressant effect
Chlorpromazine	1950	1952	Antipsychotic effect
Reserpine	1953	1953	Antipsychotic effect
Meprobamate	1950	1955	Anxiolytic effect
Imipramine	1940s	1957	Antidepressant effect
Haloperidol	1958	1958	Antipsychotic effect
Chlordiazepoxide	1955	1960	Anxiolytic effect
Clozapine	1961	1971	Antipsychotic effect

[a]Naturally occurring camphor was obtained from *Cinnamomum camphora* since ancient times
[b]In 1871, there was the first recorded use of lithium for the treatment of mania and in 1886 lithium carbonate was used for the first time to prevent depression

psychiatry began in the 1850s, with the invention of the hypodermic needle. Potassium bromide, first isolated from seawater in 1826, was initially used to treat scrofula and only later as an anticonvulsant. Its sedative effects began to be widely exploited in psychiatry in the 1850s. Chloral hydrate was synthesized in 1832 by Justus von Liebig and first used as an hypnotic by Otto Liebreich in the late 1860s, based on the wrong assumption that it would be metabolized to chloroform in the body. The awful taste of chloral hydrate did not prevent this drug from becoming a very popular hypnotic even outside the lunatic asylum. The anticholinergic alkaloids atropine (and its levorotary isomer hyoscyamine) and scopolamine were isolated from plants of the Solanaceae family in 1831 and 1881, respectively. Their ability to induce a state of drowsiness led to their wide use in psychiatric institutions.

In the first decades of the twentieth century, many psychiatrists advocated the use of bromides and ▶ barbiturates to induce a prolonged state of hypnosis (sleep-therapy). A variant of sleep-therapy was represented by coma-therapy induced with barbiturates and later with insulin. Indeed, the lack of effective psychiatric treatments made the psychiatrists ready to try the riskiest procedures (heroic treatments). In the late 1930s, Ladislas Von Meduna popularized the use of camphor and then of pentylenetetrazol to induce convulsions for the treatment of ▶ schizophrenia. Paracelsum (sixteenth century), Robert Whytt (1751), Leopold von Auenbbrugger (1776), and William

Oliver (1785) had previously advocated the use of camphor for the convulsive therapy of the mentally ill. In the 1930s, Manfred Sakel developed another type of convulsive therapy, based on the use of insulin. In 1939, with the introduction of ► electroconvulsive therapy by the Italian psychiatrists Ugo Cerletti and Lucio Bini, camphor and pentylenetetrazol were rapidly abandoned, whereas insulin therapy remained in fashion at the fringes of mainstream psychiatry.

It should be noticed that the pharmacotherapeutic approaches outlined earlier were initially used to treat virtually all types of mental disorders and did not lead to any "chemical" theory of mental function. Drugs were seen mostly as tools to restrain the patients or to produce dramatic changes in the state of brain activity (convulsions or coma) that might help "resetting" mental functions.

Experimenting with Hallucinogenic Drugs (1880s–1940s)

One of the most fascinating aspects of early psychopharmacology is represented by the great deal of interest in ► hallucinogens in both academic and industrial environments. This phenomenon is perfectly exemplified by the book *Phantastica* (1931), into which the German pharmacologist Louis Lewin poured his life-long interest in the ► classification of psychoactive substances, based on their subjective and behavioral effects. He identified *Inebriantia* (e.g., ► alcohol and ether), *Exitantia* (e.g., ► cocaine and ► Khat), *Euphorica* (e.g., ► opiates), *Hypnotica* (e.g., Kava), and *Phantastica* (e.g., Peyote or Ayahuasca). As early as 1887, the pharmaceutical company Parke Davis became interested in the active principle of peyote and other cactuses used by native Americans of the southwest for ritual purposes. Arthur Heffter finally isolated mescaline in 1897. In the following three decades, a number of psychologists and psychiatrists investigated the strange effects of mescaline hoping to find a lead into the nature of psychotic hallucinations. The interest in hallucinogens had almost died out when, in 1938, a chemist working at Sandoz, Albert Hofmann, isolated ergonovine from *Claviceps purpurea,* an ► ergot fungus growing on rye, and subjected it to a number of chemical modifications. Hofmann's aim was to find a drug could induce labor without endangering mother and child, as was the case with the ergot preparations used by midwives since the Middle Ages. Five years later, Hofmann tested lysergic acid diethylamide-25 (LSD-25) on himself, with spectacular results.

The psychedelic effects of LSD brought, for the first time in history, psychoactive substances to center stage of public discourse in North America and Europe, originating a subculture oriented toward spiritual enlightenment. Even the military became interested in LSD, in view of its possible use for manipulating mental functions. At a therapeutic level, LSD was used to facilitate psychotherapy, supposedly by reducing ego defenses (psycholytic therapy), the 1950s and 1960s being the heydays of psychoanalysis. More level-headed research was aimed at understanding the mechanisms of action of LSD in the hope of finding the neurobiological substrate of mental insanity. In 1953, John Gaddum discovered that LSD had anti-serotonin effects and in the same year, Betty Twarog found serotonin in the brain. In 1954, Gaddum proposed that serotonin was required for normal mental functions. It was later discovered that at recreational doses, LSD acted as a partial agonist at various subtypes of serotonin receptors (which is compatible with the anti-serotonin effect described by Gaddum, given that partial agonists act as antagonists in the presence of full agonists), including ► 5-HT2A receptors. The serotoninergic hypothesis of schizophrenia would gain further support with the discovery that many ► antipsychotics could block 5-HT_{2A} receptors.

The First "Antidepressant": Amphetamine (1930s–1950s)

It is often forgotten that ► amphetamine was the first antidepressant drug to enter the psychiatric outpatient market. Phenylisopropylamine (which received the name amphetamine only in 1939) was synthesized for the first time in 1887 by Lazar Edeleanu and then again in 1928–1929 by Gordon Alles, who was searching for an epinephrine analog that could be administered orally for the therapy of asthma. Amphetamine proved to be a failure as an antiasthma medication and in 1934 Alles sold the patent to Smith, Kline and French, which initially marketed it as a decongestant (Benzedrine). Soon it became clear that there was much more to amphetamine than its decongestant effect. In 1935, Benzedrine came to the attention of Abraham Myerson, a prominent American psychiatrist, who thought that its "energizing" effects could be beneficial in minor ("neurotic") depression. Myerson obtained clinical data supporting his hypothesis, and in 1937 SKF began pursuing the psychiatric market with a circular sent to virtually all American doctors stating that "the main field for Benzedrine Sulfate will be its use in improving mood." In 1939–1940, there was a first major campaign in nonspecialist medical journals advertising Benzedrine's effectiveness in "neurotic" depression. Further advertising runs throughout the 1940s reinforced the notion that amphetamine could serve as a stand-alone therapy for those mild forms of ► depression

that were most likely to fall within the scope of family doctors' practice. In the 1950s, with the ascent of psychoanalysis in the USA, amphetamine began to be marketed as an adjuvant to psychotherapy and it was only in the 1960s that its popularity among psychiatrists declined. For about two decades, amphetamine represented the only antidepressant available and was widely prescribed by psychiatrists and general practitioners alike. It was also used for the therapy of ▶ narcolepsy and of ▶ attention deficit disorders. In the mid-1940s, about one million daily doses of amphetamine were used for the therapy of mood disturbances and another one million for weight loss. Other uses of amphetamine, linked to its addictive and performance-enhancing effects (exploited to the full during WWII by civilian and army personnel alike), are beyond the scope of this essay. An important aspect of the amphetamine story was its role in advancing theoretical thinking in biological psychiatry. Myerson thought that the central feature of "neurotic" depression consisted of a state of anhedonia caused by an abnormal dominance of the, supposedly cholinergic, brain circuits responsible for sleep and restfulness over the supposedly adrenergic, brain circuits responsible for activity and wakefulness. Myerson was clearly ahead of his time because when he expounded his theory, in the late 1930s, the notion of chemical transmission in the brain was still highly speculative. In any case, amphetamine may be regarded not only as the first mass-marketed psychoactive drug but also as the first drug whose psychoactive and therapeutic effects could be framed in the context of a neurobiological theory of mental functions.

The Revolutionary Decade: Antipsychotic, Antidepressant, Anxiolytic, and Antimanic Drugs (1949–1958)

The clinical efficacy of the prototypical psychotherapeutic drugs was discovered in a serendipitous manner during a 10-year span, from 1949 to 1958. The starting point of this psychotherapeutic revolution was the substituted ethylamine group at the core of the phenothiazines, an ethylamine group present not only in histamine, but also in ▶ norepinephrine, ▶ dopamine, and serotonin.

Antipsychotic ▶ phenothiazines were first synthesized in 1883 by August Bernthsen, who, as many other industrial chemists of the time, was searching for synthetic dies that could replace the expensive natural dyes. However, in the first half of the twentieth century, it was common practice, given the dearth of effective medications, to screen the biological actions of available compounds in the hope of finding something with potential therapeutic value. In the 1940s, Rhône-Poulenc researchers found that phenothiazines were effective antihistamines, and therefore could be useful for the therapy of allergic reactions. It was later discovered that phenothiazines had many other effects, such as the ability to induce hypothermia, muscle relaxation, sedation, and mild euphoria. The French surgeon Henry Laborit thought that these effects might help in reducing the risk of postsurgical shock, a potentially fatal complication of surgical stress, and included one of these compounds, ▶ promethazine, in his preanesthetic "lytic" cocktail. Laborit was sufficiently impressed by the central nervous system effects of promethazine to ask Rhône-Poulenc for a more potent analog. Such a compound was already available: ▶ chlorpromazine (halogens such as chlorine are known to increase the biological potency of organic molecules). Chlorpromazine exhibited additional effects relative to other phenothiazines, including the ability to induce a state of detachment and to reduce hallucinatory and delusional symptoms in psychotic patients. The large spectrum of chlorpromazine actions led Rhône-Poulenc to market the drug under the name of Largactil. In 1952 and 1953, the French psychiatrists Jean Delay and Pierre Deniker published a series of papers reporting on the possible use of chlorpromazine in the treatment of severe depression, mania, and, most importantly, of ▶ schizophrenia. The hope was that because of its ability to induce drowsiness, chlorpromazine could be used in sleep therapy. The almost miraculous antipsychotic effect of chlorpromazine went beyond the wildest dreams of the psychiatrists, unlocking the doors of psychiatric wards to schizophrenics who had been considered hopeless until then. The frequent appearance of symptoms reminiscent of ▶ Parkinson's disease and other "extrapyramidal" side effects did not dampen the enthusiasm of psychiatrists for the first "▶ neuroleptic" (a term introduced by Delay) and chlorpromazine soon became a blockbuster.

In 1953, another antipsychotic drug, ▶ reserpine, made its appearance in the psychiatric wards. For centuries, traditional Indian medicine had made use of extracts from *Rauwolfia serpentina* for the treatment on insanity, hypertension, and other conditions. In 1931, G. Sen and K.C. Bose reported on the effectiveness of Rauwolfia in calming psychotic patients and lowering blood pressure, but their paper was published in an Indian medical journal and received little attention in Europe and North America. Nonetheless, in the early 1950s, pharmaceutical companies such as Squibb and Ciba become interested in Rauwolfia and in 1953 Ciba's chemist Hugo Bein found that its active principle was reserpine. In 1954, Nathan S. Kline reported on the antipsychotic effect of reserpine and the drug remained in use throughout the 1950s before it

became apparent that it was less effective and more toxic than chlorpromazine and other neuroleptics.

In the 1960s and 1970s, the search for new antipsychotic drugs followed two main paths. The first one (the "me-too" approach) consisted in altering the structure of phenothiazine; e.g., by adding a trifluoromethyl group to promethazine to obtain ► trifluoperazine. A slightly different approach consisted in using, instead of the phenothiazine rings, other tricyclic (e.g., thioxanthine) or heterocyclic rings as starting points for chemical modifications. A striking example of the latter case was the synthesis, in 1961, of ► clozapine, the first, and, according to many, the only truly atypical antipsychotic (that is, an antipsychotic with little extrapyramidal toxicity). A second line of development originated in the late 1950s with the synthesis by Paul Janssen, of a compound that exhibited both opioid-like analgesic effects and neuroleptic-like sedative and motor effects. Further structural modifications, aimed at boosting the antipsychotic effect, led to the synthesis of first butyrophenone, ► haloperidol, another blockbuster antipsychotic drug.

The discovery of effective antipsychotic drugs did not lead to an immediate understanding of their mechanism of action. It was known, however, that chlorpromazine and other antipsychotic phenothiazines could affect monoaminergic transmission in various ways: alpha-receptor blockade, norepinephrine reuptake inhibition, and norepinephrine release inhibition. Furthermore, tests in the rat had shown that antipsychotic phenothiazines were able to block the motor stereotypies induced by amphetamine, which was a notorious psychotomimetic drug. Although the mechanism of action of amphetamine was still uncertain, it was widely thought that it could be related to adrenergic mechanisms. Finally, it was shown that reserpine reduced ► norepinephrine levels in the brain. Even so, other pharmacological actions of chlorpromazine, such as the ability to block serotonin reuptake and to induce the formation of free radicals through oxidoreduction, were still considered potentially relevant for the antipsychotic effect. Then, in the early 1960s, the focus shifted to ► dopamine. In 1958–1959 Arvid Carlsson and colleagues demonstrated that dopamine was not a mere precursor of noradrenaline and adrenaline but a neurotransmitter in its own right, and soon afterward Oleh Hornykiewicz, Theodore Surkes, and colleagues demonstrated that dopamine depletion was at the basis of Parkinson's disease. In 1963, Carlsson and Margit Lindquist suggested the existence of dopamine receptors with high affinity for chlorpromazine and haloperidol, but the first to hypothesize that the antipsychotic effect was due to the blockade of dopamine receptors was Jacques van Rossum, in 1967. Finally, in 1975, Philip Seeman and Solomon H. Snyder demonstrated the existence of dopamine receptors. A striking correlation between the potency of antipsychotic drugs and their affinity for dopamine D2 receptors was found immediately thereafter. For the first time in history, there was a robust neurobiological hypothesis for a mental disorder as well for its symptomatic therapy. It is fair to say that the "► dopamine hypothesis" of schizophrenia represents a mere *ex-adjuvantibus* outcome of the serendipitous discovery of the antipsychotic effects of phenothiazines and reserpine.

Despite all efforts, none of the antipsychotics synthesized after chlorpromazine represented a significant improvement in effectiveness. The only important progress has consisted in developing antipsychotics with lesser autonomic and extrapyramidal toxicity or with better dispositional profiles (e.g., esterified compounds for depot preparations). Indeed, it is somewhat sobering to realize that the last breakthrough in the therapy of psychosis was achieved about 50 years ago with the synthesis of clozapine, and that the only pharmacological target that has yielded effective antipsychotics is still represented by the blockade of D2 receptors.

The high affinity of many neuroleptics for the 5-HT_{2A} receptors, as well as the serotoninergic mechanism of action of LSD and naturally occurring hallucinogens, has been at the base of much research for selectively serotonin antipsychotic drugs. Another potential target was identified in the glutamate receptors, given the ability of ► NMDA receptor antagonists, such as PCP and ketamine, to produce psychotic episodes. Yet, all attempts at developing antipsychotics with selective serotoninergic or glutamatergic mechanisms of action have been unsuccessful, at least so far. The excitement aroused in 2007 by reports of the antipsychotic efficacy of LY2140023, a prodrug of the mGlu2/3 receptors agonist LY404039, has been considerably dampened by Seeman and colleagues' demonstration of the affinity of a structural congener of these drugs for dopamine D2 receptors.

Antidepressants. Besides promethazine, promazine, and chlorpromazine, other drugs with a substituted ethylamine group were tried in the 1950s with the aim to improve sleep therapy. In 1899, Johannes Thiele and Otto Holzinger of the Bavarian Academy of Sciences in Munich synthesized an iminodibenzyl nucleus that differed from phenothiazines for having an ethylene bridge instead of a sulfur bridge and in the late 1940s, Geigy's chemists synthesized a number of derivatives of this basic structure while searching for new antihistamines. Ronald Kuhn, a Swiss psychiatrist, tried compound G22150 (► imipramine) on more than five hundred psychiatric

patients and found a dramatic improvement only in individuals with severe ► depression and only after many days or weeks of treatment. In 1957, Kuhn communicated his findings to a half-empty room at the Second World Congress of Psychiatry in Zurich, encountering general skepticism, even from Geigy's headquarters. Among the few who took notice, there was Heinz Lehmann, who conducted the first clinical trial in North America, reporting on the antidepressant effect of imipramine in 1958.

Even before imipramine, other drugs with antidepressant effect were available but it took some time before their efficacy could be proved conclusively. Isoniazid and iproniazid were synthesized by Hoffman-La Roche's chemists through the modification of hydrazine, a rocket fuel, of which large stores remained at end of WWII. The goal was to obtain drugs against tuberculosis, still a worldwide scourge at the time. These drugs were also tested, according to a well-established tradition, in psychiatric patients. The first report concerning isoniazid, by Jean Delay and colleagues, appeared in 1952 whereas the first report concerning iproniazid, by R. G. Bloch, appeared in 1954. The putative antidepressant effect of isoniazid was not confirmed by subsequent studies and was probably due more to the enthusiasm with which TB patients received the new treatment than to its pharmacological usefulness. It took several more years before it was understood that the apparent vagaries in the clinical effectiveness of iproniazid depended on the short duration of the treatment regimens. In 1957, Nathan Kline and colleagues of the Rockland State Hospital in Orangeburg, New York, reported that iproniazid seemed to work as a "psychic energizer" in depressed in- and outpatients.

The antidepressant effect of imipramine was readily attributed to its ability to block norepinephrine reuptake whereas that of iproniazid to the ability to block ► monoamine-oxidase, the enzyme that degrades norepinephrine and other monoamines. As seen for the antipsychotics, a relatively straightforward *ex-adjuvantibus* line of reasoning resulted in the "noradrenergic" hypothesis of depression. This hypothesis sat well with the finding that, when administered to rats, reserpine produced effects reminiscent of depression, such as immobility.

The "me-too" approach, which had been so successful with neuroleptics, was immediately adopted to obtain drugs with a pharmacological profile similar to, or better than, that of imipramine. For example, the halogen substitution strategy that had yielded chlorpromazine led to the synthesis of ► clomipramine. Contrary to the other ► antidepressants then available, clomipramine exhibited elevated serotonin reuptake blocking capabilities but its metabolite desmethylclomipramine, was a selective inhibitor of norepinephrine reuptake. Not everybody, however, subscribed to the noradrenergic hypothesis of depression. In the late 1960s, some researchers, including Carlsson, Lindqvist, G. F. Oxenkrug, and I. P. Lapin, proposed, on the strength of sparse lines of evidence, that the most important effect of antidepressants was the inhibition of serotonin reuptake. The ► serotonin hypothesis was pursued by Carlsson and Hans Corrodi, who modified the structure of the antihistamine pheniramines to obtain, after many years of work at Astra, zimelidine, the first selective serotonin reuptake inhibitor (► SSRI). Zimelidine was marketed in 1982 but was soon withdrawn because of neurological toxicity. Two other SSRIs were marketed in 1983 (indalpine, later withdrawn because of hematological toxicity) and 1984 (► fluvoxamine), but it was ► fluoxetine (marketed in 1986) that became a byword for SSRI and the most spectacular blockbuster in the history of psychopharmacotherapy, also because of an aggressive marketing campaign by Ely Lilly. However, no consistent relationship has been shown between the therapeutic efficacy of antidepressants and their selectivity for the ► norepinephrine transporter vs. the ► serotonin transporter. Despite all efforts, none of the antidepressants synthesized in the last 50 years exhibited a better therapeutic profile than imipramine, the most important advantage of the newer antidepressants being represented by lesser toxicity, cardiac toxicity in particular.

Anxiolytics. The first drugs with selective ► anxiolytic effects were the ► barbiturates. Barbital (diethylbarbituric acid) was first synthesized in 1902 by Bayer's chemists Emil Fischer and Joseph von Mering, who discovered that it was a very effective hypnotic. ► Barbital was marketed as Veronal in 1904 and along with ► phenobarbital (marketed in 1912 as Luminal) dominated the market of anxiolytic and hypnotic medication until the mid-1950s. Barbiturates, however, become known for the risk of potentially lethal overdosing, their habit-forming properties, and their ability to induce severe ► physical dependence. Thus, it is not difficult to see why, in 1955, the arrival on the market of ► meprobamate (described by Wallace Laboratories as a safe non-addictive alternative to barbiturates) took the medical establishment by storm. Meprobamate was derived from mephenesin, a drug that was developed as a would-be antibiotic but that turned out to have muscle relaxant, sedative and anxiolytic effects. For 10 years, meprobamate was a worldwide best-seller, under the trade names Miltown and Equanil, until it was understood that its toxicity and ► abuse potential was not much different from that of barbiturates. By that time, a much safer alternative to both meprobamate and

barbiturates had become available. The precursors of ▶ benzodiazepines were synthesized in the mid-1930s by Leo Sternbach, a Polish post-doctoral fellow in Krakow who was actually interested in finding new artificial dyes with quinazolinic structure. In 1954, Sternbach, now a chemist at Hoffman-La Roche, resumed working on the quinazolinic structure with the hope of finding a compound that could compete with meprobamate. All derivatives but one were tested and proved to be inactive. Three years later, the last compound, RO5-0690, was found sitting on a shelf by an assistant during a clean up. The results of testing in mice indicated that RO5-0690 had hypnotic and sedative effects similar to that of meprobamate and structural analysis indicated that it was not a quinazoline but a 1, 4 benzodiazepine, which explained why it differed so markedly from the other derivatives. After a further mishap due to the use of extremely high dosages in the first human trial, RO5-0690 (▶ chlordiazepoxide) turned out to be a very promising drug and in 1959 the first meeting focusing on a benzodiazepine was held in Galveston, Texas. Chlordiazepoxide proved to be extremely safe, although it exhibited habit-forming properties and induced physical dependence. In the last 50 years, the me-too strategy has led to the synthesis of more than 100 benzodiazepine analogs, which seem to differ predominantly in terms of ▶ pharmacokinetics. The risk of inducing severe ▶ sedative–hypnotic–anxiolytic dependence has represented the major shortcoming of all anxiolytic treatments until the introduction of ▶ buspirone (a partial agonist to 5-HT_{1A} receptors) in the mid-1980s.

▶ Lithium. Of all psychotherapeutic drugs, lithium has the most bizarre story. During the nineteenth century, lithium bromide was used, like other bromides, to sedate agitated patients although a more specific use as an antimanic drug was advocated as early as 1871 by the American neurologist William A. Hammond. Lithium was also used as an antirheumatic drug and, given the association that was believed to exist between rheumatism and depression, many physicians in Europe recommended it for the therapy of ▶ mania and depression. However, by the early 1940s, the widespread use of lithium chloride, instead of sodium chloride, by hypertensive patients, unveiled its serious neurological and cardiac toxicity, which led the Food and Drug Administration to ban it. Not surprisingly, the 1949 report by John Cade, a previously unknown Australian physician, claiming that lithium was highly effective in manic patients was met with a high degree of skepticism, not to say outright hostility. The naive pathogenic theory proposed by Cade to explain his findings did not help either. Finally, yet importantly, pharmaceutical companies had little or no interest in developing medications that no patent could protect. Mogens Schou, a Danish psychiatrist, and his collaborators, in a series of studies published between 1954 and 1970, demonstrated, beyond any reasonable doubt, that lithium carbonate was indeed an effective antimanic drug. Despite the recent introduction of "▶ mood stabilizers" such as ▶ lamotrigine, ▶ valproic acid, and ▶ carbamazepine, lithium remains the first-line treatment for mania.

Conclusions

The discovery of antipsychotic and antidepressant drugs in the 1950s, albeit of a largely serendipitous nature, powerfully catalyzed the research on chemical neurotransmission that had been going on since the early twentieth century, culminating in the identification of neurotransmitters. Another consequence of the interaction between psychiatry and pharmacology has been the development of ▶ animal models of schizophrenia (e.g., ▶ startle response, ▶ prepulse inhibition), ▶ animal models of depression (e.g., ▶ social stress, ▶ chronic mild stress, and other types of stress), and a variety of other ▶ animal models (e.g., attention hyperactivity disorders, eating disorders, anxiety, addictive disorders). These models have been increasingly employed in conjunction with techniques from molecular biology involving genetically modified animals. As a result, spectacular advances in our understanding of the neurobiology of normal and abnormal mental functions have occurred in the last 50 years and it seems reasonable to expect that this increment in knowledge will eventually lead to major therapeutic discoveries. Some limited success has already been achieved, as in the pharmacotherapy of heroin, alcohol, and tobacco addiction (e.g., ▶ methadone and ▶ buprenorphine for heroinism; ▶ varenicline, tobacco-free nicotine delivery devices, and ▶ bupropion for tobacco addiction; benzodiazepines, ▶ naltrexone, ▶ disulfiram, and ▶ acamprosate for alcoholism). Yet, the fact remains that the last major breakthrough in the pharmacotherapy of psychiatric disorders occurred about 50 years ago and that relatively little is presently available for the pharmacological therapy of obsessive–compulsive disorders, autism, eating disorders, aggressive behavior, dementia, etc.

Cross-References

▶ Addictive Disorder: Animal Models
▶ Alcohol
▶ Alcohol Abuse and Dependence
▶ Aminergic Hypotheses for Depression
▶ Aminergic Hypotheses for Schizophrenia

- ▶ Animal Models for Psychiatric States
- ▶ Anticonvulsants Drug
- ▶ Antidepressants
- ▶ Antipsychotic
- ▶ Barbiturates
- ▶ Benzodiazepines
- ▶ Caffeine
- ▶ Cannabinoids and Endocannabinoids
- ▶ Classical (Pavlovian) Conditioning
- ▶ Classification of Psychoactive Drugs
- ▶ Cocaine
- ▶ Depression: Animal Models
- ▶ Drug Discrimination
- ▶ First-Generation Antipsychotics
- ▶ Glutamate Receptors
- ▶ Hallucinogens
- ▶ Hypnotics
- ▶ Khat
- ▶ Lithium
- ▶ Monoamine Oxidase Inhibitors
- ▶ Mood Stabilizers
- ▶ Nicotine
- ▶ Operant Behavior in Animals
- ▶ Opioids
- ▶ Placebo Effect
- ▶ Ritual Uses of Psychoactive Drugs
- ▶ Schizophrenia
- ▶ Schizophrenia: Animal Models
- ▶ Sedative, Hypnotic & Anxiolytic Dependence

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Homeothermy

Definition

It refers to the maintenance of a constant body temperature in warm-blooded animals. This is typically achieved by the use of physiological processes to compensate for heat loss or gain when environmental temperatures change. Strategies typically recruited include generation of heat by metabolism, muscle contraction, and heat radiation by sweating or panting. Homeotherms generally have an insulating material to retain heat such as fur or fat. Infants of some species including rats and mice achieve homeothermy postnatally.

Homosynaptic

Definition

When events at a single synapse or group of synapses occur but do not involve interactions between synapses or groups of synapses.

Hormones

Definition

Hormones are substances produced by an organ and released into the bloodstream to have their effect on a target organ some distance away.

HPA

▶ Hypothalamic–Pituitary–Adrenal Axis

HPLC

Synonyms

High pressure liquid chromatography

Definition
High pressure liquid chromatography (HPLC) is a form of column chromatography used frequently in biochemistry and analytical chemistry in order to separate, identify, and quantify compounds. HPLC utilizes a column that holds chromatographic packing material (stationary phase), a pump that moves the mobile phase(s) through the column, and a detector that shows the retention times of the molecules. Retention time varies depending on the interactions between the stationary phase, the molecules being analyzed, and the solvent(s) used.

HPPD

▶ Hallucinogen Persisting Perception Disorder

HRT

▶ Habit Reversal Therapy
▶ Habit Reversal Training

5-HT

▶ Serotonin

5-HT_{1A} Receptor

Cross-References
▶ Antidepressants
▶ 5-HT_{2A} Receptor
▶ Serotonin

5-HT2A Receptor

Definition
A member of the serotonin 5-HT_2 receptor family – one of the Type A family of G-protein-coupled receptors. It is a seven-transmembrane helical bundle that responds to binding of serotonin by activating second messengers within the cell. Typically, one of the major signals is generation by coupling to Gaq, which leads to phosphoinositide hydrolysis. The receptors are highly expressed on apical dendrites of cortical pyramidal cells, where their activation enhances the gain of cortical cell signaling.

Hug Drug

▶ Methylenedioxymethamphetamine (MDMA)

Human Medicinal Product

▶ Medicine

Hunger

Definition
A subjective feeling, comprising the visceral and emotional components associated with the desire to eat. Occurs in response to energy need (such as after fasting), or may be stimulated in response to external food stimuli irrespective of bodily need. Commonly occurs as a conditioned response to the expected delivery of food at regular, predictable mealtimes. The term is also used to refer to an inferred drive to consume food. Hunger is not purely biologically driven but is also context- and time-specific. At certain times and in certain situations, organisms expect to eat and hunger may be a conditioned response. Hunger is also stimulated by food cues and food availability.

Cross-References
▶ Appetite
▶ Eating and Appetite
▶ Satiety

Hunger-Mimetics

▶ Appetite Stimulants

Huntington's Disease

Synonyms
HD

Definition
An autosomal-dominant neurodegenerative disease due to a single mutation involving polyglutamine expansion

of >38 CAG repeats in exon 1 of the *huntingtin* gene on chromosome 4. HD is associated with a complex of motor cognitive and psychiatric symptoms, with a mean age of onset around 40 years (the actual age in individual patients correlates inversely with the CAG repeat length), and progressing to death over a course of 15–20 years. The huntingtin protein is involved in multiple subcellular processes including protein trafficking, nuclear uptake, and energy metabolism. The mutation results in intracellular aggregation and formation of nuclear inclusions of fragments of the mutant huntingtin protein and degeneration of the affected cells. ► Neurodegeneration is focused initially in the neostriatum (caudate nucleus and putamen), but spreads to associated cortical areas as the disease progresses, ultimately resulting in widespread neurodegeneration and brain atrophy. HD is most usually modeled in experimental animals by neurotoxic lesions of the neostriatum and more recently in a number of strains of transgenic mice and rats carrying the expanded CAG mutation in the huntingtin gene.

Hydrocodone

Synonyms
Dihydrocodeinone

Definition
Hydrocodone belongs to the opioid (narcotic) analgesic medication class as well to the antitussive medications class. It is a semisynthetic opioid derived from two natural opioids: ► codeine and thebaine. Hydrocodone is available only in combination with other ingredients and different product combinations are prescribed for different uses. Some hydrocodone products are used to relieve moderate to severe pain, whereas others are used for cough relief. Hydrocodone may cause side effects typical of opiate drugs such as nausea, vomiting, constipation, drowsiness, dry throat, itching, and constriction of the pupils.

Cross-References
► Analgesics
► Dependence
► Opioids
► Pain
► Tolerance
► Withdrawal Syndromes

Hydromorphone

Synonyms
Dihydromorphinone; Dimorphone

Definition
Hydromorphone is an opioid narcotic medication acting mainly on μ-opioid receptors. It is used in the treatment of pain in emergency situations and in patients suffering from chronic long-term pain. Like ► morphine, it has the potential to lead to abuse and long-term dependence on the drug, but some studies show that hydromorphone has a lesser tendency for these actions compared to morphine. Like morphine, it can produce physical dependence and a ► withdrawal syndrome.

Cross-References
► Analgesics
► Opioid Dependence and Its Treatment
► Opioids
► Physical Dependence

14-Hydroxy-Dihydromorphinone

► Oxymorphone

6-Hydroxydopamine

Synonyms
6-OHDA

Definition
6-hydroxydopamine (6-OHDA), a hydroxylated analog of dopamine, is a neurotoxin commonly used in neurobiological research to lesion dopaminergic and/or noradrenergic pathways. Its biological effects were initially described in the hearts of mice in the early 1960s. 6-OHDA was subsequently shown to produce anterograde degeneration of the nigrostriatal dopaminergic system when injected in the substantia nigra pars compacta. It has since extensively been used to produce animal models of Parkinson's disease and, more recently, of ADHD and other neurobehavioral deficits.

Cross-References
► Attention Deficit Hyperactivity Disorders: Animal Models
► Neurotoxicity
► Neurotoxins

3-Hydroxy-l-Tyrosine

► Levodopa

9-Hydroxyrisperidone

► Paliperidone

5-Hydroxytryptamine

► Serotonin

Hyoscine

► Scopolamine

Hyperactive Delirium

Definition

The hyperactive delirium is a subtype of delirium that is commonly characterized by restlessness, agitation, hypervigilance, hallucinations, and delusions. Hyperactive delirium is correlated with alcohol and drug withdrawal, drug intoxication, or medication adverse effects.

Hyperactivity

Synonyms

Hyperkinesias; Hyperlocomotion; Restlessness

Definition

In behavioral neuroscience, hyperactivity is a state of abnormally elevated locomotor and muscular activity. Especially in children, hyperactivity is often accompanied by impulsiveness, aggressive tendencies, and difficulties to concentrate. These and other symptoms are usually found together in the combined type of the ► ADHD syndrome. Paradoxically, psychomotor stimulants are widely used to reduce pathological hyperactivity in both humans and animal models of ADHD.

Cross-References

► Attention Deficit and Disruptive Behavior Disorders
► Attention Deficit Hyperactivity Disorders: Animal Models
► Impulse Control Disorders
► Impulsivity
► Methylphenidate
► Psychomotor Stimulants

Hyperalgesia

Definition

Hyperalgesia is an exaggerated response to a painful stimulus that can occur after tissue injury or nerve ligation. Some drugs may also induce hyperalgesia.

Cross-References

► Analgesics
► Opioids

Hyperkinesias

► Hyperactivity

Hyperkinetic Child Syndrome

► Attention Deficit and Disruptive Behavior Disorders
► Attention Deficit Hyperactivity Disorder

Hyperlocomotion

► Hyperactivity

Hyperphagia

Synonyms

Overconsumption; Polyphagia

Definition

An excessive consumption of food beyond that needed for basic energy requirements, which may occur in

association with central nervous system disorders. In animals, overeating or over consumption of calories is usually produced when an animal is given prolonged access to a highly palatable energy-dense diet. It can also be induced by administration of ► appetite stimulant drugs (orexigens). Hyperphagia is essential in animal models of dietary-induced obesity. Hyperphagia is more difficult to induce through pharmacological intervention than hypophagia.

Cross-References
► Appetite
► Appetite Stimulants
► Hunger
► Hypophagia

Hyperphagics

► Appetite Stimulants

Hyperpolarization

Definition
A transient increase in the relative negativity of the intracellular potential, usually causing a reduced excitability of the neurone.

Hyperprolactinemia

Synonyms
Elevated prolactin; Elevated luteotropic hormone

Definition
The presence of abnormally high levels of prolactin in the blood. Prolactin is primarily produced and secreted by lactotrope cells of the anterior pituitary gland (adenohypophysis), which in turn is regulated by neuroendocrine neurons in the ► hypothalamus. Specifically, dopamine released from the median eminence into hypophysial portal blood acts on dopamine D_2 receptors to inhibit prolactin release. Conversely, blockade of dopamine D_2 receptors, as can occur with ► antipsychotics, leads to hyperprolactinemia. All ► first-generation antipsychotics are associated with elevated prolactin. As a class, the ► second-generation antipsychotics demonstrate a decreased risk in this regard, with the exception of the substituted benzamides (e.g., amisulpride, sulpiride), risperidone, and paliperidone (9-hydroxy-risperidone). That these agents represent exceptions appears related to a combination of factors including ► elimination half-life and ► blood–brain barrier permeability. For example, substituted benzamides are administered in higher doses as they cross the barrier relatively poorly; however, the median eminence is termed a "circumventricular organ" that allows for permeability in this region.

Symptoms related to elevated prolactin in women include amenorrhea, oligomenorrhea, galactorrhea, infertility, and decreased libido. In males, symptoms include gynecomastia, galactorrhea, infertility, decreased libido, and reduced muscle mass. Hyperprolactinemia has also been linked to several types of cancer (breast, endometrial), increased platelet aggregation, and osteopenia with sustained elevations. At present, treatment of hyperprolactinemia generally involves switching to one of the atypical antipsychotics not linked to this particular side effect.

Cross-References
► Antipsychotics
► Sex Differences in Drug Effects

Hyperserotoninemia

Definition
Hyperserotoninemia stands for elevated, whole blood serotonin level. This is one of the most consistent biological findings in autism found in 30% of patients. Elevated serotonin blood level has also been found in families of autistic patients.

Cross-References
► Autism: Animal Models
► Autism Spectrum Disorders and Mental Retardation

Hypersomnias

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Synonyms
Excessive daytime sleepiness; Excessive sleep; Hypersomnia; Narcolepsy

Definition

The hypersomnia disorders, or hypersomnias of central origin, are those in which the primary complaint is daytime sleepiness and in which the cause of the primary symptom is neither a circadian rhythm sleep disorder nor a sleep related breathing disorder nor any other cause of disturbed nocturnal sleep (ICSD-2). Daytime sleepiness is defined as the inability to stay awake and alert during the major waking episode of the day, resulting in unintended lapses into drowsiness or sleep.

Role of Pharmacotherapy

Daytime sleepiness is not a homogeneous concept. It can manifest itself as bouts of sleepiness building up into irresistible and refreshing sleep episodes. In other cases, it is associated with large increases in total daily amount of sleep with a major difficulty waking up at the end of the night or of a nap and no feeling of restoration. Rarely it can consist of periods of a week or so of almost continuous sleep, recurring at several months' interval. More frequently the pattern is one of sleepiness most apparent in the afternoon and early evening and awakening later on weekends or on days off.

The occurrence of excessive daytime sleepiness in the general population ranges from 5 (severe) to 15% (moderate) (Ohayon et al. 1997).

Daytime sleepiness has a clear impact on the life of the patient with the risk of automobile or work accidents, impaired academic or work performance, disruption of family life, and impaired cognitive function.

The severity of daytime sleepiness can be quantified subjectively, using the Epworth Sleepiness Scale, a scale rating the probability of dozing in eight more or less soporific daily situations (Johns 1994), and objectively, using the Multiple Sleep Latency Test, a test measuring the tendency to fall asleep in a quiet situation, repeated five times throughout the day (Littner et al. 2005).

Diagnostic Categories

The ICSD-2 includes ten diagnostic categories under the heading of hypersomnia of central origin:

- Narcolepsy with cataplexy is characterized by two cardinal symptoms – excessive daytime sleepiness/sleep attacks and cataplexy, and other clinical features, hypnagogic and hypnopompic hallucinations, sleep paralysis and disturbed nocturnal sleep, that are not necessarily part of the actual clinical picture.
- Narcolepsy without cataplexy includes the same symptoms except cataplexy.
- Narcolepsy due to medical condition. The distinctive feature of this subtype of narcolepsy is the existence of a significant underlying medical or neurological disorder accounting for the excessive daytime sleepiness/sleep attacks and/or cataplexy.
- Recurrent hypersomnia, most classically the Kleine–Levin syndrome, characterized by recurrent episodes of hypersomnia associated with behavioral and cognitive abnormalities.
- Idiopathic hypersomnia with long sleep time. In this condition, the patient has a complaint of excessive daytime sleepiness associated with prolonged nocturnal sleep and major difficulty in awakening at the end of night sleep or of a nap.
- Idiopathic hypersomnia without long sleep time is remarkable for excessive daytime sleepiness only.
- Behaviorally induced insufficient sleep syndrome occurs when a subject persistently fails to obtain the amount of sleep required to maintain normal levels of alertness and wakefulness.
- Hypersomnia due to medical condition depends on a coexisting medical or neurological disorder that produces hypersomnia.
- Hypersomnia due to drug or substance covers hypersomnias associated with tolerance to or withdrawal from various prescribed or street drugs.
- Hypersomnia that is not due to substance or known physiological condition (psychiatric hypersomnia) is a type of hypersomnia temporally associated with a psychiatric disorder.

According to a recent study that reviewed the diagnoses of 1,243 patients referred to a Japanese outpatient clinic for complaint of excessive daytime sleepiness, the most frequent diagnosis (34.7%) was obstructive sleep apnea syndrome (not a disorder of hypersomnia of central origin), followed by idiopathic hypersomnia (10.9%), narcolepsy (8.8%), behaviorally induced insufficient sleep syndrome (7.1%), ▶ circadian rhythm sleep disorders (6.1%) (not a disorder of hypersomnia of central origin), and hypersomnia not due to substance or known physiological condition (4.3%) (Komoda et al. 2008). Hypersomnia due to medical condition and hypersomnia due to drug or substance were not listed and recurrent hypersomnia accounted only for 0.2% of the diagnoses.

Prior to committing to long-term therapy of hypersomnia, an accurate diagnosis is important in order to choose an appropriate therapy. The ICSD-2 specifies necessary diagnostic tests and criteria for each disorder of hypersomnia of central origin. Treatment objectives should include control of excessive daytime sleepiness

and other sleep-related symptoms, such as cataplexy in the case of narcolepsy or the underlying condition in case of hypersomnia due to medical condition. A range of drugs is available to treat hypersomnia (Table 1).

Efficacy

All the listed drugs have been systematically studied in narcoleptic patients. Moreover only the new drugs, ► modafinil and sodium ► oxybate, have been subjected to a series of randomized, double blind, placebo-controlled trials (The US Xyrem Multicentre Study Group 2002; The Xyrem International Study Group 2005; US Modafinil in Narcolepsy Multicenter Study Group 1998; US Modafinil in Narcolepsy Multicenter Study Group 2000). Modafinil and sodium oxybate have been approved by the European Medicines Agency (EMEA) and the US Food and Drug administration (US FDA), and ► methylphenidate by some European countries (Belgium, Denmark, France, Germany, and Switzerland) and the US FDA.

Hypersomnias. Table 1. Drugs used as stimulants.

Drugs	Mechanisms	Starting/ maximum dose	Adverse effects/remarks
Long used drugs			
Amphetamines			
D-amphetamine	Induces dopamine release and, to a lesser extent, norepinephrine and serotonin	5 mg/60 mg	Increase in heart rate and blood pressure Irritability, nervousness Anorexia, nausea
Methamphetamine	Induces dopamine release and, to a lesser extent, norepinephrine and serotonin	5 mg/60 mg	Increase in heart rate and blood pressure Irritability, nervousness Anorexia, nausea
Amphetamine-like drugs			
Methylphenidate	Induces dopamine release	10 mg/60 mg	Same as with amphetamines but less marked
Pemoline	Blocks dopamine reuptake	37.5 mg/75 mg	Minimal sympathomimetic effects Potential hepatotoxicity (withdrawn from the market)
Mazindol	Induces a weak dopamine release Also blocks dopamine and norepinephrine reuptake	2 mg/8 mg	Sympathomimetic effects Rare cases of pulmonary hypertension and valvular abnormalities (withdrawn from the market in several countries)
Selegiline	Selective monoamine oxidase B Inhibitor (metabolically converted to amphetamine and methamphetamine)	10 mg/40 mg	Sympathomimetic effects Interaction with other drugs (tryptophan, serotonin) (only occasionally used)
Newer drugs			
Modafinil	Unknown mechanism but presumably involves dopamine reuptake inhibition	100 mg/400 mg	Headache, nausea, nervousness, rhinitis Induction of human hepatic cytochrome P450 enzymes
Sodium oxybate	The sodium salt of GHB, a neuromodulator of GABA, serotonin, dopamine and endogenous opioids	4.5 g/9 g	Headache, nausea, dizziness, enuresis

If one considers the most recent drugs, modafinil and sodium oxybate, the first has been approved in France in 1994 and in the USA in late 1998, while sodium oxybate has been approved more recently in 2005.

A conservative therapy, based on the well-tested efficacy of the drug and its limited adverse effects, consists in using modafinil first, in a split dose strategy with 200 mg in the morning and 200 mg at 12:00. In case of insufficient efficacy or of a secondary relapse, modafinil is supplemented with either methylphenidate (on an as-needed basis) or sodium oxybate at a dose of 4.5 g in two divided doses at night (Billiard 2008).

A more recent therapeutic approach consists in using sodium oxybate as a first-line treatment, based on the efficacy of the drug on the three main symptoms of narcolepsy, excessive daytime sleepiness/sleep attacks, cataplexy, and disturbed nocturnal sleep. The initial dose is 4.5 g in two divided doses at night, one at bedtime and another one 2.5–4 h later. The dose may be increased to a maximum of 9 g/night, divided into two equal doses of 4.5 g (Billiard 2008). Most patients will start to feel better within the first few days, but optimal response at any given dose may take as long as 8–12 weeks. In case of insufficient efficacy, sodium oxybate is supplemented with either modafinil or methylphenidate. In either case, the place for other stimulants, ► amphetamines and amphetamine-like drugs, has become extremely limited, due to potential adverse effects.

In addition to pharmacotherapy, behavioral treatment measures are always advisable in the case of narcolepsy. Essentially, the studies available support the recommendation for planned naps during the day, as naps decrease sleep tendency and shorten reaction time. Because of limitations on work or home times, naps are best scheduled on a patient-by-patient basis.

As concerns the other hypersomnias of central origin, pharmacotherapy depends on the disorder. In the case of recurrent hypersomnias, all attempted therapies have been disappointing. Idiopathic hypersomnia with or without long sleep time is treated by modafinil or methylphenidate. Results range from good to poor. Behaviorally induced insufficient sleep syndrome is best treated in encouraging patients to increase their time in bed either at night and/or in taking naps. The treatment of hypersomnia due to a medical condition, such as stroke, encephalitis, tumor, and neurodegenerative disease, is always challenging because excessive daytime sleepiness is often a multifactorial phenomenon including poor sleep at night, depression, effects of medication(s), and the effect of the disease itself. Hypersomnia due to drug or substance is to be treated by withdrawal of these, which is most often difficult to achieve. Psychological supportive therapy is required. Hypersomnia not due to substance or known physiological condition comes under the treatment of the psychiatric condition. However, the addition of modafinil is often necessary (Morgenthaler et al. 2007).

Tolerability

The different possible adverse effects of the various stimulants are listed on Table 1. Modafinil is probably the drug with the least adverse effects. As far as sodium oxybate is concerned, if one follows the titration rules strictly, that is, an initial prescription of 4.5 g divided into two equal doses of 2.25 g/night, and then increase to a maximum dosage of 9 g/night, by increments of 1.5 g at a 2-week interval, the likelihood of adverse effects is relatively limited.

Risks of tolerance and dependence

► Tolerance to amphetamine and amphetamine-like stimulants. may develop in up to one-third of patients, but abuse potential is generally low in narcoleptic patients. There is no evidence of tolerance and ► dependence with modafinil. In the case of sodium oxybate, the most problematic adverse effect was expected to be drug abuse. However, the monitored prescription program in the USA revealed that this is a very low risk in narcoleptic patients.

Future treatments

At present, there is not much research oriented toward the treatment of the different categories of hypersomnias, except for narcolepsy. In this case, the major development in understanding the neurobiological basis of the condition has led to several focuses for future treatments, namely symptomatic neurotransmitters, endocrine therapy, immunotherapy, and hypocretin-based therapies (Mignot and Nishino 2007).

Novel compounds currently in development include armodafinil, the R-enantiomer of the racemic compound modafinil, and an inverse H-3 receptor agonist (tiprolisant). The first one has already been evaluated in humans and seems promising, while the second has been tested with success in canine and murine models of narcolepsy and in a pilot single-blind trial of narcoleptic patients receiving a placebo followed by tiprolisant, both for one week. Thyrotrophin-releasing hormone has been shown to increase wakefulness in canine narcolepsy.

Based on the not yet confirmed autoimmune hypothesis of narcolepsy, treatments such as intravenous immunoglobulins have been tried in children with some uncontrolled but promising results.

Now, as ► hypocretin/orexin deficiency is the cause of most narcolepsy in humans, the best standard for narcolepsy treatment is likely to aim at replacing the missing neurotransmitter. Various approaches are being considered including administration of hypocretin-1, cell transplantation, and gene therapy.

Conclusion

The treatment of hypersomnias of central origin varies with the actual disorder. The most advanced treatment is the one for narcolepsy, due to the fact that the approved drugs have undergone several randomized, double blind, placebo-controlled clinical trials. Moreover, due to major advances in the understanding of the neurobiological basis of narcolepsy, new treatments are being tested in animal models and some of them in humans. Other hypersomnias have not benefited from systematic pharmacological trials and there is a need for studies testing commonly used stimulants in these disorders.

Cross-References

► Hypersomnia of Central Origin
► Psychostimulants

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Hypersomnias of Central Origin

Definition

Hypersomnias in which the primary complaint is daytime sleepiness and the cause of this symptom neither a circadian rhythm sleep disorder nor a sleep-related breathing disorder or another cause of disturbed nocturnal sleep.

Hyperventilation

Definition

Hyperventilation is when a person breathes abnormally, both too quickly and too deeply.

Cross-References

► Agoraphobia
► Panic

Hypnagogic Hallucination

Definition

A vivid, dream-like sensation of seeing, hearing, or feeling something that occurs just before sleep onset. Although described as one of the symptoms of narcolepsy, taken alone is considered a normal phenomenon.

Hypnotic Dependence

► Sedative, Hypnotic, and Anxiolytic Dependence

Hypnotics

Definition

Drugs used for the treatment of insomnia.

Hypoactive Delirium

Definition

Hypoactive delirium is a subtype of ► delirium that is characterized by psychomotor retardation, lethargy, sedation, and reduced awareness of surroundings. The hypoactive subtype of delirium is commonly misdiagnosed as depression. Hypoactive delirium has generally been found to occur due to hypoxia, metabolic disturbances, and hepatic encephalopathies.

Hypochondria

► Somatoform and Body Dysmorphic Disorders

Hypocretins

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Synonyms

Orexins

Definition

The hypocretins (Hcrt1 and Hcrt2), also known as orexin A and orexin B, are two ► neuropeptides expressed in a few thousand neurons in the lateral hypothalamus (de Lecea et al. 1998; Sakurai et al. 1998), which are critical for arousal stability. Lack of Hcrt neurons or peptides leads to narcolepsy with or without cataplexy.

Pharmacological Properties

Hcrt peptides are derivatives of a longer precursor of 130 residues, with an apparent signal sequence.

The C-terminal 19 residues of these two putative peptides – Hcrt2 (28 residues; RPGPPGLQGRLQRLLQA NGNHAAGILTM-amide) and Hcrt1 (33 residues; EPL PDCCRQKTCSCRLYELLHGAGNHAAGILTL-amide) – share 13 amino-acid identities, suggesting that the peptides have related structures and functions. This region of Hcrt2 contains a seven-amino acid match with secretin. Hcrt1 contains two intrachain disulfide bonds. Human Hcrt1 is identical to the rodent peptide, whereas human Hcrt2 differs from rodent Hcrt2 at two residues. The non-amidated forms of the peptides are electrophysiologically inactive.

Receptors and Signaling Cascades

The initial orphan GPCR, Hcrtr1, binds Hcrt1 with high affinity, but Hcrt2 with 100–1,000-fold lower affinity (Sakurai et al. 1998). A related GPCR, Hcrtr2, sharing 64% identity with Hcrtr1, was identified by searching database entries with the Hcrtr1 sequence and has a high affinity for both Hcrt2 and Hcrt1. These two receptors are highly conserved (95%) across species. Radioligand-binding studies and calcium flux measurements have shown Hcrt1 to have equal affinity for Hcrtr1 and Hcrtr2, whereas Hcrt2 has ~10-fold greater affinity for Hcrtr2 than Hcrtr1.

The mRNAs that encode the two Hcrt receptors and the receptor proteins themselves, detected by immunohistochemistry, are both enriched in the brain and moderately abundant in the hypothalamus, but have different distributions within the brain.

Hcrt receptors are also widely expressed in the periphery, especially in endocrine tissues including the pituitary, adrenal gland, testis, gastrointestinal tract, pancreas, and pineal gland.

Both Hcrtr1 and Hcrtr2 act through a family of GTP-binding proteins (Gq) that activate protein kinase C (PKC) and mobilization of intracellular calcium. Gq-activated signaling cascades result in phosphorylation of Ca^{2+} channels, which can increase Ca^{2+} conductance and neuronal excitability.

Biological Actions Within the Brain

Experimental administration of Hcrt peptides to animals stimulates food intake, affects motivation and rewarding behavior, and modifies arousal.

Feeding and Metabolism

Sakurai et al. (1998) found that intracerebroventricular (ICV) administration of either Hcrt1 or Hcrt2 increased short-term food consumption in rats. Other findings suggest that the hypocretins are not critical players in feeding activities, but rather play roles in increasing arousal and motivation. Continuous administration of Hcrt1 for seven days in rats does not significantly alter daily food intake, body weight, blood glucose, total cholesterol, or free fatty acid levels, suggesting that many of hypocretin's effects may be limited to short-term, immediate stimulation of feeding behavior consequent to the increased wakefulness. Hcrt deficient mice show very modest, if significant, differences in food intake. Hypocretin-► ataxin 3 transgenic mice, which are genetically depleted of hcrt

neurons and would be expected to be lean, show obesity, and hypolocomotion, and this effect appears to be dependent on diet and genetic background. During fasting, Hcrt1 accumulation in the CSF does not exceed concentrations normal for the waking period. In addition, hcrt ataxin-3 mice, unlike wild-type animals, do not show an increase in locomotor activity after fasting. All these data suggest that some of the food-uptake effect may result from arousal rather than direct feeding pressure.

Motivation and Addiction

Hcrt neurons are highly responsive to ► morphine and their activation is linked to preferences for cues associated with drug and food reward and also naltrexone-precipitated withdrawal. Moreover, Hcrt reinstates extinguished drug-seeking behavior, an effect blocked by an Hcrt1 antagonist (Boutrel et al. 2005) (► Addictive disorder: animal models). Hcrt1 infusion into the ventricle or the VTA leads to a dose-dependent reinstatement of alcohol and cocaine-seeking behavior (► Alcohol abuse and dependence; ► Cocaine dependence; ► Reinstatment of self administration; ► Operant behavior in animals) and it also increases intracranial self-stimulation thresholds. Hcrt-induced reinstatement of cocaine-seeking was prevented by the blockade of noradrenergic and corticotropin-releasing factor systems. Accordingly, a Hcrt1 receptor antagonist blocks footshock-induced reinstatement of previously extinguished cocaine-seeking behavior leading to the conclusion that Hcrt is a major gate in driving stress-mediated drug seeking behavior.

Arousal

In vivo recordings of Hcrt neurons have revealed that these cells do not fire tonically, but rather show bursts of activity at the transitions between sleep and wakefulness, and during exploratory or consummatory behavior (Mileykovskiy et al. 2005). More recently, Adamantidis et al. (2007) used ► optogenetic methods to demonstrate that activation of Hcrt neurons is sufficient to induce wakefulness (Adamantidis et al. 2007).

(a) Rodent models

Continuous recording of the behavior of Hcrt gene deleted mice (Hcrt knockout mice) revealed periods of ataxia, which were especially frequent during the dark period. (Chemelli et al. 1999) EEG recordings showed that these episodes were not related to epilepsy, and that the mice suffered from cataplexy-like attacks with their EEGs showing episodes of direct transition from wakefulness to REM sleep, the hallmarks of narcolepsy (Chemelli et al. 1999). Similar observations were made in rats in which the hypocretin neurons of the lateral hypothalamus were inactivated by ► saporin targeting, although in this model, cataplexy was not observed. Mice with an inactivated Hcrtr 2 gene have a milder narcoleptic phenotype than the Hcrt knockouts; Hcrtr 1 knockouts exhibit only a sleep fragmentation phenotype, whereas double Hcrtr 1 and Hcrtr 2 mutants recapitulates (almost) the full Hcrt knockout phenotype, suggesting that signaling through both receptors contributes to normal arousal, although the role of Hcrtr 2 is greater than that of Hcrtr 1.

Mouse and rat models of ► narcolepsy have been generated by expressing a mutant form of ataxin 3. These transgenic animals show progressive depletion of Hcrt neurons, and display a narcolepsy-like phenotype.

(b) Human narcolepsy

Nishino et al. (2000) studied Hcrt-1 concentrations in the cerebral spinal fluid (CSF) of normal controls and patients with narcolepsy by radioimmunoassay. Hcrt-1 was undetectable in 37 of 42 narcoleptics and in a few cases of Guillain-Barré syndrome. CSF Hcrt-1 was in the normal range for most neurological diseases, but was low, although detectable, in some cases of CNS infections, brain trauma and brain tumors (► Hypersomnias). The absence or very low levels of CSF Hcrt-1 have been replicated independently in narcolepsy patients with or without cataplexy.

Peyron, Thannikal and their teams of collaborators (Peyron et al. 2000; Thannickal et al. 2000) found that, in the brains of patients with narcolepsy, only few or no Hcrt-producing neurons could be detected. Hcrt neurons are likely selectively depleted, as other markers that colocalize in these neurons such as preprodynorphin are also absent in the hypothalamus of narcoleptic patients, whereas co-distributed MCH neurons are unaffected. Furthermore, a single patient with a non-HLA-linked narcolepsy carries a mutation within the Hcrt gene itself. The mutation results in a dominant negative amino acid substitution in the secretion signal sequence that sequesters both the mutant and heterozygous wild-type Hcrt nonproductively to the smooth endoplasmic reticulum. These findings leave no doubt as to the central role of the Hcrt system in narcolepsy. Because most cases are sporadic, mutations in the Hcrt gene or those for its receptors can account for no more than a small subset of the human narcolepsies. The HLA association, loss of neurons with signs of gliosis, and age of disease onset are consistent with autoimmune destruction of the Hcrt neurons accounting for the majority of narcolepsy, although a nonimmune-mediated degenerative process has not been ruled out.

Current treatment of narcolepsy includes ► modafinil and psychostimulants to promote alertness during the day and sodium oxybate to consolidate sleep during the rest period. Modafinil has been shown to activate Hcrt neurons in the hypothalamus, although this effect is not selective.

Several Hcrtr 1 selective antagonists have been reported. Recently, a nonselective orally bioavailable Hcrt receptor antagonist (almorexant) has been shown to promote sleep in dogs and humans (Brisbare-Roch et al. 2007). This small molecule Hcrt receptor antagonist has great promise in the treatment of insomnia (► Hypnotics) as well as prevention of relapse of drug seeking and modulation of metabolism.

Cross-References

► Addictive Disorder: Animal Models
► Alcohol Abuse and Dependence
► Animal Models of Psychiatric States
► Circadian Rhythms
► Cocaine Dependence
► Hypersomnias
► Hypnotics
► Modafinil
► Operant Behavior in Animals
► Reinstatement of Self Administration

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Hypocretins/Orexins

Definition

The hypocretin peptides, hypocretins 1 and 2, were discovered and named in 1998. The name "hypocretin" was derived to reflect the primary localization of hypocretin-producing cells in the hypothalamus and a sequence similarity with the hormone secretin.

In parallel, endogenous ligands to two orphan receptors with homologous structures had been identified and called orexins A and B because of their stimulating effects on appetite.

The orexin peptides turned out to be the same as hypocretins.

Hypometria

Definition

An undershoot in saccade amplitude, that occurs most acutely for internally generated saccades, often observed in patients with Parkinson's disease or medicated patients with schizophrenia.

Hypophagia

Definition

The suppression of caloric intake in animals usually resulting from a reduction in feeding behavior brought about by drug administration or other biological (e.g., surgical) or environmental interventions (such as change in diet). This is usually the first indication of a drug's

appetite-suppressing potential. However, drugs can reduce caloric intake through a variety of non-appetite mechanisms such as nausea, behavioral disruption (sedation or hyperactivity), or malaise.

Cross-References

► Appetite Suppressants

Hypophagics

► Appetite Suppressants

Hypothalamic–Pituitary–Adrenal Axis

Synonyms

HPA

Definition

Refers to a coordinated pattern of stimulation and feedback interaction between hypothalamic paraventricular neurons, pituitary corticotrophs, and the adrenal cortex with the aim to facilitate adaptation to stress and synchronize daily and sleep-related events.

Hypothalamus

Definition

A portion of the brain that contains a number of small nuclei with a variety of functions. The main function of the hypothalamus is to maintain homeostasis. Some cells of the hypothalamus detect changes in the levels of metabolites and hormones and participate in the control of metabolic and neuroendocrine functions.

Hypothermia

Definition

The situation where the body temperature of a warm-blooded creature is reduced to being lower than normal for that species. Hypothermia can be produced by either exposure of the animal to low ambient conditions or can be induced by administration of certain chemical compounds.

Hypovase®

► Prazosin

I

IACUC

Synonyms
Institutional animal care and use committee

Definition
Institutional Animal Care and Use Committee is a local committee composed of practicing scientists experienced in research involving animals, specialists in veterinary medicine, animal care technicians, nonscientists, and lay representatives who oversee the care and use of animals used in biomedical research.

ICD

Definition
International Statistical Classification of Diseases and Related Health Problems (currently in its tenth edition). Provides codes for classifying symptoms and diseases, and includes a section on mental and behavioral disorders.

ID

► Intradimensional

Idiopathic

Definition
This is a term used in medicine for a condition that arises spontaneously or where the cause is unknown.

Illness Anxiety

► Somatoform and Body Dysmorphic Disorders

Imaging Mass Spectrometry

Synonyms
IMS; Mass spectrometry imaging; MSI

Definition
IMS allows an image of a brain tissue section to be acquired at a specific molecular weight and provides the investigator with spatial and quantitative information of proteins and peptides. It is commonly possible to generate individual maps to verify the presence, the molecular weight, and the location of proteins. IMS can produce hundreds of image maps each at a discrete molecular weight value. Applications range from low-resolution images of peptides, proteins, drugs, and their metabolites in selected areas of tissue to high-resolution images of tissue cross sections.

Cross-References
► Mass Spectrometry (MS)
► Matrix-Assisted Laser Desorption Ionization (MALDI)
► Metabolomics
► Neuropeptidomics
► Post-Translational Modification

Imipramine

Definition
Imipramine is a ► tricyclic antidepressant with a tertiary amine chemical structure. The first tricyclic to be developed, it acts by inhibiting the reuptake of ► norepinephrine and ► serotonin. Its primary use is in the treatment of depression. It is metabolized to desmethylimipramine (desipramine), a tricyclic associated with relatively selective norepinephrine reuptake inhibition, which is itself marketed as an antidepressant. Usage of imipramine has declined in recent years in conjunction with the general decline in the use of tricyclics. Imipramine has a side-effect profile similar to that of other tricyclics, including drowsiness, cardiovascular effects, and anticholinergic

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effects (e.g., constipation, dry mouth, blurred vision, urinary retention). As with other tricyclics, its potential for lethality in overdose is high.

Cross-References

► Antidepressants
► Tricyclic Antidepressants

Immunotherapy

► Vaccines and Drug-Specific Antibodies

Immunotoxins

► Neurotoxins

Impairment of Functioning; Measurement Scales

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Synonyms

Activities of living scales; Disability scales; Impairment of functioning scales; Quality of life scales

Definition

Psychiatric disorders can have a variety of negative psychosocial consequences such as unemployment, homelessness, or difficulties in communicating with others. Recently, the World Health Organization (WHO) developed a new scheme for the description and classification of these negative consequences (International Classification of Functioning, Disability, and Health – ICF; WHO 2001). In this context, "disorders of activity/capacity" means the ability of what an individual can do or not do. "Disorder of participation" means the degree in which an individual can fulfill role requirements in the job, the family, or in leisure times.

Principles and Role in Psychopharmacology

Assessments of the outcome of morbidity focused traditionally on deaths and reduction of symptoms. While mortality data or data on symptoms are important in their own right, they do not adequately capture health outcomes of individuals. Especially when analysing psychiatric interventions, symptom assessment alone does not explain what patients can do, what they need, and what their prognosis will be (Üstün et al. 2004).

Psychiatric disorders are an important cause of long-term disability. The most recent report of the WHO attributed about 29% of all years lived-with-disability to psychiatric disorders: the five major were unipolar affective disorders (10%), substance use and alcohol-use disorder (4%), ► schizophrenia (2%), ► bipolar affective disorders (2%), and ► dementia (2%). However, the interaction between mental disorder and disability is more complex than what the WHO report suggests. For example, ► depression is an important predictor for the onset and progression of both physical and social disability. In contrast, disability due to physical diseases is an important risk factor for depression in older adults (Mathers and Loncar 2006; Prince et al. 2007). A variety of studies have shown that psychiatric disorders frequently result in impairment of functioning, such as keeping social contacts, living independently, or to stay in the job (Rössler et al. 2005). The distinctions of the in-part similar and sometimes overlapping constructs such as impairment of functioning, disability, impaired activities of living, and quality of life are not fully clear (Katschnig et al. 1997).

When investigating the effects of psychiatric treatment such as psychotropics, psychotherapy, or social interventions, clinicians usually focus on the reduction of symptoms and avoiding relapses (usually defined as recurrence of symptoms). For this purpose, a variety of condition-specific assessment tools had been developed (e.g., ► Hamilton Rating Scale for Anxiety (Hamilton 1959), Positive and Negative Syndrome Scale (Kay et al. 1987)). Nevertheless, it has been shown that psychiatric treatment might reduce symptoms but does not have an impact on functioning. Thus, several authors suggested analysing the effects of treatment not only on symptoms, but also on functioning.

The idea of measuring functioning, disability, or similar concepts is not new in psychiatry. There are a lot of assessment tools, but many have been criticized because they are not comprehensive or mix functions with symptoms. Considering these aspects, the WHO adopted a new scheme in 2001 for the description and classification of illnesses, including disability and functioning, called the the International Classification of Functioning, Disability, and Health (ICF; WHO 2001). The ICF aims to provide a unified and standard language and framework for the description and classification of health and health-related states. It belongs

to the group of classifications developed by the WHO, such as the International Classification of Diseases (Baron and Linden 2008).

In addition to symptoms, the ICF describes disorders of activity/capacity (i.e., what an individual can do or not do). Of course, symptoms essentially influence what an individual can do. Disorders of activity/capacity can result in disorders of participation (i.e., the degree in which an individual can fulfill role requirements in the job, the family, or in leisure times). For example, reduced drive is typical for persons with depressive episodes (=symptom). Reduced drive impairs the ability to leave the apartment (=disorder of activity/capacity). If somebody cannot leave the apartment, he/she will not be able to work resulting in sick leave or unemployment (=disorder of participation). Further, we must not forget that the ability to fulfill role requirements can also be influenced by environmental factors (Baron and Linden 2008). The risk for unemployment will be increased for this person suffering from depression if the unemployment rate in the city is overall high.

Nevertheless, there is a complex interrelationship between symptoms, capacities, and participation. Different symptoms can lead to the same or different disorders of capacity. For example, reduced drive, negativism, ► hallucinations, or ► anxiety symptoms can impair an individual's ability to leave his/her apartment. Similarly, different disorders of capacity can lead to the same or different disorders of participation, and context factors might have an essential influence on the ability to fulfill role requirements. A person whose anxiety reduced his/her ability to communicate with other persons might be able to work as a data typist, but may be incapable to work as a salesperson in a supermarket.

A classification considering such complex interrelationship becomes very impractical for daily clinical use. For this reason, the WHO developed several instruments based on the ICF, like the ICF-Checklist (WHO, 2002) and the WHO Disability Assessment Schedule II (Üstün et al. in press). The ICF-Checklist is a short selection of items for everyday clinical practice. Its items were selected by experts to cover the most frequently used aspects. The WHO Disability Assessment Schedule II is a scale that gives a total score of disability based on the activities and participation domains of the ICF (Üstün et al. 2004). While the theoretical framework of ICF is a sound basis to understand the complex interactions between symptoms, capacities, and participation, it is not widely used in clinical practice or research. For these reasons, the following types of scales are often used for these purposes.

Impairment of Functioning and Disability

Both concepts mix impairments in capacities and impairments in participation. Instruments covering these domains are often used to describe the consequences of psychiatric disorders. It has been criticised that the number of randomized controlled trials using such scales is much smaller (Burns and Patrick 2007). Among others, the "Personal and Social Performance" (PSP; Morosini et al. 2000) scale, the "Global Assessment of Functioning" (GAF; Hall 1995) scale and the "Groningen Social Disability Schedule" (GSDS; Wiersma 1986) scale are frequently used.

Activities of Living

The theoretical concept of activities of daily living is focussing on activity/capacity, but scales often include items covering impairments in participation. Examples are the "Katz Index of Activities of Daily Living" (ADL; Katz et al. 1963) or the "Instrumental Activities of Daily Living" (IADL; Lawton and Brody 1969) scales (Baron and Linden 2008). These scales are frequently used in dementia research and studies investigating other mental disorders among the elderly.

Quality of Life

Quality of life is conceptualized by some authors as the opposite to impairment of functioning and disability. There is no clear distinction between activity/capacity and participation. In addition, often aspects of well-being, happiness, or satisfaction with treatment are included (Katschnig et al. 1997). While some instruments assess the subjective views of patients, others focus on the expert views. Since subjective well-being and happiness are diminished in depressive disorders, some authors discussed if there is a systematic error in the assessment of quality of life among persons suffering from depression. Nevertheless, a recently published study revealed no evidence for a globally biased negative evaluation of subjective quality of life by depressed patients (Kuehner 2002). Instruments were developed in order to cover all types of psychiatric and physical disorders (e.g., "WHO Quality of Life" scale – WHOQOL (The WHOQOL Group 1998), Medical Outcome Study Approach – MOS-SF-36 (Ware and Sherbourne 1992)), and others were developed specifically for those with psychiatric disorders (e.g., "Lancashire Quality of Life Profile" (Becker et al. 1993), "Quality of Life Index for Mental Health" (Becker et al. 1993)).

Cross-References

► Hamilton Rating Scale for Anxiety
► Quality of Life

► Rating Scales and Diagnostic Schemata
► Social Impairment

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Impairment of Functioning Scales

► Impairment of Functioning; Measurement Scales

Implicit Expectancies

Definition

Implicit expectancies are automatic anticipatory cognitions about the effect of some phenomenon. Related to the use of psychoactive substances, expectancies describe an individual's beliefs about the expected outcomes of consuming the substance. Implicit expectancies are automatic and unconscious. Individuals are often unaware of implicit expectancies.

Cross-References

► Expectancies and Their Influence on Drug Effects

Imprinted Genes

Synonyms

Genomic imprinting

Definition

Imprinted genes are a subset of genes (mostly found in mammals) that are subject to germline epigenetic modification in a parent-of-origin-specific manner. This usually results in expression of these genes from only one parental copy of the genome, despite the presence of a copy from both mother and father.

Impulse Control

► Behavioral Inhibition

Impulse Control Disorders

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Synonyms

Behavioral addictions; Impulsivity; Urge-driven behaviors

Definition

In the fourth edition of the Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-IV-TR), the category "impulse control disorders not elsewhere classified" includes kleptomania, intermittent explosive disorder, pyromania, pathological gambling, and ▶ trichotillomania. The impulse control disorders share common core qualities: (1) repetitive or compulsive engagement in a behavior despite adverse consequences; (2) diminished control over the problematic behavior; (3) an appetitive (▶ urge) or craving state prior to engagement in the problematic behavior; and (4) a hedonic quality during the performance of the problematic behavior (▶ impulsivity).

Despite being fairly common among adolescents and adults, impulse control disorders (ICDs) have been relatively understudied (Grant 2008). Currently in the USA, for example, there are no Food and Drug Administration (FDA)-approved medications for the treatment of any of the impulse control disorders. These essays review the available research on the pharmacological treatments of kleptomania, intermittent explosive disorder, and pyromania (pathological gambling and trichotillomania are discussed elsewhere), the advantages and disadvantages of different agents, as well as the reason for the preference of one medication over another.

Role of Pharmacotherapy

Kleptomania

Kleptomania is characterized by repetitive, uncontrollable stealing of items not needed for one's personal use, and is associated with significant morbidity and morality. The onset of this disorder occurs typically in early adulthood but has been reported in cases as young as four and as old as 77. The course of the illness is generally chronic, with waxing and waning of symptoms. Women appear twice as likely to suffer from kleptomania as men. Individuals with kleptomania frequently hoard, discard, or return stolen items. Less than half of the married kleptomaniacs disclose their behavior to their spouses.

Most individuals with kleptomania try unsuccessfully to stop stealing. The inability to stop this behavior often leads to feelings of shame and guilt. The majority of individuals with kleptomania have been apprehended at some time due to their stealing behavior. High rates of co-occurring psychiatric disorders (e.g., depression, anxiety, and other impulse control disorders) are common in individuals with kleptomania (McElroy et al. 1991).

Pharmacological Treatments

There is a very limited amount of data regarding treatment for kleptomania. Most of the available data are confined to one (▶ double-blind) study, two (▶ open label) studies, and case reports. Although there are no medications approved to treat kleptomania, pharmacotherapy has shown some early promise in treating this disorder.

Opioid Antagonists

Since subjects with ICDs, such as kleptomania often report uncontrollable cravings and excitement upon stealing an item, the hypothesis of a reward-triggered release of dopamine has been implicated as underlying these symptoms. Alterations in dopaminergic pathways may produce the feelings of pleasure often associated with kleptomania. As a result, ▶ opioid antagonist, such as ▶ naltrexone, which are thought to decrease dopamine neurotransmission in the ▶ nucleus accumbens and the corresponding linked motivational neurocircuitry, have been proposed as beneficial agents in dampening the excitement and cravings often reported in kleptomania.

The first (open-label) study for kleptomania involved the use of the (opioid antagonist) naltrexone. Ten subjects with kleptomania were treated over 12 weeks with escalating doses of naltrexone (50 to 200 mg/day) in an open-label design. A mean dose of 145 mg/d resulted in a significant decline in the intensity of urges to steal, stealing thoughts, and stealing behavior in nine of the ten subjects compared to baseline symptoms. A naturalistic study of naltrexone produced similar results. Seventeen subjects were followed over a 3-year period while being treated with naltrexone (mean dose of 135.3 mg/day). The study showed that 41% of the subjects reported complete abstinence from stealing and 76% of the subjects reported significant reductions in their urges to steal.

In the only placebo-controlled, double-blind study of kleptomania, 25 subjects were randomized in a 1:1 fashion to either naltrexone or placebo for 8 weeks (Grant et al. 2009). By study endpoint, 66.7% of the naltrexone group compared to 7.7% of the placebo group ($p<0.001$) demonstrated symptom remission. The mean effective dose of naltrexone was 116.7 mg/day.

Although the double-blind study of naltrexone did not report any elevations of liver enzymes, (opioid antagonists), particularly at doses higher than 50mg/day, have been associated with ▶ hepatotoxicity. Other common side effects of opioid antagonists include nausea, dizziness, insomnia, headaches, and loose stools.

Antidepressants

Because low levels of the serotonin metabolite 5-hydroxyindole acetic acid (5-HIAA) and blunted serotonergic response within the ▶ ventromedial prefrontal cortex have been associated with impulsive behaviors,

serotonergic antidepressants have also been examined in the treatment of kleptomania.

The only controlled study of an antidepressant involved 7 weeks of open-label ▶ escitalopram treatment followed by having the responders randomized to either escitalopram continuation or placebo for an additional 16 weeks (Koran et al. 2007). When the responders were randomized, 43% of those on escitalopram relapsed compared to 50% on placebo, thereby showing no drug effect in terms of response. Although escitalopram is generally well tolerated, the selective serotonin reuptake inhibitors may cause sedation, constipation, weight gain, headache, sexual dysfunction, and dry mouth.

Other Agents

Case series and case reports have also illustrated the benefit of mono- or combination pharmacotherapy for the treatment of kleptomania. In the case of monotherapy, the following medications have shown benefit: ▶ topiramate, ▶ paroxetine, ▶ fluoxetine, ▶ valproic acid, and ▶ fluvoxamine.

In terms of combination therapy, the following have been reported as successful in treating kleptomania: paroxetine plus valproic acid plus naltrexone; topiramate plus paroxetine; naltrexone plus ▶ venlafaxine; ▶ lithium plus fluoxetine; ▶ trazodone plus ▶ tranylcypromine; ▶ sertraline plus ▶ methylphenidate; and ▶ imipramine plus fluoxetine.

Conclusions

Kleptomania, a largely unrecognized disorder, presents as a chronic illness for many individuals and causes significant psychological, social, and legal repercussions. Since presentation specifically of kleptomania is quite rare, it is important that clinicians recognize the disorder and screen patients appropriately. Treatment recommendations are difficult to make, given the extremely limited amount of information regarding pharmacotherapy of kleptomania. The opioid antagonist naltrexone has demonstrated benefit in a placebo-controlled, double-blind study and therefore should be considered a first-line treatment. There is a substantial need for systematic studies in the treatment of this disorder.

Intermittent Explosive Disorder (IED)

Intermittent explosive disorder (IED) involves recurrent, significant outbursts of (aggression), often leading to assaultive acts against people or property, which are disproportionate to outside stressors and not better explained by another psychiatric diagnosis. Recent research suggests IED may be common, with 6.3% of a community sample meeting criteria for lifetime IED (Coccaro et al. 2004).

IED appears as early as childhood (i.e., prepubertal) and peaks in mid-adolescence with a mean age of onset ranging from about 13 to 18 years. The average duration of symptomatic IED has variably been reported to range from nearly 12 to 20 years to nearly the entire lifetime. Individuals suffering from IED regard their behavior as distressing and problematic. Aggressive outbursts in IED have a rapid onset, often without a recognizable prodromal period. They are short-lived (<30 min) and involve verbal assaults, destructive and nondestructive property assaults, or physical assaults. Aggressive outbursts most commonly occur in response to a minor provocation by a close intimate or associate and individuals may have less severe episodes of verbal and nondestructive property assault in between more severe assaultive/destructive episodes. Episodes are associated with substantial distress, impairment in social functioning, occupational difficulty, and legal or financial problems.

Pharmacological Treatments

While there are no approved medications for the treatment of IED, several psychopharmacologic agents appear to have effects on aggression. Classes of agents shown to have "anti-aggressive" effects in double-blind, placebo-controlled trials of individuals with "primary" aggression (i.e., not secondary to psychosis, severe mood disorder, or organic brain syndromes) include mood stabilizers (e.g., ▶ lithium), 5-HT uptake inhibitors (e.g., fluoxetine), and anticonvulsants (e.g., diphenylhydantoin, ▶ carbamazepine). Findings from (double-blind), placebo-controlled, clinical trials suggest that anti-aggressive efficacy is specific to *impulsive*, rather than non-impulsive, aggression.

Although pharmacotherapies have been studied in the treatment of aggression, there is only one controlled study specific to IED. In a 12-week study in the treatment of impulsive aggression, 96 subjects with Cluster B personality disorders, 116 subjects with IED, and 34 subjects with post-traumatic stress disorder were randomized to receive either divalproex sodium or placebo (Hollander et al. 2003). In the intent-to-treat analysis, the study found that divalproex had no significant influence on aggression in the subjects with IED. Although divalproex is generally well tolerated, it can cause somnolence, nausea, weight gain, hair loss, and (hepatotoxicity).

Several other medications have shown efficacy in treating IED in case reports, including lithium, ► clozapine, carbamazepine, and ► propranolol.

Conclusions

Given the paucity of treatment studies for IED, no empirically supported pharmacological treatment recommendations can be offered. The only pharmacological study to date failed to demonstrate benefit. Given the personal and publics health issues of IED, treatment studies are of immediate and inevitable need.

Pyromania

Pyromania is considered to be a rare psychiatric condition characterized by (1) deliberate and purposeful fire-setting on more than one occasion; (2) tension or affective arousal before the act; (3) fascination with, interest in, curiosity about, or attraction to fire and its situational contexts; and (4) pleasure, gratification, or relief when setting fires or when witnessing or participating in their aftermath.

Although thought for a long time to be a disorder primarily affecting men, recent research suggests that the gender ratio is equal in adults and may be slightly higher among females in adolescence. The mean age of pyromania onset is generally late adolescence, and the behavior appears chronic if left untreated. Urges to set fires are common in individuals with this behavior and the fire setting is almost always reported as pleasurable. Severe distress follows the fire-setting, and individuals with pyromania report significant functional impairment (Grant and Kim 2007). High rates of co-occurring psychiatric disorders (e.g., ► depression, ► substance use disorders, and other ► impulse control disorders) are common in individuals with pyromania.

Pharmacological Treatments

There are no randomized, controlled clinical trials examining pharmacotherapy for the treatment of pyromania, and no medications have been approved for its treatment.

Medications that have been described in case reports have shown benefit in the treatment of pyromania include ► topiramate, ► escitalopram, ► sertraline, ► fluoxetine, ► lithium, and a combination of ► olanzapine and sodium ► valproate. An equal number of medications have also shown no benefit in the treatment of pyromania in case reports, including fluoxetine, valproic acid, lithium, sertraline, olanzapine, escitalopram, citalopram, and clonazepam.

Pyromania is a largely unrecognized disorder that causes significant psychological, social, and legal repercussions. Because few individuals volunteer information regarding their fire-setting, it is important that clinicians recognize the disorder and screen patients appropriately. Various treatments have been helpful in case studies but more research on examining etiology and treatment is needed.

Recommendations for Pharmacological Treatment of Impulse Control Disorders

In the area of ICDs, the systematic study of pharmacotherapy is in its infancy. With few studies published, it is not possible to make treatment recommendations with a substantial degree of confidence for most ICDs. No drugs are currently approved by the US FDA for the treatment of any of these disorders. Nonetheless, specific drug therapies may offer promise. Although naltrexone might be considered a promising treatment for kleptomania, the data are limited to one small placebo-controlled study. For IED and pyromania, there are even less available data to generate empirically supported treatment recommendations. For all of these disorders, issues such as which medication to use and for whom, or the duration of pharmacotherapy, cannot be sufficiently addressed with the available data. In conjunction with emerging epidemiological data supporting a relatively high prevalence of impulse control disorders, the small amount of data in the area of effective treatments highlights the clinical need for additional research in this area.

Cross-References

► Double-blind
► Hepatotoxicity
► Impulsivity
► Nucleus Accumbens
► Open-label
► Opioid Antagonist
► Urge
► Ventromedial Prefrontal Cortex

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Impulsive Aggression

Definition

Refers to the rapid display of intense aggressive acts without regard of the long-term consequences.

Cross-References

► Aggressive Behavior: Clinical Aspects

Impulsive–Compulsive Gambling

► Pathological Gambling

Impulsivity

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Synonyms

Inability to delay gratification; Failure of response inhibition or behavioral inhibition; Self-control failure

Definition

The term impulsivity is used in two distinct ways. First, it is used to indicate a lack of inhibition, or a tendency to behave without regard to the potential negative consequences of the action. Second, it is used to indicate a failure of self-control or inability to delay gratification, and refers to selecting an outcome that occurs sooner rather than an outcome that is objectively larger but will occur later.

Impact of Psychoactive Drugs

Contexts in Which the Impulsivity Construct is Used

Impulsivity is a multifaceted construct that is used in psychology, psychiatry, and economics. It can refer to both normal and abnormal functions, and to both a stable ► trait of an individual and a transient ► affective state. In the healthy population, impulsivity changes throughout development, with peak levels during childhood and adolescence, and there is also considerable variability in the trait among healthy adults. In psychiatric populations, impulsivity is a common symptom of several psychiatric disorders, including, but not limited to, the category of "Impulse Control Disorders."

In a clinical context, heightened levels of impulsivity are a diagnostic symptom for a number of psychiatric disorders in the DSM-IV TR (APA, 2000) and ICD-10 (WHO, 1990). These disorders are commonly classified as ► externalizing disorders, e.g., ► Attention-Deficit/Hyperactivity Disorder, Substance Use Disorders, Conduct Disorder, and Pathological ► Gambling. There is also some speculation that abnormally low levels of impulsivity may be associated with psychiatric conditions. For example, obsessive-compulsive behavior is characterized by repetitive behaviors and intrusive thoughts, which may reflect an exaggerated focus on the potential negative consequences of behavior and heightened behavioral inhibition.

In the normal population, inter-individual variation in impulsivity is a key element of most personality theories. Within this context, impulsivity is viewed as a stable trait loosely related to sensation or novelty seeking, boredom susceptibility, ► risk taking, unreliability, disorderliness, and sometimes even sensitivity to reward. For example, in the Five-Factor Model of personality, impulsivity is assessed through three of the five factors: It is a component of the domains of Neuroticism, Conscientiousness and Extroversion. In the Myers–Briggs Type Indicator, impulsivity is associated with a focus on the external world (extroversion), and staying open to new information and options (perceiving). Yet other questionnaires ask respondents to assess their behavioral predispositions, creating an operational definition of the impulsive personality. These include: (1) urgency or the tendency to behave quickly or without consideration of the consequences when experiencing strong positive or negative emotional states, (2) lack of planning, or behaving without forethought, (3) lack of perseverance, or an inability to remain on task, and (4) sensation seeking, the tendency to seek novelty or thrilling situations. These operational definitions provide an objective basis by which to study impulsivity and its underlying mechanisms.

Dimensions of Impulsivity

Impulsivity is a theoretical concept that can be deconstructed into several factors. Researchers, including those interested in the impact of psychoactive drugs, have

focused in particular on two factors: (1) an impairment of behavioral or response inhibition and (2) an inability to delay gratification or a pronounced devaluation of delayed outcomes (delay or intertemporal discounting). These two factors have been refered to variously as motor and cognitive impulsivity, motor and choice impulsivity, impulsive action and impulsive ▶ decision making. These terms have in common the distinction between preventing or terminating an ongoing behavior (inhibition), and preferring a more immediate to delayed reward outcome (delay aversion). Even though these factors are thought to represent basic behavioral tendencies, the factors are themselves the product of other, more basic, underlying neuropsychological processes. For example, the ability to inhibit behavior is influenced by the ability to learn and remember appropriate cues, and requires knowledge of the adverse consequences of failing to inhibit the behavior. Inhibition also requires attention to recognize "act" (go) versus "inhibit" (no-go) signals and discriminate appropriate signals from distractors, and it requires the ability to emit the appropriate motor response. Decision making about immediate versus delay outcomes requires an understanding of the duration of the delay, and either a memory for the delayed reward that spans the waiting period or an accurate concept of the value of the future reward.

Both inhibition and delay aversion have been measured using both self-report questionnaires and behavioral tasks. In general, questionnaires are more appropriate as measures of a stable trait because they typically refer to habitual behaviors occurring over a period in time, whereas behavioral measures may be more appropriate to assess momentary changes in the behaviors. Most of the commonly used impulsivity questionnaires, to a greater or lesser extent, incorporate both the inhibition and delay aversion aspects of impulsivity. The behavioral measures are typically more specific, and are used in both human and nonhuman models to assess responses to specific experimental interventions including the administration of psychoactive drugs.

Questionnaires are used to assess both clinically significant levels of impulsivity as well as variations in the normal range. One scale commonly used to assess clinically significant impulsive tendencies in children is the Conner's Behavioral Ratings, which is a parent and teacher rating scale used to diagnose attention-deficit/hyperactivity disorder. The items include behavioral descriptions such as difficulty sitting still in a classroom setting, inability to inhibit inappropriate behaviors such as running around the classroom. A self-report scale typically used to assess impulsivity in the normal population is the Barratt Impulsiveness Scale, which assesses variations in the tendency to engage in behaviors indicative of impulsivity. Factor analysis is commonly used to separate the responses on this questionnaire into the more fundamental neuropsychological processes underlying the behavior, such as attention, perseveration, motor, cognitive instability, self-control, and cognitive complexity. Other self-report questionnaires that include measures of impulsive behaviors are the Multiphasic Personality Inventory, Eysenck Impulsivity Questionnaire and the UPPS Impulsive Behavior Scale.

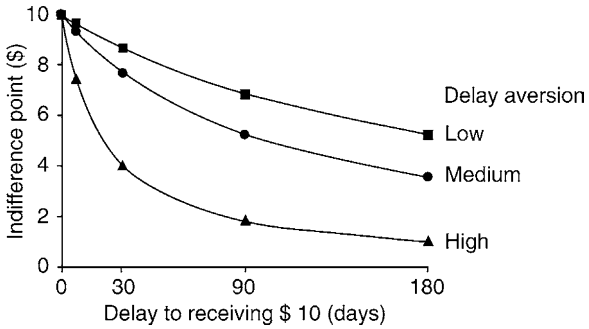
Both questionnaires and behavioral tasks have been used to measure delay aversion by quantifying relative preference for immediate rewards over delayed rewards. Typically, these tasks require individuals to choose between two alternatives, one of which is a smaller reward available sooner, e.g., $9 available now or $40 available now, and the other is a larger reward available later, e.g., $10 in 7 days or $100 in 5 years. The rewards may only be available hypothetically, or the rewards may actually be delivered though usually on a probabilistic basis. In these tasks, the ▶ subjective value of the delayed reward is assessed in terms of an equally valued reward available now (Table 1).

By providing a range of later options, e.g., $10 in 30 days, $10 in 90 days, it is possible to create a response-to-delay profile or a discount function (Fig. 1).

Individuals who exhibit a stronger tendency to accept small rewards rather than wait, and thus discount the value of the delayed reward more steeply, are considered more impulsive than individuals who prefer the larger, delayed reward. In Fig. 1, the delay profile is best described using a hyperbolic function: delayed amount/ 1+k * delay, where k represents the gradient of the

Impulsivity. Table 1. Participants choose between the alternatives in each row. The size of the immediate reward is varied in the left column. The subject's preference is indicated with stars. In this example, $9 now is the minimum value of immediate reward accepted instead of waiting a week for $10. The point of subjective equality or indifference point is defined as halfway between this minimum accepted amount and the largest rejected amount ($9.00 and $8.50), i.e., $8.75.

Which do you prefer?		
$10 now *	OR	$10 in 7 days
$9.50 now *	OR	$10 in 7 days
$9 now *	OR	$10 in 7 days
$8.50 now	OR	$10 in 7 days *
$8 now	OR	$10 in 7 days *



Impulsivity. Fig. 1. Indifference points for a series of delays in three hypothetical individuals, who show different levels of delay aversion.

discount function. However, there is some debate about whether discounting occurs exponentially or hyperbolically (Green and Myerson, 2004). The extent of discounting can be quantified using an index of the gradient, or by calculating the area under the discount curve.

Delay aversion, or delay discounting, has also been assessed in other species including pigeons, mice, rats and nonhuman primates. The studies with nonhumans use food, water, sucrose or drug rewards, and usually involve delays of up to 60 s. Notably, the animals experience the entire delay period, as well as receiving the delayed (larger) reward during the experimental session. This is in contrast to most studies with humans that involve prospective delays and rewards occurring in the future. There are two basic types of discounting tasks. One type is the "within session" procedure, in which the delay to large reward increases in a fixed, systematic way over trials within a session. Subjects choose between a small, sooner (often immediate) reward and a larger, later reward, e.g., three food pellets immediately and six pellets in 10 s, on a fixed number of consecutive trials. The delay to the large reward is 0 s on the first block of trials, but systematically increases over blocks within an experimental session. The within session procedure measures the percent of occasions on which the animals choose the small immediate reward or larger delayed reward at each delay. The other type of task is the "adjusting procedure," which requires multiple sessions to determine a discounting function. In adjusting procedure studies, the reward size or delay on each trial is adjusted, according to the animal's behavior on the previous trial, and different amount or delay conditions are determined on different sessions. There are two main variations of the adjusting procedure. In the adjusting amount procedure, the size of the smaller, sooner reward varies across trials, while the size of the large reward and its delay is fixed throughout the session. If the animal chooses the immediate reward then on subsequent trials the immediate reward is decreased, whereas if the animal chooses the delayed reward the size of the immediate reward is increased. Delay is varied between sessions. In the adjusting delay procedure, the delay to the large reward varies while the smaller reward has a fixed size and delay. Choices of the small reward cause the delay to the large reward to decrease, and choices of the large reward cause its delay to increase. In both adjusting procedures, subjects' choices cause the adjusting alternative to change systematically until subjects become indifferent between the smaller, sooner and larger later rewards, i.e., the ▶ indifference point is achieved. The dependent measure in the adjusting amount procedure is the size of the immediate reward at indifference, making this procedure similar to the questionnaire method shown in Table 1. As in the human assessment, the extent to which the animal accepts smaller immediate amounts is the measure of impulsivity. The dependent measure in the adjusting delay procedure is the length of the delay to the large reward at indifference. Less impulsive individuals will tolerate a longer delay to the larger reward. All of these tasks are used to assess the effects of experimental treatments, for example, the effects of drugs hypothesized to increase or decrease delay aversion.

Several tasks measure the ability to inhibit a prepotent response, i.e., a response that the organism is strongly inclined to make. Different tasks have been developed for humans and nonhumans. One response conflict task used in humans is the Stroop task, in which participants must suppress extraneous salient information. They are required to name the color of ink of a word that names a different color. Thus, there is a conflict between the response that is required (naming the ink color) and the response that occurs when reading the color word. In other tasks, the prepotent response is created by manipulating the relative frequencies of behaviors. The Conner's Continuous Performance Task is a ▶ Go/No-Go task, which requires a button press whenever a new letter of the alphabet is shown on a computer screen, except when the letter is a certain specific, designated letter. Errors of commission or false alarms refer to the tendency to emit the prepotent, but incorrect, response. More false alarms are indicative of greater impulsivity. In yet other tasks, the prepotent behavior has been signaled to be appropriate but the individual is required to terminate that behavior or switch to a different behavior (Logan et al., 1997). In these tasks, the dependent measure is the time needed to stop a response. For example, in the Stop task, an individual is signaled to press a button or make a saccadic

eye movement in a specific direction when a "Go" signal is presented. On a small percentage of trials, some milliseconds following the Go signal, a "Stop" signal is presented, signaling the individual to terminate the initiation of the button press or saccade. The amount of lead time needed to inhibit a Go response provides a measure of impulsivity, longer Stop Times indicate less ability to inhibit and thus more impulsivity.

The tasks used to assess conflict and response inhibition across species include some tasks that resemble the tasks used in humans and some are different. There are both human and nonhuman versions of Go/No-Go conflict procedures. In these procedures, typically the organism is rewarded for correct Go responses, and may either be rewarded for correct inhibitions or punished for not inhibiting appropriately (errors of commission). Higher numbers of false alarms, or failures to inhibit, indicate higher levels of impulsivity. One example of a widely used Go/No-Go procedure used with nonhumans to examine behavioral inhibition is the ► 5-Choice Serial Reaction Time Task (5CSRTT; Robbins, 2002). One of five response options is briefly illuminated, and the animal is required to respond at the correct location within a short time window to earn reward. This task measures the number of premature responses as the indicator of impulsivity, under conditions when premature responses are punished with a brief time out. Another example of a Go/No-Go procedure used with nonhumans but not humans is the differential reinforcement of low rates (DRL) schedule, in which the animals are required to refrain from pressing a lever until a certain minimum time (e.g., 72 s) has elapsed. In this case, the Go signal is internal, and ability to inhibit responding is viewed as largely reliant on timing processes.

Impulsivity and Substance Use Disorders

Impulsivity plays a significant role in substance use disorders. Individuals diagnosed with substance use disorders score higher on both behavioral and personality measures of impulsivity than comparison groups (Perry and Carroll, 2008). Thus, drug users score higher on personality measures of impulsivity, they exhibit a steeper devaluation of delayed rewards and they are also less able to inhibit prepotent responses. Impulsive behavior may be related to drug use in several ways. Impulsivity may affect the likelihood of initiating use, or it may affect the progression to problematic use or persistence of use in inappropriate situations. It may also affect the ability to abstain, or remain abstinent for extended periods. Drug use itself may in turn affect impulsive behavior, either through direct pharmacological effects or through mild toxicity related to chronic use. Finally, impulsivity and drug abuse may be related to a common etiological factor, such as genetic predisposition for both drug use and impulsive behavior. These various hypotheses are not mutually exclusive and indeed data support each point of view (see Perry and Carroll, 2008). It remains a challenge for behavioral scientists to identify the basic underlying constructs of impulsive behaviors and their role in substance abuse.

A substantial number of controlled studies have examined the effects of drugs of abuse on measures of impulsivity. Whereas in studies with humans, the measures of delay discounting have proven relatively insensitive to the acute effects of drugs, studies with nonhumans provide a rich body of data regarding the effects of drugs on delay aversion. Drugs such as ► alcohol, ► cocaine, and ► morphine reportedly increase discounting, whereas other drugs, such as ► amphetamine, may actually decrease discounting. Studies with laboratory animals have also investigated the neural basis of discounting by making selective lesions in brain regions associated with reward sensitivity and decision making. Studies with both humans and nonhumans demonstrate that certain drugs of abuse also impair behavioral inhibition, although again, there is evidence that certain drugs, especially stimulant drugs, may also improve inhibition at low doses. The effects of drugs on measures of impulsivity depend on many factors including the procedure, the animals, the drug doses, and the individuals' baseline levels of impulsivity. In general, however, drugs of abuse are associated with increased delay aversion as well as decreased behavioral inhibition.

Neural and Genetic Mechanisms of Impulsivity

Researchers are actively investigating the neural and genetic mechanisms underlying impulsivity, and several brain areas and neurotransmitter systems have been implicated (see Cardinal, 2006; Pattij and Vanderschuren, 2008). There is evidence that impulsive behavior is related to dysfunction in the ► nucleus accumbens and ► prefrontal cortex. Lesions of the nucleus accumbens and of the orbitofrontal cortex, a part of prefrontal cortex, lead to higher levels of delay aversion and impairments in behavioral inhibition. In humans, ► functional magnetic resonance imaging (fMRI) studies indicate that choosing between immediate and delayed rewards activates the caudate-putamen and prefrontal cortical areas, whereas tasks involving behavioral inhibition activate the rostromedial prefrontal cortex. Other brain areas implicated in impulsive behaviors include the mesial prefrontal cortex, the orbitofrontal cortex, the dorsolateral striatum, the insula, and the ► amygdala. Research has also implicated both dopamine and serotonin in the performance of impulsive

behaviors. For example, D2 receptor antagonists increase delay discounting while D1 receptor antagonists have little effect. Lesions of brain areas rich in ► dopamine result in increases in impulsive behaviors. Correlational studies assessing ► serotonin function, including the measurement of serotonin metabolites, have linked low levels of serotonin to higher impulsivity. Advances have also been made in identifying genetic determinants of impulsive behaviors (Verdejo-Garcia et al., 2008). For example, genes related to dopaminergic function such as DAT1, D2DR, COMT and MAO-A have been associated with impulse control disorders including ► substance use disorders, ► attention-deficit/hyperactivity disorder and other externalizing disorders.

In sum, impulsivity is a heterogenous construct, consisting of behaviors relating to poor inhibitory control, bias for immediate versus delayed rewards, and an insensitivity to negative consequences. Impulsivity is a characteristic of a number of psychiatric diagnoses such as externalizing disorder and drug use, and it also varies in the normal populations. The underlying constructs of impulsive behaviors are an active subject of research, as are efforts to identify the neural circuitry and genetic predispositions to the behavior.

Cross-References

► Attention Deficit and Disruptive Behavior Disorders
► Attention Deficit Hyperactivity Disorders: Animal Models
► Behavioral Economics
► Impulse Control Disorders
► Pathological Gambling

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IMS

► Imaging Mass Spectrometry

In vivo

Definition

In vivo is when a treatment is given in real life rather than in imagination. The person therefore has to perform a certain task, for example, walk to the end of the road. It also refers to experiments carried out in whole, living organisms, as contrasted with studies of isolated cells or organs.

Cross-References

► Agoraphobia

Inability to Delay Gratification

► Impulsivity

Inability to Sleep

► Insomnias

Inbred Strains

Definition

Inbred strains are the result of breeding between two animals that are closely related. This process of repeatedly breeding close relatives (usually for more than 20 generations) allows all animals within that strain to be genetically similar. Inbred strains allow investigators to assess genetic influences on behavioral traits. The use of inbred strains allows any behavioral differences seen within inbred strains to be attributed to factors other than genes.

Incentive Learning

► Reward-Related Incentive Learning

Incentive Motivation

► Appetitive Responses
► Conditioned Taste Preferences

Incentive Properties of Drug Cues

► Attentional Bias to Drug Cues

Incoherent Thinking

Definition

Breakdown in the grammatical structure of what is expressed.

Independents

Synonyms

Autonomous; Separated; Unrelated

Definition

Independents have no relationship between the independent and the alternative – a change in price in either the alternative or the independent will not affect the demand for the other.

Cross-References

► Behavioral Economics

Indifference Point

Synonyms

Point of subjective equality

Definition

Subjective value of one alternative in a choice situation that equivalent to the other alternative. Used to quantify the value of a delay reward in the delay-discounting tasks. Mathematical description of the relationship between subjective value and delay to reward is a delay discount function.

Indirect-Acting Dopamine Agonists

Definition

Indirect-acting dopamine agonists are drugs that block and/or reverse the dopamine transporter, thereby producing elevated levels of dopamine in the synapse. Effects of these drugs, such as ► amphetamine and ► cocaine, are greatly diminished by prior brain amine depletion. Direct-acting dopamine agonists, such as ► apomorphine, interact directly with dopamine receptors and can produce ample behavioral effects in amine-depleted animals.

Cross-References

► Amine Depletion Techniques
► Amine Depletors
► Dopamine Transporter
► Psychostimulants

Indoleamine

Definition

Neurotransmitters derived from the amino acid tryptophan that contains an indole ring. The best example is serotonin.

Indoleamine Hypothesis

► Aminergic Hypotheses for Depression

Inducible Knockout

Synonyms

Temporal knockout; Time-specific knockout

Definition

The use of a system where the experimenter controls the timing of gene removal. The tetracycline inducible system is frequently used to produce animals where a simple injection of tetracycline will either terminate or initiate gene transcription.

Cross-References

► Ethopharmacology
► Genetically Modified Animals
► Phenotyping of Behavioral Characteristics

Infantile Autism

► Autism Spectrum Disorders
► Autism Spectrum Disorders and Mental Retardation

Informed Consent

Definition

In severe psychiatric cases, the capacity for giving an informed consent may be impaired and it depends on the level of the mental capacity of the patient. There are differences in the legislation in different countries concerning the requirement of consent on the part of psychiatric patients. The fact that a patient is legally admitted does not automatically allow involuntary treatment; therefore, an informed consent should be looked for; if this is not possible, the clinician has to follow the rules of good clinical practice and, above all, fulfill his duties as a clinician.

Cross-References

► Ethical Issues in Human Psychopharmacology
► Legal Aspects of Psychopharmacology

Inhalant and Solvent Abuse

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Synonyms

Solvent abuse; Volatile substance abuse

Definition

Abused inhalants contain volatile substances that are self-administered as gases or vapors to induce a psychoactive or mind-altering effect. These volatile substances are available in legal, relatively inexpensive, and common household products, which can be gases, liquids, aerosols, or, in some cases, solids (Balster et al. 2009). The use and abuse of these substances are referred to as inhalant use and abuse. ► DSM-IV defines Inhalant Abuse and Inhalant Dependence disorders using the same diagnostic symptom criterion sets employed for other Substance Use Disorders, with the exception that a characteristic withdrawal syndrome (or substance use for relief of withdrawal symptoms) is not included. Similarly the 2007 version of the International Classification of Diseases-10th edn (► ICD-10) provides Harmful Use and Dependence diagnoses for volatile solvent-related disorders. In some regions of the world, the terms "solvent abuse" or "volatile substance abuse" are preferred, but not all of the products contain solvents, so a broader term such as "inhalant abuse" or "volatile substance abuse" should generally be used.

Current Concepts and State of Knowledge

It is important to distinguish between abused inhalants and other drugs that are used by smoking or inhalation, such as opium or crack cocaine. "Sniffing," "snorting," "huffing" (soaking a rag with the abused product and inserting it into the mouth to breathe fumes), "bagging" (filling a plastic bag with the abused product and holding it over the nose and mouth), and "spraying" (directly spraying the abused product into oral cavities) describe various routes of administration for abused inhalants. Inhalant abusers can be identified by signs such as organic solvent odors on the breath or clothes, chemical stains on the clothes or around the mouth, and empty spray paint or solvent containers. They may exhibit neurological signs and symptoms and have other mental health or substance abuse problems.

Inhalant use is a very prevalent behavior, especially among youth aged 12–25 years. For example, in the US, lifetime prevalence in 18–25 year olds is about 15% and past year use is about 2% of the population (Wu and Ringwalt 2006), placing inhalant use as just below alcohol, tobacco, and cannabis use in this age group and making the use far more prevalent than the use of more widely studied drugs such as cocaine and heroin. Among 12–13 year olds, inhalant use is even more prevalent than cannabis use (http://www.oas.samhsa.gov/2k8/inhalants/inhalants.cfm). In addition, among all past year inhalant users, the prevalence of dependence was 8%. The association of early inhalant abuse with increased risk of many substance use disorders has also been described (Neumark et al. 1998), and there is also a very high rate of ► comorbidity of inhalant use and other psychiatric disorders. For example, Wu and Howard (2007) recently reported a very high rate of psychiatric disorders among inhalant abusers in the general US population. For example, 70% of inhalant users in this sample met criteria for at least one lifetime mood, ► anxiety, or personality disorder, and 38% of them experienced a mood or anxiety disorder in the past year. Females were more likely than males to have multiple comorbid psychiatric illness. Conduct disorder, mood

disorders, and suicidality are common among adolescent inhalant abusers (Sakai et al. 2004). Inhalant abuse is a worldwide problem, and there is some evidence that the public health impact of this behavior is a particular problem in some developing countries (http://international.drugabuse.gov/information/pubs_presentations.html; Kozel et al. 1995).

It is widely believed that inhalant abuse is associated with neurological problems and other organ toxicity, although the epidemiological evidence that these rates are significantly greater than the rates of neurological problems among other substance abusers is lacking. Nonetheless, inhalants clearly have the capability to produce central and peripheral nervous system toxicity as well as damage to other organs such as the liver and kidney (Balster 2003). Each abused chemical has its own profile of toxicity, and some are known to be more toxic than others. The fact that many products contain mixtures of solvents and other ingredients as well makes the problem of showing individual products or types of products as the sole cause of health problems among abusers a significant scientific challenge.

Background

There are several dozen abused inhalant chemicals available in thousands of commercial products, many of which are unique to a particular country or region. In addition, many of the products contain mixtures of chemicals. The products are available in several forms, including gases, vapors, aerosols, liquids, and solids. The complexity and diversity of abused inhalants have presented a problem in developing a useful, scientifically-based subclassification (Balster et al. 2009). It has been argued that, as with the classification of psychoactive drugs, abused inhalants would be best classified by different profiles of pharmacological and subjective effects. Using this approach, three different groups of inhalants have been proposed (Table 1).

Abuse of volatile ► nitrites has been decreasing. These chemicals apparently produce their abuse-related effects by peripheral vasodilatation resulting in blood pooling and brain anoxia. This results in dizziness and feelings of light-headedness. Engorgement of the penis may also be a factor in nitrite abuse. ► Nitrous oxide is a gas at room temperature and is primarily obtained by the diversion of tanks used in medicine as a source of nitrous oxide for anesthesia. Nitrous oxide was sometimes referred to as "laughing gas." The cellular mechanisms for the abuse of nitrous oxide are unknown although there is some evidence that opioid systems may be involved.

Many chemicals constitute the class of solvents, fuels, and anesthetics. The abuse of vapor anesthetics goes back to the use of ether, both by inhalation and orally. Of course, alcohol is a good solvent and a weak anesthetic, and the abuse of chemicals in this class is often compared to ► alcohol abuse and dependence and other ► sedative, hypnotic and anxiolytic drug dependence (Balster 1998; Bowen et al. 2006). An important difference is that the effects of abused inhalants are almost immediate and are very short acting, much like those of vapor anesthetics. Prototypal chemicals from this class include ► toluene and ► trichloroethane, and most of the animal and neurobiology research on abused solvents has utilized one or both of these compounds. Abuse of lighter fluid containing butane has emerged as a particular problem in some regions, and gasoline, which contains toluene and many aliphatic hydrocarbons, is also subject to abuse. As with ► alcohol and other depressant drugs, the enhancement of ► inhibitory amino acid neurotransmission and the ► antagonism of excitatory amino acid neurotransmission have been implicated as the neural basis for the abuse-related effects of compounds such as toluene and trichloroethane (Bowen et al. 2006).

There are no known pharmacotherapies for inhalant use disorders nor have there been any published controlled trials of potential medications for this condition. Because inhalant abusers are generally young, behavioral interventions used with adolescents are typically employed to assist users to reduce their use or to prevent future use episodes. It is widely believed that prevention is

Inhalant and Solvent Abuse. Table 1. Subclassification of abused inhalants, providing examples from each class and product sources

Class	Examples	Sources
Volatile nitrites	Amyl nitrite, butyl nitrite	Antianginal medication, room odorizers
Nitrous oxide	Nitrous oxide	Anesthetic
Solvents, fuels, and anesthetics	Toluene, trichloroethane, trichloroethylene, xylene, butane, isopropane, isoflurane	Adhesives, paint removers and thinners, inks, nail polish and remover, industrial solvents, cleaning fluids, compressed air dusters, correction fluids, lighter fluids, anesthetics

a key component of the control of inhalant abuse. Normal, regulatory strategies for drug abuse control have little use because so many of the abused products have widespread household use. Several broad strategies for inhalant abuse prevention have been proposed (http://www.inhalants.org/; http://www.doe.virginia.gov/VDOE/Instruction/Inhalantbook.pdf; http://www.health.gov.au/internet/main/publishing.nsf/Content/73AFC6ADE4DEED9CCA25746B00834DA8/$File/vol-sub-mis-rvw-int.pdf). In addition, a few specialized treatment programs for inhalant abusers, such as the network established by the Youth Solvent Addition Committee in Canada have been developed (http://www.members.shaw.ca/ysac/Who%20Are%20We/whoarewe.htm).

Cross-References

- ▶ Abuse Liability Evaluation
- ▶ Alcohol Abuse and Dependence
- ▶ Classification of Psychoactive Drugs
- ▶ DSM-IV
- ▶ Ethical Issues in Human Psychopharmacology
- ▶ Excitatory Amino Acids and Their Antagonists
- ▶ ICD-10
- ▶ Inhibitory Amino Acids and their Antagonists
- ▶ Nitrites
- ▶ Nitrous Oxide
- ▶ Physical Dependence
- ▶ Rating Scales and Diagnostic Schemata
- ▶ Sedative, Hypnotic and Anxiolytic Dependence
- ▶ Toluene
- ▶ Trichloroethane
- ▶ Withdrawal Syndromes

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Inhibition of Memory

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Definition

The pharmacological inhibition of memory refers to the ability of certain compounds to impair the laying down of new memories, disrupt the consolidation of others, speed up the extinction of memory ("un-learning"), or lead to the forgetting of old memories.

Impact of Psychoactive Drugs

A startling number of both used and abused substances share the capacity to impair memory. Indeed, memory is often cited as a reason for ingesting psychoactive substances, for example, people will say they drink alcohol to "forget." But for many years, it was thought that pharmacological compounds only impaired the learning of new information (i.e., anterograde amnesia) but could not destroy the old memories (i.e., retrograde amnesia). More recently, however, it seems that several pharmacological compounds may be effective in erasing some – particularly recently acquired – memories.

Overview

Recent advances in psychopharmacology and neuroscience have allowed us to explore further the mechanism of memory-impairing compounds. Their final common pathway appears to be the blockade of the induction of ▶ long-term potentiation (LTP) and related processes most notably in the ▶ hippocampus. LTP is the process by which "neurons that fire together wire together," such that there is an increase in synaptic strength following activation of two neurons. A drug itself may impact on any one of a number of processes involved in memory

formation or destruction. Some key ways a drug may alter memory are

- By interfering with encoding or consolidation
- By changing the degree of interference from previous memories
- By affecting retrieval of a memory
- By capitalizing on the instability of memories on reactivation
- By enhancing "extinction" learning, i.e., learning a new memory that takes precedence over the old – this is particularly important in the case of conditioning, a nondeclarative form of memory

The use of amnestic agents in psychopharmacology and neuroscience has been valuable in learning not only about the effects of drugs that are used clinically or taken for recreational purposes, but also in teaching us about the memory itself.

Inhibiting the Formation of New Memories

The mechanism of most amnestic drugs is the inhibition of new learning. Some types of memories appear to be more vulnerable than others. Human memory has been subdivided – on the basis of findings from neuropsychological, neuroimaging, psychological, and psychopharmacological studies – into five different "memory systems": ▶ episodic memory, ▶ semantic memory, ▶ working memory, procedural learning, and the perceptual representation system. Different drugs have different profiles of memory-inhibiting effects on these types of memory. Episodic memory, our memory for events and occurrences encoded from a subjective perspective and accompanied by contextual details (what, where, when), appears to be the most susceptible to pharmacological inhibition. Drugs that principally act on varying neurotransmitter systems from GABA (e.g., ▶ benzodiazepines, ▶ alcohol) to glutamate (e.g., ▶ ketamine, PCP, alcohol) and acetycholine (e.g., ▶ scopolamine), all produce reliable, dose-dependent inhibition of the formation of new episodic memories. Working memory is also broadly inhibited by a variety of compounds, especially at higher doses, including some noradrenergic blocking drugs (e.g., ▶ propanalol, clonidine), dopamine antagonists (e.g., ▶ haloperidol), and ▶ NMDA-receptor antagonists such as ketamine.

The inhibition of other memory systems appears to be less widespread, with the caveat that those systems have, relative to episodic and working memory, been less thoroughly researched in psychopharmacology. Semantic memory is our memory for language and facts; it is not time locked and is thought to be formed via transfer of information from episodic memory. For example, when one first learns that the UK prime minister is Gordon Brown, it is an episodic memory; however, with time, he/she is no longer able to recall the occasion upon which he/she first learnt this information but just *knows* that Gordon Brown is the prime minister, this is termed as semantic memory. Psychopharmacological studies have assessed the impact of compounds on retrieval from semantic memory rather than their impact on the formation of new semantic memories. The glutamatergic NMDA-receptor antagonist, ketamine, has been shown to acutely inhibit semantic memory retrieval, whereas levodopa has been shown to increase retrieval from semantic memory on a semantic priming task. Other studies have suggested similar disinhibition of retrieval after a single dose of Δ9-tetrahydrocannabinol (THC) or when recreational users smoke cannabis (▶ Cannabinoids and endocannobinoids)

Interfering with Memory

Theories of forgetting in memory research initially suggested that interference from previously learnt material – proactive interference – was responsible for forgetting, where the prior existence of old memories makes it harder to recall newer memories. NMDA-receptor antagonists like ketamine have been found to increase proactive interference in rodents, impairing performance on a ▶ spatial memory task. However, nowadays research suggests that although proactive interference plays a part, a retroactive interference has more direct role in forgetting. Retroactive interference refers to the ability of more recently learnt information to inhibit previous memories. There is some suggestion that ketamine also increases retroactive interference in humans in a word-learning task. Administering amnestic agents such as scopolamine, prelearning of the second item in memory has been found to prevent retroactive interference in rodents.

One particularly interesting application of retroactive interference is retroactive facilitation. This happens when an amnestic compound, such as those described above, ingested after some information has been learnt, actually *facilitates* memory for this information. This phenomenon has been observed with a variety of compounds including ▶ alcohol, ▶ benzodiazepines, scopolamine, and NMDA-receptor antagonists. The mechanism of retroactive facilitation has begun to be identified: these amnestic agents cannot disrupt induction of LTP in the hippocampus for information learnt before they were ingested (what is known as retrograde amnesia), therefore their facilitatory effects are likely to occur by blocking the induction of new LTP without impairing the

maintenance of old information. This then protects new memory traces from interference when they are in a fragile state and are still being consolidated and reconsolidated. Preclinical studies confirm this assertion. The synthetic induction of LTP impairs recall of the prior learning of the ▶ Morris Water Maze; however, giving an NMDA-receptor antagonist post learning blocks this interference and performance is left intact.

Wiping Out Memories

The ability to forget information is important, for if we remembered every single event and stimulus encountered in our environment then the brain's workspace would be crowded with irrelevant information. The amnestic power of compounds such as alcohol and benzodiazepines as discussed above, can facilitate memory for information learnt before consuming or being administered drugs. Other compounds, however, appear to be able to destabilize the previously learnt information such that it becomes quickly "unlearnt," leading to the suggestion that it may be possible to "erase" certain unwanted memories.

It has long been known that smoked herbal cannabis, from the *Cannabis sativa* plant, in particular the active ingredient THC, impairs memory and like other drugs, it is known to prevent the induction of hippocampal LTP. However, recently the exact mechanism by which the drug exerts its effects on memory has begun to be studied. Mice lacking the cannabinoid 1 (CB1) receptor show enhanced memory and ▶ perseveration in their behavior, along with an impairment in both short- and long-term extinction of memories. It seems that in these animals memory is improved, but memories become almost impossible to erase. This has led to the suggestion that the ▶ endocannabinoid system may be involved in preventing the automatic ▶ consolidation of memories and destabilizing memories for forgetting. Hence, the drug cannabis may inhibit memory by modulating the brain's endogenous forgetting system.

Although interfering with the endocannabinoid system may destabilize memories, other compounds appear to be able to inhibit the consolidation of recently formed memories. ▶ Noradrenaline is thought to play a role in memory consolidation, via enhancement of LTP in the hippocampus and amygdala, such that memories become more quickly consolidated. Giving antagonists of the β-adrenergic receptor (beta-blockers) has been suggested as a potential means of inducing retrograde emotional amnesia in humans. Clinically, this has been suggested as a treatment for ▶ posttraumatic stress disorder (PTSD), as a means of weakening and erasing traumatic emotional memories. Emerging evidence, indeed, suggests that such drugs, when administered after a traumatic event, have the capacity to reduce the physiological responses associated with recalling a traumatic event. Further, these compounds appear to prevent full consolidation of emotional memories in the amygdala. One problem with using drugs like propanalol to treat PTSD is that the disorder itself cannot be diagnosed until at least a month after the traumatic event. However, animal studies have found that when memories are reactivated they become destabilized and vulnerable to destruction. Recent research has demonstrated that if propanolol is given following *reactivation* of a trauma memory, it also reduces physiological responsivity and intrusive images associated with the event.

Researchers have also capitalized on the vulnerability of reactivated memories to pharmacological modulation in treating other clinical disorders such as addiction. Infusing an NMDA-receptor antagonist into the ▶ amygdala prior to the reactivation of drug memories also has been found to disrupt drug-associated memory in rodents and their drug-seeking behavior. This impairment of memory for the drug was found to persist for 4 weeks following treatment. Highly experimental treatments of alcohol and heroin addiction in humans may also have inadvertently used a similar mechanism. Alcohol and heroin addicts given the NMDA-receptor antagonist, ketamine, prior to psychological therapy, also showed a reduction in drug-seeking behavior and relapse.

Inhibiting the Retrieval of Old Memories

Memory inhibition in retrieval is an important facet of any functioning memory system. A memory system would be rendered virtually useless if we were to recall all previously learnt information at once. An adaptive memory system selects only the relevant information from memory and inhibits the recall of huge swathes of irrelevant, but related, information. For example, if I wish to remember a friend's phone number, I need not recall all the phone numbers that I know, or even those that my friend ever had, so all of these must be inhibited in memory. As mentioned previously, there is indirect evidence that certain pharmacological compounds "inhibit the inhibition of memory" or *disinhibit* the retrieval from semantic memory, which can be as detrimental as impairing the encoding of new information. This disinhibition of retrieval has been inferred from increased semantic priming – a reduction in reaction time when a prime word is followed by a related word – with ▶ L-dopa and

cannabis. Following the ingestion of these compounds, it is suggested that activation spreads more quickly through semantic networks and retrieval is disinhibited. This is reflected in the quicker response time when two words are related than when they are unrelated. Similarly, increased priming has been observed in individuals with ▶ psychosis and ▶ mania, and it has been suggested that this is a cognitive basis of symptoms such as thought disorder and flight of ideas.

Memory retrieval can also be overinhibited; this too can be problematic. On the basis of the "encoding specificity principle" it was thought that information encoded while intoxicated with a drug would be most efficiently retrieved when again intoxicated with the same drug. In other words, retrieval would be best when in the same drug state as when information was initially acquired. Retrieval of information when not under the influence of a drug would thus be inhibited. The drug state was thought to act as a contextual cue around the memory, aiding retrieval. However, this effect is not reliably observed and even when it is, it is quantitatively very small.

Extinguishing the Past

Extinction learning itself is thought to involve active suppression of memories via processes different from normal forgetting. In humans, extinction learning has been powerful in the psychological treatment of ▶ anxiety disorders which involves "exposure therapy." Recent research has shown the strength of combining psychological treatments with pharmacotherapies in enhancing extinction learning. Preclinical studies have demonstrated the potential of augmenting extinction learning by boosting central glutamatergic neurotransmitter system functioning. In particular, the previously widely used antituberculosis drug, D-cycloserine (DCS) – which is a partial agonist at central glutamatergic NMDA-receptors – enhances the response to exposure therapy in patients with social phobia, fear of heights, and ▶ obsessive–compulsive disorder. In addition to these trials of DCS-related facilitation of exposure therapy, animal behavioral research also suggests that DCS may facilitate extinction of cocaine-induced ▶ conditioned place preference (CPP). This facilitative effect on extinction is also long-lasting and resistant to reinstatement (i.e., relapse). In humans, however, DCS has shown limited efficacy in enhancing fear extinction, but appears to enhance fear memory consolidation.

Cannabidiol (CBD) is a naturally occurring compound extracted from the *Cannabis sativa* plant. The pharmacology of CBD is not completely understood, but it is thought that it weakly binds to CB1 and CB2 receptors, functionally blocking the reuptake and hydrolysis of ▶ anandamide, an endogenous cannabinoid. As discussed above, the endocannabinoid system is thought to play a key role in the brain's natural forgetting mechanisms. There is now also an extensive preclinical literature examining the role of CB1 receptors in extinction learning. CB1-receptor knock-out mice exhibit impaired extinction learning and administration of exogenous CB1-receptor antagonists impairs the extinction of fear behaviors. Conversely, CB1 receptor agonists, eCB membrane transport inhibitors and CBD itself have been shown to facilitate fear extinction. CBD, like DCS, has also been found clinically to enhance the extinction of cocaine- and amphetamine-related CPP.

There is a clear parallel between fear extinction in animals and exposure therapy in humans. In the future, therefore, compounds which aid extinction of memories may have an important therapeutic role in treating clinical conditions such as addiction and anxiety.

Should Parts of the Past Be Extinguished?

Pathological memories – trauma, addiction, anxiety – may have a devastating impact on an individual's life. Therefore, there is an understandable excitement at the possibility of treating these conditions by manipulating the very memories that produce them. However, the notion of erasing memories carries with it a host of potential ethical problems. In the film "Eternal Sunshine of the Spotless Mind" individuals are able to choose "cosmetic" memory surgery to remove unwanted memories of painful life experiences or attachments. This raises the question: is it morally acceptable to remove parts of people's memories, given they are so fundamental to one's identity?

Bioethical committees have also considered the notion of the "erasing" of memories as a potentially hazardous endeavor. They have concluded that memories, however negative and distressing, are integral to one's continuity of experience. Ethically, this area is still largely controversial, and developments will depend on furthering our understanding of the effects of extinguishing memories. For example, how does inhibiting one type of memory impact on other forms of memory? It is possible that the removal of a memory itself may have psychological, and even neurobiological, consequences. However, thus far any induction of pharmacological retrograde amnesia seems limited to nondeclarative forms of memory, and as such the impact on *conscious* experience may be minimal. As science progresses and the sophisticated inhibition of

memory becomes a reality, there may be emerging, as yet unconsidered, ethical considerations. However, we should also bear in mind that reports of the use of compounds producing anterograde amnesia like alcohol and cannabis date back thousands of years. Indeed, this seems to be one of the appealing properties of drugs of abuse. When asked in surveys, drug and alcohol users often cite the memory-impairing capacities of drugs as a pleasurable effect. Given it seems accepted that individuals erase "memories" of the present by using drugs and alcohol, will it in future be acceptable for them to erase memories of the past?

Conclusions

Many psychoactive substances have a capacity to inhibit memory. Abused substances, for example, alcohol, cannabis, MDMA, and ketamine often acutely impair the laying down of new memories, and this can be perceived as a pleasurable effect which users often report as an experience of "living in the moment." Episodic memory is the type of memory most commonly inhibited by these amnestic psychoactive substances, chiefly via blockade of induction of hippocampal LTP. For a long time, it was thought that psychoactive substances could only cause anterograde amnesia and impair the laying down of new memories; indeed, for the majority of compounds, this is the case. Yet recently, research has demonstrated the capacity of some compounds to pharmacologically inhibit prior memories and produce a retrograde impairment. There is now evidence that when reactivated, memories can become destabilized and then "erased," and adrenergic receptor antagonists have emerged as potential treatments for PTSD. Creating stronger extinction memories, using compounds such as DCS, may compliment psychological treatments of anxiety and addiction. While the clinical potential of such treatments is clear, the ethical implications are not. The pharmacological inhibition of memory is an exciting field of research which has the potential to yield novel pharmacotherapies for psychiatric disorders as well as further insights into the very nature of memory itself.

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Inhibitory Amino Acids and Their Receptor Ligands

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Definition

Normal brain function is based on a delicate balance between inhibition and excitation of neuronal activity. Neuronal inhibition is primarily due to the neurotransmitter ▶ GABA (γ-aminobutyric acid) and also includes the neurotransmitter glycine. They exert inhibition via their respective receptors, i.e., ionotropic $GABA_A$ receptors, metabotropic $GABA_B$ receptors, and ionotropic glycine receptors. In this article, the role of GABA and glycine in brain function, their respective receptor pharmacology, and their therapeutic impact are briefly described.

Pharmacological Properties

GABA and the Inhibitory Interneuron "Clocking" Networks

Complex brains have developed specialized mechanisms for the grouping of principal cells into temporal coalitions of local or distant networks, the inhibitory interneuron "clocking" networks. They consist of ▶ GABAergic interneurons of rich diversity. In cortical circuits, these neurons control spike timing of the principal cells, sculpt neuronal rhythms, select cell assemblies, and implement brain states (Klausberger and Somogyi 2008). To achieve this regulatory control, distinct GABAergic interneurons innervate distinct subcellular domains of pyramidal cells and act in discrete time windows. Such a compartmentalized structure of pyramidal cells allows spatially segregated activities to occur at the same time. Also, the same domain of pyramidal cells can receive differentially timed GABAergic input from distinct sources. For instance, subcortical state-modulating input from brain stem nuclei is received by CCK expressing GABA neurons. Finally, cortical long-range GABA projections appear to prime and reset activity in multiple target areas in cognitive processes (Klausberger and Somogyi 2008).

Despite the daunting complexity of the inhibitory interneuron network, the search for a relevant pharmacological control target led to the discovery of the role of $GABA_A$ receptors in cognitive and emotional processing and in the regulation of behavior. This discovery arose

from the recognition that a major class of psychoactive drugs, the ► benzodiazepines, exerted their effects via an ► allosteric modulatory site of $GABA_A$ receptors, termed benzodiazepine receptors (Möhler and Okada 1977). Initially, this discovery was pertained to the regulation of ► anxiety, but was subsequently extended to the GABAergic regulation of vigilance, memory, ► schizophrenia, and pain. The clinical validity of this approach has been demonstrated by the emergence of a new pharmacology of $GABA_A$ receptor subtypes and first clinical proof of concept studies in patients with anxiety disorders and schizophrenia.

Functional Distinction of $GABA_A$ Receptor Subtypes

The diversity of GABAergic interneurons in network regulation is paralleled by a diversity of $GABA_A$ receptors. $GABA_A$ receptors are GABA-gated pentameric chloride channels, mediating largely tonic and phasic inhibition. They are generally composed of three types of subunits (α, β, γ) with multiple variants (α_{1-6}, β_{1-3}, γ_{1-3}). Receptors containing α_1, α_2, α_3, or α_5 in combination with β_2 or β_3 and γ_2 are benzodiazepine-sensitive, whereas those containing α_4 or α_6 or δ instead of γ_2 fail to be responsive to these drugs. Together with the structural diversity of receptor subtypes, the morphological distribution pattern suggested specific functional roles for specific receptor subtypes in distinct neuronal networks and associated cognitive processing. The $GABA_A$ receptor subtypes were taken as markers for behavior-relevant circuits (Möhler 2007a, b).

The behavioral relevance of the $GABA_A$ receptor subtype was identified using a point mutation strategy in mice. Each of the four benzodiazepine-sensitive $GABA_A$ receptor subtypes was rendered benzodiazepine-insensitive by a genomic point mutation in the α_1, α_2, α_3, or α_5 subunit gene, which converted a canonical serine residue in the drug-binding pocket to a histidine residue. The point-mutated receptors were diazepam-insensitive, but maintained their cellular and subcellular expression pattern. In these mice, the physiological response to GABA was unaltered. It was only when a benzodiazepine drug was administered that a particular drug response was absent in the mutant. The behavioral deficit could be ascribed to the particular mutated receptor subtype. In the wild type, this receptor subtype was expected to mediate the corresponding response. In addition, by means of their distinct expression patterns, the $GABA_A$ receptor subtype in question identified the neuronal network, which mediated the respective behavior (Möhler 2007a, b).

Three rho subunits, expressed mainly in retina, constitute $GABA_A$ receptors, which have also been termed $GABA_C$ receptors based on structural and pharmacological distinctions (potential homomeric subunit composition; insensitivity to bicuculline, picrotoxine, and benzodiazepines). However, these properties do not qualify for a terminology distinct from $GABA_A$ receptors (Barnard et al. 1998).

Regulation of Sedation and Sleep via $GABA_A$ Receptors

The sedative component of benzodiazepines, measured by the reduction of locomotor activity, is attributed to neuronal circuits expressing α_1GABA_A receptors, the most prevalent receptor subtype in the brain. Ligands with preferential affinity for α_1 receptors, such as ► zolpidem or ► zaleplon, are used as ► hypnotics (Table 1). However, the changes in sleep architecture (suppression of REM sleep) and EEG-frequency profiles (reduction of slow-wave sleep, increase in fast β-frequencies) induced by classical benzodiazepines are largely due to the effects mediated by receptors other than α_1. The most pronounced effect of diazepam on the sleep EEG in wild-type mice is derived from the enhancement of α_2GABA_A receptors. Thus, the hypnotic EEG fingerprint of ► diazepam can be dissociated from its sedative action. Future hypnotics might target changes in the EEG pattern, which are the characteristics of physiological sleep, and thereby aim at improving the sleep quality. For instance, the GABA-mimetic gaboxadol (4,5,6,7-tetrahydroisoxazolo [5, 4-c]pyridine-3-0l hydrochloride; synonym THIP), which interacts preferentially with $\alpha_4\beta_3\delta$ $GABA_A$ receptors in vitro, was found to enhance slow-wave sleep in vivo (Möhler 2008).

Anxiolysis via α_2 $GABA_A$ Receptors

The differentiation of $GABA_A$ receptors by knock-in point mutations showed that it was the α_2- but not the α_3- or α_5-$GABA_A$ receptor that mediated the ► anxiolytic activity of diazepam. In α_2(H101R) mice, but not α_3(H126R) or α_5(H105R) mice, diazepam failed to induce anxiolytic activity (light–dark paradigm, ► elevated plus maze). In keeping with this notion, the benzodiazepine site ligand L-838417, which showed efficacy at α_2, α_3, and α_5, but not at α_1GABA_A receptors, was proved to be anxiolytic in wild-type rats (Table 2). Similarly, the benzimidazo-derivative NS11394 acting as ► partial agonist at α_2, α_3, and α_5, but not at α_1 receptors, was found to show anxiolytic activity in rodents (Table 2). It remaines to be clarified to what extent the α_3GABA_A receptor component

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Inhibitory Amino Acids and Their Receptor Ligands. Table1. $GABA_A$ receptor subtypes[a].

Subunits	Localization	Pharmacology
$\alpha_1\beta_2\gamma_2$	Major subtype (60%), Synaptic and extrasynaptic	Benzodiazepine-sensitive. Mediates sedative and anticonvulsant activity
$\alpha_2\beta_3\gamma_2$	Minor subtype (15–20%). Synaptic	Benzodiazepine-sensitive. Mediates anxiolytic and analgesic activity
$\alpha_3\beta_n\gamma_2$	Minor subtype (10–15%)	Benzodiazepine-sensitive. Mediates sensori-motor gating. Anxiolytic activity only at high receptor occupancy. Partly mediates analgesic activity
$\alpha_5\beta_{1,3}\gamma_2$	Less than 5% of receptors. Extrasynaptic (cerebral cortex, hippocampus, olfactory bulb)	Benzodiazepine-sensitive. Mediates modulation of temporal and spatial memory
$\alpha_4\beta_n\delta$	Less than 5% of receptors. Extrasynaptic	Insensitive to benzodiazepines. Sensitive to low concentration of ethanol
$\alpha_4\beta_n\gamma$	Less than 5% of receptors. Extrasynaptic	Insensitive to benzodiazepines
$\alpha_6\beta_n\delta$	Small population. Extrasynaptic (only in cerebellum)	Insensitive to benzodiazepines. Sensitive to low concentration of ethanol
$\alpha_6\beta_{2,3}\gamma_2$	Less than 5% of receptors. Synaptic (only in cerebellum)	Insensitive to benzodiazepines

[a]The term benzodiazepine refers to diazepam and structurally related agents in clinical use. The % values are estimates taking all brain $GABA_A$ receptors as 100%. For details see text and Möhler (2007a)

contributed to the anxiolytic activity of these ligands. In mice lacking α_3GABA_A receptors, the anxiolytic activity of diazepam was undiminished. However, TP003, a ligand with selective efficacy at α_3GABA_A receptor did show anxiolytics activity, an effect which was, however, apparent only at high receptor occupancy. Classical benzodiazepines exert anxiolysis at low receptor occupancy, suggesting that the α_2GABA_A receptors and not the α_3GABA_A receptors are the major mediators of this activity. Thus, the strategy to develop novel day-time anxiolytics, which are free of sedation, focuses on α_2GABA_A receptors, although α_3 receptors are not excluded. Such ligands are expected to display low or no dependence liability. The α_2 receptors take up strategic positions mainly on the soma and the axon initial segment of pyramidal cells in cerebral cortex and ► hippocampus and also occur in the ► amygdala. This selective inhibitory control seems to be sufficient to exert anxiolysis and defines a medically relevant anxiety circuit (Atack 2008; Löw et al. 2000; Möhler 2007a).

Regulation of Learning and Memory via α_5 $GABA_A$ Receptors

Spatial and temporal memory is linked to oscillatory neuronal activity in the hippocampus, where the NMDA-type glutamate receptors on principal neurons have attracted most attention in modulating memory performance. However, there is a balancing control by GABAergic tonic inhibition. α_5GABA_A receptors are located at the base of the dendritic spines, which receive the excitatory input. When α_5 receptors were partially reduced genetically, associative learning in the form of trace ► fear conditioning, a hippocampus-dependent memory task was enhanced, but not delay or contextual conditioning, which are hippocampus-independent. Similarly, spatial memory in water maze learning was reduced in mice lacking α_5 receptors. Thus, for the first time, a defined GABAergic control of temporal and spatial memory had been established. Indeed, a partial ► inverse agonist acting at α_5GABA_A receptors enhanced the performance of wild-type rats in the water maze test (Atack 2008; Möhler 2007a).

Schizophrenia: Alleviating the Cognitive Deficit and Regulating Sensorimotor Gating Through α_2 and α_3 $GABA_A$ Receptors

A large number of neurophysiological and neuroimaging studies of patients with schizophrenia have furnished in vivo evidence for dysconnectivity, i.e., abnormal functional integration of brain processes. This dysconnectivity could arise from aberrant wiring of connections during development or from aberrant synaptic plasticity. Among the various clinical symptoms of the disease, the cognitive deficits are associated with a deficit in EEG γ band

Inhibitory Amino Acids and Their Receptor Ligands. Table 2. $GABA_A$ receptor subtype ligands[a].

Drug	Main activity	Interaction with recombinant $GABA_A$ receptors[b,c]
A. Benzodiazepine site ligands		
Zolpidem	Hypnotic	Preferential affinity for α_1
Zaleplone	Hypnotic	Preferential affinity for α_1
Indiplon	Hypnotic	Preferential affinity for α_1
L-838 417	Anxiolytic Antihyperalgesic	Comparable affinity at α_1, α_2, α_3, α_5 subtype. Partial agonist at α_2, α_3, α_5 (not α_1) subtype
NS11394	Anxiolytic Antihyperalgesic	Partial agonist at α_2, α_3 (not α_1) subtype, nearly full agonist at α_5 subtype
Ocinaplon	Anxiolytic	Comparable affinity at α_1 α_2, α_3, α_5 subtype. Partial agonist at α_2, α_3, α_5 subtype nearly full agonist at α_1
SL 651 498	Anxiolytic	Agonist at α_2, α_3, partial agonist at α_1 and α_5 subtype
TPA 023	Anxiolytic	Partial agonist at α_2, α_3 subtypes, antagonist at α_1, α_5 subtypes
TPA 003	Anxiolytic	Partial agonist at α_3 subtype. Effective only at high receptor occupancy.
ELB 139	Anxiolytic	Selective receptor profile uncertain
α_3IA	Anxiogenic	Weak inverse agonist at α_3
L-655 708	Memory enhancer	Partial inverse agonist with preference for α_5 subtype
B. Modulatory site other than benzodiazepine site		
Ethanol	Anxiolytic Sedative	High sensitivity ($\geq$3 mM) at $\alpha_4(\alpha_6)\beta_3\delta$[d]; Medium sensitivity ($\geq$30 mM) at $\alpha_4(\alpha_6)\beta_2\delta$[d]; Low sensitivity ($\geq$100 mM) at $\alpha_4(\alpha_6)\beta_3\gamma_2$
Neurosteroids (e.g., 3α,5α-THDOC)	Anxiolytic Sedative Anesthetic	High sensitivity at δ-containing subtypes[d] and at α_1, α_3 receptors in combination with β_1
Intravenous anesthetics (Etomidate, Propofol)	Sedative Anesthetic	Act on receptor subtypes containing β_3, i.e., mainly α_2 and α_3 subtypes
C. GABA site		
Gaboxadol	Hypnotic	Partial agonist at α_1, α_3 subtypes, full agonist at α_5, and superagonist at $\alpha_4\beta_3\delta$ receptors[b]

[a]This table is a summary from Rudolph and Möhler (2006), Möhler (2007a, 2008), and Atack (2008)
[b]Classical partial agonists, which do not differentiate between $GABA_A$ receptor subtypes such as Bretazenil or Pagoclone, are not considered in this review
[c]Data should be treated with caution as properties of recombinant receptors that are expressed in foreign host cells might not give an accurate reflection of their neuronal counterparts
[d]GABA is a weak partial agonist on δ-containing receptors, which largely explains the strong modulatory response of ligands acting on δ-containing receptors. THDOC, 5α-pregnane3α,21-diol-20-one

activity, pointing to a potential deficit in GABAergic control. Indeed, in postmortem studies, GABAergic Chandelier neurons in frontal brain were found to be dysfunctional. These neurons are known to act via α_2GABA_A receptors. Furthermore, in mice, a deficit of α_3GABA_A receptors resulted in sensorimotor gating deficits and a hyperdopaminergic phenotype. These results pointed to a new GABAergic strategy in treating cognitive deficits, sensorimotor gating deficits, and possibly negative symptoms in schizophrenia. Restoration of GABA was expected to restore oscillatory synchronicity and cognitive function. MK0777, an α_2/α_3 $GABA_A$ receptor modulator, was therefore tested in the treatment of schizophrenia patients. In a proof of concept study, a 4-week treatment with MK0777, as add-on to the standard antipsychotic therapy, resulted not only in an increased level of ► attention and ► working memory, but also restored the oscillatory power of the γ band, when the patients performed a cognitive task. Thus, a GABA substitution therapy proved effective in reconstituting the phenotype and the biotype

of cognition. This example is expected to trigger further clinical trials to support an entirely new therapeutic concept of cognitive deficits based on α_2/α_3 $GABA_A$ receptors (Lewis et al. 2008).

Modulation of Chronic Pain: Spinal α_2 and α_3 $GABA_A$ Receptors

The canonical circuits of GABAergic control of principal cells also applies to circuits in the spinal cord with particular reference to sensory pain processing. Using the point-mutated mice described earlier, spinal α_2 (and α_3) $GABA_A$ receptors were identified as powerful gatekeepers of pain (Knabl et al. 2008). The experimental α_2/α_3 receptor ligand L-838 417 (Table 2) was highly effective in suppressing inflammatory and neuropathic pain, yet devoid of unwanted sedation and motor impairment. Most importantly, in contrast to ► morphine, L-838417 failed to show any ► tolerance in analgesic efficacy, as tested over nine days. The α_2/α_3 receptor ligand reduced not only the nociceptive input, but also reduced the activity in brain areas associated with the associative-emotional component of pain (fMRI) (Knabl et al. 2008). Similarly, NS11394, acting as ► partial agonist at α_2 and α_3 receptors and as almost full agonist at α_5 receptors, was effective in rat models of inflammatory and neuropathic pain (Table 2) (Mirza et al. 2008). These results provide a rational basis for a new class of drugs for the treatment of chronic inflammatory and neuropathic pain, based on a pain-related inhibitory interneuron network in brain and spinal cord.

$GABA_A$ Receptors for Consciousness

In the quest for neuronal correlates of consciousness, various avenues are being followed including the quest for the mechanism of action of anesthetic drugs by which consciousness is safely, painlessly, and reversibly switched off and on again for surgical interventions. Various molecular targets have been invoked in mediating the clinical effects of general anesthetics. Recent work focused on the role of $GABA_A$ receptors, based on the analysis of point-mutated knock-in mice, which carried point mutations in the β_3 and β_2 subunits of the $GABA_A$ receptor. These mutations rendered the $GABA_A$ receptors containing the respective subunits insensitive to modulation by the intravenous anesthetics propofol and etomidate and certain volatile anesthetics, e.g., enflurane. It was found that β_3-containing $GABA_A$ receptors mediated in full the immobilizing action of etomidate and propofol (Table 2), which correspond to the stage of surgical tolerance. Thus, β_3GABA_A receptors are a major control element for anesthesia.

$GABA_B$ Receptors and their Pharmacology

Besides ionotropic $GABA_A$ receptors, GABA acts on metabotropic $GABA_B$ receptors, which are heterodimers formed by the subunits B1 and B2, of which B1 occurs in two isoforms (B1a, B1b). The receptors are located both pre and postsynaptically, coupled to K^+ and Ca^{2+} channels. Therefore, when the receptor is activated, a variety of effects might be expected. The normal result is a long-lasting neuronal hyperpolarization, mediated by an increase in membrane conductance to K^+, and a reduction in the postsynaptic potential produced by a decrease in the release of excitatory transmitters, e.g., ► glutamate or ► substance P, via presynaptic $GABA_B$ receptors. $GABA_B$ receptors contribute to inhibitory events throughout the cerebral axis but are particularly preponderant in the spinal cord. In higher brain centers, $GABA_B$ receptors largely lack a direct innervation and are activated by "spill-over" from adjacent GABAergic synapses. In spinal cord, however, innervation of post and presynaptic $GABA_B$ sites does appear to occur (Bowery 2006).

There is a paucity of potent and selective $GABA_B$ receptor agonists. Through its muscle relaxant and antispastic activity, baclofen is the only $GABA_B$ receptor agonist in clinical use. Nevertheless, other uses of baclofen have been proposed in animal studies, such as the alleviation of pain, reduction of anxiety, and amelioration of drug addiction. Antagonists, acting at $GABA_B$ receptors, have yet to prove their therapeutic benefit. In animal models, antagonists, such as CGP36742, were shown to improve cognition, alleviate absence epilepsy, and improve depression-like behavior. At present, it remains to be seen how these apparent functional distinctions of $GABA_B$ receptor ligands can be equated with the lack of diversity in receptor structure (Bowery 2006).

Glycine Receptors and their Pharmacology

Besides GABA, glycine is the second major inhibitory neurotransmitter being highly concentrated in the ventral and dorsal horn of the spinal cord, but occurs also in higher brain regions. Glycine receptors (GlyR) are pentameric glycine-gated chloride channels and – like $GABA_A$ receptors, ► nicotinic acetylcholine receptors, and $5HT_3$ receptors – belong to the ligand gated ion channel family. GlyR are composed of α and β subunits in a ratio of 2α:3β. Four different genes encoding GlyRα subunits (α_1– α_4) and a single GlyRβ subunit gene have been identified in vertebrates (Betz and Laube 2006; Betz et al. 2001). Compared to $GABA_A$ receptors, the pharmacology of GlyR is much less developed. Among GlyR agonists, β-alanine and taurine, besides glycine, display inhibitory activity in vitro and may well do so also in vivo.

By inhibiting glycine binding, strychnine represents a unique tool to distinguish glycinergic from GABAergic inhibition. Consistent with a systemic disinhibition of motorneurons, strychnine poisoning leads to motor disturbances accompanied by unusual sensory impressions owing to the disinhibition of afferent pathways. Intoxicated persons report hyperactivity of vision and hearing and also acute pain. Indeed, the α_3 GlyR, which is primarily expressed in dorsal horn, is an essential target for pain regulation (Harvey et al. 2004). Agonists for α_3GlyR might qualify as future analgesics. The role of glycine as co-agonist of glutamate at NMDA receptors in excitatory synapses is described elsewhere in the Encyclopedia.

Summary

The roles of neuronal inhibition by GABA and glycine are increasingly incorporated into functional models of neuronal networks to understand complex brain functions. Based on the recognition of receptor subtypes, major advances were made in a new $GABA_A$ receptor pharmacology. Anxiolytics lacking sedation, novel nonopioid analgesics, and cognitive enhancers in schizophrenia are among the major achievements with clear potential of clinical benefit.

Cross-References

► Benzodiazepines
► Dementias and Other Amnestic Disorders
► Generalized Anxiety Disorder
► Inhibitory Amino Acids and Their Antagonists
► Latent Inhibition
► Molecular Mechanisms of Learning & Memory
► Schizophrenia
► Social Anxiety Disorder

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Inhibitory Postsynaptic Potentials

► EPSPs and IPSPs

Insomnias

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Synonyms

Inability to sleep; Sleeplessness; Unsatisfactory sleep.

Definition

► Primary insomnia is a complaint of difficulty in initializing or maintaining ► sleep or nonrestorative sleep that

lasts for at least 1 month and causes clinically significant distress or impairment in social, occupational, or other important areas of functioning. The disturbance in sleep does not occur exclusively during the course of another sleep disorder or mental disorder and is not due to the direct physiological effects of a substance or a general medical condition (► DSM1V).

Role of Pharmacotherapy

One third of our time is spent asleep. For years, sleep remained an enigma but modern scientific techniques such as the polysomnograph (► polysomnography) have given us useful insights (Lader et al. 2006). Recently, the discovery of several chemical agents involved in the regulation of sleep has emphasised the complexity of this state.

Polysomnographic recordings analysed by visual recognition of characteristic patterns have revealed two main types of sleep characterised by the presence of Rapid Eye Movements (REM sleep) or absence of these movements (non-REM sleep). The latter is divided into four stages – from light sleep through to two deeper stages, so-called slow wave sleep. The individual goes through a typical series of cycles of REM and non-REM sleep during the average 7–8 h of sleep. These patterns ("sleep architecture") change radically from the new-born, infants, adolescence, and adulthood to old age.

Sleep complaints are extremely common. Approximately, 10% of the population has a complaint of insomnia, which occurs every night for two weeks or more, whereas 3–4 times this number has the occasional sleep disturbance. However, despite this prevalence, only 5–10% approach a physician to discuss their sleep problems.

Diagnostic Categories

There are four main diagnostic categories of Sleep Disorders, according to presumed etiology (DSM-IV, APA 2000). These are:

(a) Sleep Disorder related to another mental disorder (usually ► depression or ► anxiety)
(b) Sleep Disorder due to a general medical condition,
(c) Substance-induced Sleep Disorder, and
(d) Primary Sleep Disorders, in which none of the above etiologies can be identified.

Primary sleep disorders are therefore presumed to arise from endogenous abnormalities in sleep−wake generating or timing mechanisms or conditioning factors.

The specific type of sleep complaint may vary over time with difficulty in falling asleep at one time and difficulty in staying asleep at other times. Maladaptive sleep habits may set in with erratic sleep schedules: these perpetuate the disorder patients to complain about decreased attention, energy, and concentration and increased feelings of fatigue and malaise. Many sufferers have previous history of increasing sleep difficulties culminating in complaints of insomnia: these may be delayed into late middle age. The polysomnograph (polysomnography) usually but not invariably shows impairment in sleep continuity such as increased sleep latency or frequent awakenings.

Other conditions that can give rise to sleep disorders are breathing-related sleep disorder (obstructive sleep apnoea) and circadian rhythm sleep disorder (delayed sleep phase, jet lag, and shift work) (American Sleep Disorders Association 1990). Mental disorders associated with insomnia include ► Major Depressive Disorder, ► Mania, Anxiety Disorders, ► schizophrenia, and organic disorders such as ► dementia. General medical disorders that are associated with insomnia are numerous and encompass all systems. Substances that impair sleep include ► caffeine, ► alcohol, ► nicotine, and medicines, such as ephedrine, and withdrawal of opioids, sedatives, anxiolytics, and hypnotics.

A range of drugs is available to treat primary insomnia on a symptomatic basis. Before doing so, it is a good practice to consider whether:

1. There is any cause that has not yet been identified such as depression, anxiety, breathing difficulties, pain, etc., even at a subclinical level? If so, treat the primary cause appropriately.
2. Is substance misuse, especially of alcohol, a problem? If so, treat the substance abuse and be very circumspect about prescribing psychotropic drugs, particularly benzodiazepines.
3. To rationalise any other medications, for example, do not give arousing drugs at night.
4. The patients' expectations of sleep is realistic and the patient napping during the day is thereby reducing night-time sleep requirements?
5. All relevant "sleep hygiene" stratagems have been mobilised? These include:
   (a) Increase daily exercise in the afternoon but not the evening
   (b) Reduce daytime napping
   (c) Reduce caffeine, alcohol, and nicotine intake, particularly in the evening
   (d) Reserve the bed for sleeping and not for watching TV

(e) Adhere rigidly to a regular time of retiring and rising at the same time each day, including weekends
(f) Learn and use anxiety management or relaxation techniques

Drugs Used as Hypnotics

The most widely prescribed drugs used as hypnotics are the ► benzodiazepines and chemically dissimilar but pharmacologically similar medications, the so-called "z-drugs" (see Table 1).

In treating insomnia, the expected duration of the disorder needs consideration. It is traditional to divide these into:

1. Transient insomnia, which occurs in those who are usually good sleepers. It may be due to extraneous factors such as jet-lag following time-zone crossings, temporary noise, and shift work. A clear end to the problem can be seen, and it is thought justifiable to prescribe a short-acting hypnotic for the duration of the expected disruption or until the sufferer adapts to it.
2. Short-term insomnia, which usually reflects disruption caused by emotional stress or serious medical illness. It is expected to last for a few days to a few weeks but may recur. It is often quite variable from night to night. A hypnotic may be helpful but should be used only for a few weeks. If the patient can reserve the medication for those nights when he or she feels that the insomnia is likely to be disturbing (i.e., intermittent use on an "as necessary" basis), the risk of inadvertent chronic use can be minimised. Again, a short-acting drug is usually preferred as it enables the insomniac to maintain a clear mind to deal with the day's problems.
3. Chronic insomnia, which is a much more contentious topic. It is the commonest form of primary insomnia and was long rather neglected. More recently, a consensus conference under the auspices of the US National Institutes for Health (2005) concluded that it was a common and major problem that caused a great deal of stress. Even more contentiously, there are wide differences of opinion as to whether this chronic disorder justifies long-term hypnotic use (Benca 2005). Again, identification of possible causes such as a chronic subclinical depression (dysthymia-like) should be undertaken and the primary cause such as pain, pruritus, or nocturnal respiratory distress should be treated.

A fairly large group of chronic insomniacs is left. Women are more likely to suffer from this condition than men; the elderly more likely than younger adults. The question as to whether prescribe a hypnotic focuses on three aspects – efficacy, tolerability, and risk of dependence.

1. *Efficacy*. Doubts have not been fully allayed about the long-term efficacy of hypnotics (Glass et al. 2005). Very few controlled studies have extended beyond a month. Some attenuation of effect has been noted and attributed to ► tolerance. However, some trials show that ► placebo effects persist and lessen drug-placebo

Insomnias. Table 1. Drugs used as hypnotics.

Drug	Usual therapeutic dose (mg/day)		Time until onset (min)	Duration of action
	Adult	Elderly		
Lormetazepam†	0.5–1.5	Quarter to half the adult dose 3	30–60	Short
Oxazepam†	15–30		20–50	Medium
Nitrazepam†	5–10		20–50	Long
Temazepam†	10–20		30–60	Short
Zaleplon	10		30	Very short
Zopiclone	3.75–7.5		15–30	Medium
Zolpidem	5–10		7–27	Short
Eszopiclone	6		15–30	Medium
Promethazine	25–50		Unclear but may be 1–2 h	Long
Ramelteon	8	8	15–30	Short
Melatonin -Extended Release (ages >55 only)	3	3	15–30	Short

†, benzodiazepines

differences. More recently, a few studies have shown convincing evidence of efficacy for at least six months, eszopiclone being a notable example.

2. *Tolerability.* This has been extensively evaluated for the benzodiazepines and the z-drugs, ► zopiclone, ► zolpidem, and ► zaleplon. Unwanted effects have been coruscatingly quantified with respect to residual ("hang-over") effects the next day. But even more important are cognitive and psychomotor impairment 2–4 h after ingestion, at the peak effects of the drug. The elderly are the main users of hypnotics and they are prone to nocturnal wakenings and trips to the bathroom. The problem of unsteadiness and falls has been studied both in a clinical and an epidemiological context. A recent warning from the FDA concerned bizarre nocturnal activity. Daytime functioning covers many topics of which driving behaviour has received most attention.
3. The third topic, ► *tolerance*, ► *dependence*, and *withdrawal problems*, is even more contentious (Lader 1998). First, long-term users may overestimate the benefits of continuous use. It is difficult for them, their carers, and doctors to distinguish between:
   (a) recurrence of the insomnia on discontinuation;
   (b) rebound when the symptoms of insomnia recur temporarily in exaggerated form;
   (c) Withdrawal when newly emergent symptoms supervene; they are usually transient but some patients complain of persistence of these symptoms, often muscle stiffness and perceptual heightened sensitivity.

Yet another problem is misuse, where doses escalate to higher than therapeutic levels; withdrawal is both difficult and protracted. Hypnotic drugs, particularly flunitrazepam and ► temazepam, can be abused either as primary agents or in conjunction with other drugs of addiction such as ► opioids, ► cocaine, and ► amphetamines. Personal health problems and social harm develop despite the "addict's" perception of the risks.

For all these reasons, the benefit/risk ratio of the benzodiazepines remains disputed. It has been known that they should not be prescribed indiscriminately; instead, shorter-acting compounds are to be preferred; they are not given to children or the elderly; their usage should be carefully monitored; attempts have been made to avoid their long-term use; and warnings have been given about drug interactions, particularly with ► alcohol, resulting in "paradoxical" overreactions. The patient should be warned that withdrawal may not be uneventful. The z-drugs are probably less likely than benzodiazepines of similar duration of action, such as triazolam, to cause adverse reactions. Nevertheless, one UK official body, the National Institute for Clinical Excellence, in a Technology Appraisal (2004), did not see z-drugs as a preference over the benzodiazepines.

Other Medications

Other medications, such as ► melatonin analogs, are also licensed for insomnia. An extended release form of melatonin has been licensed in Europe for primary insomnia aged 55 and over. A melatonin analog, ramelteon, which acts on M_1 and M_2 receptors, is available in the USA. It acts mainly to shorten the onset of sleep but slightly prolongs sleep as well. Both these compounds are largely devoid of adverse effects, such as sedation, and dependence and withdrawal problems.

Some antihistamines that penetrate to the brain are highly sedative; ► promethazine and diphenhydramine are examples. In some countries, they are available over the counter, but they can cause sedation the next day. Over-the-counter herbal remedies include valerian and hops.

With insomnia secondary to mental or medical causes, the presence of this comorbidity may influence the choice of medication for the primary disorder. For example, a depressive with distressing insomnia would prefer a sedative ► antidepressant rather than a neutral or stimulant one.

Conclusion

Insomnia in its many forms remains a therapeutic challenge. Careful elucidation and evaluation of the symptom pattern and possible etiological factors is essential to its successful management. Nondrug and drug treatments are both available, but use of the latter involves difficult judgments regarding the benefits and risks in each patient.

Cross-References

► Polysomnography
► Primary Insomnia
► Sleep

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Institutional Animal Care and Use Committee

► IACUC

Instrumental Aversive Conditioning

► Operant Behavior in Animals
► Operant Conditioning
► Passive Avoidance

Instrumental Behavior

► Operant Behavior in Animals

Instrumental Conditioning

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Synonyms

Operant conditioning

Definition

Instrumental conditioning occurs when a response is acquired and controlled by a contingency between the response and a reinforcer or outcome. In the case where there is a positive relationship between the response and the reinforcer, so that the response causes the reinforcer, two processes control responding: an S-R/reinforcement process mediating habitual behavior and an R-O process underlying goal-directed action. The conditions of training determine whether the habitual or goal-directed process predominates. Moreover, these two processes can be dissociated within the ► prefrontal cortex and striatum with the dopamine system being particularly implicated in habit learning. Stimuli serve multiple functions in instrumental conditioning. First, they act as ► discriminative stimuli in that they control when a response is performed. Although this control acts by the direct elicitation of the response in the case of habitual behavior, goal-directed action can be based on knowledge of the triadic relationships between stimulus, response, and outcome. Second, not only can a signal for an appetitive reinforcer motivate and prime an instrumental responding, but such a stimulus can also act as a ► conditioned reinforcer for instrumental behavior. Taken together, these processes and functions allow an agent to exert sophisticated and highly adaptive control over its environment in the service of needs and goals.

Principles and Role in Psychopharmacology

The capacity for instrumental conditioning is probably the most important form of behavioral learning. Although other forms of learning allow an animal to anticipate the occurrence of biologically significant events, it is only through instrumental learning that an animal can learn to control these events in the service of its needs and desires, whether it be learning how to exploit a new food resource, how to court a new mate, how to avoid a potential predator, or even how to procure and self-administer an addictive drug (see ► Self-administration of drugs). By definition, instrumental conditioning is a change in behavior controlled by a relationship between the target response and consequent event or outcome.

In practice, it is not always a straightforward matter to decide whether an acquired response is instrumental. Consider a simple case in which a hungry chick learns to approach a food bowl. Although the approach response is instrumental in gaining access to the food, it is far from clear that the approach behavior is actually controlled by this relationship. Consider an environment in which the usual response–outcome relationship is reversed so that the chick has to learn to move away from the bowl in order to gain access to the food. Under this reversed relationship, the bowl recedes at twice the speed the chick approaches it, and in order to feed, the chick has to learn to move away from the bowl because it will then

catch it up at twice the rate that the bird withdraws from it. If the chick's locomotion with respect to the food bowl is instrumental, then learning this reversed response–outcome relationship should not be a problem. In fact, chicks never learn to withdraw from the bowl to gain the food but rather persist in chasing it away. This maladaptive behavior suggests that the original approach response under the normal, nonreversed relationship may not be controlled of the instrumental approach-food relationship but rather reflect the natural propensity of chicks to approach a stimulus, in this case the food bowl, that has been rendered attractive by its association with food.

The reversed contingency procedure is an example of the bidirectional assay of the instrumental status of a response. To establish that a response is under instrumental control, it is necessary to demonstrate that both of the two opposing responses can be acquired under the appropriate response–outcome relationship. For example, not only should a rat be able to learn to push a lever to the left for food but also to reverse the direction of pushing when pushing to the right is required. The fact that it is often difficult to implement such a bidirectional assay with many nominally instrumental learning tasks, such a running in a runway or maze for a reward, has led contemporary researchers to favor operant tasks (see ► Operant behavior in animals), such as lever pressing for food, in which a discrete and relatively arbitrary response is used.

In the example of a hungry rat learning to press a lever for a food outcome, the outcome is referred to as the reinforcer because it is the event responsible for strengthening or reinforcing the response. Moreover, the acquisition of the lever pressing is an example of positive reinforcement because the food strengthens responding through a positive response-reinforcer contingency in that the response causes food delivery. Aversive events can also act as instrumental reinforcers, but in this case they reinforce the response through a negative response–reinforcer relationship so that performance of the response actively avoids or escapes the occurrence of the reinforcer, which would then be an example of ► negative reinforcement (see ► Active avoidance). If an aversive outcome is presented under a positive response–outcome relationship, it acts as a punisher and reduces responding, thereby allowing the animal to passively avoid the outcome (see ► Passive avoidance and ► punishment procedures). This essay will focus on the processes mediating positive reinforcement.

When Thorndike first characterized instrumental conditioning, he explained response acquisition by his "Law of Effect." According to this law, the presentation of a positive reinforcer strengthens an association between any stimuli present at the time of responding and the response itself so that subsequent presentation of the stimuli is more likely to elicit the response. We now know that this characterization of the instrumental learning in terms of stimulus–response (S-R) learning is insufficient in at least two respects. The Law of Effect assumes that the strength of the S-R association depends solely on the number of times and the probability that the response is followed by a reinforcer (paired reinforcement). However, if instrumental learning was solely dependent on paired reinforcement, performance could be insensitive to the causal relationship between the response and reinforcer. For example, if the probability of paired reinforcement is kept constant, the responding can be rendered causally ineffective by increasing the probability of the reinforcer in the absence of the response (unpaired reinforcement) until when the probability of paired and unpaired reinforcement are equal, when responding has no effect on the overall amount of reinforcement. The fact that such noncontingent schedules maintain a very low rate of responding shows that instrumental conditioning is in fact sensitive not only to response–reinforcer pairings but also to their contingency.

The second major limitation of the S-R/reinforcement theory is that it does not support goal-directed instrumental behavior. Specifically, an animal cannot select an appropriate response on the basis of the current incentive value of the associated outcome through an S-R mechanism and, therefore, responding is insensitive to changes of incentive value without undergoing reacquisition with the revalued outcome. Consider a case in which a rat initially learns to press a lever for a particular type of food before acquiring an aversion to the food (see ► Conditioned taste aversions). According to the S-R/reinforcement theory, the acquisition of this food aversion should have no impact on the animal's initial propensity to respond when once again given access to the lever. The only function of the food outcome during the initial training was to reinforce an association between the stimulus of the lever and the response of pressing it, so that the subsequent devaluation of the food should have no impact on the propensity to press the lever until the now-devalued food is once again presented contingent on the lever press. At variance with this prediction of S-R theory, there is now wealth of evidence that instrumental performance can be immediately sensitive to outcome revaluation. Sensitivity to outcome revaluation requires that the animal encodes the response–outcome (R-O) contingency during initial training so that a subsequent change in the

value of the outcome can immediately impact on responding through this R-O learning. In the absence of R-O learning, there is no mechanism by which a change in outcome value can directly modulate instrumental performance.

Instrumental performance mediated by R-O learning is characterized as goal-directed, whereas responding based on S-R learning is habitual (Dicknson 1994). In contrast to S-R learning, which is nondeclarative in form, R-O learning is declarative in that performance is mediated by a representation of the response–outcome relationship (see ▶ Declarative and nondeclarative memory). Clearly, goal-directed behavior, being immediately responsive to changes in outcome value, is much more flexible that habitual responding (see ▶ Behavioral flexibility). Instrumental contingencies engage both goal-directed and habitual learning with the relative contribution of these two forms of learning to the control of performance being determined by the conditions of training. Overtraining on a single response–outcome contingency produces insensitivity to outcome devaluation, thereby indicating habitual S-R control. However, responding remains sensitive to outcome devaluation, and therefore goal-directed action, even after overtraining on a more complex schedule in which different responses produced different outcomes. Another factor that determines whether performance is autonomous of the current incentive value of the outcome is the nature of the reinforcement schedule. On ratio schedules, there is constant probability of reinforcement and therefore a linear relationship between response and reinforcement rates, which should lead to good R-O learning. In contrast, under an interval schedule the reinforcement source depletes when a reinforcer is taken and time has to elapse before another reinforcer is available. This regeneration rate therefore sets an upper limit on the rate of reinforcement so that when responding is sufficient to procure a reinforcement rate near this upper limit, there is only a weak relationship between response and reinforce rates and consequently little R-O learning. Therefore, it is not surprising that responding more rapidly becomes habitual with training on an interval rather than on a ratio schedule. Variations in the type and parameters of reinforcement schedules allows the study of the economics of behavior (see ▶ Behavioral economics).

The behavioral distinction between goal-directed action and habitual responding has now been validated by neurobiological dissociations in the rodent by using the outcome devaluation and contingency manipulation assays (Balleine and Ostlund 2007; Cardinal et al. 2002). Lesions of the dorsomedial (prelimbic) prefrontal cortex prior to, but not following, training render performance insensitive to outcome devaluation and the degradation of the R-O contingency brought about by enhancing the probability of unpaired reinforcers. Therefore, dorsomedial prefrontal cortex functioning appears to be critical for the acquisition of goal-directed action but not for the retention and deployment of R-O learning. These latter functions depend on the integrity of the dorsomedial striatum in that both pre- and post-training lesions of this structure render responding insensitive to outcome devaluation and contingency degradation. In summary, goal-directed instrumental learning and performance depends on the interaction of the dorsomedial prefrontal cortex and striatum. A parallel cortico-striatal system is critical for the acquisition of S-R habits in the rat. The lesions of a more ventral area (infralimbic) of the rodent prefrontal cortex and of the dorsolateral striatum ensure that instrumental responding remains goal-directed in spite of a degree of overtraining that produces habitual responding by intact animals.

Ever since the discovery that dopamine antagonists produce extinction of instrumental responding, the importance of this neurotransmitter in instrumental conditioning has been well established. However, the exact functions of ▶ dopamine in instrumental performance remain unclear. It is known that the decrement in instrumental performance is observed under doses of neuroleptics that do not interfere with consumption of the food reinforcer nor with motor performance. Three lines of evidence suggest that dopamine may play a critical role in habit reinforcement. First, lesions of nigro-striatal dopamine system render performance sensitive to outcome devaluation under training conditions that produce S-R habits in control animals. Second, a regime of pre-treatment with dopamine agonists (see ▶ Psychomotor stimulants), which is thought to sensitize a dopamine-based reinforcement system, enhances the rate at which instrumental responding becomes habitual with training (see ▶ Reinforcement disorder). Finally, addictive drugs, which enhance dopamine function, are more effective reinforcers of habitual responding than are natural food rewards (see Self-administration of drugs). However, there is evidence that dopamine may also play a role in goal-directed performance in that dopamine infusions into the ▶ ventromedial prefrontal cortex restore sensitivity to outcome devaluation following a training regime that renders responding habitual in control animals.

Furthermore, dopamine also has a motivational function that is most clearly revealed by the so-called Pavlovian-instrumental transfer (PIT) paradigm. The rationale for

PIT lies in the fact that an instrumental contingency not only embodies the critical R-O relationship but also a predictive, or Pavlovian, stimulus–outcome (S-O) relationship. When a rat is trained to press a lever for food, not only does it experience the instrumental press-food contingency, but also pairings of the stimulus of the lever and, indeed, of the contextual cues of the operant chamber with the food. The PIT paradigm demonstrates the functions acquired by these stimuli by separately training the R-O and S-O relationships. When, on test, the stimulus that has been paired with the reinforcer is presented for the first time while the animal has the opportunity to perform the instrumental response (usually in extinction), the presence of the stimulus is found to enhance instrumental responding, a transfer effect that is reduced by the presence of dopamine antagonists either during training or during testing.

In part, PIT is thought to reflect a general motivating effect of reinforcer-associated stimuli on instrumental performance in that it is modulated by the motivational state of the animal at the time of testing and observed even if the stimuli and responses are associated with different appetitive reinforcers (Dickinson and Balleine 2002). For example, a stimulus associated with a starch solution potentiates lever pressing trained with food pellets more when the animal is hungry rather than sated. In contrast to this general form of PIT, a second, outcome-specific form of PIT is observed when the stimulus shows greater potentiation of a response with which it shares a common outcome. Unlike the general form, magnitude of outcome-specific PIT is relatively independent not only of the animal's current motivational state but also of the current incentive value of the stimulus-associated outcome. Whereas general PIT is evidence for the motivational influence of the conditioned stimuli, outcome-specific PIT suggests that such stimuli also has prime responses with which they share a common outcome. The behavioral distinction between these two forms of PIT is bolstered by their neurobiological dissociation within the amygdala. Whereas lesions of the central nucleus attenuate general PIT, it is dysfunction of the basolateral nucleus that abolishes outcome-specific PIT (Balleine and Ostlund 2007). A parallel dissociation is found following lesions of the ► nucleus accumbens with dysfunction of the core impacting on general PIT and that of the shell on outcome-specific PIT.

The ► amygdala also plays a role in mediating a second function of a reinforcer-associated stimulus, that of ► conditioned reinforcement (Cardinal et al. 2002). A stimulus that has been previously established as a predictor of an appetitive reinforcer will strengthen an instrumental response when delivered contingently on performance of that response. So, for example, rats will learn to press a lever for the presentation of light that has been paired with food delivery, an effect that depends on the integrity of the basolateral amygdala. Moreover, the effectiveness of the conditioned reinforcement is greatly enhanced by psychostimulants, a potentiation that is mediated by the nucleus accumbens. Conditioned reinforcement serves at least two important functions in the maintenance of complex behaviors. First, it enables animals to acquire a chain of responses that ultimately leads to primary reinforcement. The stimuli associated with each link in the chain act as conditioned reinforcers of responding in the prior link in the chain, thereby maintaining responding early in the chain. Second, conditioned reinforcers can act as tokens of primary reinforcement and so maintain behavior at times when access to the primary reinforcer is not available.

The final instrumental function of stimuli is as ► discriminative stimuli, signaling when a particular response–outcome relationship is operative. So, for example, an animal can learn that one of two responses, for example a left lever press, delivers the reinforcer in presence of one stimulus, a light, whereas the another stimulus, a tone, signals that the other response, a right lever press, is required for reinforcement. In the case of habitual responding, the discriminative function is a direct consequence of the S-R associations established by the reinforcement process. However, the discriminative control of goal directed behavior is more complex in that there is evidence that animals can learn about the three-term relationship between stimulus, response, and outcome (Rescorla 1991). Consider the following training contingencies between two stimuli, two responses and two outcomes:

S_A: $R_1 \Rightarrow O_X$ $R_2 \Rightarrow O_Y$ S_B: $R_1 \Rightarrow O_Y$ $R_2 \Rightarrow O_x$

The contingencies signaled by each stimulus are the same except for the fact that the relationship between the responses, R_1 and R_2, and the outcomes, O_Y and O_x, are reversed across the two stimuli, S_A and S_B. Evidence that rats learn about the specific R-O relationships signaled by each stimulus come from the effects of devaluing one of the outcomes. For example, if O_X is devalued, the animals should preferentially perform R_2 in S_A, but R_1 in S_B. The fact that rats show just such a pattern of test responding following the outcome devaluation demonstrates that goal-directed behavior can be controlled by knowledge of the three-term contingency.

In summary, instrumental conditioning occurs when a response is acquired and controlled by a contingency

between the response and a reinforcer or outcome. In case where there is a positive relationship between the response and reinforcer, so that the response causes the reinforcer, two processes control responding: an S-R/reinforcement process mediating habitual behavior and an R-O process underlying goal-directed action. The conditions of training determine whether the habitual or goal-directed process predominates. Stimuli serve multiple functions in instrumental conditioning. First, they act as ► discriminative stimuli in that they control when a response is performed. Although this control acts by the direct elicitation of the response in the case of habitual behavior, goal-directed action can be based on knowledge of the triadic relationships between stimulus, response, and outcome. Second, not only can a signal for an appetitive reinforcer motivate and prime an instrumental responding, but such a stimulus can also act as a conditioned reinforcer for instrumental behavior. Taken together, these processes and functions allow an agent to exert sophisticated and highly adaptive control over its environment in the service of needs and goals.

Cross-References

► Active Avoidance
► Behavioral Economics
► Behavioral Flexibility: Attentional Shifting, Rule Switching, and Response Reversal
► Conditioned Taste Aversions
► Declarative and Nondeclarative Memory
► Operant Behavior in Animals
► Passive Avoidance
► Psychomotor Stimulants
► Punishment Procedures
► Reinforcement Disorder
► Schedules of Reinforcement
► Self-Administration of Drugs

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Instrumental Performance

► Operant Behavior in Animals

Insulin-Resistant Brain State

Synonyms

IRBS

Definition

Reduction or loss of insulin action; reduced binding to insulin receptors in regions of interest for AD, hippocampus, or cortical areas.

Integral Membrane Protein

Definition

A protein that is permanently incorporated in a cell membrane; such protein can only be separated from the cell membrane using detergents.

Intellectual Disability

► Autism Spectrum Disorders and Mental Retardation
► Mild Cognitive Impairment

Intensive Care Unit Psychosis

► Delirium

Intermittent Claudication

Definition

Intermittent claudication refers to muscle pain (ache, cramp, numbness, or sense of fatigue), which occurs during exercise, in individuals with peripheral vascular disease caused by the obstruction of large arteries in the arms and legs. It is often a symptom of severe atherosclerotic disease of the peripheral vascular system. The PDE3

inhibitor cilostazol has been approved for the treatment of intermittent claudication.

Cross-References
► PDE3 Inhibitors

Internalization

Definition
Translocation of receptors including GPCRs and ionotropic receptors from the surface membrane to intracellular compartments.

Interpersonal Psychotherapy

Synonyms
IPT

Definition
A brief form of psychotherapy that focuses on enhancing interpersonal skills in order to ameliorate interpersonal factors that may be contributing to psychological distress. IPT appears to be effective in the treatment of depressive disorders of mild to moderate severity.

Inter-Temporal Choice

► Delay Discounting Paradigms

Interval Timing

Definition
Interval timing refers to the perception, estimation, and discrimination of durations in the range of seconds-to-minutes-to-hours. It is crucial for fundamental cognitive processes related to obtaining reward, estimating the rate of event occurrence, decision making, and neuroeconomics (see behavioral economics).

Cross-References
► Behavioral Economics
► Timing Accuracy
► Timing Behavior

Intracellular Recording

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Synonyms
Sharp microelectrode recording; Whole cell recording

Definition
► Intracellular recording denotes a group of electrophysiological techniques used to study the electrical properties of cells. These techniques permit the recording and manipulation of a cell's ► membrane potential, and the measurement of the ionic currents flowing across the plasma membrane. As such, these techniques allow for the study of a cell's membrane potential and its relationship to active and passive macroscopic ionic currents.

Principles and Role in Psychopharmacology
Living cells exhibit a membrane potential that is the result of the asymmetrical distribution of ions across the plasma membrane and the ion fluxes carried through the ion channels expressed by the cell. Excitable cells, and neurons in particular, express a rich complement of ion channels that produce not only a hyperpolarized membrane potential, but also endow the plasma membrane with a complex electrogenesis (Hille 2001; Kandel et al. 2000).

Foremost among the electrical phenomena of neurons is the ability to generate action potentials, which constitute the basic computational unit of neuronal networks. Action potentials reflect a brief increase in sodium permeability that causes a transient reversal of the membrane potential. Because action potentials represent a relatively large change in voltage across the membrane, they can be detected using extracellular recording techniques which allow for the assessment of neuronal activity under a variety of experimental conditions (see ► extracellular recording). However, most of the computational work of individual neurons involves changes in membrane potential at voltages below the threshold for the generation of action potentials. Direct investigation of this phenomenon requires recording of membrane voltage and ionic currents using intracellular recording techniques.

The simplest modality of intracellular recording monitors the membrane potential of a cell as a function of time. This is accomplished using a high input impedance "intracellular" amplifier that measures the voltage difference across the cell membrane using a fluid-filled

electrode whose lumen is continuous with the cell cytoplasm. The bath is generally considered to be at 0 mV (ground) and thus the cell's membrane potential is negative. This recording modality is known as ► current clamp, because the current flowing through the electrode, be it a sharp microelectrode or a patch electrode, is held "clamped" at a fixed level and the cell's membrane voltage is allowed to vary. This allows for recording of not only action potentials, but subthreshold excitatory and inhibitory synaptic potentials as well as the slow depolarizing and hyperpolarizing responses signaled by G protein-coupled receptors. The alternative to current clamp recording is ► voltage clamp recording, a less naturalistic recording modality where the amplifier actively controls the voltage across the membrane by current injection, and thus allows for the direct measurement of the ionic currents flowing across the membrane.

Current clamp and voltage clamp recordings can be implemented using either sharp microelectrode or patch clamp electrodes. In ► sharp microelectrode recordings, a glass capillary is heated and pulled at high velocity to produce a minute "sharp" tip. The electrode is then filled with a concentrated salt solution of high conductivity (e.g., 3 M KCl) and the cell is impaled with the electrode to obtain electrical continuity between the electrolyte filling the microelectrode and the cell cytoplasm. In ► patch clamp recording, a glass capillary is heated and pulled in multiple stages to produce a large tip electrode (generally 1–3 m diameter) that is filled with an intracellular solution, osmotically balanced to the cytoplasm. The electrode tip is then gently pressed against the plasma membrane with slight suction through the lumen of the electrode to obtain a "tight seal" between the smooth glass tip and the cell membrane. Further negative pressure is applied to the interior of the electrode to disrupt the membrane underneath the electrode tip and gain access to the cytoplasm, a recording configuration known as ► whole cell recording (Sakmann and Neher 2007).

Intracellular recording techniques constitute an important cluster of electrophysiological methods that allow for the mechanistic investigation of neuronal physiology and the study the cellular actions of neurotransmitters and their receptors. The use of these techniques on vertebrate and invertebrate experimental preparations over the last several decades has allowed us to gain important insight into multiple aspects of neuronal function including, for example, the microscopic physiology of ion channels and synapses, how ionotropic receptors excite and inhibit neurons and how G protein-coupled receptors regulate neuronal excitability (Hille 2001). Equally important, intracellular recording techniques combined with pharmacological (see ► Receptors: Functional Assays) and molecular biological interventions (see ► Genetically Modified Animals) have allowed us to explore cellular signaling *in situ*. This has permitted substantive advances in our understanding of the cellular and molecular mechanisms that underlie neuronal excitability and that are used by neurotransmitters receptors to signal their physiological responses.

All of the intracellular recording modalities outlined above can contribute to our understanding of neuronal physiology. However, each of them offers a unique set of advantages and disadvantages. ► Current clamp recordings offer a "naturalistic" approach to the study of neuronal physiology in that this methodology allows us to monitor the voltage across the cell membrane while it fluctuates while it would in a neuron *in situ*. A powerful experimental feature available during current clamp recordings is the ability to inject direct current into the cell to manipulate the cell's membrane potential. Of course, current injection through a high resistance electrode leads to the development of an additional voltage across the electrode in series with the membrane, but most modern current clamp amplifiers include a bridge circuit that allows for the cancelation of this voltage. The ability to inject direct current into the cell opens many experimental avenues for the study of neuronal physiology. In fact, current clamp recordings implemented using sharp microelectrodes form the experimental foundation upon which our current understanding of neuronal physiology and the actions of neurotransmitters was built. For example, they have allowed us to learn that synaptic potentials are composed of discrete quanta, that ► glutamate is the main fast excitatory neurotransmitter in central neurons and that ► G protein-coupled receptors exert their effects by regulating not only membrane potential but also by modulating a host of calcium- and voltage-activated currents. Sharp microelectrodes, however, tend to exhibit high resistances, which result in electrically noisy recordings and exhibiting limited current passing capacity. These factors limit the power of this technique to address subtler mechanistic issues.

Voltage clamp recordings offer a powerful alternative for the study of neuronal physiology. In this recording modality, the cell membrane potential is clamped at a set voltage controlled by the experimenter and the amplifier injects current as needed to maintain the set voltage. This injected current, of course, is the mirror image of the ionic current flowing through the membrane, thus allowing for its direct measurement. Voltage clamping is a powerful technique that allows for the direct study of the ion currents activated or modulated by

neurotransmitters. However, it is difficult to implement using sharp microelectrodes because of their limited and nonlinear current passing capacity. As such, voltage clamping with microelectrodes requires that the current injection be separated from the recording of voltage either through the use of two microelectrodes or of a discontinuous ("sample and hold") voltage recording protocol where current injection is temporarily dissociated from the recording of voltage. These technical difficulties delayed the widespread use of voltage clamp methodologies to the study of neuronal physiology until the maturing of patch clamp recordings techniques.

The development of patch clamp recording methodologies starting with the work of Sakmann and Neher in the 1980s revolutionized the study of neuronal electrophysiology (Hamill et al. 1981). One important aspect of this revolution was the development of whole cell recordings, which allowed for the use of low resistance patch electrodes to voltage clamp a variety of cell types. Because the resistance of a patch electrode (series resistance) is generally much lower than the resistance of the recorded cell, this allows for the easy implementation of whole cell voltage clamp recordings using a single electrode. This opened the ability to conduct sophisticated electrophysiological studies aimed at understanding the precise mechanisms by which neurotransmitters regulate ion currents and neuronal excitability. Additionally, the low electrical noise associated with whole cell recordings has made it possible to study synaptic transmission in central neurons at a level previously impossible due to the small amplitude of unitary synaptic potentials or synaptic currents. These developments led to profound insights into the mechanisms underlying the regulation of synaptic transmission and synaptic plasticity (see ► Synaptic Plasticity).

While whole cell recording offers a powerful avenue for the investigation of neuronal electrophysiology, it is not without limitations. Most importantly, the large tip of the patch electrode allows for the rapid exchange of the cell's cytoplasm with the electrode's filling solution, a process that is generally referred to as "dialysis" of the cell's interior. This results in the loss of diffusible components from the cytoplasm and can lead to the loss or "wash-out" of cellular responses. Similarly, responses that are dependent on complex enzymatic cascades for recovery may also be rendered artifactually irreversible upon prolonged whole cell recording. One alternative to the use of whole cell recording that does not suffer from this problem is "perforated patch" recording, where the membrane patch blocking access into the cell is permeabilized using an ionophore such as nystatin. Alternatively, sharp microelectrode recordings afford the ability to conduct long lasting intracellular recordings from neurons with little if any "wash-out" of cellular responses.

A second limitation results from the fact that neurons are complex cable structures (Bar-Yehuda and Korngreen 2008). Voltage clamp of such cells, even when conducted using whole cell recording techniques, allow for precise control of voltage only at one point of the cable structure, generally at the soma. This means that a large fraction of the dendritic arbor is, more likely than not, imperfectly voltage clamped. This severely restricts what can and cannot be inferred from voltage clamp recordings.

The usefulness of the electrophysiological approaches outlined above has been greatly magnified by the development of imaging techniques capable of visualizing neurons in living brain slices (Sakmann and Neher 2007). This allows for the routine targeting of visually identified neurons for whole cell recording. As such, it makes it possible to record from neurons that have been genetically-tagged or genetically-modified by the expression or co-expression of fluorescent proteins. It also allows for the targeting of specific cells' subpopulations defined by their axonal projections and identified through the use of fluorescent retrograde tracers. These developments provide electrophysiologists with the ability to conduct rigorous single cell work even within the highly heterogeneous cell populations that characterize most brain regions.

In summary, intracellular recording in its many implementations allows investigators to interrogate single neurons about the actions and mechanisms used by neurotransmitters to regulate their function. As such, this technique helps bridge the gap between native tissue physiology and the mechanistic insights originating from work in model systems. This in turn helps in the development of experimental assays capable of contributing to drug discovery and the characterization of novel therapeutic compounds. As such, intracellular recording constitutes a key technique in neuropsychopharmacology.

Cross-References

► Extracellular Recording
► Genetically Modified Animals
► Receptors: Functional Assays
► Synaptic Plasticity

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Intracerebral Microdialysis

► Microdialysis

Intracranial Self-Stimulation

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Synonyms

Brain stimulation reward

Definition

Intracranial self-stimulation (ICSS) is the performance of an instrumental act, such as lever pressing, to trigger delivery of electrical brain stimulation.

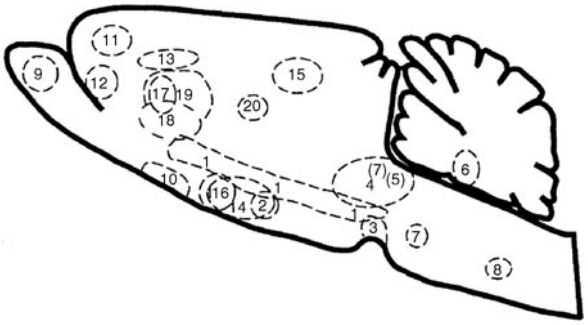
Impact of Psychoactive Drugs

Rats and other vertebrates will work avidly to trigger delivery of electrical stimulation to certain brain sites. The potent rewarding effect produced by the stimulation ("brain stimulation reward," BSR) can compete with, summate with, and substitute for the rewarding effects of natural goal objects, such as food and water. Thus, the stimulation appears to inject a signal into the central nervous system (CNS) that mimics those produced by natural rewards. Given that the electrically induced rewarding effect originates as a volley of observable action potentials in axons coursing past identifiable CNS sites, the phenomenon of BSR has long been regarded as a gateway to tracing the neural circuitry involved in the pursuit of natural rewards. It has also been proposed that dependence-inducing drugs gain their grip over behavior, at least in part due to their ability to alter neurotransmission in the circuitry underlying BSR. If so, working out the structure and operating principles of the circuitry responsible for BSR should shed light on issues central to modern psychopharmacological research.

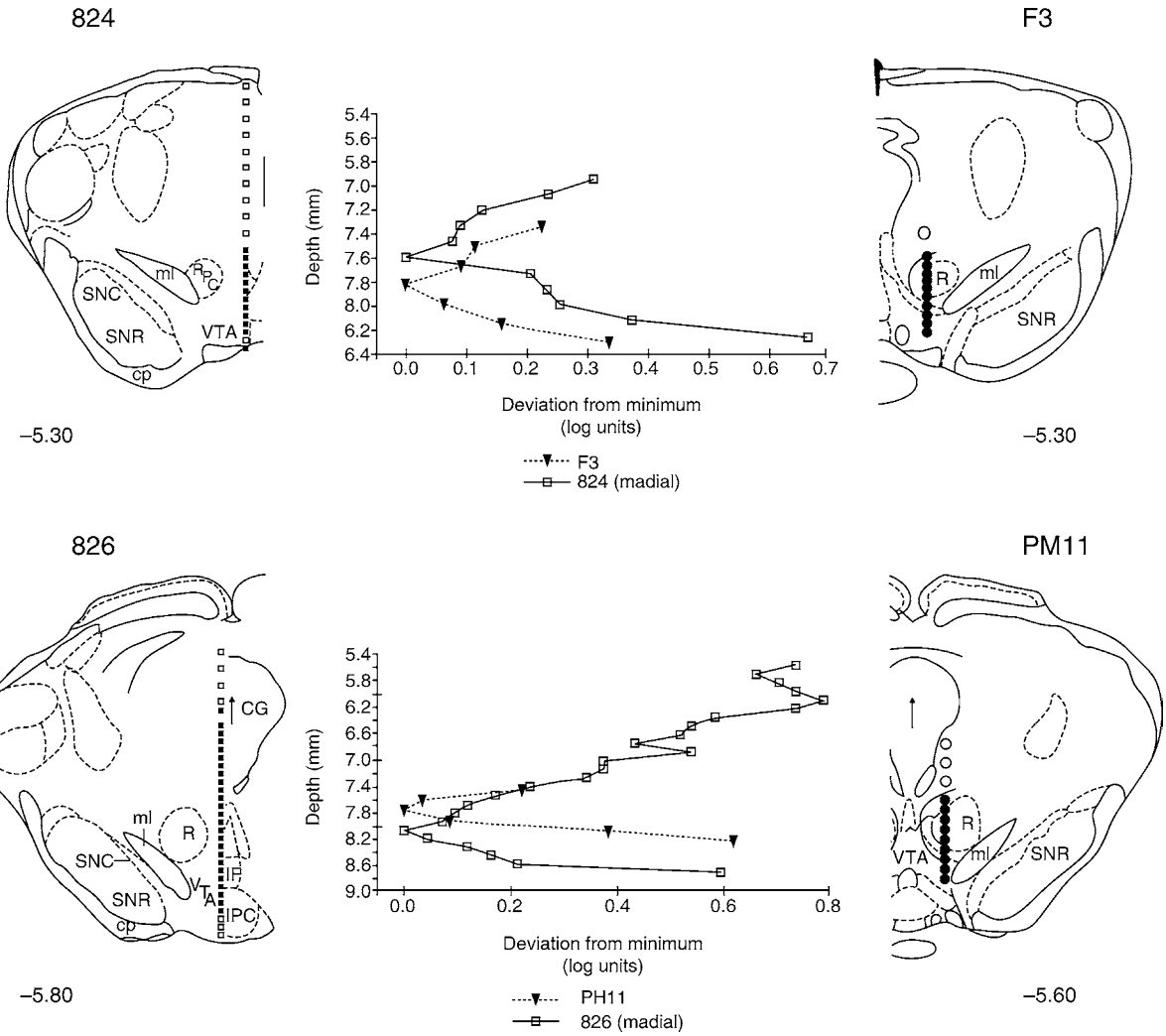
Figure 1 summarizes the location of ICSS sites in the rat brain. This image drives home the spatial extent of reward-related circuitry, which is best conceived as a distributed network, rather than as a restricted set of "centers." Figure 2 complements Fig. 1 at a finer scale. This image shows that when a stimulation electrode is advanced through the brain in fine steps (at coronal planes near the level of #3 in Fig. 1), the strength of the simulation required to sustain a given level of responding varies sharply with depth. A simple interpretation of such data is that the neural circuitry underlying BSR is tightly concentrated within the broad areas depicted in Fig. 1.

Methods have been developed for inferring whether there are direct axonal links within the reward circuitry between pairs of BSR sites and, if so, which end of such links points toward the terminals that transmit the reward signal to efferent stages (Shizgal 1997). These methods demonstrate axonal continuity within segments of the medial forebrain bundle (MFB), as well as between the hindbrain/midbrain core and the MFB; the segment of the MFB between the lateral hypothalamus (LH) and the ventral tegmental area (VTA) includes neurons in which conduction in the descending (rostro-caudal) direction leads to efferent stages of the circuitry.

Figure 3 provides a minimal model of how the signals induced in the directly activated neurons that give rise to the rewarding effect (at the left of the figure) are translated into behavioral output, such as lever-pressing for BSR. In the directly stimulated neurons, the electrically induced



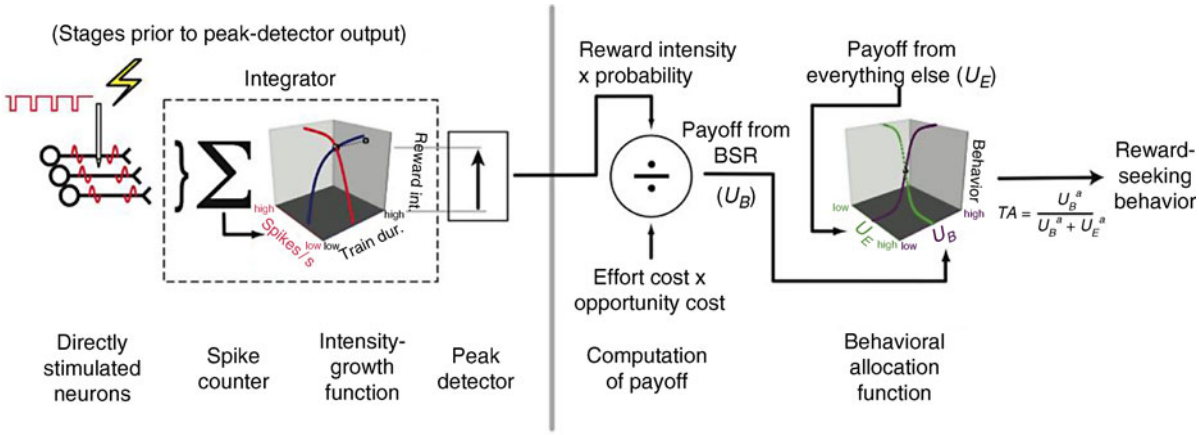
Intracranial Self-Stimulation. Fig. 1. Sagittal outline of a rat brain showing the approximate location of regions supporting ICSS. (Reproduced from Wise RA (1996) Annu Rev Neurosci 19:319–340.) Please see original for the numeric key.



Intracranial Self-Stimulation. Fig. 2. Variation of self-stimulation threshold as a function of electrode depth. (Reproduced from Forgie ML, Shizgal P (1993) Behav Neurosci 107(3):506–524. Data on the left are from Rompre PP, Miliaressis E (1985) Brain Res 359:246–259.)

reward signal is represented by a rate code, which sums impulse flow across the population of activated neurons within a time window defined by the stimulation train. The resulting spike count is then transformed nonlinearly into a single time-varying quantity representing the intensity of the reward; growth of the reward signal decelerates over time and eventually levels off (darker curve). Within a time window of given duration, the reward signal grows as a function of the stimulation-induced spike count and eventually saturates (lighter curve). The peak reward intensity achieved during a stimulation train is recorded in memory (not shown) and translated ultimately into behavior.

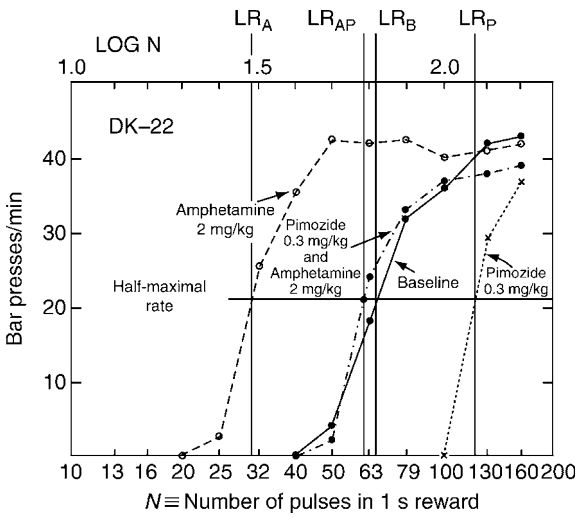
A vertical gray line in Fig. 3 demarcates the boundary between the BSR-specific and more general processes involved in the control of the reward-seeking behavior. The elements to the left of the gray line include the directly stimulated neurons and the circuitry that integrates their output over time and space, compressing the effects of the electrically triggered volley into a single quantity recorded in memory. To the right of the gray line, this stored reward-intensity signal is combined with information about a) the probability that a reward will be delivered once the response requirement (e.g., pressing the lever a given number of times) has been satisfied, b) the physical effort ("effort cost") and time



Intracranial Self-Stimulation. Fig. 3. Translation of the volley of action potentials triggered by the electrode into reward-seeking behavior. (Based on Fig. 1 in Arvanitogiannis and Shizgal (2008).)

("opportunity cost") required to do this, and c) the delay (not shown) between meeting the response requirement and delivery of the reward. In keeping with the generalized form of the ▶ matching law and behavioral decision theories in general, the subjective values of all these variables are combined in scalar fashion to yield an estimate of the payoff the subject can expect in return for satisfying the response requirement. Finally, in the spirit of the generalized single-operant matching law, the payoff from BSR (U_B, suitably transformed) is compared with the sum of all the (suitably transformed) payoffs available in the test environment, which include the payoffs (U_E, suitably transformed) from behaviors such as grooming, exploring, resting, etc. The result determines the proportion of time ("time allocation" (TA)) devoted to the pursuit of the electrically induced reward. Time allocation grows as the payoff from BSR is increased (darker curve) and as the payoff from competing activities falls (lighter curve).

Preliminaries: measuring the effects of drugs on BSR. The first psychopharmacological study of BSR was published within 3 years of the discovery of the phenomenon by Olds and Milner in 1953. The rate of lever pressing served as the behavioral measure of drug action. The deficiencies of that measurement method rapidly became clear. As can be seen at the right of Fig. 3 ("behavioral allocation function"), the payoff from BSR is translated into observable behavior by a saturating function. Thus, different levels of payoff can result in the same maximal level of time allocation, response rate, etc. For example, once the stimulation current or frequency are sufficiently high, response rates are not boosted by further



Intracranial Self-Stimulation. Fig. 4. Cancelation between the effects of amphetamine and pimozide on ICSS. (Reproduced from Gallistel CR, Karras D (1984) Pharmacol Biochem Behav 20(1):73–77.)

increments, but when offered a choice, rats will exhibit a preference for the stronger stimulation. A more general problem stemming from the use of response rates as the dependent variable can be seen in Fig. 4. As is typically the case, sigmoidal functions translate stimulation strength into behavioral output; a third variable, doses of two drugs that exert opposite influences on dopaminergic neurotransmission, displaces the sigmoidal psychometric functions laterally along the logarithmic axis representing stimulation strength. If only a single value of stimulation

strength (in this case, the pulse frequency) had been employed, the measured effects of the ► neuroleptic drug and the combination of the neuroleptic with a ► psychomotor stimulant would have depended on the arbitrary choice of pulse frequency. For example, had 160 pulses s^{-1} been selected, little influence of the drugs would have been apparent, but a profound influence would have been seen had 63 pulses s^{-1} been chosen instead. In contrast, if the curves are sectioned horizontally, rather than vertically, the measured effects of the drugs are essentially independent of the chosen criterion; similar shifts are apparent at behavioral criteria of 25%, 50%, and 75% of the maximal response rate. Thus, by measuring responding for the stimulation over a broad range of pulse frequencies, the countervailing influences of the two drugs can be discerned.

Quantifying the influence of drug treatments on ICSS by measuring lateral displacements of psychometric functions is called the "curve-shift" method (Miliaressis et al. 1986). In addition to the benefits described above, it is also argued that this method can distinguish changes in performance caused by disruptive effects of drugs, such as sedation or stereotypy, from *bona fide* influences on BSR. Performance disruption is said to alter the maximal rate of responding and the slope of the psychometric functions, whereas, changes in reward effectiveness are said to produce lateral shifts. If correct, this statement would confer a most convenient property on the curve-shift method. Unfortunately, there is contradictory evidence demonstrating that performance variables, such as alterations in the force required to depress the lever, produce systematic lateral curve shifts. Figure 3 argues that such effects should be expected: increases in effort cost decrease payoff but can be offset by increases in reward intensity.

Arvanitogiannis and Shizgal (2008) have delineated a related problem with the curve-shift method. They show that a given curve shift can arise from changes in different variables controlling reward pursuit. In effect, the same shift produced by an action of a drug to the left of the vertical gray line in Fig. 3, such as potentiation of spatio-temporal integration, can be mimicked by an action to the right of the vertical gray line, such as a reduction in subjective effort cost.

The curve-shift method has become the dominant means of assessing the influence of drugs on BSR, and it was employed in most of the work summarized in this essay. However, a new method is required to distinguish actions of drugs on the two sides of the vertical gray line in Fig. 3. Arvanitogiannis and Shizgal (2008) have proposed that by varying both the strength and cost of reward, the influence of drugs on components of the reward circuitry prior to the output of the spatiotemporal integrator in Fig. 3 can be distinguished unambiguously from influences brought to bear on downstream components. Successful application of their method would bring the field into the third turn of a spiral course of progress.

Experiments performed using the rate measurement proved useful in identifying drugs that are effective in altering performance for BSR. The curve-shift method provided a clear methodological advance by eliminating the dependence of drug-induced changes on arbitrarily selected stimulation parameters. The three-dimensional method developed by Arvanitogiannis and Shizgal (2008) promises to better distinguish the influence of drugs on different components of the circuitry underlying pursuit of the rewarding stimulation and to better distinguish effects of drugs on performance capacity from effects on reward integration. However, Fig. 3 points to a limitation of this new method: numerous interacting variables (depicted to the right of the vertical gray line) influence performance in ways that will be indistinguishable unless the mapping of the objective to the subjective values of these variables is nonlinear and these nonlinearities can be exploited experimentally. Thus, there will be a need for continued methodological advances in order to fully account for the effects of drugs on BSR and to maximize the contribution of such experiments in determining the neurochemical basis of reward.

The neurochemical basis of BSR. In the following sections, we summarize the contributions of the most extensively studied neurotransmitter systems to ICSS.

► *Dopamine* is the neurotransmitter most closely associated with BSR (Wise and Rompré 1989). Reductions in dopaminergic neurotransmission lower the effectiveness of the electrical stimulation in supporting ICSS, leading to rightward displacements of psychometric functions measured by the curve-shift method; as can be seen in Fig. 4, a higher stimulation strength is required to produce a given rate of lever pressing following administration of a dopamine receptor blocker ("► Pimozide 0.3 mg/kg"). Conversely, drugs that enhance dopaminergic neurotransmission increase the effectiveness of the electrical stimulation in supporting ICSS and thus, produce leftward shifts ("► Amphetamine 2 mg/kg"); such drugs reduce the simulation strength required to produce a given level of behavioral output. When two drugs that exert opposing influences on dopaminergic neurotransmission were coadministered, their effects on performance for BSR canceled ("Pimozide 0.3 mg/kg and Amphetamine 2 mg/kg"). Similar cancelation has been achieved by pitting the selective ► dopamine transporter blocker, GBR-12909 against the D-1 receptor blocker, SCH-23390. Drugs that

block D-2 receptors have also been shown to produce rightward curve shifts, and there is evidence that D-1 and D-2 receptors exert synergistic influences in this regard.

Dopamine neurons manifest multiple activity states. Under resting conditions, roughly 50% of the midbrain population is quiescent. Two active states have been described: sustained low-frequency (tonic) firing and intermittent high-frequency (phasic) bursting. Self-stimulation of the MFB is accompanied by a prolonged increase in tonic output, which is manifested in an increased extracellular concentration of dopamine, as observed by means of in vivo microdialyis probes in dopamine terminal fields. Phasic release, as measured by means of fast-scan cyclic voltammetry, is also observed in self-stimulating rats. In an early report, these brief increases in the local extracellular concentration of dopamine were described as transient, falling below the detection limit within a minute or so of the onset of self-stimulation. However, in more recent experiments that incorporate a 10-s post-reward time-out, a dopamine transient was recorded in the nucleus accumbens following each and every pulse train delivered via electrodes at the ventral tegmental level of the MFB.

As the evidence reviewed above suggests, there is wide agreement that dopaminergic neurotransmission is deeply implicated in ICSS. Nonetheless, a lively debate continues over exactly what role(s) dopaminergic neurons and their different activity states play. For example, many authors assume that the rewarding effect of stimulating the MFB is due to direct activation of dopaminergic fibers. However, the properties of these fibers are largely incompatible with this idea. The axons of dopamine neurons are unmyelinated and of fine caliber; their thresholds for activation by extracellular currents are high. Thus,relatively few such fibers should be excited directly under the typical conditions of BSR experiments, which entail the use of stimulation electrodes with large exposed tips and currents that are low with respect to the thresholds of dopaminergic fibers at the short-pulse durations commonly employed. The refractory periods of dopaminergic fibers are long and their conduction velocities low in comparison with the estimated values for the directly stimulated axons mediating self-stimulation of the MFB. Given the limited overlap between the excitability properties of dopaminergic fibers and those of the directly stimulated fibers mediating BSR, it would appear that activation of midbrain dopaminergic neurons during ICSS is achieved largely via a trans-synaptic route (Shizgal 1997). As predicted by this proposal, blockade of ► glutamate receptors in the VTA decreases the magnitude of ventral striatal dopamine transients elicited by rewarding VTA stimulation.

Moisan and Rompre (1998) have proposed a way to reconcile the influence of dopaminergic manipulations on ICSS with the mismatch between the properties of dopaminergic neurons and those of the directly activated neurons underlying BSR. They first varied the current and pulse frequency of rewarding MFB stimulation so as to determine two sets of stimulation parameters that produced the same level of behavioral responding: one that activated many directly stimulated neurons at low frequency and a second that activated fewer directly stimulated neurons at higher frequency. They then showed that putative midbrain dopamine neurons trans-synaptically activated by the rewarding stimulation fired at similar rates in response to the two different sets of stimulation parameters. Thus, the firing of the dopamine neurons reflects the "counter property" of spatiotemporal integration previously described in behavioral studies of BSR (depicted by the Σ symbol in Fig. 3). On this basis, Moisan and Rompré proposed that midbrain dopamine neurons may compose an integral part of the spatiotemporal integrator or relay its output to efferent stages of the circuit.

Salomone has developed an alternative perspective (Salamone 2002). In his view, dopaminergic neurons influence the proclivity to invest effort in the pursuit of reward; changes in the activity of these neurons do not alter reward intensity. Thus, Salomone's view is compatible with an influence of dopamine on subjective effort costs (Fig. 3) or the motivation to pay such costs to obtain reward.

Hypotheses concerning the contribution of dopamine to reward intensity or investment of effort in meeting work requirements are based directly or implicitly on curve-shift data, obtained using either stimulation strength or the work requirement as the independent variable. Arvanitogiannis and Shizgal (2008) have argued that such data cannot link the influence of dopamine unambiguously to processes operating at either side of the vertical gray line in Fig. 3; data obtained by varying both the strength and cost of reward are required to do so. The results of such an experiment have yet to be published as of this writing.

The following sections summarize the contributions of various other neurotransmitters to ICSS. The centrality of midbrain dopamine neurons to the phenomenon remains evident, as several other neurotransmitters appear to exert their influence on ICSS by means of their interactions with dopaminergic neurons.

► *Noradrenaline* figured heavily in early psychopharmacological research on BSR. The early interest waned after the reductions in response rate produced by agents that decrease noradrenergic neurotransmission were attributed to sedation, and early claims that

self-stimulation of sites in the vicinity of the locus coeruleus were due to activation of noradrenergic neurons were disputed. Nonetheless, neurons in the locus coeruleus and lateral tegmental A7 cluster do show increased double labeling for the rate-limiting enzyme in noradrenalin synthesis, tyrosine hydroxylase, and the immediate early-gene product, Fos, following self-stimulation of the MFB. Injection of the α_1 receptor antagonist, terazosin, into the locus coeruleus has been shown recently to produce rightward shifts in rate-frequency curves obtained from rats working for electrical stimulation of the MFB. Given the evidence that activation of α_1 receptors excites noradrenergic neurons in the locus coeruleus, this finding suggests that the firing of these neurons contributes in some way to the pursuit of rewarding MFB stimulation.

► *Acetylcholine* has been implicated in self-stimulation by experiments entailing manipulation of projections to midbrain dopamine neurons from cholinergic cell bodies in the pedunculopontine and lateral dorsal tegmental nuclei (Yeomans et al. 1993). Activation of these excitatory projections potentiates MFB self-stimulation and drives dopamine release in the ► nucleus accumbens. Neurotransmission in the cholinergic projections to the VTA is suppressed by the action of cholinergic agonists at autoreceptors on or near the cholinergic somata or by the action of cholinergic antagonists in the VTA terminal field. These manipulations reduce self-stimulation of the MFB (i.e., they cause rightward curve shifts). Disinhibition of the cholinergic projections by administration of cholinergic antagonists in the vicinity of the cholinergic cell bodies potentiates MFB self-stimulation, as evinced by leftward curve shifts. Enhanced release of acetylcholine is observed during self-stimulation of the MFB, both in the vicinity of the cholinergic cell bodies and in the VTA terminal field. Although modest effects on MFB self-stimulation have been reported following nicotinic manipulations of the cholinergic projections to the VTA, muscarinic receptors, the M_5 sub-type in particular, appear to mediate most of the effect of the cholinergic drive on MFB self-stimulation and on dopamine release in the nucleus accumbens. Administration into the VTA of ► antisense oligonucleotides for the M_5 receptor suppresses MFB self-stimulation. The potent modulation of MFB self-stimulation by cholinergic agents suggests that the effects of activating MFB fibers are relayed to VTA dopamine neurons, at least in part, by constitutively active cholinergic afferents.

► *Serotonin.* An important role in emotional and behavioral control has been attributed to serotonergic neurons. However, the multiplicity of serotonergic receptors, the widespread distribution of the serotonergic projections, and the action of serotonin both at the cell bodies and in the terminal fields of dopamine neurons make it challenging to build a comprehensive account of the action of serotonin on brain reward circuitry. Nonetheless, there is good agreement on the overall pattern of the results obtained to date in studies of the role of serotonin in ICSS: Release of this neurotransmitter generally exerts a suppressive influence on ICSS and opposes the influence of dopamine release (Harrison and Markou 2001). For example, stimulation of inhibitory cell-body autoreceptors decreases the activity of serotonergic neurons in the rostral raphé nuclei and potentiates self-stimulation of sites along the LH-VTA segment of the MFB. The effects of systemically administered agonists vary as a function of dose, stimulation site, and affinity for different subtypes of serotonin receptors. That said, rightward curve shifts or related increases in ICSS thresholds have been observed following administration of agonists for the 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{2C} receptors. Systemic administration of antagonists for these receptors and the 5-HT_3 receptor usually leaves ICSS unaltered but can reverse changes produced by concurrent administration of serotonergic or dopaminergic agonists.

Histamine. A reward-inhibiting role has been proposed for histamine-containing neurons in the tuberomammillary regions of the posterior hypothalamus (Wagner et al. 1993). These neurons project to the nucleus accumbens, where blockade of H_1 receptors increases the extracellular concentration of dopamine. Ipsilateral damage to the tuberomamillary histamine neurons or blockade of H_1 receptors in the nucleus accumbens increases the rate of LH self-stimulation. It remains to be determined whether leftward curve shifts can be produced by such manipulations.

Glutamate and GABA. Given the ubiquity of these amino-acid neurotransmitters in the brain, it would be surprising indeed if they did not play important roles in the rewarding effects of electrical brain stimulation.

► Glutamate is released in the VTA during MFB self-stimulation. Numerous nuclei provide glutamatergic input to the VTA, and it is not yet known which subset of glutamatergic neurons are responsible for the release of this neurotransmitter during ICSS. Identifying these neurons is of substantial potential interest because they may well contribute to the directly activated stage of the circuit responsible for BSR. The notion that directly activated MFB fibers provide excitatory input to dopamine cells is compatible with the abovementioned hypothesis of Moisan and Rompré.

Experience with ICSS of the MFB has been shown to downregulate the expression of the GluR1 subunit of

AMPA receptors, a phenomenon that has been proposed as an explanation of the lack of sensitization observed over the course of long periods of ICSS testing. Viral-induced increases in the expression of GluR1 in the shell region of the nucleus accumbens produce rightward curve shifts, whereas, increased expression of the GluR2 subunit in the above region shifts the psychometric curves leftward (Todtenkopf et al. 2006).

Microinjection of GABAergic agonists or antagonists into the VTA or into basal forebrain regions such as the sublenticular extended amygdala can produce systematic shifts in rate-frequency curves obtained from rats working for MFB stimulation (Waraczynski 2006). In the case of VTA injections, the level of activity of the local dopaminergic cell bodies appears to determine the sign of the effect. For example, the $GABA_A$ agonist, muscimol, produces rightward curve shifts when injected alone, but can reinstate self-stimulation after it has been abolished by intra-VTA injection of a large dose of ► morphine in rats pretreated with the dopaminergic receptor blocker, pimozide. This effect has been interpreted to reflect the restoration of firing in dopamine cell bodies that had been driven into depolarization block by the combination of autoreceptor blockade and strong opioidergic excitatory drive; the ► $GABA_A$ stimulation is posited to have hyperpolarized the dopamine cells sufficiently to restore their ability to generate action potentials (Wise and Rompré 1989).

Endorphins. The role of ► endogenous opioids in reward has been investigated extensively, and studies of ICSS have played an important role in this endeavor. Peripherally administered opiates and ► opioids to drug-naïve rats exert a biphasic influence on performance for BSR: an initial decrease in the vigor of responding is followed by an increase above baseline levels. The initial depression tolerates with repeated administration of the drug whereas the enhancement of performance does not, and thus the potentiation of ICSS by systemically administered opiates and opioids emerges as the principal effect of these drugs as a regimen of repeated administration proceeds.

Injection of opioid receptor agonists into either the VTA or the nucleus accumbens terminal field of VTA dopamine neurons can produce leftward shifts in psychometric curves obtained from rats working for rewarding MFB stimulation. In the case of the nucleus accumbens injections, such effects are observed following administration of agonists for either μ- or δ-opioid receptors. In contrast, systemic administration of the ► κ opioid agonist, U-69,593 produced rightward curve shifts and counteracted the left-shifting influence of cocaine.

The modulation of ICSS by opiates and opioids is linked strongly, but not exclusively, to the effects of these drugs on dopaminergic signaling. For example, GABAergic interneurons in the VTA are hyperpolarized by ► μ-opioid agonists, thus disinhibiting dopaminergic cell bodies. Opioid agonists have also been shown to increase release of dopamine in the nucleus accumbens. That said, opposite effects on dopamine tone in the core and shell subregions of the nucleus accumbens were observed following local administration of μ- and δ agonists. Given that opioid receptors are found both pre- and postsynaptically in the nucleus accumbens and have been identified on dopaminergic, cholinergic, glutamatergic, and GABAergic neurons, there are multiple ways that opiates and opioids could influence the processing of reward-related signals in the ventral striatum.

► *Cannabinoids.* An abundant literature links the endogenous cannabinoid system to the pursuit and evaluation of rewards, and there is evidence that cannabinoid agonists activate both dopaminergic and opioidergic neurons. Within this literature, the data on ICSS are anomalous: in the hands of different investigators, drugs that alter ► cannabinoid signaling have been observed to enhance, suppress, or fail to alter pursuit of BSR. Methodological issues could be at the root of these conflicting reports, and application of the 3D model described in Fig. 3 may help shed light on these issues. Given the steep slope of the "intensity-growth function" (lighter curve in the left-hand graph), substantial changes in the values of variables on the right-hand side of the figure can produce only modest shifts in 2D projections of the 3D surface, such as rate-frequency curves, which can prove hard to discern through the measurement noise, individual differences in drug sensitivity, etc. However, such changes should be readily detectable when the 3D-measurement method is used.

Concluding remarks. Together with the conditioned place-preference and drug self-administration paradigms, ICSS has been, and continues to be, a mainstay of research on the psychopharmacology of reward. As this essay suggests, rather a lot has been learned from ICSS experiments about the roles of different neurotransmitter systems in brain reward circuitry. Nonetheless, much additional work will be required to fully account for the powerful influence of drugs on ICSS. Advances in behavioral measurement methods promise to tie the effects of pharmacological manipulations to specific psychological processes that contribute to the pursuit of BSR, and new methods, such as techniques for optical stimulation and inhibition of neurons expressing particular neurotransmitter-related genes, promise to refine our understanding of reward processing at the cellular and circuit levels.

Cross-References

- ▶ Addictive Disorder: Animal Models
- ▶ Behavioral Economics
- ▶ Cannabinoids and Endocannabinoids
- ▶ Conditioned Place Preference and Aversion
- ▶ Excitatory Amino Acids and Their Antagonists
- ▶ Histaminic Agonists and Antagonists
- ▶ Instrumental Conditioning
- ▶ Operant Behavior in Animals
- ▶ Opioids
- ▶ Psychomotor Stimulants
- ▶ Reinforcement Disorders
- ▶ Self-administration of Drugs

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Intradimensional

Synonyms

ID

Definition

In the context of a ID/ED task, the intradimensional (ID) stage involves discriminating between two (generally novel) stimuli that differ from each other in at least two dimensions (e.g., color and shape), but for which the relevant discriminative dimension (e.g., color) has been primed by prior experience.

Intrathecal

Definition

An injection into the space surrounding the spinal cord, avoiding the blood–brain barrier.

Intrinsic Sympathomimetic Activity

Definition

The term used with β-blocking drugs that show both agonism and antagonism at a given β-receptor, so that, for example, there is improved cardiac function without cardiac rate being reduced significantly. Drugs that have intrinsic sympathomimetic activity are also known as ▶ partial agonists.

Inventories

- ▶ Rating Scales and Diagnostic Schemata

Inventors Delusion

- ▶ Delusional Disorder

Inventors' Psychosis or "Inventors" Delusion ("Erfinderwahn" or "Erfindungswahn")

- ▶ Delusional Disorder

Inverse Agonists

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Synonyms

Negative antagonists

Definition

Inverse agonists are ligands that inhibit spontaneous (ligand-independent) receptor activation.

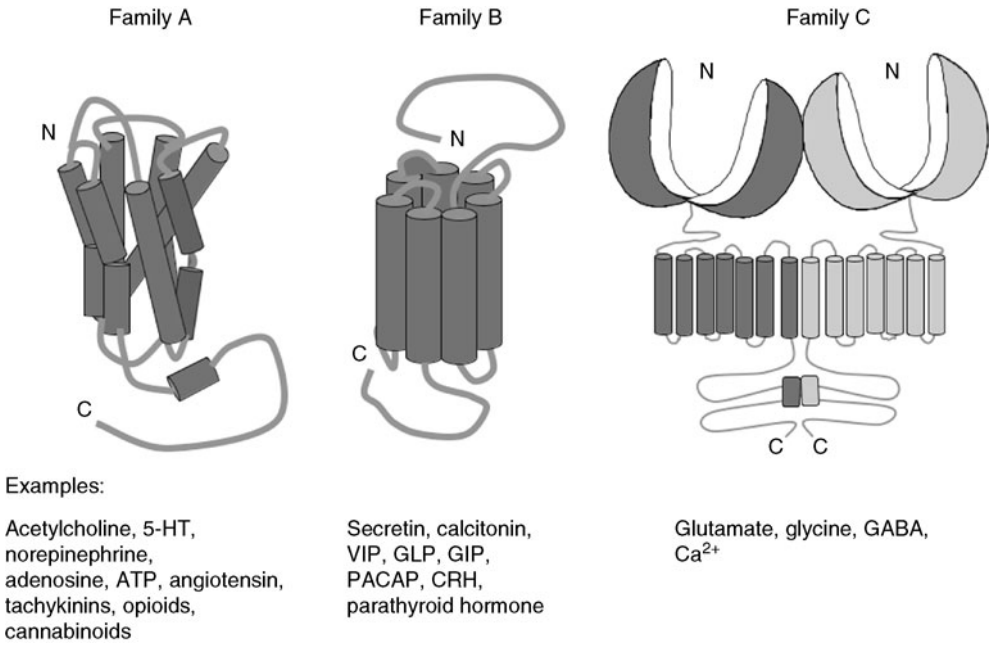
Pharmacological Properties

Introduction

► G-protein-coupled receptors (GPCRs) are the largest family of receptors in the human genome, are ubiquitously expressed on the surface of all cells, and constitute the predominant signaling system in living organisms. Given that hormone and neurotransmitter activity at GPCRs is such a prevalent phenomenon in virtually every physiological process, it is not surprising that aberrations in GPCR-mediated signal transduction have been associated with many disease states, including CNS disorders, metabolic disorders, cardiovascular disease, and many cancers. Approximately 30% of all medicines currently on the market target GPCRs, but this figure only relates to a small fraction of the total number of GPCRs that could be effectively exploited therapeutically. Thus, these receptors remain one of the most tractable and widely pursued groups of drug targets.

Structurally, GPCRs are defined by a common architecture composed of an extracellular N-terminal domain, an intracellular C-terminal domain, and seven transmembrane domains linked by three extracellular and three intracellular loops (Fig. 1). Despite this common architecture, GPCRs exhibit a remarkable diversity in the range of ligands that they recognize and the intracellular signal transduction cascades that they couple to, which is indicative of a very flexible and dynamic nature. Mammalian GPCRs are further subdivided into three groups: Family A or Class I GPCRs ("rhodopsin-like"), the largest family comprising receptors for prototypical neurotransmitters and hormones such as biogenic amines (epinephrine, norepinephrine, ► serotonin, ► dopamine, histamine, acetylcholine), adenosine, ► cannabinoids and angiotensin; Family B or Class II GPCRs, incorporating peptide hormone receptors such as calcitonin, parathyroid hormone, glucagon, and secretin receptors; and Family C or Class III GPCRs, including receptors for small molecules such as ► glutamate, ► GABA, and calcium (Fig. 1).

For many years, the traditional view of signaling via GPCRs posited that these receptors were quiescent in the absence of ligand, and that activation was mediated by a ligand-induced conformational change that subsequently promoted coupling to a variety of members of the heterotrimeric G-protein family to initiate intracellular signal transduction. This simplistic view was considered consistent with the (even older) phenomenological classification of drugs as either ► agonist or ► antagonist, i.e., compounds that activated the system were agonists, whereas compounds that had no apparent effect on the system but could block the actions of agonists were classed as antagonists. However, it is now known that GPCR-mediated signaling is a more complex process than originally envisaged, and a number of important developments in the field have led to a reclassification of the molecular nature of drugs and a change in the approaches used to screen for them. One of these developments was the discovery that GPCRs, like many other proteins, can spontaneously adopt one or more active states in the absence of ligand. This ligand-independent activity is termed ► constitutive activity and is now acknowledged as a naturally occurring phenomenon for nearly all GPCRs to varying extents. A second, more recent, development is the recognition that different active states of a GPCR can be coupled to markedly different signal transduction processes, some of them in a G-protein-independent manner, and that not all states are promoted by all ligands that recognize the GPCR. This dynamic, "multi-conformational," view of GPCR activity has led to a re-evaluation of the molecular nature of drug efficacy and highlighted the inadequacy of the simple agonist/antagonist paradigm for describing the effects of drugs. In particular, it is now evident that the role of a ligand is to stabilize one or more GPCR states for which it has the highest affinity and, by doing so, bias the possible conformations of the receptor toward those states. In this new paradigm, agonists are ligands that promote GPCR active states over and above those states that occur spontaneously, whereas ligands that promote inactive states, i.e., reduce the constitutive (basal) activity of a signaling pathway, are termed inverse agonists (Fig. 2). Compounds that bind to the GPCR but do not bias the distribution of active to inactive states are termed ► neutral antagonists.



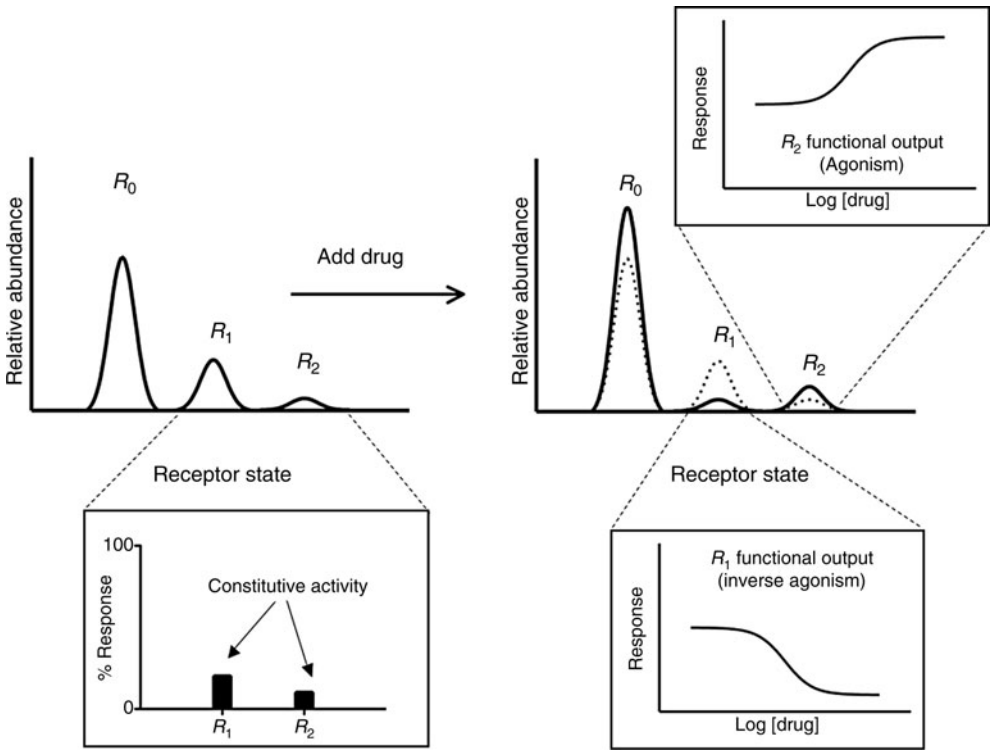
Inverse Agonists. Fig. 1. The three major families of mammalian G-protein-coupled receptors (GPCRs) with some representative examples of their endogenous agonists.

This chapter briefly considers the implications of these ligand behaviors for drug action and therapeutics.

Cellular and Molecular Basis of Constitutive Activity and Inverse Agonism

The term "inverse agonist" was first used to describe the actions of certain compounds, such as the β-carbolines, at the ionotropic $GABA_A$ receptors, where it was observed that the compounds not only antagonized the actions of ► benzodiazepines at the receptor, but also appeared to evoke an effect opposite to that of the benzodiazepine in the absence of the latter (Costa and Cotecchia 2005). However, given that the mechanism of action of benzodiazepines is to act as positive ► allosteric modulator of the endogenous agonist, ► GABA, rather than as true agonists in their own right, compounds such the β-carbolines are more appropriately classed as "negative allosteric modulators" rather than true inverse agonists; the reversal of "basal" activity in this instance reflects allosteric antagonism of the endogenous agonist. This is an important pharmacological consideration that extends beyond the specific $GABA_A$ example. Namely, the in vivo effects of drugs that reduce basal activity may reflect the true inverse agonism of a constitutively active receptor, or they may reflect the antagonism of an endogenously released agonist of that receptor.

Given that the unambiguous demonstration of inverse agonism requires the experimental observation that the effect is not due to antagonism of an endogenous agonist, most observations and assays of inverse agonist behavior are routinely made using a variety of cell-based in vitro bioassays. It was in this context that the earliest report of true inverse agonism occurring at a GPCR was presented by Costa and Herz, who demonstrated the constitutive activation of guanosine triphosphatase (GTPase) activity by the δ-► opioids receptor expressed natively in NG108-15 cell membranes and its reversal by compounds that were previously classed as simple opioid receptor antagonists (Bond et al. 2000). Moreover, that same study was the first to differentiate antagonists on the basis of the ability to inhibit constitutive activity (inverse agonists) from the ability of not perturbing constitutive activity but still antagonizing the actions of both agonists and inverse agonists (i.e., act as neutral antagonists). Since the initial report of constitutive GPCR activity and inverse agonism, there has been an explosion in the number of ligands identified to express this type of pharmacology (Bond et al. 2000), including compounds acting at prototypical Family A neurotransmitter receptors, such as the adrenoceptors (α_1, α_2, and β_2), ► muscarinic receptor (M_1, M_2, M_3, and M_5), histamine H_2 receptors, serotonin receptors ($5\text{-}HT_{1A}$, $5\text{-}HT_{2A}$, $5\text{-}HT_{2C}$, $5\text{-}HT_4$, $5\text{-}HT_6$, and



Inverse Agonists. Fig. 2. Agonism and inverse agonism arising due to ligand-induced redistribution of multiple receptor conformational states. The figure shows the distribution of three theoretical receptor states: R_0 inactive; R_1 active conformation that induces functional output 1; R_2 active conformation that induces functional output 2. In the absence of ligand (left side), most of the receptors exist in an inactive state, but some constitutive activity may be detected. In the presence of ligand (right side), the conformations of the receptor change such that the behavior of the system is altered; in this example, the abundance of receptors in the R_1 is reduced, and thus the ligand would be classified as an inverse agonist in an assay measuring functional output 1. However, the R_2 state is increased by ligand, and so an assay of functional output 2 would classify the ligand as an agonist.

5-HT_7), and dopamine receptors (D_2, D_3, and D_5), as well as Family B and C GPCRs, such as the vasoactive intestinal peptide (Kenakin 2004) and metabotropic glutamate (Bond and Ijzerman 2006) receptors. Importantly, a number of established or potential ▶ antipsychotics, ▶ antidepressants, and other psychopharmacological drugs have inverse agonist activity at such targets, e.g., serotonin, dopamine, histamine, opioid, cannabinoid, and muscarinic receptor subtypes (Bond and Ijzerman 2006). As mentioned earlier, GPCRs are highly dynamic proteins, and their ability to fluctuate between various conformational states is a natural property common to most proteins governed at the molecular level by random thermal fluctuations in the energy of the protein in its microenvironment. Physiologically, however, organisms have evolved to keep most constitutive receptor activation at relatively low levels; it would be metabolically wasteful to maintain a permanent state of cellular activation, in addition to reducing the dynamic response range available for signal transduction. For GPCRs, this is generally governed by key microdomains of the receptors that have evolved to minimize the spontaneous isomerization of the proteins into active conformations (Pontier et al. 2008). Thus, at any point in time, only a small fraction of a given population of GPCRs will be in a ligand-independent active state (Fig. 2). An important question, thus, is under what conditions is constitutive activation of a GPCR appreciable such that inverse agonist activity of various ligands is readily detected? Perhaps, a more important consideration is under what circumstances does the phenomenon become therapeutically relevant?

Overexpression of GPCRs Can Result in Detectable Constitutive Activity

If only a small fraction of the total population of a GPCR is constitutively active in a given cellular background, then a common mechanism by which such activity can be regulated is by the control of the total amount of the receptor. Indeed, the overexpression of various wild-type GPCRs in ►recombinant cell line represents one of the most common strategies for amplifying low levels of constitutive receptor activation to a degree that is readily detected in many cell-signaling assays. Overexpression of GPCRs has thus been instrumental in the detection of constitutive activity in both native tissues and recombinant cell lines (Milligan 2003). Furthermore, the use of receptor overexpression systems permits the study of constitutive activity of most GPCRs, and it is largely for this reason that the surge of inverse agonist reports in the literature coincides with the rise of the molecular biology era of the 1980s onwards; as is often the case, it is not the biological phenomenon that is new but, rather, it is the new technologies that facilitate the detection of the phenomenon. This can also explain why, in the past, compounds were more simply classified as either agonists or antagonists – in the presence of low levels of constitutive activity, or in a bioassay that did not have the sensitivity to detect such activity, an inverse agonist would appear indistinguishable from a neutral antagonist.

Constitutively Active Receptor Mutants in (Patho) Physiology

Another common means of engendering constitutive activity in a GPCR is through the introduction of mutations that reduce the energy barrier for transition of the protein between inactive and active states. There are a number of key regions of GPCRs, such as the bottom of transmembrane domains 3 and 6 as well as parts of the intracellular loops, that are well known to govern receptor isomerization into an active state. Hence, in addition to overexpression, mutational strategies that target these key activation regions to engender constitutive GPCR activity are another mainstay of studies that have identified inverse agonist actions of ligands previously classified as simple antagonists. A common criticism of such studies is that, in many instances, the mutations that are introduced to make a receptor constitutively active are not naturally occurring and it is thus possible that the pharmacology described for various ligands at these mutant receptors in artificial systems will not be predictive of their behavior in a more physiological environment. However, even overexpression studies of wild-type receptors in recombinant cell lines can be criticized as not necessarily being physiologically predictive.

In addition to the intracellular domains of GPCRs as key activation regions, more recent studies have identified hitherto unappreciated roles of the extracellular loops of some GPCRs in controlling receptor activation, both in the absence and presence of ligand. For instance, the receptors for sphingolipids, melanocortin, and cannabinoids lack a pair of key disulfide bond-forming cysteine residues in the extracellular loops, which are conserved across many other Family A GPCRs; it has been hypothesized that the lack of these cysteines leads to a reduction in ground-state receptor stability and, therefore, may explain the notably high constitutive activity of these receptors (Milligan 2003). This latter situation is an example of a naturally occurring structural feature of some GPCRs that may predispose them to high levels of constitutive activation in a physiological setting.

Another means by which GPCRs can display robust constitutive activity in the absence of overexpression is as a result of ►polymorphism or ►splice variant (Bond and Ijzerman 2006). Three interesting examples of the latter include the serotonin 5-HT_{2C} receptor, the histamine H_3 receptor, and the β_1-adrenoceptor. The serotonin 5-HT_{2C} receptor achieves this as a consequence of RNA editing. This is a process of posttranscriptional modification of the receptor's mRNA transcript, which results in changes in the second intracellular loop at amino acid positions 156, 158, and 160. In the nonedited 5-HT_{2C} receptor, these positions correspond to isoleucine, asparagine, and isoleucine, respectively, and predispose the receptor to exhibiting very high constitutive activity. Depending on the degree of RNA editing, the amount of constitutive activity observed is markedly decreased, with the fully edited 5-HT_{2C} receptor isoform containing valine, glycine, and valine in the same intracellular loop 2 positions and displaying virtually no constitutive activity (Bond and Ijzerman 2006). The histamine H_3 receptor undergoes alternative splicing to generate many isoforms, two of which have a propensity to display high levels of constitutive activity. The β_1-adrenoceptor is associated with a number of single nucleotide polymorphisms, one of which (S49G) has been identified in patients with cardiac failure and is characterized by high constitutive activation (Bond and Ijzerman 2006). Collectively, these observations suggest that the inherently labile nature of some GPCRs that allows them to readily adopt a ligand-independent active state may have either physiological and/or pathophysiological relevance.

There are also naturally occurring mutations in some GPCRs that yield constitutive receptor activation and

have been linked to congenital diseases. These include constitutively active mutants of the thyrotropin receptor, which was found to be the cause of hyperfunctioning thyroid adenoma, the luteinizing-hormone receptor, which leads to inappropriate testosterone release and early onset male precocious puberty, the parathyroid hormone receptor, leading to Jansen-type metaphyseal chondrodysplasia, and the rhodopsin receptor, which leads to the development of retinitis pigmentosa (Bond et al. 2000).

Endogenous Inverse Agonists

Some GPCRs utilize endogenous inverse agonists as important regulators of their function. A primary example is the endogenous ligand for rhodopsin, 11-*cis*-retinal, which in the resting state exists covalently bound to the receptor to ensure that it stays in an inactive state; it is only when exposed to light that the ligand isomerizes to all-*trans*-retinal and allows signal transduction (and hence the perception of vision) to proceed. Without this tight inverse agonist-mediated mode of regulation, even slight constitutive activation of rhodopsin would be calamitous for the fidelity of signaling required to ensure appropriate vision. Another example is the peptides, agouti and ► agouti-related peptide (AgRP), both endogenous inverse agonists of the melanocortin MC1 (agouti) and MC4 (AgRP) GPCRs (Bond et al. 2000; Costa and Cotecchia 2005). The MC1 receptor plays an important role in melanin production and the control of pigmentation (Milligan 2003), whereas the MC4 receptor is a key mediator of feeding behaviors and body weight regulation. Although it is not clear why these particular systems require tonic input from both endogenous agonists and inverse agonists, their existence implies a need for very tight regulation.

In a pathophysiological setting, the Kaposi's sarcoma-associated herpes virus encodes a constitutively active chemokine GPCR, ORF-74, as part of its viral replication mechanism. The very high constitutive activity of this virally encoded GPCR promotes cell proliferation to achieve increased viral replication. Interestingly, the endogenous chemokine *agonist* of the interleukin-8 receptor (the mammalian homolog of ORF-74), stromal cell-derived factor-1, acts as an *inverse agonist* at ORF-74 (Bond et al. 2000). In addition to its therapeutic implications, the finding that the same ligand can act as an agonist of one GPCR and an inverse agonist at another GPCR highlights the multidimensional nature of ligand efficacy, and the fact that the cellular assay system can have a profound effect on the classification of ligand pharmacology.

Inverse Agonists or Neutral Antagonists: Clinically, Which Is Better?

The majority of current therapeutic agents on the market are clinically utilized as antagonists. With respect to GPCRs, it has been estimated that approximately 85% of ligands classified as antagonists are actually inverse agonists (Kenakin 2004), assuming the endogenous receptor is constitutively active (which may well depend on tissue expression and/or disease). This finding has both theoretical and practical implications. On theoretical grounds, it is to be expected that most ligands will possess some degree of efficacy, either in a positive direction (agonists) or negative direction (inverse agonists). According to current models of ligand–receptor interaction, the act of binding to a GPCR will bias its conformations such that its properties in the presence of ligand are unlikely to be coincident with its properties in the absence of ligand. Thus, neutral antagonists, which in theory should display similar affinities for all GPCR states such that they do not perturb the conformational equilibrium on binding, should not represent a substantial proportion of the chemical space encompassing GPCR-recognizing compounds. Table 1 shows a representative sample of inverse agonists currently on the market, most of which were believed to be neutral antagonists at the time of their release.

At a practical level, the abundance of inverse agonists relative to neutral antagonists raises the question as to which type of ligand is preferred as a therapeutic agent for disorders where receptor antagonism is a desired endpoint. At this point in time, the question remains to be adequately addressed. Certainly, for diseases where the cause is directly attributable to a constitutively active GPCR, such as some of the congenital disorders described above, it can be reasoned that an inverse agonist would be preferable to a neutral antagonist. However, these disorders are relatively rare, and both types of agents (inverse or neutral) would still effectively antagonize the endogenous agonist for the target receptors. Nonetheless, recent studies in heart failure and asthma models (see below) suggest that the balance may indeed be in favor of inverse agonists (neutral antagonists are apparently devoid of effect). With respect to neuropsychiatric disorders, it is of particular note that the 5-HT_{2C} receptor has various levels of constitutive activity depending on the degree of RNA editing (as outlined above). Consequently, it is conceivable that in certain disease states, such as ► depression, the level of constitutive activity of the receptor may increase significantly, suggesting that inverse agonism may be a treatment of choice rather than neutral antagonism. This is currently largely speculative, as it remains to

Inverse Agonists. Table 1. Examples of therapeutics with inverse agonist activity and their receptor targets. (Adapted from Bond and Ijzerman 2006.)

Receptor target	Example drug(s)	Disorder
α_1-Adrenoceptor	Prazosin, terazosin	Hypertension
β_1-Adrenoceptor	Metoprolol, carvedilol, bisoprolol	Heart failure
Muscarininc M_1	Pirenzipine	Gastric ulcers
Muscarinic M_3	Darifenacin, tolterodine	Bladder dysfunction
Histamine H_1	Cetirizine, loratadine	Allergy
Histamine H_2	Cimetidine, ranitidine, famotidine	Duodenal and gastric ulcers
Angiotensin AT_1	Candesartan, irbesartan	Hypertension, heart failure
Oxytocin OT	Atosiban	Preterm labor
Cysteinyl leukotriene $CysLT_1$	Montelukast, zafirlukast	Asthma
Cannabinoid CB_1	Rimonabant	Obesity, smoking cessation
Histamine H_3/Serotonin 5-HT_2	Mianserin	Depression
Serotonin 5-HT_2/Dopamine D_2	Risperidone	Psychosis
Dopamine/Serotonin	Chlorpromazine	Psychosis
μ-Opioid	Naloxone	Drug overdose
α_2-Adrenergic/Serotonin 5-HT_2	Mirtazapine	Depression
Dopamine D_2	Haloperidol, clozapine	Schizophrenia

be established that 5-HT_{2C} receptor modulation is clinically relevant, although animal data may suggest so.

It is possible that further insight into clinical differences between inverse agonists and neutral antagonists may currently be gleaned not from the acute effects of these compounds, but rather from their long-term effects; this is particularly pertinent given that most drug therapies require chronic administration. Specifically, GPCRs are subject to dynamic, postsignaling regulatory mechanisms, such as desensitization, phosphorylation, internalization, and downregulation, and drugs can differentially modulate these processes. As occurs with most receptors on long-term exposure to agonists, constitutively active receptors are nearly always downregulated. It may thus be anticipated that prolonged exposure to inverse agonists will have the opposite effect, i.e., an upregulation in GPCR number or function over time. This has indeed been shown to be the case for many (but not all) GPCRs (Bond et al. 2000). Consequently, the upregulation of the receptor mediated by an inverse agonist may produce unwanted side-effects during treatment or postwithdrawal. For example, inverse agonist-mediated upregulation of the histamine H_2 receptor has been proposed as a mechanism for patients developing tolerance to antiulcer drugs such as cimetidine and ranitidine, as well as rebound effects on cessation of their therapy (Bond and Ijzerman 2006). A similar mechanism has been proposed for adverse events associated with withdrawal from antipsychotic medications, including ► clozapine (Moncrieff 2006). Unfortunately, this mechanism may also cross over to produce off-target or -tissue side-effects. At least two cases have been reported of patients who were treated with the dopamine receptor inverse agonist, metoclopramide, for abdominal discomfort, vomiting, and nausea, but who subsequently experienced psychotic episodes on cessation of treatment.

On a positive note, long-term adaptive changes in system responsiveness that are promoted by inverse agonists may also be linked to improved therapeutic outcomes. Recent large-scale placebo-controlled clinical trials of patients being chronically treated with ► β-adrenoceptor blockers for heart failure have demonstrated significant decreases in morbidity and mortality for the inverse agonists, carvedilol, metoprolol, and bisoprolol, but not the neutral antagonist, bucindolol (Parra and Bond 2007). A similar hypothesis has now been proposed as a putative chronic treatment for asthma (Parra and Bond 2007). In each instance, the acute effects of the inverse agonist would be anticipated to initially worsen the symptoms of the disorder, but chronic compensatory mechanisms may eventually lead to improved and potentially sustained clinical outcomes. This is currently a controversial area of

research, but one that definitely warrants further study given that many other types of established therapeutic agents have inverse agonist properties; it is remarkable, for instance, that a number of clinically used antipsychotics acting at either dopamine D_2 and/or serotonin 5-$HT_{2A/2C}$ receptors have inverse agonist effects.

Extending the Paradigm: The "Pluridimensional" Nature of Drug Efficacy

The discovery and acceptance of inverse agonism as a widespread phenomenon in the mode of action of many drugs has led to additional studies on the molecular nature of drug efficacy and its manifestations. There are now numerous examples where the same ligand, acting at the same receptor, can display totally different degrees of efficacy, ranging from positive to inverse, depending on the cellular background and/or the signal pathway being measured. For example, ► propranolol is an inverse agonist for the cAMP accumulation pathway linked to the β_2-adrenoceptor, but an agonist for the phosphorylation of extracellular signal-regulated kinases 1/2 (ERK1/2) mediated by the same receptor; proxyfan, a histamine H_3 receptor ligand, is a partial agonist for both ERK1/2 and cAMP signaling, but an inverse agonist for arachidonic acid release (Galandrin et al. 2007). These types of observations are becoming increasingly prevalent and indicate that the classification of a ligand's efficacy depends on one's signaling vantage point (Fig. 2). Furthermore, they also indicate that ligand efficacy is not "linear" in the sense that receptor occupancy and stimulus generation by a given ligand does not necessarily trigger all possible receptor behaviors in a sequential (linked) fashion. This nonlinear view of drug efficacy has been associated with a variety of terms, including "protean agonism," "biased agonism," "collateral efficacy," "stimulus-trafficking," and "functional selectivity" (Urban et al. 2007). The potential for terminological confusion notwithstanding, these recent discoveries highlight the fact that ligands can have a plethora of effects at the cellular level but that, in many instances, there is no proven relationship between the magnitude and direction of ligand efficacy at a given cellular pathway and clinical outcome. This means that when screening for new drugs, multiple assay formats are required to capture as many potential ligand behaviors as possible. In addition, more studies are clearly warranted to correlate clinical efficacy with cellular efficacy(ies).

Concluding Comments

Within the last two decades, the concepts of constitutive receptor activity and inverse agonism have gone from being pharmacological curiosities to accepted paradigms in drug and receptor behavior. Constitutively active receptors are now used routinely in drug discovery research in order to classify potential hits in terms of their possible spectrum of efficacies. Moreover, most compounds that have previously been classed as (neutral) antagonists are very likely to be inverse agonists. However, the clinical relevance of inverse agonists remains largely unknown. The challenge now is to be able to better correlate improved mechanistic understanding of the pluridimensional nature of drug efficacy with improved clinical outcomes.

Cross-References

► Antipsychotic Drugs
► Benzodiazepines
► Beta-Adrenoceptor Antagonists
► Cannabinoids and Endocannabinoids
► Histaminic Agonists and Antagonists
► Muscarinic Agonists and Antagonists
► Opioids

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Inverse Problem

Definition

The inverse problem refers to an underdetermined problem that researchers encounter when trying to identify the locus or loci of neural activity that give rise to a particular ERP scalp distribution. The problem is that there is, in principle, an infinite number of possible source configurations that can produce any given scalp distribution. Therefore, additional assumptions and information about the brain are needed to arrive at a unique solution.

Cross-References

► Event-Related Potentials
► Source Localization Techniques

Iontophoresis

► Microiontophoresis and Related Methods

Iowa Gambling Task

Definition

A neuropsychological test invented by Bechara and Damasio for measuring decision-making deficits in brain-damaged patients especially with lesions of the ventromedial prefrontal cortex.

IPT

► Interpersonal Psychotherapy

IRBS

► Insulin-Resistant Brain State

Irreversible Trapping

Definition

A pharmacokinetic model used in PET imaging in which a radiotracer partially follows the metabolic pathway of an endogenous compound but stops or undergoes much slower metabolism than the endogenous compound at a certain point in the process. The radiolabel (it is no longer attached to the original tracer at this point, but rather, to one of its metabolic byproducts) is considered trapped at this stage, and the model is used to estimate the rate of the metabolism of the endogenous compound up to this point.

Isocarboxazid

Synonyms

Marplan

Definition

Isocarboxazid is a nonselective and irreversible monoamine oxidase inhibitor (MAOI) with a hydrazine chemical structure. It acts by inactivating the enzyme monoamine oxidase, which is involved in the catabolism of several key neurotransmitters, including norepinephrine, serotonin, and dopamine. Its primary use is in the treatment of ► depression, but it is also used for treating ► panic disorder. Because of the potential for serious toxicity common to all nonselective, irreversible MAOIs, isocarboxazid is reserved for treating patients who have proven refractory to other antidepressants. Isocarboxazid may cause mild dry mouth and sexual dysfunction; more troublesome side effects may result from orthostatic hypotension, including dizziness and syncope. Like other MAOIs, isocarboxazid may interact with foods containing tyramine and with certain catecholaminergic drugs to result in a hypertensive crisis. Similarly, isocarboxazid and other nonselective, irreversible MAOIs can interact with serotonergic drugs and compounds to result in ► serotonin syndrome, characterized by hyperpyrexia, hyperreflexia, and myoclonus. Hypertensive crisis and serotonin syndrome, when severe, can be fatal without proper treatment.

Cross-References

► Antidepressants
► Monoamine Oxidase Inhibitors (MAOIs)

ISOFORM

Synonyms

Splice variant

Definition

The term isoform, when discussing ► corticotrophin-releasing factor (CRF) receptors, refers to the alternative splicing of the CRF receptor mRNA, shortening the final amino acid sequence. The CRF_1 receptor has no known isoforms, while the CRF_2 receptor has three: CRF_{2A}, CRF_{2B}, and CRF_{2C}. These receptor isoforms have identical primary structure until the N-terminus, where they differ in their N-terminal domains. It is likely that they have identical secondary and tertiary structure in their transmembrane domain.

Cross-References

► Gene Expression and Transcription

Isolation Calls

► Distress Vocalization

Isolation Rearing

Definition

An animal model in which rats, immediately after weaning (usually postnatal day 21), are housed in isolation from siblings for an extended period (usually several weeks). In adulthood, these animals show many characteristics also seen in patients with schizophrenia.

Cross-References

► Schizophrenia: Animal Models
► Simulation Model

Isomers

► Stereoisomers

Isozyme

Definition

Isozymes are enzymes that catalyze the same reaction but have differences in their amino acid sequences.

J

Justifications

► Ethical Issues in Animal Psychopharmacology
► Ethical Issues in Human Psychopharmacology

Ian P. Stolerman (ed.), *Encyclopedia of Psychopharmacology,* DOI 10.1007/978-3-540-68706-1,

K

Kanner Syndrome

► Autism Spectrum Disorders
► Autism Spectrum Disorders and Mental Retardation

Kappa-Opioid Agonists

Definition

These are drugs acting selectively on the kappa receptors of the endogenous opioid system. For example, U-50 488.

Cross-References

► Endogenous Opioid
► Opioids

Kappa-Receptor

Definition

The term κ-opioid peptide receptor represents the ► G-protein-coupled receptor that responds selectively to a group of largely experimental opioid drugs, initially based on ketocyclazocine (hence κ). It is usually named the κ-receptor or KOR. It is expressed in areas of the nervous system that moderately mediate analgesia with a side-effect profile distinct from μ-opioids. The KOP receptor protein is produced by a single gene. When activated, the KOR receptor predominantly transduces cellular actions via inhibitory G-proteins. The electrophysiological consequences of KOP receptor activation are usually inhibitory.

Kat

► Khat

Kath

► Khat

K_D

► Equilibrium Dissociation Constant

K_D^{-1}

► Affinity

Kel

► First-Order Elimination Kinetics

Keratotic Lesion

Definition

A skin lesion characterized by an abnormal development of keratin, a proteical constituent of hair and nails, and is usually induced by excessive sunlight. It is considered a precancerous condition.

Ketamine

Synonyms

Special K

Definition

Ketamine is a ► dissociative anesthetic used in human and veterinary medicine. Its primary mechanism of

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action is as a noncompetitive ► NMDA receptor antagonist. In humans, ketamine is mainly used as a general anesthetic, usually in combination with other compounds. However, it can also be used at sub-anesthetic doses as a sedative, analgesic, and bronchodilator although its dysphoric psychoactive side effects limit such use to emergency clinical situations only. These side effects include detachment, depersonalization, altered perception and thought processes, loss of normal time sense, ► hallucinations, and amnesia. Some of these side effects underlie ketamine's high-abuse potential and its recreational use of this drug (mainly intranasally but occasionally intravenously). In small doses, the experience is often pleasurable and many users report feelings of euphoria, whereas at larger doses unpleasant and uncontrollable effects emerge, including hallucinations and out-of-body experience labeled "passing through the K-hole." One of the main short-term problems associated with ketamine abuse is a potentially fatal interaction with depressant drugs such as alcohol, heroin, and barbiturates which, at higher doses, results in complete suppression of vital functions. It impairs cognition and its long-term abuse can lead to addiction as well as urinary tract problems.

Ketazolam

► Benzodiazepines

Khat

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Synonyms

Chat; Gat; Kat; Kath; Mairungi; Miraa; Murungu; Q'at; Qat; Tschat

Definition

Khat, derived from the plant *Catha edulis* Forsk, is a social stimulant drug whose effects are mainly due to cathinone, a psychoactive alkaloid also referred to as a "natural amphetamine" for its pharmacological profile.

Pharmacological Properties

Introduction

Khat is the transliteration of an Arabic word that indicates the leaves and shoots of *Catha edulis* Forsk, a small tree of the ► Celastraceae family endemic of the highlands of the Horn of Africa and Arabic peninsula. In these regions, recreational khat chewing for experiencing its psychostimulant effects is deeply rooted in the everyday life and recent efforts to control this use are facing strong resistance. Moreover, in the last three decades the khat habit has followed the stream of migration moving away from the countries where the plant is cultivated. Among the many alkaloids that have been isolated from khat, alpha-aminopropiophenone (cathinone) and (+)-norpseudoephedrine (cathine) are considered responsible for the psychostimulant effects of khat. Cathinone appears to be between seven and ten times more potent than cathine and accordingly, the commercial value of khat at markets has been found to relate to its actual cathinone content. Experienced chewers are aware that the fresher the leaves and shoots, the stronger the subjective effects to be expected. Indeed, cathinone is an unstable molecule, and apart from being converted to cathine during plant maturation, it also degrades during harvesting and drying processes. For this reason, khat leaves are usually wrapped up in banana leaves in order to preserve the freshness and buyers do not allow more than 2 or 3 days before consumption.

Mechanism of Action, Pharmacokinetics and Effects

Cathinone structure and mechanism of action resemble quite closely that of ► amphetamine. Indeed, cathinone increases ► dopamine, ► noradrenaline, and ► serotonin release from the postsynaptic terminals (Kalix and Braenden 1985). Additionally, it prevents neurotransmitters reuptake by inhibiting the relative transporters, as observed in the striatum of drug-treated rats (Fleckenstein et al. 1999). In vivo ► microdialysis studies showing an increase in striatal dopamine metabolites are coherent with these actions.

The ► pharmacokinetic profile of khat emerged in detail when typical "khat sessions" were arranged in an experimental setting, where subjects chewed the leaves enabling active principles to be gradually released and absorbed by the buccal and gastrointestinal mucosa. Results showed that cathinone plasma concentration, which reaches its peak at about 1.5–3.5 h from the start of the sessions, declines over nearly 7 h from ingestion, being metabolized to norephedrine and cathine (Widler et al. 1994). Cathine shows a slower clearance,

contributing to the extension of the overall effects of khat ingestion and to the prolonging of analytical evidence of this ingestion.

The effects induced by chewing khat are typically amphetamine-like. Euphoria, elation, logorrhea (excessive and often incoherent talking), and increased feelings of alertness are experienced, usually in a milder form with respect to amphetamines. This is intrinsic to the modality of consumption, which usually requires hours to allow subjective effects to gradually build up and be perceived by the chewer. Khat-induced "arousal" facilitates interpersonal relations in a convivial setting, as subjects, enhanced in mood and loquacity, feel confident to engage in animated discussions, although their attentional abilities may be negatively affected. Reduced fatigue, insomnia, anorexia, and increased libido are also often reported. Sympathetic stimulation determines an increase in body temperature, mean arterial pressure, and heart and respiratory rates (Nencini et al. 1984), though a certain degree of ▶ tolerance typically develops in habitual consumers.

Stimulation of the central nervous system may also lead to mood disturbances and irritability, especially at the end of a khat session, but dysphoric responses during consumption are not infrequent, and may be due to an inappropriate setting interfering with the experience of mood elevation.

Dependence

As an amphetamine-like stimulant, the addiction potential of khat has been a matter of debate among the expert committees questioned by national authorities on the effective risk for public health and social functioning caused by khat chewing. Indeed, similar to amphetamine, khat users may experience craving, as shown by the buyers' behavior at markets, and a certain degree of tolerance to the neurovegetative and endocrine effects seems to develop (Nencini et al. 1984). Drowsiness and ▶ dysphoria experienced the morning after the session may be considered the expression either of hangover or of mild ▶ withdrawal syndrome. Nevertheless, a proper withdrawal syndrome has not been described yet, although interrupting prolonged use may result in mild depression, anergia, and sleep disturbances. Animal studies have been of great help in elucidating khat's behavioral pharmacology inherent to addiction in comparison with other stimulant substances. Animal models of ▶ self-administration of psychoactive drugs have been proved to be highly reliable in predicting human abuse when exposed to the same drug. As expected, cathinone, similar to amphetamine but two to four times weaker, maintains self-administration in a variety of species (Johanson and Schuster 1981), thus demonstrating considerable reinforcing properties. Moreover, its properties in ▶ drug discrimination experiments, which determine the emission of specific behavioral responses only in the presence of the drug, generalize to amphetamine and ▶ cocaine. Pharmacological studies with dopamine antagonists have pointed out the major role of dopaminergic neurotransmission in mediating these effects, a common thread among psychostimulants that exert positive reinforcing effects. Given the tight qualitative similarity between khat's most active alkaloid and amphetamines, it may seem odd that only a few cases of ▶ dependence have been reported. This, however, should not come as a surprise, since the addictive potential of a drug is usually related to the rapidity of onset of action and ultimately to the route of administration. Hence, since khat intake by chewing is intrinsically limited by the bulkiness of the plant material and 2–3 h are required to reach maximal plasma levels, in the natural setting the reinforcing properties of the drug are weaker compared to amphetamine or cocaine; thus, it is improbable that dependence develops to the same extent and severity. This is perhaps the reason why habitual users usually do not show serious problems when stopping use.

Psychiatric Adverse Effects

Repeated exposure of rodents to khat extract or to cathinone causes a variety of behavioral effects that model psychotic disturbances. It is important to note that experimental results may differ when using khat extracts instead of cathinone, since standardized bioavailability of the extract cannot be easily obtained. With this caveat in mind, parenteral administration of cathinone in rats and mice determines an increase in locomotor activity and stereotyped movements, which are considered indexes of a psychomotor stimulant effect, although not as potent than that of amphetamine (Kalix and Braenden 1985). A dose-related increase in locomotor activity in rats was also seen after bilateral microinjections of cathinone directly into the brain's ▶ *nucleus accumbens*, again consistent with the hypothesis of a dopaminergic mediated phenomenon. Other paradigms have pointed out khat's potential for inducing strong and long-lasting behavioral ▶ sensitization (Banjaw and Schmidt 2005), since its repeated administration caused an augmented number of rearings and upward and downward sniffing, which persisted after discontinuation of treatment. Behavioral sensitization to psychostimulants models many aspects of the development of toxic psychosis in human addicts. Recently, khat extract and cathinone have been found to cause a deficit in ▶ prepulse inhibition (PPI), which is also disrupted in schizophrenic patients and thus serves as a model of sensorimotor gating for the study of psychotic disorders. The deficit develops

gradually after repeated administration and is attenuated by the atypical antipsychotic ► clozapine. Another experimental behavior elicited by cathinone that is strongly linked to human psychosis is the excessive water consumption observed in rats after repeated administration (Graziani et al. 2008). In fact, it may model psychotic polydipsia, a potentially fatal complication of ► schizophrenia. The hyperdipsic effect in conditions of free access is common to other dopaminergic drugs, such as amphetamine and quinpirole. Interestingly, cathine does not induce per se excessive water consumption in rats, but can reinstate the polydipsic response to amphetamine.

The psychotic potential of khat is partially confirmed by several reports of onset of paranoid psychosis in khat users. Manic-like psychosis and persistent ► hypnagogic hallucinations have also been described in human literature. These adverse psychiatric sequelae, however, are thought to be mainly correlated with both traumatic experiences, such as combat, and severity of khat use, in terms of daily intake and early onset of heavy use (Odenwald et al. 2005). A large survey among Yemeni adults has excluded any correlation between khat chewing and psychopathological alterations (Numan 2004). Although the causality between the two variables remains difficult to ascertain and would benefit from further and better-designed investigations, there have been growing reports of khat-induced psychosis in immigrants residing in Europe and USA. The estrangement of the immigrant condition and the lack of social support once the use is dislocated from their native culture might create a setting that favors the risk of experiencing the negative effects of the drug in vulnerable subjects.

Experimental and Clinical Toxicology

Studies on acute and chronic toxicity of khat on organs and functions have often led to contrasting or even misleading results. Potential toxic effects on organs have been experimentally reported, but modalities and doses of administration reflect an unrealistically heavy daily consumption. A negative impact on reproduction has been documented, both in mice (fertility reduction and postimplantation loss) and humans (higher incidence of low birth weight in regular female khat chewers). Cathinone, as well as cathine-induced vasoconstriction in the placenta may account for these detrimental effects. In males, data on the effects of khat on testosterone plasmatic levels and ► capacitation function of spermatozoa are far from being clear and vary with the species in exam.

A mutagenic and ► teratogenic effect of khat was evidenced in rats and cellular lines, suggesting that the drug may induce chromosomal aberrations and a selective type of cell death similar to ► apoptosis. However, teratogenic effects in pregnant women have never been reported.

Along with mood and psychotic disorders, oral lesions and adverse cardiovascular events are thought to represent the major concerns in terms of public health. In the buccal cavity, irritant and proinflammatory action of terpenoids and tannins released from khat leaves may be responsible for the onset of chronic inflammatory processes and ► keratotic lesions. Although evidence are once again contradictory, khat consumption, especially when associated with ► alcohol and tobacco use, might be a potential cause of oral leukoplakia and malignant lesions, as suggested by the micronucleus test for genetic damage in buccal mucosa cells of consumers. The already mentioned sympathetic activation caused by chewing khat is unequivocally involved in the genesis of cardiovascular accidents. Cathinone acts as a competitive antagonist of the noradrenaline transporter, increasing monoamine action on the cardiac ventricles of rats. Several case reports and an epidemiological study showing a 39-fold increase of risk of acute myocardial infarction in heavy khat chewers seem to remove all doubts on this topic (Al-Motarreb et al. 2005).

Socioeconomic Considerations

The spreading of the habit of chewing khat has roused a political debate in those countries where the plant is cultivated and deeply rooted in the everyday life. The number of habitual consumers is growing rapidly, mostly in Yemen: children under the age of 12 and especially women, who refrained from using in the past mostly because it was considered a male habit, are additional to the 90% of the adult male population already consuming daily. Apart from the detrimental health consequences, khat is pointed out by its detractors as one of the leading causes of family disintegration and increasing the economic burden in home countries. When commenting adversely, one should nevertheless consider the profound negative impact on the local culture of a hypothetical ban. In fact, immigrants have kept alive the tradition of chewing in Europe and USA, confirming khat as tightly bonded to their former social culture and thus an expression of identity.

Although the active alkaloids of the plant, cathinone and cathine, have been labeled Schedule I and Schedule III substances respectively by WHO since 1988, the legal status of khat in western countries is not uniform. At the moment, it is prohibited in Finland, France, Ireland, Italy, Norway, Sweden, Switzerland, and also in the USA if it contains cathinone or cathine, but legal in the Netherlands and in the UK. In several countries of Africa khat is

considered legal. Recently, the WHO committee, revising the international literature, has judged the potential for abuse and the threat to public health of khat as not significant and not requiring any scheduling (WHO 2006).

Cross-References

- ► Leucoplakia
- ► Microdialysis
- ► Prepulse Inhibition
- ► Psychostimulants
- ► Self-Administration of Drugs

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K-Hole

Definition

The term "K-hole" is a slang term for a state of dissociation occurring when large doses of ► ketamine are ingested. These effects, which mimic the schizophenic symptoms, result in the user feeling trapped in a state in which they may feel detached from their bodies and unable to move. Other symptoms include distortion of the senses, particularly vision, result in disorientation, and can cause nausea and vomiting. Distortions in bodily awareness, perceptions of falling and flying, and intense hallucinations may also be experienced. The combination of these effects leave the user feeling trapped in a frozen state, as if stuck in a hole peering out.

Cross-References

- ► Dissociative Anaesthetics
- ► Self-Administration of Drugs

Kinase Inhibitors

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Synonyms

Protein kinase inhibitors

Definition

Protein kinases, one of the largest human gene families, play a key regulatory role in cell functioning. The common feature of all protein kinases is to function as a catalyst in the transfer of the terminal phosphoryl group of ATP, covalently attaching it to a free hydroxyl group of their protein substrates' amino acids – tyrosine (tyrosine kinases), or serine or threonine (serine/threonine kinases). A number of kinases can also act on all three amino acids (dual-specificity kinases). Based on sequential and structural similarities, approximately 518 protein kinases encoded in the human genome could be classified into seven major groups (further divided into families and subfamilies): tyrosine kinase (TK); tyrosine kinase-like (TKL); cyclin-dependent kinases (CDK), mitogen-activated protein kinases (MAPK), glycogen synthase kinase 3 (GSK-3), and CLK (CMGC); homologs of Sterile 7, Sterile 11, and Sterile 20 kinases (STE); casein kinase 1 (CK1); protein kinase A (PKA), protein kinase G (PKG), and protein kinase C (PKC (AGC)); calcium/calmodulin-dependent protein kinase (CAMK); and a group of unclassified and atypical protein kinases (Manning et al. 2002).

Protein phosphorylation is involved in a myriad of complex biological and physiological cellular processes, including receptor tyrosine kinases, second-messenger generators, ► signaling cascades participation, and kinases regulating cell life cycle. Thus, deregulation of kinase function has been associated with an equally diverse number of pathophysiological processes. These include immunological disorders (inflammatory and infectious disease), metabolic disorders, cancer, and central nervous system (CNS) diseases (including neurodegeneration-related disorders). Thus, protein kinase regulation (through activation or inhibition) presents as a logical molecular target for the treatment of these conditions.

Different types of inhibitors, as discussed below in more detail, can be classified based on their kinetic characteristics, including substrate-competitive inhibitors (inhibitors that directly compete with protein substrate binding), ATP-competitive inhibitors (inhibitors that directly interact with the ATP-binding site), activation inhibitors/allosteric modulators (allosteric inhibitors that primarily alter protein kinase conformation to block ATP binding), and irreversible inhibitors. However, despite the large body of knowledge currently available, protein kinase inhibition persists as a challenge for targeted drug development due to the structural similarity among kinases (and the inherent difficulties of selectively inhibiting them without affecting normal physiology), their functional redundancy for specific signaling, and the still unclear connections between these pathways and specific disease processes.

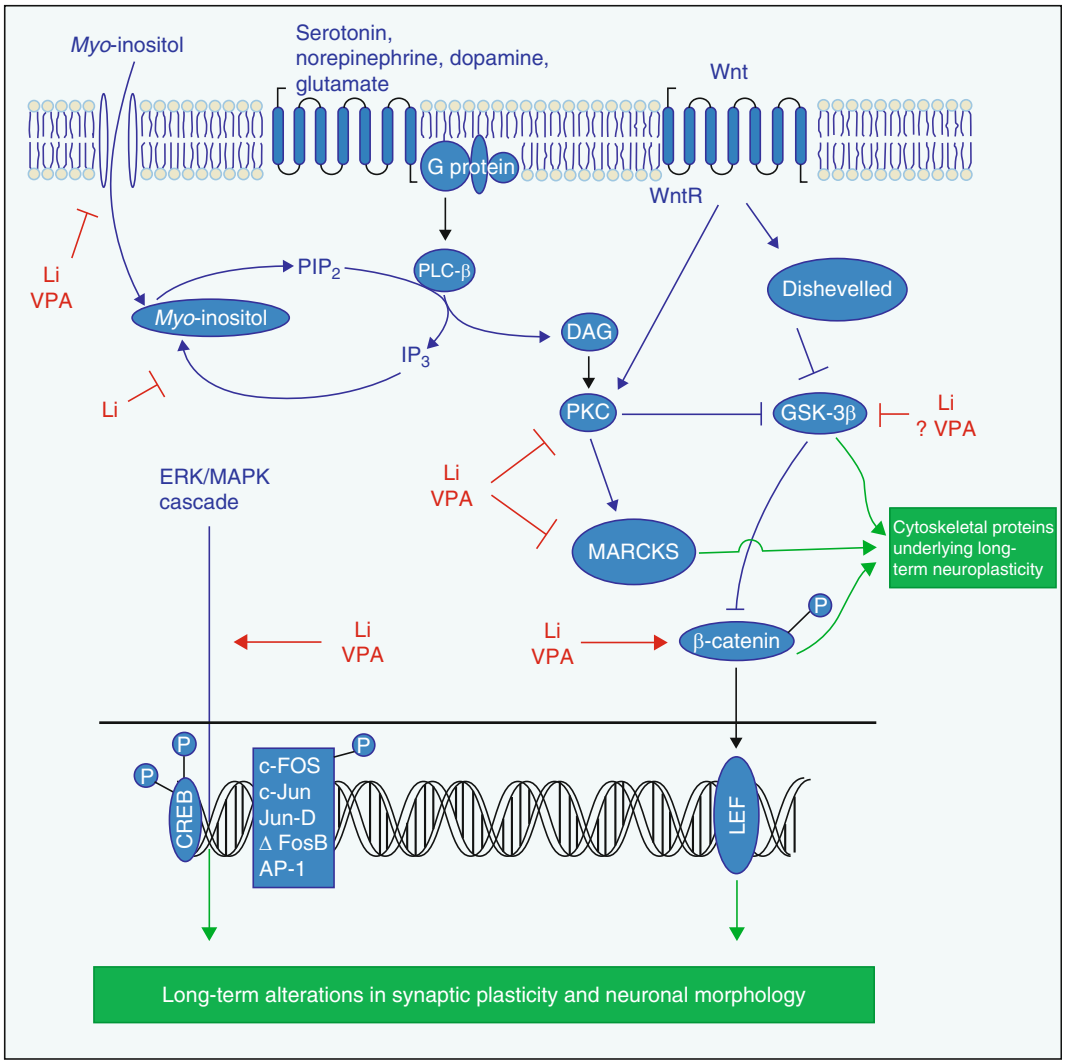
Pharmacological Properties

While discussing the potential strategies and particular issues regarding the targeting of kinases in the treatment of CNS disorders, we focus here on the protein kinase inhibition of two signaling molecules that represent targets for novel therapies for ► bipolar disorder: glycogen synthase-3 (GSK-3) and protein kinase C (PKC). Both have been identified as therapeutically relevant biochemical targets of currently available and effective medications, holding the possibility of mediating more refined and sophisticated treatment for this devastating illness.

Although many drugs that target kinase inhibition are in clinical development for various medical illnesses and even more are being investigated at the preclinical level, the use of modulators of ubiquitous kinases in the CNS still raises concerns of specificity, tolerability, and safety. However, the success of a number of kinase-targeted drugs in cancer treatment, including Gleevec (Imatinib, an inhibitor of tyrosine kinase BCR-Abl), Iressa (Gefitinib, an inhibitor of tyrosine kinase EGFR), and Herceptin (Trastuzumab, an antibody against tyrosine kinase receptor HER2), has initially proved the feasibility of such strategy. Modulators that target the brain are, for the most part, still in the preclinical stages of development. However, ► lithium, a mood stabilizer that targets signaling cascade molecules, including the inhibition of protein kinases as GSK-3, has been a mainstay of treatment for bipolar disorder for almost 60 years, provides a key example of a safe and effective modulator of signaling systems in the CNS. Tamoxifen, mainly an antiestrogen agent, is another regulator of CNS signaling molecules including PKC inhibition with an acceptable efficacy and safety profile. Both drugs modulate signaling pathways that are involved in diverse brain functions, and possibly other CNS disorders, demonstrating relatively circumscribed clinical effects. Thus, developing other CNS kinase-targeted drugs with adequate specificity and tolerability is possible, albeit challenging.

PKC Inhibition

PKC is a family of serine/threonine kinases that are involved in the transduction of signals for cell proliferation, differentiation, ► apoptosis, senescence, and angiogenesis. The family is comprised of at least 12 isoforms, which are subdivided into three classes (classical/conventional, novel, and atypical) on the basis of calcium- and diacylglycerol (DAG) dependence. PKC isoforms differ in structure, subcellular localization, tissue specificity, mode of activation, and substrate specificity. Activation of PKC results in its translocation, and subcellular localization is thought to regulate accessibility to activators and substrates. PKC is activated by such varied upstream signals as ► G protein-coupled receptors (GPCRs), receptor tyrosine kinases (RTKs), and nonRTKs via DAG activation (Fig. 1). Several PKC isoforms are independently activated by the phospholipase C (PLC) and phosphoinositide-3 kinase (PI3K) pathways. Of PKC's numerous substrates, a major target is the MEK–ERK pathway, also thought to be involved in the activation of Raf1 (Serova et al. 2006) (The Raf–MEK–ERK pathway is a signaling cascade – the first entirely mapped from the cell membrane with many substrates both in the cytosol and the nucleus). PKC has been identified as a potential target for the treatment of a number of medical diseases, including diabetes, cancer, and ► bipolar disorder. With respect to its potential role in bipolar disorder, it is significant that lithium and valproate bring about strikingly similar effects on the PKC signaling cascade (Manji and Lenox 1999), as discussed below.



Kinase Inhibitors. Fig. 1. Intracellular signaling cascades involved in the long-term stabilization of mood by lithium (Li) and valproic acid (VPA). Activation of receptors coupled to PI hydrolysis results in the breakdown of phosphoinositide 4,5-biphosphate (PIP_2) into two second messengers: IP_3 and diacylglycerol (DAG), which is an endogenous activator of PKC. Lithium is an uncompetitive inhibitor of inositol monophosphatases, whereas both lithium and VPA, upon chronic administration, decrease *myo*-inositol uptake. These perturbations by mood stabilizers likely contribute to the reduction in PKC activity and the reduced levels of PKC-α, PKC-ε, and myristoylated alanine-rich C kinase substrate (MARCKS), a major PKC substrate in the CNS (MARCKS proteins play important roles in multiple cell functions, including cell architecture, cell cycle, and exocytosis, and are regulated by Ca^{2+}/calmodulin and PKC.) In the Wnt signaling pathway, binding of the Wnt signal to the Wnt receptor (WntR) activates an intermediary protein, Disheveled, which regulates GSK-3β. GSK-3β regulates cytoskeletal proteins, and also has an important role in determining cell survival and cell death. Lithium (and possibly VPA) directly inhibits GSK-3β, which may underlie, at least in part, the increases in β-catenin that occur after chronic treatment with these agents. The ERK MAP kinase cascade regulates several important transcription factors, most notably CREB and activator protein-1 (AP-1) (AP-1 is a transcription factor that regulates gene expression in response to diverse stimuli.) Recent studies have demonstrated that both lithium and VPA activate the ERK MAP kinase cascade, which may contribute to the long-term changes in synaptic plasticity and morphology that follow chronic treatment. Together, regulation of these signaling pathways through selective kinase inhibition might bring about an enhancement of synaptic connectivity, potentially necessary for long-term stabilization of mood. (Reprinted from Manji C (2002) Nat Med 8:557–558 With permission.)

Preclinical and Clinical Evidence of the Role of PKC Inhibition in the Pathophysiology and Treatment of Bipolar Disorder

Evidence from numerous studies using widely varying methodologies implicates PKC in the pathophysiology and treatment of ► bipolar disorder. These include peripheral blood cell studies that have showed altered PKC isozyme levels and activity in bipolar subjects, and postmortem studies similarly demonstrate altered PKC levels and activity in subjects with bipolar disorder. Importantly, lithium and ► valproate – two efficacious medications with mood-stabilizer properties, widely utilized in the treatment of bipolar disorder – decrease PKC levels in an isozyme-specific manner and decrease PKC activity. Lithium interacts with the PI/PKC pathway via the inhibition of inositol mono-phosphatase (IMPase), resulting in decreased free myo-inositol and the subsequent production of DAG, with the downstream effect of decreasing PKC levels and activity. Valproate – structurally dissimilar from lithium – also appears to inhibit PKC, suggesting that this inhibition is important to the common therapeutic effects of both medications.

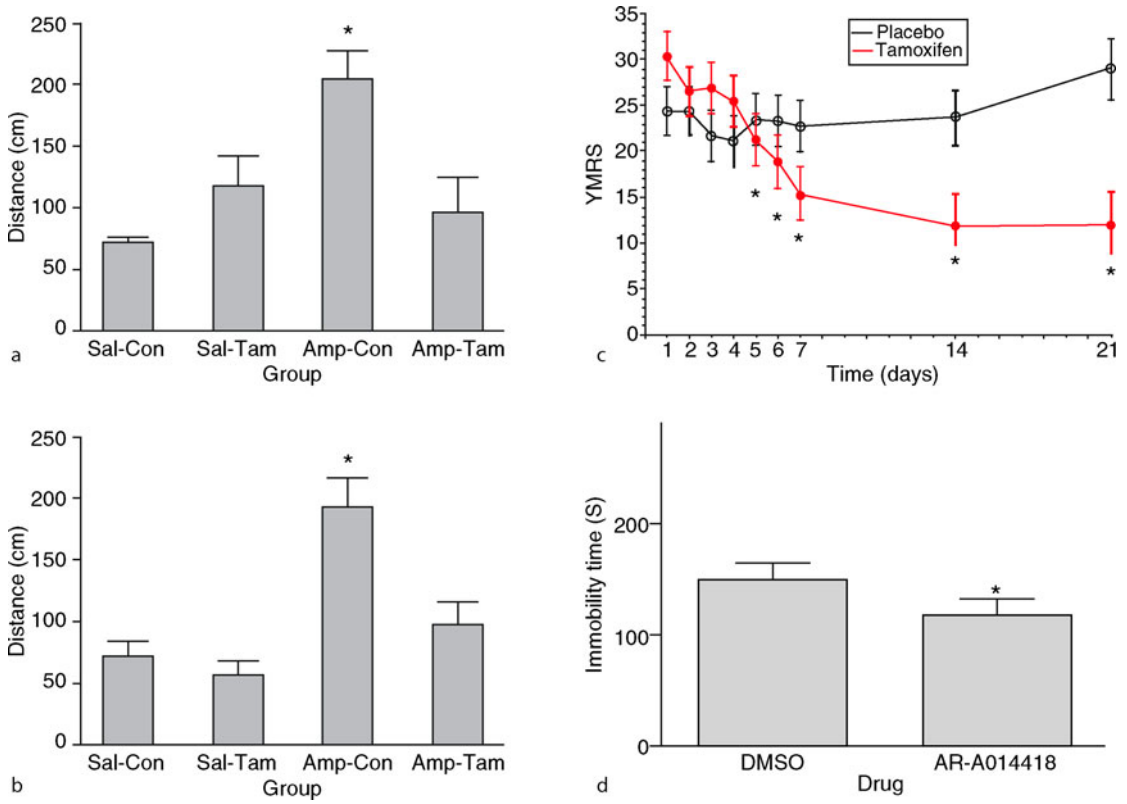
Based on the clinical observation that ► psychostimulants (amphetamine and cocaine) worsen manic symptoms in hypomanic patients and induce manic relapses in subjects with a personal or family history of bipolar disorder, stimulant-induced behavioral alterations in rodents are utilized as experimental models of mania. Lithium treatment prevents these forms of psychostimulant-induced behaviors, which provides additional validation to these models. Notably, the behavioral alterations induced by psychostimulants in rodent are associated with changes in PKC, and furthermore, pharmacological inhibitors of this kinase-attenuate amphetamine-induced hyperlocomotion (Fig. 2a, b). In fact, excessive activation of PKC dramatically impairs cognitive functions of the prefrontal cortex, while PKC inhibition protects it, suggesting that PKC might play a role in some of the cognitive features of mania.

The first study in humans with a fairly selective PKC inhibitor was a small, open-label trial, in which treatment with tamoxifen produced a greater than 50% decrease in manic symptoms in five of seven subjects. Noticeably, this effect was recently confirmed in a ► double-blind, placebo-controlled, 3-week study of 16 manic patients (Zarate et al. 2007), effects found as early as day 5 of treatment with the PKC inhibitor (Fig. 2c). The potential role of the PKC signaling pathway in the pathophysiology of bipolar disorder has been further strengthened by the identification of a bipolar susceptibility gene, which is an upstream regulator of this kinase. Diacylglycerol kinase eta (DGKH), a major regulator of DAG that activates all known classical and novel isoforms of PKC, was identified as a risk gene for bipolar disorder in two recent independent genome-wide association studies (Baum et al. 2008; Wellcome Trust Case Control Consortium 2007).

Development of PKC Inhibitors

A large number of structurally distinct PKC inhibitors have been identified or developed, mostly for use in cancer treatment, and Tamoxifen has been investigated and found efficacious in three independent clinical trials for bipolar disorder. PKC inhibitors that are used in treatment or have undergone clinical trials for cancer include the already-mentioned tamoxifen (treatment for estrogen receptor-positive breast cancer); the lipid analogs safingol (Phase-I trial with doxorubicin for solid tumors) and miltefosine (Phase-II trial of topical treatment for cutaneous breast cancer metastases); the indolocarbazoles UCN-01 (Phase-II trials for several cancers) and PKC412 (Phase-II trials for solid tumors); the bisindolylmalemide enzastaurin (Phase-II trials for glioblastoma and B-cell lymphoma); and the PKCα-specific antisense oligonucleotide ISIS3521 (several Phase-II and Phase-III trials) (Serova et al. 2006). The PKC inhibitors that have been investigated thus far are relatively nonspecific, with the exception of the ► antisense oligonucleotides, that unmodified, however, very rarely cross the brain–blood barrier and will probably require forms of central delivery or adaptations to increase its lipophilicity. The potential of isoform-, cell type-, and substrate-selective PKC inhibitors has therefore not been fully explored.

The development of highly selective PKC inhibitors is critical for the possibility of novel therapies with good efficacy, tolerability, and safety profiles. As mentioned, strategies such as the use of non-ATP-competitive inhibitors, or inhibitors that target binding proteins or substrates that are less promiscuous than the target kinase, may prove useful in the development of anti-PKC agents. A substrate-competitive inhibitor has been designed for PKCα, and peptides corresponding to PKC-anchoring proteins like RACK (receptors for activated C kinases) selectively inhibit specific PKC isozyme activity. A related strategy is to target PKC in specific subcellular locations. Because PKC isoforms are translocated upon activation, targeting location-specific anchoring proteins may produce isoform- and/or substrate-specific inhibition. Finally, combination strategies may prove beneficial for increasing specificity and sustained therapeutic effectiveness and reducing resistance. Examples of target combinations might include kinase-targeted agents with (a) binding or scaffolding proteins that are location- and/or



Kinase Inhibitors. Fig. 2. Preclinical and clinical behavioral evidence of the effect of protein kinase inhibition: (**a**) Effects of two injections of tamoxifen, a PKC inhibitor, (1 mg/kg) on amphetamine-induced hyperactivity in rats, measured in a large open field after acute or (**b**) chronic (7 daily injections) amphetamine treatment. The y-axis represents total distance traveled during the 45-min test session. Both acute and chronic amphetamine increased total distance traveled, and this increase was attenuated by tamoxifen pretreatment without affecting nonamphetamine-treated rats. Sal = Saline; Con = vehicle; Amp = amphetamine; Tam = tamoxifen; Sens = sensitized. * $p<0.05$. (**c**) Clinical study: change in scores on the Young Mania Rating Scale (YMRS) over three weeks ($n=16$). Subjects on tamoxifen showed significant improvement in mania when compared with placebo as early as 5 days, an effect that remained significant throughout the 3-week trial. * $p<0.05$. (**d**) Immobility time in the forced swim test (in seconds) in Rats; $n=14$ per group; bar graphs represent mean $\pm$ SE. Animals treated with AR-A014418 (a selective GSK-3 inhibitor) demonstrated significantly reduced immobility time (suggesting an antidepressant-like action) when compared with vehicle-treated animals. * $p<0.05$. DMSO = Vehicle. (Modified and reproduced from Einat, Yuan, Szabo, Dogra, Manji (2007) Neuropsychobiology 55:123–131 (**a** and **b**); Zarate et al. 2007 (**c**); and Gould, Einat, Bhat, Manji (2004) Int J of Neuropsychopharmacol 7:387–390 (**d**). With permission.)

isoform-specific (such as RACK); (b) up/downstream molecules within the same signaling pathway to accomplish a synergistic effect with increased specificity; or (c) functionally related molecules with narrower expression profiles. Bisubstrate inhibitors might combine, for example, ATP and a particular kinase substrate for a higher degree of specificity. Ideally, combinations of therapies are designed such that they accomplish increased effectiveness to a greater degree than increased side effects. Disadvantages of this strategy include the increased likelihood of drug–drug interactions and the potential of decreased compliance. Therapies combining PKC modulators with other anticancer agents have been investigated at the preclinical level and in clinical trials (Serova et al. 2006).

GSK-3 Inhibition

GSK-3 is a ubiquitous, multisubstrate, serine/threonine kinase that is a key component of many intracellular signaling pathways including the insulin, neurotrophin,

and Wnt pathways (Fig. 1). (The Wnt signaling pathway, which involves a large number of proteins, is initiated when Wnt proteins bind to transmembrane receptors of the Frizzled family, activating Disheveled proteins that will ultimately change the amount of β-catenin that reaches the nucleus.) GSK-3 is encoded by two genes, GSK-3α and GSK-3β, whose protein kinase domains are 98% identical. GSK-3 is regulated by many of the key players in mood-disorder pathophysiology and treatment, including serotonin, dopamine, glutamate, psychostimulants, ► antidepressants, and ► mood stabilizers (Gould and Manji 2005). GSK-3 plays a critical role in multiple cellular processes, such as metabolism, proliferation, differentiation, axonogenesis, and synaptogenesis. Its role in the regulation of apoptosis and cellular plasticity/resilience is thought to be the target of the mood-stabilizing agents, lithium and valproate.

Preclinical and Clinical Evidence of GSK-3 Inhibition in the Pathophysiology and Treatment of Bipolar Disorder

As in the case of PKC inhibition, GSK activity is also inhibited by lithium and valproate, agents with mood-stabilizing properties in humans. Lithium inhibits GSK-3 through a combination of direct binding to this kinase and increased phosphorylation of its inhibitory N-terminal serine (Martinez et al. 2006). Direct inhibition of GSK-3 at therapeutically relevant concentrations of lithium occurs in vitro and in vivo, and in diverse cell types, including cultured neurons and rodent brain, subsequently activating glycogen synthesis and Wnt/ß-catenin-dependent transcription. In mice, GSK-3 has also been shown to be inhibited by valproate (although whether this is via direct or indirect action remains controversial) and by electroconvulsive seizure, a nonpharmacological therapy utilized in the treatment of mood disorders.

At the cellular level, lithium and valproate have also been shown to promote neural viability and exert neuroprotective effects ► neuroporotection in a variety of preclinical cell-toxicity ► neurotoxicity and injury paradigms in vitro and in vivo. It is then relevant to note that GSK-3 is a major regulator of apoptosis, cellular plasticity, and resilience. In general, the increased activity of GSK-3 is proapoptotic phenomena compatible with evidence showing that treatment of cultured neurons with GSK-3 inhibitors or transfection with GSK-3 small interfering RNAs (siRNA) induce neuroprotective effects that mimic those observed under lithium exposure. In addition, additional evidence has been generated that supports the role of GSK-3 in mediating lithium's own axonogenesis effects. While N-terminal phosphorylated GSK-3ß localizes to growth cones, agents that collapse growth cone also induce dephosphorylation of GSK-3.

Pharmacological and genetic data from animal behavioral models have shown that manipulation of GSK-3 produces both antidepressant and antimanic effects. Of note, mice lacking one copy of GSK-3β exhibit antidepressant-like behavior in the forced swim test (Fig. 2d), ► Depression: animal models, and reduced amphetamine-induced locomotor activation. Very importantly, this is the only manipulation, other than that of lithium, that we are aware results in both antimanic-like and antidepressant-like effects. In addition, when the downstream effects of GSK-3 inhibition are investigated, data have shown a decrease in phosphorylation and degradation of its target β-catenin, evident that parallel lithium's increases of β-catenin and Wnt-mediated gene expression at therapeutically relevant concentrations in rodent brain. At last and of importance to clarify the functional effect of GSK-3 inhibition on decreasing β-catenin degradation, it has been observed that β-catenin overexpressed in transgenic mice have mood-stabilizing-like actions in prototypical animal models of mania (D-amphetamine hyperlocomotion) and depression (forced swim test).

Although genetic studies have not reproducibly found GSK-3 polymorphisms to be associated with bipolar disorder, a recent whole genome association study did identify ► polymorphisms in molecules in the overall GSK-3 signaling cascade to be associated with the disease. Finally, experimental data that have shown the role of GSK-3 in the modulation of ► neurogenesis, neuronal survival, and mood-related behaviors, in addition to the mediation of ► AMPA-receptor trafficking and ► circadian rhythms (in drosophila and mice), provides further support to the potential role of GSK-3 inhibition in the pathophysiology and treatment of mood disorders.

Development of GSK-3 Inhibitors

GSK-3 has emerged as a key target in the development of novel treatments for ► Alzheimer's disease, based on evidence that it is involved in formation of both amyloid plaques and neurofibrillary tangles, two pathological hallmarks of the disease. GSK-3 interacts with presenilin, which mediates the gamma-secretase cleavage step in the formation of ► amyloid-beta peptide (Phiel et al. 2003). GSK-3 also regulates the phosphorylation of the microtubule-associated ► protein tau, which, in its hyperphosphorylated form, is a main component of neurofibrillary tangles (Hernandez and Avila 2006). Preclinical studies in animal models of Alzheimer's disease have shown that

GSK-3 inhibition by lithium reduces beta-amyloid production (Phiel et al. 2003). These and other studies have raised considerable interest in the potential of GSK-3 inhibitors in the treatment of Alzheimer's and other neurodegenerative diseases and tauopathies.

More than 30 inhibitors of GSK-3 have been identified to date, represented by such diverse classes of molecules as pyridyl-oxadiazoles, malemides, thiadiazolidindiones, and pyrazolopyrimidines (Martinez et al. 2006). As with protein kinase inhibitors in general, there are many considerations regarding selectivity and safety in the development and potential use of GSK-3 inhibitors. The need for substrate-selective modulators is a critical issue, given that GSK-3 is known to phosphorylate at least 40 substrates. In fact, the selectivity of most available GSK-3 inhibitors is poorly characterized, and many demonstrate overlapping interaction with the closely related kinases, CDK2 and CDK5. In order to phosphorylate its target, GSK-3 requires a "priming phosphorylation," carried out by another kinase that is substrate-dependent. Inhibitors that target the "priming phosphate" have the potential for superior specificity. Cell-permeant phosphopeptides have been studied that bind to these sites and inhibit GSK-3 activity. A further specificity challenge is the high-sequence similarity mentioned between the catalytic domains of the two GSK-3 isoforms, making it difficult to develop isoform-selective inhibitors (Martinez et al. 2006). AR-A014418, a thiazole, and SB-216763 and SB-415286, structurally distinct malemides, are ATP-competitive inhibitors that have been shown to be highly specific for GSK-3. AR-A014418 and SB-415286 demonstrate neuroprotective properties in vitro (Faci and Skaper 2006) and AR-A014418 demonstrates antidepressant properties in animal models. In general, ATP-noncompetitive kinase inhibitors have the potential for greater target specificity than those that compete reversibly with ATP, which is the strategy of the majority of currently available inhibitors. 2,4-disubstituted Thiadiazolidiones (TDZDs) were the first class of ATP-noncompetitive inhibitors for GSK-3, demonstrating high potency and selectivity (Martinez et al. 2006), and neuroprotective properties in in vitro studies. Thienylhalomethyl ketones represent a second class of ATP-noncompetitive GSK-3 inhibitors that has yet to be fully investigated. A substrate competitive inhibitor, L803-mts, has been developed demonstrating antidepressant properties in the forced swim test.

Several strategies for reducing toxicity may be combined with the above methodologies in the development of signaling molecule-targeted drugs for psychiatric disorders. The use of partial inhibitors can be a preferred strategy in cases in which the targeted kinases are essential for life, as is the case for GSK-3. The GSK-3β knockout mouse is embryonic lethal, indicating that its function is essential and nonredundant, at least during development. Partial inhibition may not only be necessary to reduce toxicity, but may also be optimal for therapeutic effect, based on the fact that only 25% inhibition of GSK-3 is sufficient to account for lithium's behavioral effects in animal models. In addition, this partial inhibition of GSK-3 may account (at least in part) for the lack of the oncogenic effect of increasing β-catenin. Finally, CNS-selective delivery, e.g., delivery of inactive prodrug with conversion to the active drug only in the CNS, may bypass non-CNS toxicity and prove to be an effective strategy for GSK-3 inhibition.

Summary

Recent data suggest that regulation of signaling molecules is probably involved in mechanisms of action of mood stabilizers and antidepressants, and the possibility of targeting signaling molecules for treatment, particularly protein kinases such as GSK-3 and PKC, holds promising therapeutic opportunities. The debate regarding whether protein kinases can be safely targeted for directed medical therapies has focused primarily on concerns of specificity and safety. The success of several kinase inhibitors in cancer treatment, as well as the use of lithium for almost six decades, demonstrates the realistic potential of using kinase inhibitors safely and efficaciously. We have discussed a number of strategies that may be employed to increase specificity and limit toxicity with the goal of developing novel treatments with improved efficacy, tolerability, and safety.

Cross-References

- ▶ Antidepressants
- ▶ Apoptosis
- ▶ Bipolar Disorder
- ▶ Circadian Rhythms
- ▶ Depression: Animal Models
- ▶ Lithium
- ▶ Mood Stabilizers
- ▶ Neurogenesis
- ▶ Neuroprotection
- ▶ Neurotoxicity

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Kinetics

► Pharmacokinetics

Knockout/Knockin

Synonyms

Constitutive knockout; Global knockout

Definition

Knockout – The removal or complete disruption of a specific gene in an animal from the blastocyst stage through adulthood. Knockin – The introduction of a mutated version of a specific gene in place of the wild-type version.

Cross-References

► Ethopharmacology
► Genetically Modified Animals
► Phenotyping of Behavioral Characteristics

Koro

► Delusional Disorder

Korsakoff's Syndrome

Definition

Irreversible amnesic syndrome resulting nutritional deficiencies associated with prolonged alcohol abuse.

Cross-References

► Alcohol Abuse and Dependence

L

LAAM

► L-Alpha-Acetyl-Methadol

Labeled Ligand Binding

► Receptor Binding

Labeled Ligand Concentration Binding Isotherm

► Receptor Binding
► Saturation Binding Curve

Laboratory Animal Models of Minimal Brain Dysfunction

► Attention Deficit Hyperactivity Disorders: Animal Models

L-Alpha-Acetyl-Methadol

Synonyms

LAAM

Definition

LAAM is an opioid drug with limited usage in opioid agonist maintenance therapy. It is a derivative of and has a similar mode of action as ► methadone but has a longer half-life (two active metabolites) of up to 72 h. Because of a number of adverse events under LAAM, it has been withdrawn currently from the European and the American market.

Lamotrigine

Definition

Lamotrigine acts on ► GABA receptors to produce an anticonvulsant action. There are also some positive findings in the treatment of ► bipolar depression. The half-life is around 30 h and it is metabolized primarily by glucuronic acid conjugation. Serious, potentially life-threatening dermatological adverse events have been reported, albeit very rarely.

Lanreotide

Synonyms

BIM-23014; Somatuline

Definition

Lanreotide is a peptide analogue of SRIF, used to treat acromegaly and tumors in the gastroenteropancreatic tract. Lanreotide has high affinity for sst2 and sst5 receptors.

Laser Desorption Ionization

► Matrix-Assisted Laser Desorption Ionization

Late Luteal Phase Dysphoric Disorder

► Premenstrual Dysphoric Mood Disorder

Ian P. Stolerman (ed.), *Encyclopedia of Psychopharmacology,* DOI 10.1007/978-3-540-68706-1,

Latent Inhibition

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Synonyms

Stimulus pre-exposure effect

Definition

Latent inhibition (LI) is the reduced efficacy of a previously exposed, inconsequential stimulus to generate a conditioned response when paired with reinforcement, compared with a novel stimulus. LI is extremely robust, appearing across many different learning paradigms and mammalian species, including humans.

While a variety of behavioral tasks are used to demonstrate LI in rodents, all of them share a basic procedure. In the first stage, pre-exposure, animals from each of two groups are placed in an environment that will later serve as the conditioning-test apparatus. Subjects in the "stimulus pre-exposed" (PE) group are repeatedly exposed to a stimulus (e.g., tone), which is not followed by a significant consequence. Subjects in the "nonpre-exposed" (NPE) group spend an equivalent amount of time in the apparatus without receiving the stimulus. Either immediately or a certain time after the pre-exposure time is completed, all subjects enter the conditioning stage of the procedure, in which the PE stimulus is paired with a reinforcer over a number of trials. Performance is assessed by examining some behavioral index of conditioned responding, either during the conditioning stage or in a third, test stage. LI is manifested in poorer performance of the PE when compared with the NPE group.

In terms of psychological processes underlying LI, it is believed that the pairing of stimulus–no event in the pre-exposure stage results in reduced attention to, or salience of, the stimulus, which subsequently interferes with the generation of the conditioned response resulting from the stimulus–reinforcement association in conditioning (Fig. 1).

LI is a phenomenon of ► selective attention in the sense that it reflects a modulating effect of past experience on the current performance. Specifically, it reflects the ability of organisms to ignore stimuli that had been irrelevant in the past, in spite of their current relationship with a reinforcer. Since selective attention deficit is a hallmark cognitive deficit of ► schizophrenia and a central target for treatment, research that examined the effects of psychoactive drugs on LI in rodents has focused primarily on the use of LI to develop animal models of deficient attention in schizophrenia and the identification of ► anti-psychotic activity. The link between LI and schizophrenia is supported by the presence of LI abnormalities in schizophrenia patients.

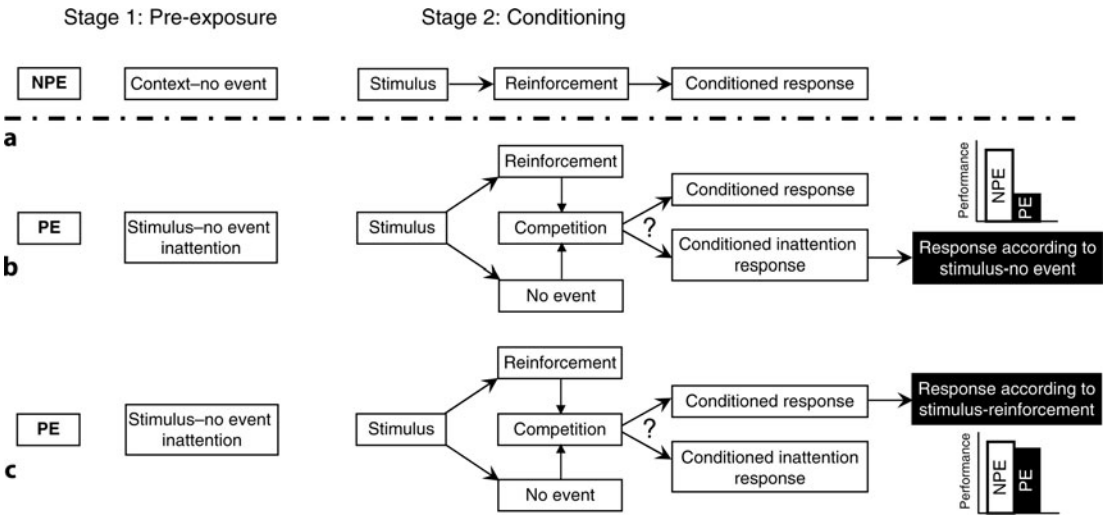
Impact of Psychoactive Drugs

Disrupted and Persistent LI

While drug effects are typically measured as a reduction or an abolition of the target behavior in comparison with its presence in drug nontreated controls, pharmacology of LI has taken a different path from its very inception, focusing on both the disruption and the *induction* of the phenomenon. The latter effect, termed interchangeably LI potentiation, enhancement, or persistence, is indexed by comparison with the *absence* of LI in drug nontreated controls. Thus, psychoactive drugs can produce two poles of LI abnormality, namely, disrupted LI under conditions that lead to LI in normal rats and abnormally persistent LI under conditions that disrupt LI in normal rats (Fig. 2). Both disruption and persistence of LI can stem from drug action in the pre-exposure stage or in the conditioning stage. In addition to unraveling the psychological mechanism by which a given drug affects LI (alterations in the acquisition or the expression of inattentional response), stage-specific action allows for a refined discrimination between the effects of different drugs on LI.

Models of LI Disruption and Persistence

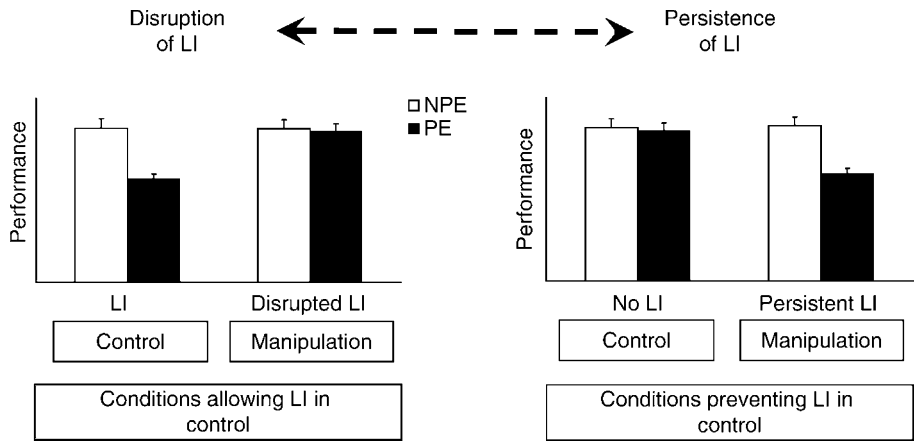
DA agonists. The notion of a hyperactive ► dopamine system in schizophrenia is supported by the capacity of the DA releaser, ► amphetamine, to induce psychosis in healthy humans and exacerbate symptoms, as well as enhance striatal dopamine release in schizophrenia patients. Because amphetamine produces only positive (psychotic) symptoms, amphetamine-induced behavioral abnormalities in animals are considered to model positive symptoms. Consistent with the expectation that the capacity to ignore irrelevant stimuli would be lost in a psychotic-like state, amphetamine disrupts LI in both rodents and humans. Amphetamine-induced LI disruption is due to the drug's action in conditioning stage rather than in pre-exposure stage, indicating that increased dopamine transmission does not produce a psychotic-like state by increasing stimulus salience but rather by weakening the inhibiting effect of reduced stimulus salience on behavior. LI is disrupted also after, as well as during withdrawal from, repeated amphetamine administration. Results with direct DA agonists are inconsistent.



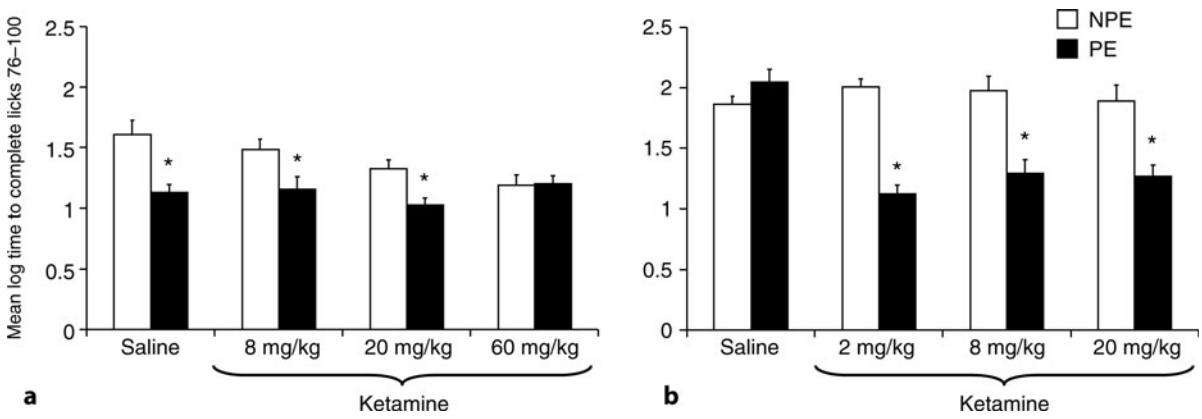
Latent Inhibition. Fig. 1. Latent inhibition as a response competition phenomenon. In the pre-exposure stage, stimulus pre-exposed (PE) animals acquire a stimulus–no event association, which results in a conditioned response of inattention to the PE stimulus. Following conditioned attention theory (Lubow et al. 1981), inattention is treated as a classically conditioned response, acquired when stimuli are consistently followed by the lack of a consequence and governed by the same rules that govern association formation during classical conditioning. In the conditioning stage, the stimulus signals conflicting outcomes, no-event vs. reinforcement, that compete for behavioral expression (conditioned inattention response vs. the conditioned response acquired in conditioning). Which of the two associations gains behavioral control depends on factors that determine their relative behavioral impact during conditioning. The three most conspicuous factors are strength of pre-exposure (usually manipulated by changing number of stimulus pre-exposures but can involve any manipulation known to affect classical conditioning such as stimulus intensity, ISI, etc.), strength of conditioning (usually manipulated by changing the number of conditioning trials or intensity of reinforcement), and context (manipulated by changing the context between pre-exposure and conditioning), but there are other factors as well, such as the time interval between pre-exposure and conditioning or the motivational state of the animal in the two stages. Pharmacological LI experiments typically manipulate number of pre-exposures and/or conditioning trials.

NMDA antagonists. The hypo-glutamatergic hypothesis of schizophrenia is derived from findings that noncompetitive NMDA antagonists such as ▶ phencyclidine (PCP) and ▶ ketamine provoke symptoms in human volunteers and exacerbate symptoms in schizophrenia patients, as well as abnormalities of glutamate neurotransmission in schizophrenia. Since NMDA antagonists also induce negative symptoms and ▶ cognitive impairments characteristic of endogenous schizophrenia, NMDA antagonist-induced behavioral effects in animals are considered to model negative/cognitive symptoms. Unlike amphetamine, low doses of noncompetitive NMDA antagonists, including PCP, ketamine, and MK-801, spare LI. While these results have led to the suggestion that NMDA antagonist-induced effects in LI cannot provide a valid model of the disorder, later studies have shown that NMDA antagonists affect LI in an opposite manner to that of amphetamine, namely, they induce persistent LI under conditions that prevent LI expression in controls (Fig. 3). Importantly, persistent LI is induced by doses of NMDA antagonists that do not produce the well-known deleterious effects of these drugs on associative learning. Higher doses that impair conditioning disrupt LI. NMDA antagonists produce LI persistence via effects in conditioning, indicating that ▶ NMDA blockade impairs rats' capacity to switch response based on changed relationships between stimuli and outcomes. The latter is consistent with numerous demonstrations of inflexible behavior following NMDA blockade in rats and humans and supports the relevance of NMDA antagonist-induced persistent LI to cognitive/negative symptoms of schizophrenia, which are characterized by inflexible and perseverative behaviors.

▶ Muscarinic antagonists. Muscarinic antagonists such as ▶ scopolamine and atropine induce a schizophrenia-like syndrome in humans, which includes positive



Latent Inhibition. Fig. 2. Two poles of LI abnormality. Based on the view of LI as a window phenomenon, namely, present under very specific and restricted conditions, two abnormalities can be produced in LI depending on the status of the phenomenon in control animals: disrupted LI under conditions producing LI in controls, and persistent LI under conditions preventing the expression of LI in controls. In psychological terms, the former reflects loss of normal ability to ignore irrelevant stimuli, whereas the latter reflects a failure to switch to respond to such stimuli when they become relevant.



Latent Inhibition. Fig. 3. Effects of ketamine on LI with weak and strong conditioning. LI was measured in a conditioned emotional response procedure in which rats were either PE to 40 tone presentations or not pre-exposed (NPE) prior to conditioning with 2 tone-shock trials (weak conditioning; Fig. 3**a**) or 5 tone-shock trials (strong conditioning; Fig. 3**b**). Time to complete 25 licks in the presence of the tone was used as a measure of fear conditioning to the tone. LI is manifested in faster times of the PE when compared with the NPE animals. The figures present mean times (logarithmically transformed) to complete 25 licks in the presence of the tone of PE and NPE rats treated with vehicle or ketamine. (**a**) Under conditions yielding LI in vehicle controls, ketamine spared LI at 8 or 20 mg/kg and disrupted LI at 60 mg/kg. (**b**) Under conditions preventing LI in vehicle controls, ketamine at doses of 2, 8, and 20 mg/kg led to persistent LI.

symptoms and cognitive impairments. Recent focus on cognitive impairments in schizophrenia has promoted attention to the cholinergic system because of its well-known role in cognition. Scopolamine can produce both LI disruption and persistence as a function of dose. Low doses of ► scopolamine disrupt LI, supporting the pro-psychotic quality of this agent. The mechanisms underlying this psychotic-like state differ however from those of amphetamine because scopolamine disrupts LI via effects at the pre-exposure stage. High doses of scopolamine spare LI under conditions yielding LI in controls, and induce persistent LI under conditions that prevent LI expression. The latter action is exerted in conditioning. Thus, scopolamine mimics both positive and negative/cognitive symptoms by

disrupting normal attentional processing, low doses preventing the development of inattention and high doses producing attentional perseveration.

Antipsychotics. In rodents, ▶ antipsychotics (APDs) are typically investigated for their ability to antagonize the effects of other drugs, but in research concerned with APD effects on LI, their direct influences on LI are also of central importance. Specifically, LI in nontreated rodents is used for indexing antipsychotic activity as well as for discriminating between typical and atypical APDs. The former is achieved under conditions of weak or absent LI in controls. Under these conditions, both typical and atypical APDs produce persistent LI. This effect, produced by a wide range of APDs differing in their in vivo and in vitro pharmacology, is also obtained in humans, and is the most widely used index of antipsychotic action in LI. The LI potentiating action of APDs is exerted at the conditioning stage, and is mediated by D2 blockade. Although APD-induced LI potentiation is very robust, it does not discriminate between typical and atypical APDs. Such discrimination is manifested under conditions that *produce* LI in controls. Whereas typical APDs do not affect LI, atypical APDs can, depending on dose and stage of administration, *disrupt* LI. The LI disruptive action of atypical APDs is exerted in the pre-exposure stage and is due to their $5HT_{2A}$ receptor antagonism. The pre-exposure-based $5HT_2$ antagonistic action competes with the conditioning-based D2 antagonistic action of these drugs. Since $5HT_2$ antagonism predominates at lower doses and D2 antagonism occurs at higher doses, depending on the dose, atypical APDs can potentiate, spare, or disrupt LI. The competition between the D2 and $5HT_2$ antagonism of atypical APDs has critical implications for interpreting the effects of these drugs on LI in animals and humans, as well as the clinical efficacy of these drugs.

In addition, since DA blockade is therapeutic against positive symptoms associated with abnormally increased DA function, but is ineffective for and may worsen negative symptoms associated with reduced DA function, recently it has been suggested that dopaminergic blockade-induced persistent LI, as exemplified by haloperidol-induced LI persistence, can model not only alleviation of positive symptoms but also induction of negative symptoms.

Reversal of Disrupted and Persistent LI

The four schizophrenia-relevant aberrations of LI, i.e., those induced by amphetamine, NMDA antagonists, and low and high-dose scopolamine, have been tested with typical and atypical antipsychotics to assess the predictive validity of these models for the identification of clinical treatments for schizophrenia. In recent years, new therapeutic strategies for schizophrenia, considered/hoped to improve negative symptoms and cognitive dysfunction, have emerged. These strategies include enhancement of NMDA transmission via the glycineB modulatory site on the NMDAR, either directly by agonists such as ▶ glycine transporter and D-serine, or indirectly by inhibiting the ▶ glycine transporter (GlyT1), and enhancement of cholinergic transmission using ▶ acetylcholinesterase inhibitors such as physostigmine, ▶ muscarinic agonists such as xanomeline, and alpha-7 nicotinic receptor agonists. Table 1 summarizes the distinct responses of five LI models (including haloperidol-induced persistence) to typical and atypical APDs, NMDA function enhancers, and cholinergic function enhancers.

Amphetamine- and low scopolamine-induced disrupted LI, although reflecting distinct psychological processes, are reversed by both typical and atypical APDs as well as by glycinergic enhancers. Scopolamine- but not

Latent Inhibition. Table 1. Summary of representative antipsychotic and other putative treatments tested against models of disrupted and persistent LI.

Drug \ Model	Disrupted LI		Persistent LI		
	Low amph	Low scop	Low MK801	High scop	Haloperidol
Haloperidol	+	+	–	–	
Clozapine	+	+	+	–	+
Glycine	+[a]	+	+	+	–
Physostigmine	–	+	+	+	–
α7 nicotinic agonist	+	?	+	?	?

+ effective; – ineffective; ? unknown; [COND] acts via conditioning stage; [PREEX] acts via pre-exposure stage

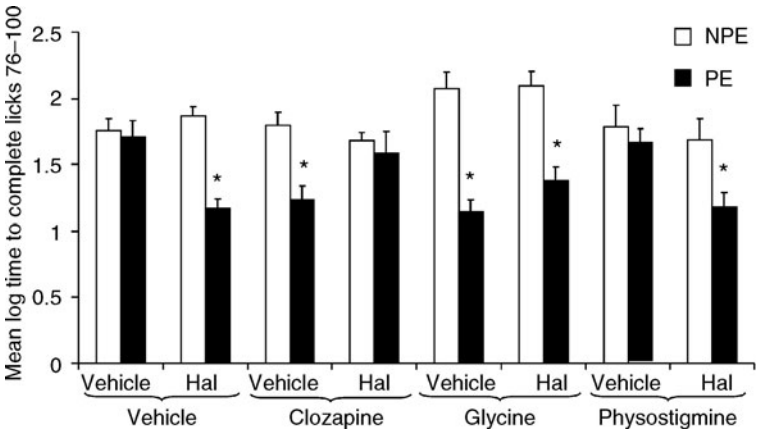
[a]The active compound is Glyt1 inhibitor SSR103800

amphetamine-induced LI disruption is reversed by ► physostigmine. *MK801-induced persistent LI* is reversed by atypical APDs (e.g., ► clozapine and ► risperidone) but not by typical APDs, as found with other NMDA antagonist-induced behavioral deficits, and in line with the differential efficacy of typical and atypical APDs in the clinic. MK801-induced persistent LI is also reversed by a wide range of compounds that potentiate NMDA transmission including glycine, D-serine, D-cycloserine (DCS), and GlyT1 inhibitors GDA, ALX5407, and the novel GlyT1 inhibitors SSR103800 and SSR504734. Importantly, MK801 is the only model that discriminates between atypical APDs and glycinergic compounds as the former reverse this abnormality via effects at pre-exposure and the latter via effects in conditioning. Finally, the novel alpha7-nAChR ► partial agonist SSR 180711 (4-bromophenyl-1,4-diazabicyclo(3.2.2)nonane-4-carboxylate-hydrochloride) is also effective in this model. *Scopolamine-induced persistent LI* is reversed by physostigmine and xanomeline, as well as glycinergic enhancers, but is resistant to both ► haloperidol and clozapine. While the inefficacy of haloperidol is expected based on its ineffectiveness in models of negative/cognitive symptoms including MK801-induced persistent LI, the inefficacy of clozapine is unexpected and sets this abnormality apart from MK801-induced as well as all other known instances of drug-induced LI persistence. *Haloperidol-induced persistent LI* is reversed by atypical APDs clozapine and risperidone but is resistant to glycine and physostigmine (Fig. 4). In addition, haloperidol-induced persistent LI is the only persistent LI that is alleviated by amphetamine, like negative symptoms in the clinic.

Using Pharmacology of Disrupted and Persistent LI to Model Domains of Pathology in Schizophrenia

Disrupted and persistent LI can be seen as two poles of dysfunctional attentional control, namely, a failure to inhibit attention to irrelevant stimuli and a failure to re-deploy attention when previously irrelevant stimuli become relevant. The former would likely give rise to the aberrantly increased salience perception and distractibility that are associated with psychotic symptoms, whereas the latter would result in the cognitive inflexibility and impaired attentional shifting that are associated with negative/cognitive symptoms. Indeed, both disrupted and excessively strong LI are found in schizophrenia patients, the former associated with acute psychosis and the latter associated with predominance of negative symptoms.

Based on their distinct pharmacological profiles, LI abnormalities produced by amphetamine, haloperidol, NMDA antagonists, and scopolamine have been suggested to represent four domains of pathology in schizophrenia (Table 2). *Amphetamine- and scopolamine-induced disrupted LI* represents the domain of positive symptoms, the only domain responsive to both typical and atypical APDs. Notably, disrupted LI is responsive to APDs irrespective of the mechanisms underlying the disruption. *NMDA antagonist-induced persistent LI* represents a (hypoglutamatergia-driven) domain of negative/cognitive



Latent Inhibition. Fig. 4. Effects of clozapine, glycine, or physostigmine on haloperidol-induced persistent LI. Mean times (logarithmically transformed) to complete 25 licks in the presence of the tone of PE and NPE rats treated with vehicle or haloperidol (hal) and pre-treated with clozapine (5 mg/kg), glycine (800 mg/kg), or physostigmine (0.15 mg/kg). No LI was evident in the vehicle control but there was LI in rats treated with haloperidol. Haloperidol-induced persistent LI was antagonized only by clozapine. Clozapine and glycine but not physostigmine led to LI persistence in vehicle-treated rats.

Latent Inhibition. Table 2. Five pharmacological LI models proposed to model five domains of pathology of schizophrenia.

Model / Pharmacological response	Disrupted LI		Persistent LI		
	Amphetamine	Scopolamine	Scopolamine	MK801	Haloperidol
Reversed by	Typical and atypical APDs and some cognitive enhancers	Typical and atypical APDs; cognitive enhancers	Cognitive enhancers	Atypical APDs; cognitive enhancers	Atypical APDs
Resistant to	Some cognitive enhancers		Typical and atypical APDs	Typical APDs	Cognitive enhancers
Symptom domain	**Positive**		**Cognitive**	**Negative/ Cognitive**	**Negative**

symptoms that respond to atypical APDs and cognitive enhancers but not to typical APDs. *Scopolamine-induced persistent LI* represents a domain of cognitive impairments that are resistant to APDs. This model may have utility in identifying effective treatments for APD-resistant cognitive impairments in schizophrenia. However, given its insensitivity to APDs, the model is likely to represent a class of behavioral inflexibility that is common to a variety of neuropsychiatric disorders, including Parkinson's disease (PD), and obsessive compulsive disorder (OCD). Indeed, both PD and OCD patients display abnormally enhanced LI. Finally, *haloperidol-induced persistent LI* represents a domain of (hypodopaminergia-driven) negative symptoms that are treatable by atypical antipsychotics but are resistant to cognitive enhancers. This abnormality may represent a class of cognitive/behavioral inflexibility that is selective to schizophrenia. The domain-specific LI model fits the future directions of drug development for treatment of schizophrenia, which will use polypharmacy strategies, with independent therapeutic agents for each domain of pathology.

Cross-References

- ▶ Acetylcholinesterase Inhibitors as Cognitive Enhancers
- ▶ Antipsychotic Drugs (APDs)
- ▶ Attention
- ▶ Cognitive Enhancers
- ▶ Excitatory Amino Acids (NMDA)
- ▶ Muscarinic Agonists and Antagonists
- ▶ Nicotinic Agonists and Antagonists
- ▶ Psychomotor Stimulants (Amphetamine)
- ▶ Schizophrenia
- ▶ Schizophrenia: Animal Models

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Latin Square Design

Definition

A systematic way of controlling the order of administration of treatments within a test session and of balancing treatments between repeated test sessions. The design enables the uncontrollable effects of unexpected events to be distributed evenly between the treatment conditions.

Lawful

► Legal Aspects of Psychopharmacology

Laxatives

Definition

Drugs taken to induce bowel movements or to loosen the stool, most often taken to treat constipation.

L-Deprenyl

► Antidepressants
► Selegiline

L-Dopa

Definition

Levo-di-ortho-phenylalanine.

Cross-References

► Anti-Parkinson Drugs
► Levodopa

Leaden Paralysis

Definition

A feature of atypical depression, leaden paralysis refers to severe fatigue creating a sensation of extreme heaviness of the arms or legs.

Learned Helplessness

Definition

First described by Seligman and colleagues in the 1970s, learned helplessness describes the impairment of learning that follows exposure to uncontrollable stress. The term "learned helplessness" implies that animals learn that they are helpless to control their environment. A variety of simpler explanations have also been proposed, and most "learned helplessness" experiments are not conducted in a manner that allows a clear interpretation.

Cross-References

► Animal Models of Psychiatric States

Learning

Definition

In its broadest sense: the fact or process of change that occurs in the relationship between a stimulus and a response as a result of experience. Also referred to as acquisition. The "black box" that relates the stimulus to the response usually refers to a whole organism but may also refer to part thereof or to an isolated biological system. Learning concerns cognitive, but also sensory, motor, emotional, and mood-related life events or items.

Learning & Memory: Molecular Mechanisms

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Definition

Alterations in gene expression have been proposed to underlie key aspects of learning and memory in diverse systems. The mechanisms by which behavioral experience, via alterations in synaptic transmission, induce changes in gene expression in specific brain regions are reviewed. Such mechanisms include alterations at the level of chromatin structure, which might be expected to mediate particularly long-lasting adaptations. There are many examples of psychotropic drugs that regulate learning and memory via their effects on gene expression.

Impact of Psychoactive Drugs

The ability of an organism to learn and remember, sometimes for extended periods of time, indicates that environmental experience can induce long-lasting changes in the brain. The nature of these changes, at the molecular and cellular levels, has accordingly been intensively studied for several decades. This work has provided an impressive appreciation of the types of adaptations that

occur in the brain in association with many types of learning and memory. It also has been possible to directly demonstrate the importance of a given molecular or cellular mechanism in mediating a particular aspect of learning and memory. However, despite these important gains, we still know relatively little about how these molecular and cellular adaptations actually summate to create a behavioral memory or enable its long-term storage and retrieval. This latter level of understanding, which represents perhaps the greatest remaining challenge in the neurosciences, requires a neural circuit level of analysis that is not yet available.

This chapter provides a brief overview of the types of molecular and cellular adaptations in the brain that have been implicated in learning and memory, and focuses on changes achieved at the level of ▶ gene expression, or gene transcription, which have been thought for over a decade to provide the long-lasting mechanisms underlying stable behavioral change.

From Synapse to Nucleus

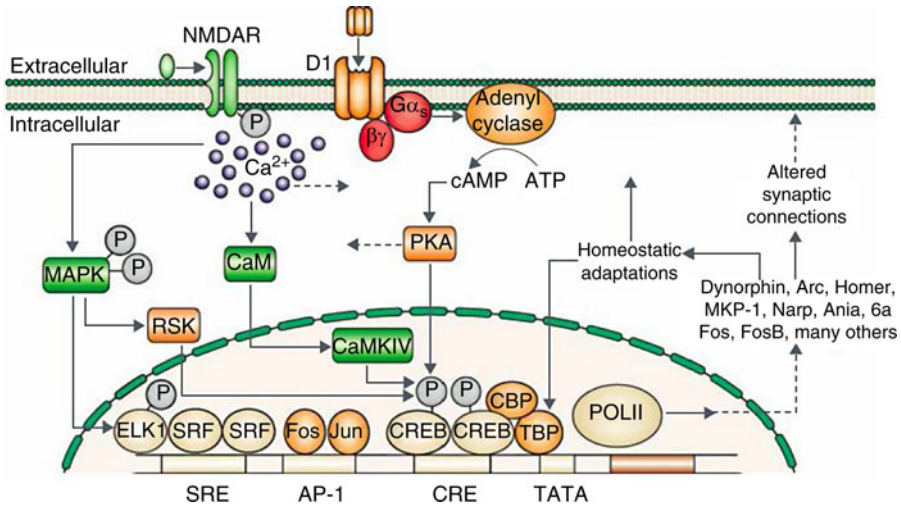
Synaptic transmission is best understood as the effects that a neurotransmitter, released by one nerve cell, exerts on a second nerve cell by virtue of its binding to a specific receptor. The activation of a receptor by its neurotransmitter triggers chemical changes inside the second nerve cell that alter its electrical activity. This occurs on the time scale of milliseconds to seconds. Operating on a much slower time scale, on the order of minutes to hours, are more complex chemical changes triggered by that very same neurotransmitter–receptor interaction. Thus, in addition to regulating ion channels, such interactions initiate cascades of chemical changes that eventually signal to the nerve cell's nucleus, where changes in gene expression – alterations in the amounts and types of proteins expressed by that cell – are induced. For example, synaptic transmission can alter the levels of ion channels or receptors expressed by a nerve cell. Consequently, at some later time point, when the first nerve cell again releases neurotransmitter onto that second nerve cell, the second nerve cell shows an altered response due to these changes in gene expression. This represents a unit of "molecular memory." Somehow, by summating these changes across the trillions of synapses in the brain, and integrating them over time, an organism learns and remembers and thereby adapts and responds to its environment.

We now know a great deal about the mechanisms by which synaptic transmission alters gene expression. The most important mechanism involves the activation of a class of proteins termed transcription factors (TFs), which bind to regulatory regions (called promoters) of specific genes and thereby increase or decrease the rate by which those genes are expressed. Hundreds of TFs are known, which exhibit three general mechanisms for their activation by synaptic transmission. Some TFs, expressed in nerve cells under basal conditions, are activated by cascades of ▶ second messenger and protein phosphorylation pathways that are stimulated (or inhibited) when neurotransmitters bind to their receptors. A prototypical example is CREB (cAMP response element binding protein), which can be phosphorylated and activated by a wide range of second messenger cascades illustrated in Fig. 1. For example, in striatum, ▶ dopamine (via activation of the cAMP pathway) and ▶ glutamate (via activation of Ca^{2+} pathways) activate several different protein kinases, each of which phosphorylates CREB on the same serine residue, resulting in the activation of its transcriptional properties. The TFs Elk1 and SRF (serum response factor) are regulated via similar mechanisms (Fig. 1). A related mechanism exists for another TF, termed NFκB (nuclear factor κB). At baseline, NFκB is bound to an inhibitor protein, IκB (inhibitor of κB), which sequesters NFκB in the cytoplasm. Upon activation of certain second messenger cascades, IκB is phosphorylated, leading to its degradation and the freeing up of NFκB to enter the nucleus where it exerts its transcriptional effects.

Other TFs are expressed at very low levels under normal conditions but are induced in nerve cells in response to neurotransmitter–receptor interactions. Examples include Fos (e.g., c-Fos, FosB) and Egr (early growth response) families of TFs. These TFs are induced because their promoter regions contain target sites for preexisting TFs such as CREB and SRF (see Fig. 1).

The third paradigm of TF activation operates for the steroid hormone receptor family of proteins, which are activated upon binding their respective hormone (e.g., glucocorticoids, gonadal steroids, etc.) and can therefore be viewed as ligand-activated TFs. Under basal conditions, steroid hormone receptors are bound by chaperone proteins which keep them in the cytoplasm. Steroid hormones, which readily permeate cell membranes, bind to the receptors and trigger their release from the chaperones and their movement to the nucleus. Once in the nucleus, the steroid receptors bind directly to responsive genes or bind to and inhibit other TFs (e.g., CREB, c-Fos).

An important principle of TF action is that most bind to DNA as dimers. Some bind as homodimers (e.g., CREB), whereas others must complex with distinct families of TFs: Elk1 dimerizes with SRF, Fos family proteins dimerize with Jun family proteins (to form an



Learning & Memory: Molecular Mechanisms. Fig. 1. Regulation of CREB activity in striatum. Stimulation of D1 dopamine receptors and glutamate receptors on striatal neurons activates several second messenger cascades. Not shown is the ability of several growth factor-associated receptors to stimulate some of the same cascades, for example, MAPK. Depicted in the cell nucleus is a model of binding sites from the *cFos* promoter including a serum response element (SRE), activator protein-1 element (AP-1), and a cyclic AMP (cAMP) response element (CRE). CBP, CREB binding protein; CREB, cAMP response element binding protein; MAPK, MAP kinase; NMDAR, NMDA receptor; PKA, protein kinase A; TBP, TATA binding protein. (From McClung CA, Nestler EJ (2008) Neuroplasticity mediated by altered gene expression. Neuropsychopharmacology 33:3–17.)

AP1 (activator protein 1) complex), and so on. Together, this results in an incredibly complex array of transcriptional regulation during the normal process of synaptic transmission.

Implicating TFs in Learning and Memory

An important role for all of the aforementioned TFs, and many others, in diverse types of learning and memory has been established over the past decade. Investigators have demonstrated the activation of specific TFs in a given brain region in response to an environmental challenge in tight temporal correlation with a form of behavioral plasticity. Examples include the phosphorylation and activation of CREB, and the induction of c-Fos and Egr, in hippocampus and amygdala in parallel to aversive learning, in some cases in parallel to a specific facet of aversive learning such as acquisition, consolidation, or extinction, among others. Likewise, exposure to a drug of abuse activates each of these TFs in drug-responsive regions (e.g., striatum, ► amygdala, ► prefrontal cortex) and such activation has been correlated with different aspects of drug-induced plasticity, such as locomotor sensitization, reward tolerance, or sensitization, etc. An interesting variation in this theme is the induction of ΔFosB, a truncated splice variant of the *fosB* gene, uniquely by chronic drug exposure. ΔFosB, normally present at very low levels in nerve cells, is induced to a small extent via CREB and SRF, but unlike all other Fos family members (which are highly unstable and therefore degrade to low basal levels shortly after the stimulus), ΔFosB is highly stable which enables it to accumulate to high levels in response to chronic stimuli. In this way, ΔFosB could mediate some of the longer-lasting effects of drug exposure on behavior.

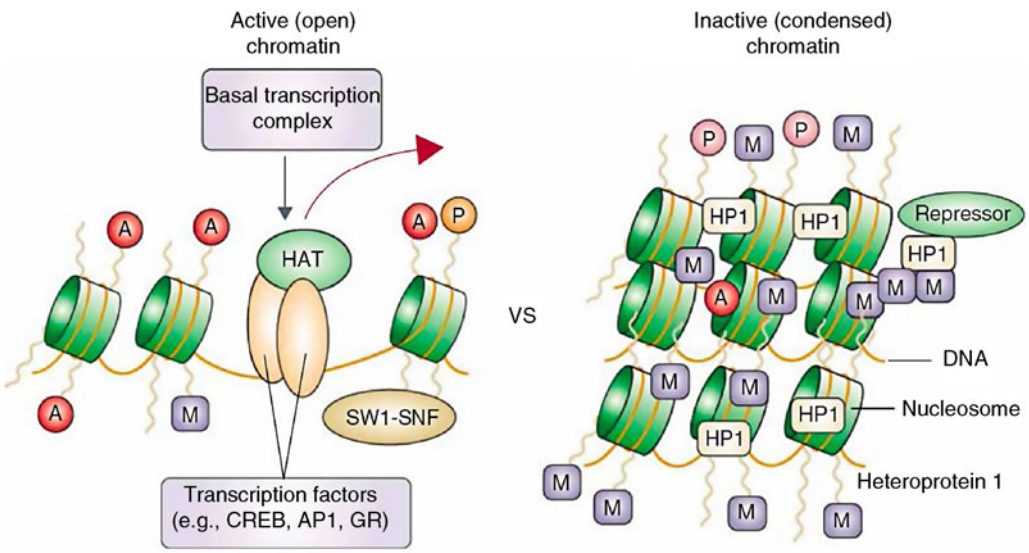
The second key step in implicating a TF in learning and memory is to manipulate that TF and demonstrate an effect on behavior. This causal information came initially from gene knockout studies, where deletion of CREB or another TF of interest was shown to obliterate an aspect of learning and memory. However, the interpretability of these early experiments was limited by the fact that the TF was knocked out from all brain regions (indeed all tissues) from the earliest stages of development, making it difficult to conclude that the TF was required in a given brain region of an adult. Such limitations have been overcome in recent years with the advent of an awesome array of powerful genetic tools, where a TF of interest – or an inhibitor (sometimes referred to as a dominant negative antagonist) – can be overexpressed in a given brain region of an adult animal or can be knocked out

selectively from that region of an adult animal. Such methods have greatly strengthened the level of proof for a TF's role in learning in memory. Overexpression of CREB specifically in ▶ hippocampus or amygdala promotes aversive learning, while overexpression of a CREB antagonist has the opposite effects. Likewise, CREB overexpression in striatum dampens an animal's sensitivity to the rewarding effects of a ▶ drug of abuse, with a CREB antagonist having the opposite effect. These latter data support the hypothesis that CREB induction by drugs of abuse represents a homeostatic mechanism mediating ▶ tolerance and ▶ dependence. Conversely, ΔFosB overexpression in striatum increases the rewarding effects of a drug of abuse, while its antagonist reduces drug reward, supporting the notion that ΔFosB induction represents a mechanism of sensitization.

From TF to Chromatin

In recent years, our level of analyzing transcriptional mechanisms in the brain has been extended to ▶ chromatin structure, where the covalent modification (e.g., acetylation or methylation) of ▶ histone proteins, around which DNA is wound in the cell nucleus, and methylation of the DNA itself, have profound effects on the ability of genes to be expressed. ▶ Chromatin exists in a continuum from a permanently inhibited (closed) state to a constitutively active (open) state (Fig. 2). Genes in closed chromatin are not expressed because they are not accessible to the cell's transcriptional machinery, whereas other genes exist in permissive chromatin where the genes are accessible to transcriptional machinery. This explains, for example, why CREB cannot induce neural gene targets in peripheral tissues where the genes exist in silenced chromatin, but can in nerve cells where the genes exist in permissive chromatin. TFs induce genes in permissive chromatin by recruiting to those genes many types of co-activator proteins. TFs recruit ▶ histone acetyltransferases, enzymes that acetylate histones; such acetylation further opens the chromatin. TFs also recruit so-called SWI-SNF factors, proteins that provide the molecular motor for histones to move across a strand of DNA as it is being actively transcribed.

This knowledge of chromatin biology has now begun to inform our understanding of gene expression regulation in the brain and, in particular, its role in learning and memory. First, changes in histone acetylation and DNA



Learning & Memory: Molecular Mechanisms. Fig. 2. Differential states of chromatin. Chromatin exists in a continuum of states from being open (i.e., active, allowing gene expression) to condensed (i.e., inactive, repressing gene expression). Changes across this continuum are mediated in part by modifications to core histone proteins. Histone acetylation (A) is associated with chromatin relaxation and the binding of TFs and coactivators, such as HATs (histone acetyl transferases) and SWI-SNF proteins that mediate the movement of histone complexes along a strand of DNA. Histone methylation (M) results in condensed chromatin and transcriptional repression (REP). Methylation of the DNA itself also results in condensed, repressed chromatin. (From McClung CA, Nestler EJ (2008) Neuroplasticity mediated by altered gene expression. Neuropsychopharmacology 33:3–17.)

methylation have been shown to occur in hippocampus in parallel to aversive learning. These findings are striking because they emphasize the degree to which fundamental mechanisms of gene regulation are affected during the course of normal synaptic transmission – on a time scale of hours. Similar changes in chromatin have been demonstrated in striatum in response to drugs of abuse. Second, it has been possible to directly implicate mechanisms of chromatin regulation in aversive learning and drug addiction by demonstrating that direct manipulations of histone or DNA modifications has profound effects on behavior. Inhibitors of ► histone deacetylases (enzymes that remove acetyl groups from histones and thereby inhibit gene expression) or of DNA methyltransferases (enzymes that add methyl groups to DNA and thereby inhibit gene expression) promote hippocampal-dependent memory as well as the rewarding effects of drugs of abuse. In contrast, overexpression of these inhibitory enzymes in specific brain regions exerts the opposite effects.

The Future

One of the major challenges of current research is to identify the target genes through which a given TF exerts its particular effects on behavioral plasticity. Small numbers of target genes have been identified for all of the TFs mentioned above; however, some TFs may regulate hundreds of targets. This has been demonstrated by use of gene expression arrays (which measure levels of all mRNAs in a tissue) and ChIP (chromatin immunprecipitation)-chip or ChIP-Seq (sequence) methods (which measure levels of chromatin modifications across the entire genome). Understanding how the coordinated regulation of such large numbers of genes summate to produce the net functional effects of a TF, and how the effects of multiple TFs are summated, remains a great technical challenge.

Ultimately, it is essential to define the many ways in which brain function is altered by transcriptional and chromatin regulation to mediate the behavioral plasticity associated with learning and memory. In addition to altering levels of ion channels and neurotransmitter receptors, and many related second messenger proteins, as stated at the outset, there is increasing evidence that environmental experience produces more profound changes in nerve cells, including alterations in their overall size and shape, and the extent of their dendritic arborizations and synaptic inputs. Work is beginning to define the changes in gene expression, and the specific TFs and chromatin modifying enzymes that underlie this long-lasting reordering of nerve cells. As we build this increasingly complete view of molecular and cellular changes that occur in concert with behavioral plasticity, it is essential to then understand at a circuit level how such changes mediate behavioral memory.

Cross-References

► Addictive Disorder: Animal Models
► Chromatin Remodeling
► Gene Expression and Transcription
► Reference Memory and Consolidation
► Spatial Learning in Animals
► Synaptic Plasticity

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Learning Set

Definition

Learning set (and the closely related concept, task set), is when a learned rule is generalized so that there is facilitation of learning a new discrimination or task when a previously learned rule or principle applies to the new situation (see Harlow, 1949). There is a corresponding impairment of new learning when a previously learned rule or principal does not apply, as exemplified by the "Einstellung effect" (Luchins, 1942).

Legal Aspects of Psychopharmacology

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Synonyms

Allowable; Constitutional; Lawful; Legitimate (aspects of psychopharmacology)

Definition

"Legal" as a topic means falling within the province of the law and its study. It also has the more specific connotation of such as is required by the law and not falling outside what is permitted.

Current Concepts and State of Knowledge

Introduction

Human societies are governed by social rules that moderate our basic biological instincts. Moreover, such social rules reflect moral and ethical principles (Harris 2002). These social institutions and conventions are governed by the rules of law. These can be complex with codes of law extending to numerous densely written tomes. In a complex society, it is almost impossible to find any human activity that is not touched on in some way by the law. Psychopharmacology, a branch of science that involves the activities of the most complex human organ – the brain – is particularly affected by rules, regulations, and the panoply of the law. Both criminal and civil laws contain swathes of material directly relevant to psychopharmacology. Rules of law may forbid certain activities or specify certain conditions that must be carried out. Rules are normative – what ought to happen, rather than factual – what actually does happen. They lay down rules of behaviour to which we are expected to conform. If we do not, the law can apply sanctions, from a fine, or restriction of liberty, right through to the death penalty, still imposed in a minority of countries.

Durkheim (1964) regarded society as ranging from a relatively simple, technologically undeveloped society to an advanced, mobile, sophisticated social structure. The purpose of laws was to maintain social cohesion by striving for balance between competing ideas and interests. If a group perceives a law as failing to recognize a strongly held belief, they may adopt extralegal measures, for example, some animal rights activists.

Legislation of Morality

This raises the question of the relationship between the law and morality. A society's code of morality is the set of beliefs, values, principles, and standards of behaviour adhered to by most members of the society. In a homogeneous society, the set of morals tends to be fairly consensual. In a multicultural society, moral values may differ greatly. To accommodate these disparate views, the law which formalizes such moral principles may have to introduce special cases, exemptions, and exceptions. Even so, some members of the society may feel unable to abide by the law, for example, human embryo research may clash with imperatives from established religions.

One cardinal example in psychopharmacology concerns the complex laws relating to the use of the oldest of psychotropic substances, ▶ alcohol. Laws outlawing alcohol in the USA ("Prohibition") were in response to pressures from those in society who took the moral high ground. These groups were organised into religious and temperance organisations that emphasised both the moral shortcomings of heavy drinking and its medical and social toll. The moral disadvantages and legal injustice of penalising moderate and occasional social drinkers were submerged under the waves of moral temperance rectitude. The Prohibition Laws failed because they were too draconian and large numbers of US citizens flouted them. But, in many countries, achieving a just balance in the licensing of alcohol still remains a distant objective, viz. ▶ binge drinking in the United Kingdom.

Legal Instruments

It is an impossible task to even outline different forms of jurisdiction. Most European countries rely on systems of law based on the Roman model and codified by Napoleon. The United States and England (but not Scotland) use a common law system, in which judges interpret and modify legislation. Some countries maintain tight central control; others devolve to the periphery. Some have both, such as Federal and State laws in the United States, the relationship between which is being constantly adjusted. In some countries, religious law such as sharia is paramount; in others it exists in parallel and may be resorted to by the religious groups. In the European community, national laws have yielded precedence to EC laws, regulations, and directives. International courts such as those in The Hague have become increasingly recognised.

Research

Legal systems, under pressure from animal rights activists, have long introduced measures to regulate the treatment of animals. As these activists vary in their attitudes from

country to country, so do the regulations. Many countries have a set of rules rather than guidelines. In some, registration of laboratories, projects, and individual experimenters is required. Particular stringency is often applied to studies on primates. Research on Great Apes may be prohibited altogether, as may that on species deemed at risk of extinction even if they are not primates (► ethical issues in animal psychopharmacology).

In the human sphere, a series of declarations followed the abhorrent practices of the Nazis. The Declaration of Helsinki (1964) states that, "It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject." Ethical committees were set up, first in the USA, and then in other countries, to regulate human research, first voluntarily but increasingly under statute (► ethical issues in human psychopharmacology). On basis of a detailed protocol, a properly constituted ethical committee containing both professional and lay members should consider the proposal, modify it if necessary, and ensure that it is adhered to. Such committees have a special (fiduciary) duty to act properly and responsibly. Any researcher failing to submit an appropriate protocol would, depending on the jurisdiction, find himself subject to the criminal code for inflicting bodily harm, or to redress under the civil code for causing a personal injury ("tort"), or expulsion from the relevant professional body. With psychotropic drugs, psychological harm could be the basis for a court action (Carson and Bull 2003).

► Informed consent is typically a sine qua non for the recruitment of experimental subjects. This entails that each potential participant be adequately informed of the purpose of the study, its methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the expected risks and potential benefits of the study, and the anticipated discomfort. The presence of a neutral witness is a useful safeguard. The volunteer should be informed of the right to withdraw from the study at any time without explanation. The investigator must be sure that the potential subject has understood the information and has been encouraged to ask questions. Consent should be in writing wherever possible. Special rules generally pertain to subjects who suffer from a severe psychiatric disorder, or lack mental capacity to give informed consent, and to children. Recently, the question of genetic privacy has been raising concern.

Two European Directives, Clinical Trials Directive (2001) and Good Clinical Practice (2005) initiated change in medical research procedures across Europe to varying extents (Brazier and Cave 2007). A Directive sets out the broad goals of the legislation but allows each EU country to determine the form and precise content of that legislation (► randomized clinical trials).

Therapeutics

It is a truism that every administration of a therapeutic substance is essentially an experiment. If that usage in a patient is grossly negligent, criminal proceedings may follow. If it falls short of that, then the injured party generally has to show that the drug administration was below acceptable clinical standards, that it caused an injury that can be quantified, at least in financial terms. Standard rates are applied to gross physical injuries such as an amputation, but psychological or psychiatric damage is difficult to quantify. Often the functional impairments are evaluated, as well as symptomatic complaints.

Psychotropic drugs have some special aspects. First, on occasion a treatment may be administered compulsorily and stringent safeguards are essential. Second, some medications have a low therapeutic index and must be monitored according to the specified protocols (e.g., ► lithium salts, ► clozapine).

No consensus exists between various jurisdictions with respect to topics such as ► withdrawal syndromes, ► neuroleptic malignant syndrome, and ► tardive dyskinesia. Currently, much concern is being expressed with regard to suicidal phenomena with ► SSRIs, especially in adolescents where evidence for efficacy is often exiguous.

In most jurisdictions, the development of an ► adverse effect, ipso facto, does not constitute grounds for action as long as the drug was administered in accord with accepted clinical standards. These can change over time, and regulatory bodies may suggest different practices. Prescribers must be aware of the latest developments and even trends.

Regulatory Affairs

How medicines are developed and licensed is dealt with elsewhere ("► Licensing and Regulation of Drugs"). Randomised Clinical Trials raise particular concerns.

Consumer Protection

Various jurisdictions (including the EU) have brought in legislation to protect consumers from defective products – those that are unfit for purpose, or those that are not of a quality that a reasonable consumer has a right to expect. Medicinal products are usually subject to such control. A group of consumers who believe that a product is defective and that they have suffered from using the product may bring an action and may subsequently recover damages. The manufacturer's usual defence is to try and prove that

the produce is not defective or that scientific knowledge at the relevant time was not sufficient for a reasonable manufacturer to detect the defect.

Misuse of Drugs

One area where psychopharmacology is closely involved with the law is in the area of drug misuse. This can relate to drugs which have no recognised therapeutic properties, such as ▶ LSD, and therefore whose use can only be a misuse, or to products that have a licit indication, such as ▶ morphine, but can be misused (Glaser and Warren 1999). A controversy attends the use of ▶ cannabis products, where some products have been licensed in some countries to establish a legitimate therapeutic usage in pain and nausea.

Jurisdictions differ widely in both the form and content of the illicit drug "scheduling" legislation. The classification of drugs of dependence is usually into several categories, and maximum penalties for use, possession, and supply vary according to the category. For example, sanctions, often swingeing, are imposed with respect to heroin and ▶ cocaine; at the other end of the spectrum, penalties are minimal with ▶ benzodiazepines, which may not even be scheduled in some countries. Cannabis is controversial and debates continue as to where it should be classified. Chemical precursors and intermediates can be scheduled.

The penalties cover a range of unlawful activities – producing a Controlled/Scheduled Drug, supplying or offering to supply one to another person, possessing a Controlled/Scheduled Drug, and in some countries, cultivating any plant of the opium or cannabis type. Exemption is available for legitimate purposes, for example, the manufacturers of morphine, the pharmacists who store and supply it, and the medical, dental, and veterinary practitioners who prescribe and administer it. Special dispensations for research purposes can be applied for but are often notoriously difficult to facilitate. Most jurisdictions lay down strict rules for safe custody.

The misuse of Controlled Drugs is further regulated in various ways. In professional circles, the prescription of a Controlled Drug usually has to follow a strictly applied proforma, and careful records are mandatory. Addicts may have to be reported to a government department or agency. Some Controlled Drugs such as heroin can only be prescribed by specially recognised doctors. Irresponsible prescribing is penalised.

Various crimes are established under legislation and involve the criminal law system, police, judges, the prison system, and customs and excise departments. Much of this is governed by the Single Convention on Narcotic Drugs signed in New York on March 30, 1961 and by the 1971 convention covering drugs more widely. Searches of individuals, possessions, and premises can usually be authorised.

Sales Outlets

Jurisdictions generally reorganise various ways in which medicinal products can be provided (Appelbe and Wingfield 2005). The most restricted is a Prescription-Only Medicine, prescribed by a recognised medical, dental, or veterinary practitioner. The least restricted is a General Sale Medicine which can be sold in shops and supermarkets. Some countries have an intermediate category of drugs which are available without prescription under the supervision of a pharmacist.

Many remedies are "alternative"; the most widely used being herbal and homeopathic "medicines." Countries vary enormously with respect to whether or how these are regulated. Finally, concoctions that are used as folk remedies are rarely encountered in legal systems unless poisonous effects are produced. Alternative medicines may also raise problems with toxic constituents (▶ herbal remedies).

Alcohol is also subject to regulation. The Scandinavian countries are typically the most stringent. Some states in the United States are also quite restrictive. The minimum age for purchasing and drinking alcoholic beverages may be 21, and the bottles containing the same cannot be openly displayed.

Cross-References

▶ Ethical Issues in Animal Psychopharmacology
▶ Ethical Issues in Human Psychopharmacology
▶ Herbal Remedies
▶ Randomized Clinical Trials

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Legitimate

▶ Legal Aspects of Psychopharmacology

Lep^{db}/Lep^{db} mouse

► db/db Mouse

Lep^{ob}/Lep^{ob} mouse

► ob/ob Mouse

Leptin

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Synonyms

OB protein

Definition

A hormone produced in and secreted primarily by adipose tissue that regulates appetite, body weight, and neuroendocrine functions.

Pharmacological Properties

History

The hormone leptin was discovered in 1994; its name is derived from the Greek word for thin, *leptos*. Like other hormones, leptin is secreted in a pulsatile manner and shows a diurnal variation with a peak during the night. Lack of leptin signaling due to a mutation of *leptin* (e.g., ► ob/ob mouse) or the leptin receptor (*lepr*) (e.g., ► db/db mouse) in rodents and humans results in increased food intake, reduced energy expenditure, and severe obesity. Leptin replacement reverses many of the phenotypes of leptin-deficient mice. However, it was quickly apparent that an absolute leptin deficiency is an extremely rare cause of human obesity. Plasma leptin levels are elevated, rather than reduced, in the majority of obese subjects and plasma leptin levels are highly correlated with total fat mass. Thus, resistance to leptin action appears to be a more likely cause of human obesity.

Leptin also plays a role in the regulation of neuroendocrine function. Mutations in the leptin gene are associated with not only obesity but also neuroendocrine impairments, including impaired reproduction and low ► sex hormones, low thyroid hormone, low growth hormone, and elevated glucocorticoids. In 1996, it was first proposed that the physiological role of leptin is the regulation of the neuroendocrine system during starvation. Fasting reduces leptin gene expression and plasma leptin levels. Leptin treatment to prevent fasting-induced fall in endogenous leptin, blunts the fasting-induced changes in the neuroendocrine system. Thus, circulating leptin serves to communicate the state of body energy stores to the central nervous system (CNS) in order to maintain normal metabolic and neuroendocrine functions. A tremendous amount of research has since then focused on the role of leptin in the regulation of metabolism and neuroendocrine function as well as CNS signaling pathways that mediate leptin action.

Mechanisms of Action

Substantial evidence shows that the leptin pathway plays a significant role in body weight regulation by communicating the status of the energy stores to the brain. Leptin has been implicated in activating a variety of intracellular signaling cascade primarily through the long-form leptin receptor, LepRb.

Leptin Receptors (LepR or ObR)

The LepR contains a single transmembrane domain and is structurally similar to the class 1 ► cytokine receptor family. There are multiple LepR isoforms, all of which are products of a single *lepr* gene containing 17 common exons and several alternatively spliced 3′-exons. In mice, the six distinct LepR isoforms that have been identified are designated LepRa–LepRf. LepR isoforms can be divided into three classes: secreted, short, and long forms. The secreted form (LepRe) contains only extracellular domains that bind circulating leptin, perhaps regulating the concentration of free leptin. Short forms (LepRa, LepRc, LepRd, and LepRf) and the long form LepR (LepRb in mice) have identical extracellular and transmembrane domains as well as the same first 29 intracellular amino acids, but diverge in sequence thereafter due to the alternative splicing of exons. Unlike the other LepR isoforms, the long form LepRb contains a 302-amino acid cytoplasmic domain that includes motifs for binding of intracellular signaling molecules, and therefore LepRb is crucial for leptin action. The *db/db* mice are deficient in LepRb, but not other LepR isoforms, as a consequence of a mutation that causes mis-splicing of the LepRb mRNA. These mice display a ► phenotype that is indistinguishable from that of mice, which are deficient in all LepR isoforms (db^{3J}/db^{3J} mice) and of leptin-deficient *ob/ob* mice. The function of short form

LepRs is less clear, although proposed roles include the transport of leptin across the ► blood-brain barrier (BBB).

CNS Leptin Action

It is currently accepted that a leptin receptor-bearing neurons within the ► hypothalamus are responsible for mediating a concerted response to fluctuations of body energy stores. Before leptin reacts with its target cells in the hypothalamus, leptin must first cross the BBB. This step is facilitated by a transporter that is an alternatively spliced product (LepRe) of the leptin receptor gene present in brain endothelial cells. Long form leptin receptors, LepRb, are expressed in the CNS and leptin injection induces neuronal activation as evidenced by c-Fos induction. Substantial evidence suggests that the brain mediates the majority of leptin's action on energy homeostasis. Intracerebroventricular injection of leptin decreases food intake and body weight. Mice with a specific deletion of LepRb in the brain are obese, but the deletion of peripheral leptin receptors does not change the normal phenotype of the animal. Expression of LepRb in neurons of LepRb-deficient mice leads to an amelioration of their obesity.

Among the various brain areas that express LepRb, the basomedial hypothalamus is implicated as playing an especially important role. There are two primary populations of neurons that express LepRb and exert potent, opposing effects on food intake and body weight in the arcuate nucleus (ARC) of the ► hypothalamus. Leptin stimulates the production of proopiomelanocortin (POMC) and its derived products including ► α-melanocyte stimulating hormone (α-MSH), which act on melanocortin 4 receptor (MC4R). Leptin also stimulates the production of cocaine amphetamine-regulated transcript (CART). Both α-MSH and CART inhibit feeding as ► appetite suppressants. In another type of ARC neuron, leptin inhibits the production of ► agouti-related peptide (AGRP), an endogenous antagonist that acts on MC4R, and ► neuropeptide Y (NPY). AGRP and NPY are potent stimulators of feeding as ► appetite stimulants. Thus, leptin decreases food intake and increases energy expenditure by simultaneously stimulating the production of α-MSH and CART and inhibiting the production of NPY and AGRP in the ARC. These ► neuropeptides are transmitted to and interact with receptors in neurons of the paraventricular nucleus (PVN) of the ► hypothalamus. These PVN neurons, in turn, generate outputs that coordinate feeding behavior and energy expenditure and send these outputs to the hindbrain. Expression of LepRb is sufficient to reduce food intake and body weight gain when directed to the ARC, but not other hypothalamic regions of leptin receptor-deficient animals. Consistently, deletion of LepR only in POMC neurons leads to a mild obesity and restoration of ARC LepRb signaling attenuates obesity and ► hyperphagia in LepRb-deficient mice. These findings constitute direct evidence that LepRb signaling in the ARC is required for normal energy homeostasis.

Leptin Signaling

The hypothalamus is a major CNS site of leptin's action. It has been proposed that several signaling pathways are involved in mediating the diverse functions ascribed to leptin.

Jak-STAT3

Leptin has been postulated to signal through the Jak kinase family (JAK)-signal transducer and activator of transcription (STAT) signal transduction pathway (Villanueva and Myers 2008). Like other cytokine receptors, LepRb does not contain intrinsic enzymatic activity, but instead signals via a noncovalently associated tyrosine kinase of the JAK family, specifically Jak2. LepRb exists as a preformed homodimer before leptin binding. Leptin binding alters the conformation of the LepRb dimer, enabling transphosphorylation and activation of the intracellular LepRb-associated Jak2 molecules. The activated Jak2 molecule then phosphorylates other tyrosine residues within the LepRb/Jak2 complex to mediate downstream signaling.

Several lines of evidence strongly support a major role of STAT3 in mediating leptin signaling in the hypothalamus. Upon leptin binding, activated Jak2 phosphorylates itself and residues Tyr985, Tyr1077, and Tyr1138 within the intracellular tail of LepRb. Tyr1138 recruits and phosphorylates STAT3 proteins, which then dimerize and translocate to the nucleus and activate a specific program of gene transcription. Leptin activates STAT3 in the hypothalamus, and neuron-specific STAT3 knockout mice develop obesity recapitulating phenotypes of leptin-deficient *ob/ob* and leptin-resistant *db/db* mice. A knockout mouse that leaves the leptin receptor intact but specifically disrupt the LepRb-STAT3 signal are hyperphagic and obese. In these animals, the cytoplasmic tyrosine residue (Tyr1138) in LepRb was replaced with a serine residue, causing a disruption of the LepRb-STAT3 signaling. These findings indicate that the cytoplasmic tyrosine residue (Tyr1138) is necessary for proper LepRb-STAT3 signaling in the hypothalamus after leptin stimulation.

STAT3 mediates the transcription of the suppressor of cytokine signaling 3 (SOCS3) which then binds to Tyr985 of LepRb to inhibit LepRb-STAT3 signaling. Deletion of SOCS3 in the brain results in prolonged leptin-induced STAT3 activation in the hypothalamus and increased leptin sensitivity. More specifically, mice with a mutation

of Tyr985 show reduced food intake and body weight. Hypothalamic STAT3 phosphorylation and anorectic and weight-reducing effect of leptin are also increased in these mice. Thus, Tyr985-dependent attenuation of LepRb signaling represents a leptin-stimulated autoinhibitory signal and SOCS3 functions as a negative regulator of leptin signaling in the hypothalamus.

The mechanisms controlling and terminating the leptin signal transduction also include the dephosphorylation and inactivation of signaling proteins, mediated by protein-tyrosine phosphatase (PTP). PTP1B dephosphorylates activated Jak2 and STAT3. Ablation of PTP1B in *ob/ob* mice attenuates obese phenotype caused by leptin deficiency. PTP1B-deficient mice show an enhanced response toward leptin-mediated weight loss and suppression of feeding. Hypothalami from these mice also display markedly increased leptin-induced STAT3 phosphorylation. Consistent with the inhibition of Jak-STAT signaling, PTP1B overexpression attenuates leptin-induced, STAT-dependent gene activation. Thus, PTP1B is another negative regulator of leptin signaling.

Shp2

Src homology-containing tyrosine phosphatase 2 (Shp2) is a widely expressed cytoplasmic tyrosine phosphatase with two Src homology 2 domains. Phosphorylation of Tyr985 recruits Shp2, which then downregulates Jak2/STAT3 activation by leptin. Thus, it is assumed that the deletion of Shp2 in the CNS enhances leptin-induced Jak2/STAT3 activation and thereby shifts to negative energy balance. However, neuron-specific Shp2 knockout mice develop obesity in the presence of enhanced leptin-induced tyrosine phosphorylation levels of Jak2 and STAT3. Leptin also induces phosphorylation of extracellular signal-regulated kinase (ERK) in the hypothalamus and leptin-induced ERK activation is attenuated in neuron-specific Shp2 knockout mice compared to wild-type mice. However, mice with a mutation of Tyr985 show increased leptin sensitivity, possibly by inhibiting Tyr985-SOCS3-mediated inhibition of LepRb signaling (Villanueva and Myers 2008). Thus, although Shp2 enhances leptin signaling by enhancing ERK signaling, the physiologic role for Shp2 in leptin action remains unclear.

MAPK

ERK, a member of the mitogen-activated protein kinase (MAPK) family, is a key enzyme for many intracellular signaling processes. Leptin induces phosphorylation of ERK1/2 in a receptor-mediated manner that involves Jak2. Leptin-induced ERK1/2 activation was restricted to the ARC POMC neurons. Activation of ERK by leptin is mediated by both Shp2 and direct interaction with Jak2. Pharmacological blockade of hypothalamic ERK1/2 reverses the anorectic and weight-reducing effects of leptin (Rahmouni et al. 2009). Thus, hypothalamic ERK plays a key role in the control of food intake and body weight by leptin.

IRS-PI3K

The phosphatidylinositol-3-kinase (PI3K)/Akt pathway in hypothalamic neurons has been implicated in the regulation of food intake and energy homeostasis. Insulin receptor substrates (IRS) proteins are members of a class of intracellular signaling molecules termed docking proteins that are phosphorylated on multiple tyrosine residues to mediate SH2-protein recruitment and downstream signaling. Although IRS proteins contain tyrosine phosphorylation sites, most of them lie in motifs that bind and activate PI3K.

LepRb signaling is also coupled to the intracellular IRS-PI3K pathway (Villanueva and Myers 2008). IRS-2-deficient mice display increased adiposity and food intake and decreased metabolic rate. Plasma leptin levels are elevated in IRS-2-deficient mice, suggesting that these mice are resistant to the metabolic effect of leptin. Deletion of any of other three IRS proteins does not cause such obese phenotype. Thus, IRS-2 plays a specific role in mediating the effect of leptin on energy homeostasis. Leptin stimulates IRS-2-associated PI3K activity in the hypothalamus, and the pharmacological blockade of hypothalamic PI3K activity blocks the anorectic effect of leptin. Although the cellular mechanisms by which LepRb couples to the regulation of PI3K remain unclear, these findings indicate that PI3K is downstream of leptin signaling. Leptin and insulin act in parallel to stimulate PI3K in POMC neurons, suggesting that the effects of leptin and insulin are integrated by these anorexigenic neurons in the hypothalamus. Thus, IRS-2-PI3K is likely to lie downstream of leptin signaling and participates in mediating the metabolic action of leptin.

AMPK

AMP-activated protein kinase (AMPK) is a heterotrimer consisting of catalytic α-subunits and regulatory β- and γ-subunits. AMPK is regulated by the cellular AMP/ATP ratio and by upstream kinase. AMPK is activated by stress and regulates cellular metabolism by inhibiting energy-consuming pathways and inducing pathways that generate ATP. Once activated, AMPK phosphorylates acetyl-CoA carboxylase (ACC) and switches on energy-producing pathways at the expense of energy depleting processes. Leptin decreases α2AMPK activity in the hypothalamus and decreases food intake by reducing the expression of ► orexigenic AGRP and NPY in the ARC. In contrast to

leptin-induced STAT3 phosphorylation in many hypothalamic regions, leptin-induced decrease in α2AMPK activity is restricted in the PVN and ARC of the hypothalamus (Minokoshi et al. 2004). Thus, AMPK signaling specifically in the PVN and ARC plays a role in mediating anorectic effect of leptin. Insulin-induced inhibition of hypothalamic AMPK activity is blocked by the PI3K inhibitor. Because the effects of leptin and insulin are integrated by hypothalamic neurons via the PI3K/Akt signaling pathway, the leptin-induced inhibition of hypothalamic AMPK activity may be mediated through the PI3K/Akt pathway.

mTORC1

The mammalian target of ▶ rapamycin complex 1 (mTORC1) protein is a serine–threonine kinase that regulates cell-cycle progression and growth by sensing changes in energy status. A number of hormones and cytokines mediate their cellular effects through the mTORC1 signaling pathway. Leptin treatment increases the phosphorylation of both S6 kinase 1 (S6K1) and S6 ribosomal protein (S6), downstream targets of mTORC1 action, in the hypothalamus. Rapamycin, an mTOR inhibitor, attenuates the anorectic and weight-reducing effects of leptin, indicating that increased mTORC1 activity is required for the leptin-induced anorexia (Villanueva and Myers 2008). Mutation of Tyr985 in *leprb* blocks S6 phosphorylation, suggesting a potential role for the Shp2-ERK signaling cascade in leptin-induced mTORC1 activation. While mTORC1 was presumed to serve as the direct cellular sensor for ATP levels, mounting evidence has implicated AMPK in the regulation of mTORC1 activity. Most neurons expressing AMPK in the ARC and PVN possess mTORC1, and leptin-induced anorexia and the AMPK activator blocks hypothalamic mTORC1 activation. Thus, AMPK and mTORC1 interact in the hypothalamus to mediate the metabolic effect of leptin.

FoxO1

The forkhead transcriptional factor subfamily forkhead box O1 (FoxO1 or Fkhr) is a downstream target of Akt. Activation of Akt phosphorylates FoxO1, leading to its nuclear exclusion and proteosomal degradation, and thereby inhibiting its action. The anorectic effect of leptin is inhibited when hypothalamic FoxO1 is activated. Moreover, rats receiving constitutively nuclear mutant FoxO1 in the ARC showed impaired satiety in response to leptin treatment. The anorectic effect of leptin was almost doubled in FoxO1 heterozygous knockout mice compared to wild-type littermate controls, indicating that the loss of FoxO1 function is associated with increased sensitivity to the anorectic effect of leptin. Conversely, the anorectic effect of leptin was greatly reduced in mice expressing FoxO1-3A, indicating that hypothalamic FoxO1 activation can attenuate the effects of leptin on food intake. Furthermore, leptin decreases the hypothalamic expression of FoxO1, a downstream target of Akt and the i.c.v. administration of the PI3K inhibitor attenuates the effect of leptin on hypothalamic FoxO1 expression, suggesting that leptin decreases hypothalamic FoxO1 expression through PI3K activation and that FoxO1 is downstream of the PI3K/Akt signaling pathway in hypothalamic neurons. FoxO1 binds to *Agrp* and *Pomc* promoters and leptin inhibits FoxO1 binding to these promoters through STAT3-mediated competition (Kitamura et al. 2006). Thus, the hypothalamic PI3K-Akt-FoxO1 signaling pathway mediates the effect of leptin on the transcriptional regulation of *Agrp* and *Pomc* and thereby mediates the effect of leptin on energy homeostasis.

Leptin Resistance and Obesity

Leptin resistance, rather than leptin deficiency, appears to be a major cause of human obesity. Although the identity of the crucial mediator(s) of leptin resistance remains unclear, there are some possibilities including the failure of circulating leptin to reach its targets in the brain and inhibition of the intracellular LepRb signaling cascade.

One possible mechanism for leptin resistance is a defective leptin transport across the BBB. The transportation of leptin into the brain is mediated via a specific transport mechanism across the BBB and/or via the ▶ circumventricular organs. Leptin is transported across the BBB by a saturable transport system that may be in part mediated by the short form of leptin receptor, LepRe. In rats, lacking all leptin receptor isoforms, there is a marked decrease in leptin transport rate from the circulation into the brain. Normal transport rate of leptin is maintained in *db/db* mice in which only LepRb is missing, but other isoforms are intact. Leptin transport rate is also reduced in high-fat diet-induced obese (DIO) rats, an animal model of leptin resistance, and DIO mice do not respond to peripherally administered leptin (Levin et al. 2004). Similar impairments are also observed in aged animals, another model of leptin resistance (Scarpace et al. 2001). Systemic administration of leptin inhibited glucose-stimulated insulin secretion in young rats, but this effect was abolished in aged rats. These findings indicate that impairments in leptin transport rates across the BBB cause leptin resistance in the CNS.

Another possible mechanism for leptin resistance is impairments in intracellular LepRb signaling system.

Leptin-resistant DIO mice and aged rats do not respond to peripherally administered leptin, but they partially respond to central injection of leptin, suggesting that the downstream signaling pathways are partially capable of mediating leptin action. This also indicates that the ability of leptin to activate hypothalamic signaling is impaired in leptin-resistant animals. For example, leptin-induced phosphorylation of STAT3 is reduced in the hypothalamus of DIO animals and aged rats. Leptin-induced activation of PI3K and mTORC1 and the inhibition of AMPK are reduced in DIO animals (Cota et al. 2008; Martin et al. 2006; Metlakunta et al. 2008). These data indicate that impairments in these LepRb signaling contribute to the development of leptin resistance. SOCS3 and PTP1B are known to be negative regulators of leptin signaling in the hypothalamus. Overexpression of each of these proteins attenuates signaling through LepRb. Thus, PTP1B and SOCS3 are important physiologic determinants of leptin signaling strength, and PTP1B or SOCS3 contribute to the development of leptin resistance and obesity by inhibiting signaling through LepRb. The LepRb-STAT3 pathway stimulates SOCS3 expression and SOCS3 expression levels correlate with the attenuation of LepRb signaling. Thus, high levels of leptin may induce SOCS3 expression and thereby attenuates leptin signaling in obesity. Theoretically, this increase in SOCS3 should inhibit LepRb signaling, which in turn reduces SOCS3 expression. However, SOCS3 levels are elevated in obese animals with elevated leptin levels. It is possible that chronically elevated leptin levels induce its own feedback inhibition through the induction of SOCS3, effectively limiting the efficacy of chronic exposure of high levels of leptin.

Conclusion

Leptin serves to communicate the state of body energy stores to the CNS in order to maintain normal metabolic and neuroendocrine functions. These actions of leptin require its transportation to the CNS across the BBB via the short form LepRe and its binding to the long form LepRb, followed by the activation of diverse intracellular signaling pathways. Resistance to the metabolic effect of leptin is a major cause of human obesity. Interventions that can enhance the rate of leptin transport across the BBB and intracellular signaling through LepRb are expected to be therapeutically effective in the treatment of obesity.

Cross-References

- ▶ Agouti related peptide
- ▶ Alpha melanocyte stimulating hormone
- ▶ Appetite stimulants
- ▶ Appetite suppressants
- ▶ Blood-brain barrier
- ▶ Body mass index
- ▶ Circumventricular organs
- ▶ db/db mouse
- ▶ Eating and appetite
- ▶ Eating Disorders: Animal Models
- ▶ Energy metabolism
- ▶ Hyperphagia
- ▶ Hypophagia
- ▶ Hypothalamus
- ▶ Neuropeptide Y
- ▶ ob/ob mouse
- ▶ Rapamycin
- ▶ Satiety

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Leucoplakia

Definition

A white-coloured thickened patch in the mucosa of the oral cavity. This lesion is primarily caused by chronic

irritative stimuli such as tobacco use or friction and may potentially evolve in cancer.

Levodopa

Synonyms
l-DOPA; l-3,4-dihydroxyphenylalanine; 3-hydroxy-l-tyrosine

Definition
Levodopa is used in the treatment of Parkinson's disease, since it is a precursor of dopamine. l-DOPA can cross the ▶ blood–brain barrier, but tends to be metabolized peripherally by both aromatic l-amino acid decarboxylase or DOPA decarboxylase (DDC) and catechol-O-methyl transferase (COMT). Therefore, l-DOPA is often associated with a DDC inhibitor (e.g., ▶ carbidopa) or a ▶ COMT inhibitor (▶ entacapone) as double combinations, or even with both a DDC inhibitor (e.g., carbidopa) and a COMT inhibitor (entacapone), as a triple combination. The combinations are used to prolong the plasma half-life of l-DOPA, but also to avoid its conversion into ▶ dopamine in the periphery, thus avoiding peripheral dopaminergic side effects. Once in the brain, l-DOPA is converted to dopamine, since the DDC inhibitors do not cross the brain barrier, and dopamine will then activate dopamine receptors; this is the basis for the treatment of ▶ Parkinson's disease or dopamine responsive dystonias. Unfortunately, l-DOPA treatment response diminishes over the years, at which point various combination therapies must be started. Also, long-term treatment with l-DOPA may be accompanied by the "on-off" phenomenon, patients oscillating between symptom improvement and abrupt onsets of ▶ akinesia.

Cross-References
▶ Anti-Parkinson Drugs

Levodopa-L-Di Ortho Phenylalanine

▶ Anti-Parkinson Drugs

Levo-Duboisine

▶ Scopolamine

Levomepromazine

Synonyms
Methotrimeprazine

Definition
Levomepromazine is a ▶ phenothiazine antipsychotic with a plasma half-life of 16–78 h. It is mainly metabolized by 1A2 and 2D6 CYP450 isoenzymes. It is said to have strong sedative properties, probably due to strong histamine H1 receptor blockade.

Cross-References
▶ First-Generation Antipsychotics

Lewy Bodies

Definition
Globular protein-rich inclusions in cell soma, characteristic of a number of diseases, in particular ▶ Parkinson's disease (PD) and certain ▶ dementias. Although dopamine depletion can occur in a number of disorders, the presence of Lewy bodies in the dopaminergic neurons of the ventral midbrain are considered as defining of idiopathic PD. The principle molecular component of the Lewy body is α-synuclein, and several of the mutations associated with familial PD involve disturbance in the α-synuclein gene or in the genes encoding-related interacting proteins.

Lewy Body Dementia

Synonyms
Dementia with Lewy bodies; DLB

Definition
Lewy body dementia is characterized by distinct ▶ cognitive impairment with fluctuating confusion, disturbance of consciousness, visual ▶ hallucinations, ▶ delusions, falls, and significant parkinsonism. The hallmark feature is the widespread ▶ Lewy bodies throughout the cortex with the presence of Lewy body and cell loss in the subcortical nuclei.

Lexington Narcotics Farm

▶ Narcotics Prison Farm

Liberation

Definition
Liberation is the process of releasing the drug from its formulation.

Cross-References
- ► Absorption
- ► Distribution
- ► Excretion
- ► Metabolism
- ► Pharmacokinetics

Libido

Definition
Libido is the capacity for sexual desire.

Cross-References
- ► Agoraphobia
- ► Sexual Disorders
- ► SSRIs
- ► SSRIs and Related Compounds

Licensing and Regulation of Medicines in the UK

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Synonyms
Drug licensing; Medicines control; Medicines regulation

Definition
The licensing and regulation of ► medicines in the United Kingdom is the statutory responsibility of their Medicines and Healthcare Products Regulatory Agency (MHRA), based in London. Before any medicine can be prescribed or sold in the UK it must have a marketing authorization (previously known as a product license). The marketing authorization specifies precisely the ► summary of product characteristics (SPC), along with the labeling and package leaflet for the product. The regulation of medicines, and the overall responsibilities of the MHRA, involves considerably more than a "once only" marketing authorization. Regulation also entails post-licensing surveillance of safety and scrutiny of any proposed variation to the clinical indications for the medicine, any changes in availability, the on-going quality of the production process, and the enforcement of regulations when required, all in respect of the Agency's principal aim, which is to safeguard the public health. Marketing authorization is given or refused on the grounds of safety, quality, and efficacy. Financial cost plays no part in regulatory decisions.

Current Concepts and State of Knowledge

Status and Function of the MHRA
The legal context within which MHRA operates is described in the Medicines Act of 1968, which became operational in 1971. The Act designated the Secretary of State for Health in England (and equivalents in Scotland, Wales, and Northern Ireland), the Licensing Authority for Human Medicines in the UK. This is a retained authority within the UK. In 2003, the then Medicines Control Agency was re-established as the MHRA, which became responsible not only for the regulation of medicines, but also medical devices and, more recently, blood and blood products. Many of the provisions of the 1968 Act have now been superseded by regulations implementing European legislation on medicines. A diminishing number of medicines are licensed on a national basis by MHRA, solely for use in the UK. Most medicines are now authorized through European procedures to ensure that they are available to, and used in the same way across, all the member states of the European Union (EU). This is either through agreement of identical national authorizations in all member states, based on the assessment of a lead member state (a mutual recognition or decentralized authorization) or through a single EU authorization issued by the European Medicines Evaluation Agency (EMEA) (centralized authorization). Under the "mutual recognition or decentralized" procedures, all EU countries in which marketing permission is sought receive the full marketing authorization application and any objections are considered and resolved through the EMEA's scientific advisory committee, the Committee for Medicinal Products for Human use (CHMP). The centralized approval system is compulsory for biotechnology products and has expanded in scope to cover drugs for AIDS, cancer, neurodegenerative diseases, and diabetes. Often the MHRA will be asked to take the

lead on the licensing process in Europe, particularly for biological and biotechnology treatments, such as a gene therapy.

The Marketing Authorization Process

Authorization to market a medicine is based on detailed requirements and elaborate processes, the scope of which is constantly changing. However, the core elements of medicines control remain essentially unchanged, the primary focus being on the evaluation of pre-licensing data (from nonclinical tests and phases 1 to 3 clinical trials) on safety, quality, and efficacy generated or commissioned by companies and submitted for approval in a Marketing Authorization Application. A medicine progresses "from bench to bedside" over a period of many years, and innovation usually involves the discovery, development, and bringing to market of a new molecular entity (NME). Often the NME is original, such as the first SSRI or atypical antipsychotic, but it may also be a relatively minor molecular modification of an existing drug. The preclinical and nonclinical assessment involves necessary animal and bench testing before administration to humans. ► Phase 1 clinical trials are also known as "first time in man" studies and are conducted usually with healthy volunteers. ► Phase 2 clinical trials are for "proof of concept"; evidence of efficacy, and safety in patients with the target condition. ► Phase 3 clinical trials represent the main clinical reference point upon which marketing authorization may be granted. These are usually large trials (involving many thousands of patients suffering from the target condition), they usually involve comparison of clinical benefits and risk between randomized samples of the target population given either the active drug or a ► placebo and/or active comparator and the results inform the labeling and patient information for the medicine when it is marketed. The benefits recorded in phase 3 clinical trials represent the main database on "► efficacy." Phase 4 trials are conducted post-marketing, the principal aim being to provide ongoing, structured safety information. Benefits recorded in Phase 4 trials are usually more appropriately termed the medicine's "► effectiveness" and more faithfully reflect every day clinical practice in that they derive from patients who have not been so strictly selected or supervised as those involved in Phase 3 studies.

Clinical Trial Authorization

Clinical trials are conducted according to Guidelines on Good Clinical Practice (GCP) as described in EU Directive 2001/20/EC, Article 1, Clause 2, which deal with ethical and scientific issues relating to the design, conduct, recording, and reporting of clinical trials that involve human subjects. The principles of GCP are outlined in Articles 2–5 in the EU Directive 2005/28/EC. The serious side effects experienced by volunteers taking part in a trial of TGN1412 in March 2006 at Northwick Park Hospital are extremely rare but indicate the importance of thoroughly testing a treatment before widespread use. Another regulatory responsibility of MHRA is to authorize any clinical trial of a medicinal product in the UK. Information on the quality of the product and its nonclinical safety will have been obtained before Clinical Trial Authorization can be obtained and any clinical trial programme commencing.

Judging the Balance of Risks and Benefits

Evidence in pursuit of authorization is submitted by the applicant (normally a pharmaceutical company) either in paper form or electronically. Thorough assessment of all of the clinical and preclinical data is conducted in-house by MHRA assessors and a recommendation is then made to one or more elements of the Agency's expert advisory structure. The main independent, expert, group advising the Agency is the Commission on Human Medicines (CHM), which came into being in October 2005. The Commission has three statutory, standing, Expert Advisory Groups – in (1) pharmacovigilance, (2) chemistry, pharmacy, and standards, and (3) biologicals and vaccines. The Chairs of the Expert Advisory Groups are members of the Commission. In addition, there are a number of established Expert Advisory Groups covering a range of specific therapeutic areas such as Psychiatry and Old Age Psychiatry. The Commission is charged with the responsibility to advise Ministers, through the MHRA, on matters relating to human medicinal products.

The Life Cycle of a Medicine

Marketing Authorizations are granted for periods of up to 5 years, when they then have to be renewed. On renewal each marketing authorization must reflect all current knowledge about the product, including any necessary action from the most recent periodic safety update report (PSUR) submitted by the applicant. Once renewed, the marketing authorization will be valid for an unlimited period unless there are justified grounds relating to pharmacovigilance, when it may become necessary to proceed with one additional 5-year renewal. Variations to marketing authorizations must be approved before introducing any changes. They take account of technical and scientific progress, introduce additional safeguards, or reflect

evolving therapeutic indications. It is common practice for new products to be varied many times, particularly in the first 2 years after marketing. Once licensed, a medicine is normally under patent protection for 10 years. Once that period has expired, the originating pharmaceutical company is deemed to have been rewarded for the costs and risks of innovation, and generic versions of the medicine may then enter the market. Such generic medicines contain the same active ingredients as the original product, and the regulatory standards for safety, quality, and efficacy, are the same as for branded products, and marketing authorization must be obtained before the generic medicine is allowed on to the market.

Safety Monitoring

No medicine is completely free of risk but sound evidence underpins all of the MHRA's decisions to ensure that an acceptable balance exists between risks and benefits. Companies applying for a marketing authorization are required to submit a risk management plan which states what is known about the medicine, identifies any gaps in knowledge about safety, and outlines plans to collect data in the post-marketing period to fill those gaps. The MHRA monitors safety and quality standards by a number of means. It conducts regular inspections of good and safe practice including medicines manufacture and supply, carries out routine sampling of marketed medicines at manufacturers' premises, considers on-going reports from health professionals, patients, and manufacturers (such as the Yellow Card scheme, see below), reviews important new evidence on products (such as the SSRIs), and assesses misleading or incorrect information contained in advertisements, product labeling, or product information leaflets (PILs).

Pharmacovigilance is the process of detection, assessment, understanding, and prevention of adverse effects of medicines, against which benefits must be weighed in coming to any decision about the need to modify, restrict, or withdraw marketing authorization. By law, manufacturers must report to the MHRA any important defects in the quality (chemical identity and purity) or clinical safety of a medicine. Any action taken by MHRA is determined by the scale of the threat posed to the public health. If a new side effect is identified, MHRA can seek advice from its external experts and/or commission further research to illuminate the issues. A number of options are available to the Agency short of requiring withdrawal of the product, and any modifications to clinical usage are reflected in the SPC. Health professionals are informed of important new information and advice in relation to medicines via a letter sent by the manufacturer, or via a direct communication from the MHRA through the Department of Health Central Alerting System. The MHRA also issues a monthly bulletin "Drug Safety Update" which includes the latest advice for users of medicines and is available on the Agency's website; www.mhra.gov.uk/mhra/drugsafetyupdate The MHRA operates a "Black Triangle Scheme" under which all new medicines, and established medicines newly authorized for a different patient population, are intensively monitored for the first few years of marketing. Products monitored under this scheme are denoted by an inverted black triangle which appears on any advertising material and in the British National Formulary (BNF). For medicines denoted by a black triangle, it is advised that *all* suspected reactions (including any considered not to be serious) should be reported. The "Yellow Card" scheme is run by the MHRA and the CHM and is used to collect information submitted spontaneously from health professionals and the general public on suspected side effects or adverse drug reactions (ADRs). For established drugs and herbal remedies, all serious adverse reactions in adults and all serious and minor adverse reactions in children under the age of 18 should be reported. Prescribers and users need not be certain about causality, and the golden rule is "if in doubt, report." Reports can be made through the MHRA website; www.yellowcard.gov.uk and paper copies of yellow cards are attached at the end of the BNF. A rich source of data on marketed medicines comes from the general practice research database (GPRD), the management of which is entrusted to the MHRA. The GPRD is the World's largest computerized database of longitudinal medical records from Primary Care. Currently, data are collected on over 3.6 million active patients from around 450 Primary Care practices throughout the UK. It is used worldwide for research by the pharmaceutical industry, clinical research organizations, regulators, Government departments, and leading academic institutions, and is an internationally recognized source of information on the safety and effectiveness of licensed medicines.

The potential for ► selective serotonin reuptake inhibitors (SSRIs) to cause withdrawal reactions, dependence, and suicidal thoughts and behavior has been the subject of controversy and public concern since the late 1980s. The safety of SSRIs was closely monitored leading to updates to the SPC and patient information as evidence accumulated. An Expert Working Group of the Committee on Safety of Medicines (predecessor of CHM) established in 2003 conducted a detailed investigation of clinical trial data, data from the Yellow Card Scheme, and from GPRD.

Their recommendations were published in 2004 and fed into the NICE clinical guideline on depression. In 2005 analyses of 17 placebo-controlled studies found that ▶ atypical antipsychotics were associated with an increased risk of death in elderly people with ▶ dementia. The product information for these medicines was updated to include warnings about this risk. There is increasing awareness of psychiatric adverse effects of non-psychiatric medicines. ▶ Rimonanbant (Acomplia) was withdrawn from the market in the EU in 2008 because the risk of psychiatric disorders, particularly depressive reactions, was considered to outweigh its benefits in the management of obesity.

Herbal Medicines

The regulation of ▶ herbal medicinal products also falls within the remit of MHRA. There are three possible regulatory routes by which a herbal remedy can reach a consumer as an unlicensed, registered, or licensed herbal medicine. By April 2011 all manufactured herbal medicines will be required to have either a traditional herbal registration or a product license. The simplified registration scheme (the Traditional Herbal Medicines Registration Scheme) began in October 2005. Registered products are required to meet specific standards of safety and quality and to be accompanied by agreed indications based on traditional usage. To be licensed a herbal medicine requires to demonstrate safety, quality, and efficacy (or effectiveness) and to be accompanied by the necessary information for safe usage. As with conventional medicines, herbal remedies may be the subject of Yellow Card reports.

Counterfeit Medicines

The detection and confiscation of counterfeit medicines represents a growing activity for MHRA. The World Health Organisation (WHO) estimates that up to 1% of medicines available in the developed world are likely to be counterfeit, and this figure rises to 10% globally. Therapeutic psychoactive drugs are no exception – counterfeit Zyprexa (▶ olanzapine) was detected and recalled in the UK by the MHRA in 2007. Counterfeit medicine is commonly available to consumers via internet online pharmacies, WHO estimating that 50% of medicines available from such sites which conceal their physical address are counterfeit. Counterfeits discovered in the UK typically contain a reduced amount of the active pharmaceutical ingredient, although the wrong ingredient or no ingredient at all have been found less frequently; therefore all counterfeit medicines are potentially dangerous.

Medicines Availability

Marketing authorization of a medicine may specify whether it can be made available either on prescription (prescription only medicines (POM)), available in a pharmacy without prescription under the supervision of Pharmacist (P), or on general sale (GSL). Prescriptions can be issued by doctors, dentists, nurse independent prescribers, pharmacist independent prescribers and supplementary prescribers. Before restrictions on the supply of a medicine can be downgraded from POM, Ministers, advised by MHRA, must be satisfied that it would be safe to allow it to be supplied without prescription. Similarly, switching from P to GSL requires demonstration of acceptable safety if sold or supplied otherwise than by or under the supervision of a pharmacist.

Orphan Drugs

The pharmaceutical industry has little interest, under normal market conditions, in developing and marketing medicines intended for small numbers of patients ("orphan drugs"), and the EU offers a range of incentives to encourage the development of these medicines, including reduced licensing fees. In that case the company applies to the EMEA requesting "orphan designation" for their product.

Powers

When regulations have been breached, the MHRA has the power to prosecute. Courts can impose fines or prison sentences when the law has been broken and the Agency has the power to require unlicensed/illegal products to be withdrawn from the market.

Cross-References

▶ Herbal Remedies
▶ Legal Aspects of Adverse Drug Effects
▶ SSRI's and Related Compounds
▶ Suicide
▶ Withdrawal Syndromes

Ligand Binding

▶ Receptor Binding

Ligand-Directed Trafficking

▶ Functional Selectivity

Ligands

Definition

Substances that bind to receptors and alter the three-dimensional shape of selected receptor proteins. The shape of a receptor protein determines the functional state of a receptor. Ligands include substrates, inhibitors, activators, and neurotransmitters.

Liking and Wanting

Definition

Liking is the hedonic quality of food and the pleasing experience of consumption, while wanting is the desire to consume food and its motivational salience. The two are distinct as we can like a food without wanting it and vice versa; however, both are probably intrinsic components of palatability. In terms of animal behavior, the strength of initial feeding response is held to indicate liking, while later feeding behavior, including returning to food source, indicates the desire to consume.

Cross-References

► Palatability

Lipid Soluble

► Lipohilic

Lipohilic

Synonyms

Fat soluble; Lipid soluble

Definition

A chemical compound that dissolves in fats, oils, lipids, and nonpolar solvents (i.e., accumulate in lipid stores in the body).

Cross-References

► Blood Brain Barrier
► Sex Differences in Drug Effects

Liquid Diet for Administering Alcohol

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Definition

This is a technique of feeding ► alcohol (ethanol) as part of a liquid diet. The technique helps to mimic in experimental animals the effects of chronic alcohol intake in man and is used in research on alcohol effects in experimental animals, especially rodents. It has been used for more than forty years in many experimental studies that investigate and evaluate the effects of ► alcohol abuse and dependence in animals.

Proper controls and dietary adequacy pose significant challenges in studies on chronic exposure to ► alcohol in rodents. Thus, a suitable ► animal model that mimics the effects of chronic alcohol intake in man has long been sought. The technique of feeding ethanol as part of a totally liquid diet was first reported in 1963 (Lieber et al. 1963). Then the liquid diet technique became the most preferred and practical method to induce alcohol physical dependence experimentally since aversions to alcohol can be overcome and the intake is sufficient to sustain high daily alcohol consumption.

The route of drug delivery is an important consideration when evaluating the long-term biobehavioral adaptations occurring in response to chronic drug administration. Before the development of liquid diet technique of alcohol feeding, alcohol was commonly given to rats as part of their drinking water. Alcohol administration in water is associated with insufficient consumption and heavy weight loss. Insufficient intake of alcohol results in low levels in blood; on the other hand, if the intake of alcohol is sufficient, there is significant liver damage due to an inadequate intake of dietary nutrients rather than to effects of alcohol (Lieber and DeCarli 1989). Esophageal and gastric ulceration may also frequently appear. Administering alcohol to experimental animals as part of a liquid diet provides an efficient model allowing investigation of chronic effects of alcohol without irrelevant harmful effects. It is also closer to chronic intake of alcohol in man. In addition to achieving a significant alcohol intake, this technique has also the advantage of following minimization of alcohol-induced liver injury.

There are several liquid diet formulae available containing a mixture of mainly carbohydrates, oils, proteins, vitamins, and mineral (Lieber and DeCarli 1989). Milk is known to be an essential nutrient for growth of mammals. Cow's milk contains the major ingredients of an ideal liquid diet. It has also been reported that cow's milk may be used as a liquid diet in rats after addition of 1% (w/v) sugar (Parale and Kulkarni 1986) or a synthetic sweetener and vitamin A (Uzbay et al. 1995). A modified liquid diet of chronic alcohol administration to rats has also been defined and used (Uzbay and Kayaalp 1995).

Principles and Role in Psychopharmacology

Some Critical Points in Liquid Diet Practice

Liquid diet mixtures with or without alcohol provide 1,000 kcal/L. The liquid diet method for administration of alcohol involves pair-feeding of control and treated animals with identical amounts of the same diet to control exposure to putative nutritional deficits. Control rats are pair-fed with an isocaloric liquid diet containing a carbohydrate such as sucrose or dextrin maltose as a caloric substitute for ethanol. It is highly recommend to have a second control group with continuous access to standard laboratory diet and water. If the alcohol-treated group differs from both control groups and the control groups do not differ from each other, effects seen will not be due to limitations in dietary intake or the liquid diet but rather to alcohol *per se* (Driscoll et al. 1990).

To prevent decrease in diet intake and weight loss, ethanol (96.5%, v/v) should be gradually presented in progressively increasing concentrations during a habituation phase. After almost a week's feeding with liquid diet without ethanol, ethanol (about 2.5% v/v) can be added to the liquid diet for 3–4 days. Then the ethanol concentration can be increased to approximately 5% for 3 days and finally to 7.0–7.5%. When ethanol concentration is increased, a carbohydrate ingredient such as sucrose or dextrin maltose is reduced to maintain isocaloricity of the diet. Then, exposure to ethanol contained in liquid diet (approximately 7%, v/v) is carried on (Uzbay and Kayaalp 1995). A simple formula is shown in Table 1.

Although the liquid diet is meant to be the sole source of fluid and food, decreases in diet consumption can be avoided by giving access to water. Animals which receive water *ad libitum* lose less weight than groups that do not receive water *ad libitum* and keep consuming the same amount of liquid diet (Piano et al. 2001).

Daily alcohol consumption and blood ethanol levels are the most critical parameters for testing the validity of a liquid diet as a vehicle for alcohol administration. Above 10 g/kg/day alcohol consumption for a couple of week and more than 150 mg/dl blood ethanol concentrations may be adequate for development of ► physical dependence on alcohol in rats (Uzbay and Kayaalp 1995). It has been recommended that in an acceptable liquid diet 36–50% of total energy should be acquired by ethanol (Lieber and DeCarli 1989; Uzbay and Kayaalp 1995). Lieber and DeCarli (1989) found that the alcohol obtained from a liquid diet containing 35% ethanol provided about 36% of the daily energy intake, with average ethanol intakes in the range of 10–14 g/kg/day. The associated blood-alcohol levels were over 100 mg/dl when pregnant rats consume the majority of their daily intake. These 100 mg/kg levels were similar to those estimated after human consumption of three drinks in 1 h, and produced most major neurobehavioral effects of ► prenatal exposure to alcohol in their offspring (Driscoll et al. 1990).

Liquid Diet for Administering Alcohol. Table 1. A simple liquid diet formula for studies on alcohol dependence.[a]

Ingredients	Liter
Cow milk	925 ml
Ethanol (%96.5)	75 ml
Vitamin A	5000 IU
Sucrose	17 g

[a]Uzbay and Kayaalp 1995; 1000.7 kcal/L

Utilization of Liquid Diet Technique in Experimental Practice

► Alcohol abuse and dependence remain among the greatest substance abuse problems worldwide. The mechanisms underlying physical dependence to alcohol are poorly understood. Generally accepted criteria for animal models of alcoholism include physical dependence upon and ► tolerance to alcohol. Tolerance is often inferred when large doses of alcohol have minimal effects on behavioral performance after chronic alcohol exposure. Physical dependence is defined by the appearance of withdrawal signs upon removal of alcohol after a period of intoxication.

The technique for the administration of ethanol as part of a liquid diet is preferable in the animal models for the development of alcohol tolerance and dependence. Alcohol ► withdrawal syndrome induced by discontinuing chronic ethanol intake is the most important evidence indicating the presence of physical dependence on alcohol (O'Brien 1996). A severe alcohol withdrawal syndrome is produced by the liquid diet technique in rats. Also, this

method can be used to assess the pharmacological profile of drugs on the alcohol withdrawal syndrome in rodents (Uzbay and Kayaalp 1995).

The liquid diet technique has been adapted to a number of animal species other than rodents. One of the most successful applications has been the baboon liquid diet. The composition of the liquid diet is adjusted to meet the primate's needs. Thus, the ethanol content of the baboon liquid diet is significantly higher than that in the rat because of a lesser aversion to ethanol in the former species (Lieber and DeCarli 1989).

Advantages of Liquid Diet Techniques

The liquid diet technique is a relevant model for alcohol consumption in humans. It provides high daily alcohol intake and sufficient blood alcohol concentrations. It does not cause severe body weight loss. Even body weight increases have been reported in rats consuming ethanol-containing liquid diet (Lieber and DeCarli 1989; Uzbay and Erden 2003).

One of the major advantages of this technique is facilitation of the pair-feeding process. Usually the alcohol-fed animals are allowed dietary consumption *ad libitum,* with amounts consumed being self-limited. Their dietary intake is monitored by determining the amount of liquid consumed (Lieber and DeCarli 1989).

The liquid diet technique has also the advantage of allowing for an accurate recording of the nutrients consumed and for an easy change of the nutritional components according to specific experimental needs. This technique has been useful in characterizing the metabolism of alcohol, in assessing the interactions between ethanol and nutrition, other drugs that are also hepatotoxic agents and carcinogens, as well as in elucidating the mechanisms of alcoholic liver injury, endocrine abnormalities, withdrawal states, developmental problems and other central nervous system changes, including some degenerative and harmful complications (Lieber and DeCarli 1989).

Another use for the liquid diet technique is investigation of prenatal exposure to alcohol in animals. When prenatal exposure to alcohol is required, pregnant rats should receive a liquid diet as their sole source of nutrition and thus a proportion of their caloric intake will consist of ethanol or an isocaloric carbohydrate such as sucrose. A commercially available liquid diet with high protein content meets the requirements during pregnancy and lactation. This technique facilitates comparisons with controls by simplifying pair-feeding procedures (Lieber and DeCarli 1989); this method also avoids effects due to inadequate maternal diets that can exacerbate the effects of ethanol (Lieber 1991).

In contrast to administering ethanol by gastric intubation, not allowing the development of physical dependence to alcohol in rats within a short time may be the main disadvantage of the liquid diet technique. More exposure time is necessary for a satisfactory model of physical dependence in animals.

Cross-References

- ▶ Abuse
- ▶ Alcohol
- ▶ Alcohol Abuse and Dependence
- ▶ Animal Model
- ▶ Physical Dependence
- ▶ Prenatal Exposure to Alcohol
- ▶ Tolerance
- ▶ Withdrawal Syndrome

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Lisdexamfetamine

Definition

Lisdexamfetamine (L-lysine-D-amphetamine) belongs to the phenethylamine and ▶ amphetamine chemical classes, and is a drug specifically developed as an alternative to

D-amphetamine for the treatment of ADHD. Lisdexamfetamine has been tailored to have a more prolonged effect than D-amphetamine, yet with a reduced abuse potential. Despite these advantages, the use of lisdexamfetamine has been associated with several side effects including dry mouth, decreased appetite, insomnia, and heart attack or stroke in individuals with preexisting cardiovascular disorders.

Cross-References

- ► Adolescence and Response to Drugs
- ► Amphetamine
- ► Attention Deficit Hyperactivity Disorder
- ► Hyperactivity
- ► Impulsivity
- ► Psychomotor Stimulants

Listening Span Test

Definition

In this test, subjects listen to sets of two to seven sentences and complete a written factual verification question for the content of each sentence. After the last sentence of each set, subjects recall the final word of each sentence in the order in which they were presented. The span (working memory capacity) represents the maximum number of sentences performed correctly on at least two out of three trials.

Lithium

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Synonyms

Lithium salts

Definition

Lithium is an alkali metal. Its salts, lithium salts, are used as a psychopharmacological drug for recurrence prevention of manic-depressive illness, in the treatment of acute mania, in augmenting the effects of antidepressants, and in cluster headache. The pharmacologically active compound is the lithium ion (Li^+).

Pharmacological Properties

History

Lithium was first used in psychiatric patients in 1871, based on a wrong pathophysiological hypothesis but abandoned shortly afterwards. In 1949, the Australian psychiatrist John Cade showed first antimanic effects of lithium in psychotic patients. Starting an intensive research in the 1950s, his Danish colleagues Mogens Schou and Poul Christian Baastrup proved the efficacy of lithium in the treatment of acute ► mania and in the prevention of affective episodes in controlled studies.

Mechanism of Action

The initial direct target of Li^+ is the competition with Mg^{2+} at circumscribed metal ion-binding sites of proteins that need the binding of this ion as a cofactor in order to function. The enzymes thus inhibited by Li^+ comprise quite a heterogeneous group of enzymes such as inositolmonophosphatase (IMPase), phosphoglucomutase (FGM), biphosphate-3′-nucleotidase (BNP1), adenylylcyclase (AC), and glycogen synthase kinase 3 (GSK-3). AC, IMPase, and GSK-3 play a critical role in cellular signal transduction mechanisms, which are believed to be the main targets in the mechanism of action of Li^+ ions. Signal transduction mechanisms transmit the information impinging at receptors on the surface of the cell into the interior of the cell. Particularly important components are the "G-proteins," a family of heterotrimeric proteins located at the inner plasma membrane consisting of an α-subunit and the tightly associated βγ-subunits. The α-subunit binds guanyl nucleotides. Interaction with an activated receptor induces exchange of the bound GDP with GTP and dissociation into free α- and βγ-subunits which can activate various effector proteins. Activation is terminated by hydrolysis of GTP to GDP by the intrinsic GTPase activity of the α-subunit and reassociation of the heterotrimeric αβγ-complex. Effector proteins encompass enzymes like AC and phospholipases (C, D, A_2), which synthesize ► second messenger-molecules such as cyclic AMP, inositoltrisphosphate (IP_3), or diacylglycerol (DAG). "Second messengers" often act via activation of protein kinases, which phosphorylate various target proteins such as ion channels or transcription factors. Given the crucial role of signal transduction in cellular regulation, it is not surprising that these systems in the brain are also critically

involved in ► neural plasticity and resilience, and are therefore candidates as potential targets in the mechanism of action of ► mood stabilizers such as lithium. Effects of lithium ions on signal transduction mechanisms have therefore been a major focus of research during the last two decades (for review, see van Calker 2006).

Effects of Lithium on the Adenylylcyclase System

The inhibition by Li^+ ions of AC is known for 30 years. It appears to be due to a competition with Mg^{2+} ions at the catalytic unit of AC. In contrast, the chronic inhibitory effects of lithium on AC are not influenced by Mg^{2+} ions, but reversed by GTP, and therefore believed to be due to actions of lithium on G-proteins (discussed below). More recent research has also confirmed an inhibitory effect of lithium on the inhibitory interaction of receptors with AC and revealed its mediation by an action of lithium on the G_i-protein. In summary, lithium ions appear to balance signal transduction via the AC system. This could dampen the excessive pathological fluctuations of signaling that might be causative related to the mood swings in bipolar disorder.

Effects of Lithium on Phosphatidylinositol (PI) Signaling

Phosphatidylinositolphosphates (PIP), minor components of the lipids in the cell membrane, play an important role in the process of receptor-activated signal transduction. Hormones and neurotransmitters stimulate via activation of particular receptor subtypes the hydrolysis of PIP_3 to two second-messenger molecules, DAG and IP_3, which activate, respectively, protein kinase C (PKC) and the intracellular release of Ca^{2+}-ions. IP_3 is metabolized to myo-inositol, which is used together with DAG for the resynthesis of PIs. The last step in the metabolism of IP_3, the hydrolysis of inositolmonophosphate to myo-inositol by IMPase, is inhibited by lithium ions in the therapeutic concentration range (K_i = 0.8 mM). The "inositol depletion hypothesis" postulates that the lithium-induced inhibition of IMPase leads to a depletion of the brain of myo-inositol and, subsequently, due to a compromised synthesis of PIs to a reduction of receptor-stimulated formation of PI-dependent second-messenger molecules. It is, however, now clear that even a 90% reduction of myo-inositol content in the brain as observed in mice with targeted deletion of the Na^+/myo-inositol-cotransporter (SMIT, discussed in detail below) does not result in functionally relevant reduction of PI synthesis (Buccafusca et al. 2008) although these mice show behavioral abnormalities reminiscent of mice treated with lithium salts (Bersudsky et al. 2008). Thus, while myo-inositol appears to play a role in the behavioral effects of lithium, effects beyond PI-formation seem to be responsible.

Measurements of the effects of lithium treatment on myo-inositol levels in the human brain are partly consistent with the inositol depletion hypothesis. Proton magnetic resonance spectroscopy (MRS) scans of bipolar patients show a significant reduction of myo-inositol content in the frontal cortex already after 5 days of lithium administration, at a time when the patient's clinical state was completely unchanged. Thus, while lithium indeed lowers the myo-inositol in the brain this action alone cannot explain the therapeutic effect but may be the initial trigger for a cascade of subsequent alterations that ultimately account for the therapeutic effect.

In addition to hydrolysis of PIs, brain cells also acquire myo-inositol from the extracellular space by virtue of the sodium/myo-inositol cotransporter (SMIT), a high-affinity myo-inositol transport system that transports myo-inositol into the cells against a steep concentration gradient. Both the activity of SMIT and the expression of its mRNA in astrocytes are downregulated after chronic treatment with therapeutical concentrations of lithium salts. Two other mood stabilizers, ► valproate and ► carbamazepine, elicit the same effect, indicating that it might represent a common mechanism of action of ► mood stabilizers.

Similar to rat astrocytes, downregulation of SMIT mRNA expression also occurs in vivo in bipolar patients chronically treated with lithium or valproate as measured in neutrophils (Willmroth et al. 2007). SMIT expression in neutrophils was increased in bipolar-1 patients. On the one hand, IP_3 and Ca^{2+} signaling were found to be compromised in peripheral blood cells of patients chronically treated with lithium salts. On the other hand, peripheral blood cells of depressive or manic patients showed an increased sensitivity of the PI-system when compared with controls. These results provide evidence for an increased sensitivity of the PI system in peripheral cells of manic-depressive patients that is compensated or even overcompensated by treatment with lithium and, perhaps, other mood stabilizers (see van Calker 2006 for review).

Effects of Lithium on the Arachidonic Acid Cascade in the Brain

Membrane phospholipids can serve as a substrate for phospholipase A_2 (PLA_2), which is also activated by receptor/G-protein coupling. The released arachidonic acid (AA) and its bioactive eicosanoid metabolites can influence many physiological processes, including membrane excitability, gene transcription, ► apoptosis, sleep, and behavior. All three mood stabilizers, lithium, carbamazepine, and valproate downregulate the ► gene expression,

protein level, and activity of the AA-specific PLA_2, and also reduce the protein level and activity of cyclooxygenase 2 (COX-2) and prostaglandin E_2. Thus, AA metabolism might be another common target of mood stabilizers (see Rao et al. 2008 for review).

Effects of Lithium on Glycogensynthase-Kinase-3 (GSK-3)

GSK-3 is recognized as an important regulator of many vital cellular functions such as apoptosis, ► synaptic plasticity, cytoskeletal rearrangement, and ► circadian rhythm. Lithium inhibits GSK-3 directly by virtue of competition with Mg^{2+}-ions and indirectly by virtue of Akt-mediated phosphorylation on the n-terminal serine (for review see Beaulieu et al. 2009). The inhibition by lithium of GSK-3 likely contributes to its antiapoptotic and neuroprotective effects.

Effects of Lithium on Protein Kinase Activities and Protein Phosphorylation

As discussed above, lithium ions modulate the basal and agonist-stimulated concentrations of the second-messenger molecules cyclic AMP, IP_3, Ca^{2+}, and DAG, and should therefore also influence the activity of the protein kinases A, C, and others that are regulated by these second messengers. Several studies have reported that lithium can modulate protein kinase A-mediated protein phosphorylation. Alterations of PKC activity by lithium have been conjectured earlier after the formulation of the inositol depletion hypothesis, since a depletion of inositol should result in a decreased consumption for PI-resynthesis and, thus increased accumulation of DAG, the activator of PKC. PKC regulates many pre- and postsynaptic aspects of neurotransmission including long-term alterations in gene expression and neuronal plasticity. Persistent activation of PKC is often followed by its rapid proteolytic degradation and downregulation of enzyme activity. This could explain why lithium after acute or subchronic treatment induces an increase, while chronic treatment results in a decrease of PKC or PKC-mediated processes. The alterations in gene expression observed after chronic lithium treatment (see below) could at least in part be mediated by effects on PKC.

Effects of Lithium on G-Proteins

As discussed above, the effects of lithium on AC and its actions on PI signaling suggest the involvement of mechanisms beyond alterations of the catalytic subunit of AC or depletion of myo-inositol, respectively. One additional mechanism by which lithium could modify the activity of these signal transduction systems is the alteration of activity of G-proteins. An influence of lithium on G-protein function can be assessed by cholera toxin and pertussis toxin, which via ADP-ribosylation directly activate or inhibit, respectively, the G_s-protein, which stimulates and the G_i-protein, which inhibits adenylylcyclase. Using this approach, it was shown by in-vivo experiments with microdialysis technique that chronic lithium treatment inhibits the function of G_i thereby increasing the basal level of cyclic AMP in the brain of rats. On the other hand, chronic lithium treatment apparently also inhibits the function of G_s, since the inhibition by chronic lithium of the receptor-mediated activation of adenylylcyclase is counteracted by GTP. The inhibition of G_i may be due to a lithium-induced stabilization of the undissociated, inactive heterotrimeric $\alpha\beta\gamma$ state of the G_i-protein. Only this form is subject to ADP-ribosylation (for review, see Manji and Lenox 2000).

Effects of Lithium on Gene Expression

As already mentioned the activation by second messengers of protein kinases can lead to phosphorylation of nuclear transcription factors that regulate gene expression. Accordingly, treatment with Li^+ ions affects the expression of a number of genes, most likely at least in part secondary to modulation of PKC and/or GSK-3 (for review, see Wang and Young 2006). Of particular interest are the actions of lithium on so-called "immediate early genes," members of the c-fos and c-jun families, which encode proteins that form the constituents of a family of transcription factors called AP-1 (activator protein 1). These genes are of pivotal importance for long-term changes in neuronal function. Genes regulated by AP-1 include neurotrophins, ► neuropeptides, neurotransmitter synthesizing enzymes, and other transcription factors. It is now well established that lithium regulates AP-1-binding activity and function. The regulation by lithium of transcription factors is obviously not restricted to AP-1, since it also modulates two other such factors, cyclic AMP-responsive element-binding protein (CREB) and nuclear factor κB (NF-κB).

Effects of Lithium on Cellular Resilience

The neuroprotective effects of lithium were only recently fully appreciated. They are at least partly explained by the finding that lithium upregulates the neuroprotective and antiapoptotic protein Bcl-2. Very recently, it has been shown that mood stabilizer also increases BAG-1, an antiapoptotic, glucocorticoid receptor co-chaperone protein. Many of these effects may be in part mediated via inhibition of GSK-3β. That neuroprotection could also be an important mechanism in vivo is suggested by the

findings that lithium induces ▶ neurogenesis in adult rodent brain and increases the total gray matter in human brain. These results are particularly important in view of the recent evidence from brain imaging and post-mortem studies that mood disorders are associated with morphometric changes suggestive of cell loss and/or atrophy.

Pharmacokinetics

After oral application lithium salts are almost completely resorbed from the intestine. Maximal plasma concentrations are reached after 1–3 h. Elimination occurs exclusively through the kidneys. Steady-state concentrations are achieved after 4–5 days of treatment.

Dosage

The dosage of lithium should be slowly escalated if possible to minimize initially more pronounced adverse effects. At steady state, i.e., 5 days after the last dose escalation, plasma levels should be determined (12 h after last intake). When determining the dose of lithium, it is important to consider that different lithium salts have quite different molecular weights. Lithium tablets must therefore be dosed according to their content of Li^+ given in mmol. When switching from one lithium salt to another, this must be accounted for to avoid, for example, severe intoxication. Thus, for example, while lithium aspartate tablets of 500 mg contain 3,2 mmol Li^+, lithium carbonate tablets of 450 mg contain 12,2 mmol Li^+. When changing 1:1 from lithium aspartate to lithium carbonate this would slightly reduce the dose measured in milligram, but, in fact, increase the dose of the active compound (Li^+) by a factor of almost 4, given the narrow therapeutic range of Li^+ – perhaps, already a toxic dose! While ordinary daily doses amount to 20–30 mmol, older patients with reduced lithium clearance often need much smaller doses.

Efficacy

Lithium salts have been proven efficacious as a monotherapy of acute mania of the euphoric type. Lithium is only a second-line treatment in mixed or dysphoric mania where valproate, ▶ atypical antipsychotics, and carbamazepine are considered first-line choices.

The second indication for lithium is the treatment of acute ▶ bipolar disorder. Lithium can be used as monotherapy as well as in combination with an ▶ antidepressant agent. The latter strategy of primarily combining lithium with an AD should not be mistaken as lithium augmentation (see below). The combination of lithium and the antidepressant should prevent the patient from switching into mania.

There is convincing evidence that lithium is the drug of first choice in the long-term treatment and prophylaxis of bipolar disorder. However, with the expansion of the bipolar spectrum, data on the effectiveness of lithium in routine care have been controversial.

Current guidelines specify that long-term lithium treatment is indicated in patients

(a) who experienced at least one single-manic episode of disruptive severity and have a positive family history;
(b) who experienced two episodes, one of them manic, and have a positive family history;
(c) who experienced three episodes.

In addition, lithium has the greatest evidence supporting an antisuicidal and mortality-reducing effect in bipolar disorder. Clinicians should thus strongly consider initiating lithium treatment in patients with mood disorders accompanied by a high risk of suicide.

Lithium augmentation of an antidepressant has been recommended as the strategy of first choice in patients with therapy-resistant unipolar depression in many of the current guidelines. The addition of lithium to a preceding antidepressant serves as a net-enhancing effect on serotonin function.

Lithium may as well be used for the long-term treatment of recurrent unipolar depression, first of all as the antisuicidal effect has been proven for this diagnostic group too, but in addition due to lithium's episode-preventing effect. However, evidence is not as solid as for bipolar illness.

Other indications for lithium treatment are

- conduct disorder including severe aggression and explosive affect in children and mentally retarded patients, based on lithium's serotonin-enhancing effects;
- cluster headache, with a minor role of lithium behind various first-choice drugs;
- prophylaxis of herpes virus infections, based on lithium's antiviral activity.

Recent research covers the immunoregulatory effects of lithium, possibly relevant in AIDS and cancer as well as neuroprotective effects that are potentially useful in the prevention of dementia and neurological diseases.

Safety/Tolerability

Long-term side effects of lithium are infrequent and serious side effects are rare, if the patients and the dosage are properly selected and monitored. Because lithium ions influence a large number of important biochemical

processes (see above), lithium has a potential to induce a relatively wide spectrum of adverse reactions in a variety of organ systems. With regard to safety and tolerability, acute and prophylactic lithium therapies follow similar basic principles. When considering side effects, it is important to distinguish between acute and long-term changes, the relatively common symptoms that can appear during the normal course of lithium prophylaxis, and the rare, intense symptoms indicative of lithium intoxication.

Table 1 shows the relative and absolute contraindications of lithium therapy.

Table 2 shows adverse effects of lithium therapy and comments on frequency and therapeutic options.

The most important laboratory tests before starting long-term lithium treatment are

- serum creatinine and creatinine clearance (estimate using the Cockcroft equation);
- T3, T4, TSH levels;
- complete blood count;
- ECG;
- fasting glucose levels.

The serum lithium level should be measured 12 ± 1 h after the last dose has been taken. The dose requirement can then be estimated proportionally. Following the initiation of lithium prophylaxis, serum lithium levels must be checked on a weekly basis. Later, monitoring should be performed approximately once per month during the first year of treatment and, subsequently, every 6–12 weeks.

In general, for most patients, a serum lithium level in the range of 0.6–0.8 mmol/l is recommended for lithium prophylaxis. In older patients, in most women, and in patients who are particularly sensitive to side effects, it may be advisable to reduce lithium levels to 0.6 mmol/l.

Serum creatinine should be monitored at least every 6–12 months. Serum calcium should be monitored every 6–12 months due to the risk of hyperparathyroidism during lithium treatment. The patient's thyroid hormone status should be checked by measuring serum T3, T4, and basal TSH once a year. Regular ultrasound examination of the thyroid is also recommended.

A complete blood count (or at least a leukocyte count) should be performed every 6–12 months.

Medical diseases occurring during lithium treatment should be carefully monitored. Serum lithium should be assessed more frequently and the dosage adjusted so that serum lithium levels remain as low as possible.

In patients with arterial hypertension, low salt diets should not be used, and diuretics should only be

Lithium. Table 1. (Absolute and relative) Contraindications to lithium.

	Absolute	Relative	Special caution with
Renal	Acute renal failure	Disorders with decreased glomerular filtration rate, tubular disorders	
Cardiovascular	Acute myocardial infarction	Cardiac rhythm disorders ("sick sinus" syndrome)	Arterial hypertension
Neurological		Cerebellar disorders Myasthenia gravis	Cerebral sclerosis Dementia; epilepsy Parkinson's disease
Dermatological		Psoriasis	
Endocrine		Hypothyroidism Addison's disease	
Gynecological		Pregnancy, 1st trimester	Pregnancy, 2nd and 3rd trimesters; childbirth; breastfeeding
Hematological		Myeloid leukemia	
General		Low sodium diet Anesthesia/surgery	Diarrhea, vomiting, fever
Medication		Diuretics	Antiphlogistics Muscle relaxants; anesthesia Anticonvulsants Tetracyclines; spectinomycin ACE inhibitors Methyldopa; neuroleptics

Lithium. Table 2. Adverse effects of lithium salts.

Organ system	Symptoms	Remarks/Therapy
Neurological/Psychiatric	Fine tremor of the fingers	Frequent side effect. Therapeutic options: dose reduction, change of dose regimen, beta-receptor blockers
	Muscle weakness	More likely at start of therapy
	Memory impairment	
Gastrointestinal	Nausea	Often at start of therapy
	Vomiting	Diarrhea and vomiting can be signs of lithium intoxication!
	Abdominal pain	
	Diarrhea	
Cardiovascular	Changes in ECG; flattening/ inversion of T wave	Reversible. Nonspecific changes are not dangerous
	Arrhythmias	Very rare. Result from initiation or conduction defects
	First-degree atrioventricular block	Regular ECG monitoring
	Sick-sinus syndrome, ventricular extrasystoles	Discontinuation of lithium
	Second- and third-degree AV block, bundle-branch block	
Renal	Polyuria, polydipsia, reduced concentration capacity	Reversible on discontinuation. Management options: dose reduction, amiloride
	Reduced glomerular filtration rate	Rare, prevent or avoid transient lithium subintoxications
	Nephrotic syndrome	Rare, reversible on discontinuation
Metabolism, electrolytes, and water balance	Weight gain	Frequent. Consider low caloric diet with normal sodium intake
	Edema	Rare. Caution when administering diuretics
Endocrine	Euthyroid goiter	Common. Suppressive therapy with L-thyroxin
	Rise of TSH, hypothyroidism	Common in long-term treatment, substitution necessary
	Hyperparathyroidism with hypocalcemia	Infrequent. Check serum calcium
Hematological	Moderate leukocytosis	Common. Reversible
Dermatological	Acne	Treat as usual
	Hair loss	Rare (check for hypothyroidism)
	Psoriasis	Can be exacerbated; maybe a relative contraindication

administered cautiously. Furthermore, in renal hypertension and diabetes mellitus, the late renal sequelae of each disease must be taken into account.

In cases of cerebral sclerosis, dementia, and other psychoorganic disorders, lithium – even at therapeutic levels – can lead to disorientation and other neurotoxic symptoms.

Pregnancy, breastfeeding

The risk of abnormal fetal development under lithium therapy has been overestimated for a long time. Based on case-control studies, the risk can be estimated as only slightly higher than normal during lithium therapy in pregnant women (at standard serum lithium concentrations). If the course of affective illness does not allow for interrupting long-term treatment, a continuation of lithium treatment during the first 3 months of pregnancy may be considered (Cohen et al. 1994). The side effects of lithium therapy apply both to the pregnant mother and the fetus. However, the toxicity threshold for the fetus is lower. A mother may nurse her child when on lithium therapy. However, the child's development must be properly monitored and the advantages of breastfeeding over formula-feeding need to be weighed against the risks.

Cross-References

► Bipolar Disorder
► Gene Expression
► Gene Transcription
► Mania
► Mood Stabilizers
► Neuroprotection

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Lithium Salts

► Lithium

Liver Toxicity

► Hepatotoxicity

Local Field Potentials

Synonyms

Field potentials

Definition

The electrophysiological recorded local field potential (LFP) is thought to represent the synchronized input (sum of somato-dendritic potentials) into a neuronal ensemble, as opposed to output neuronal spiking activity. This signal is typically recorded using a low impedance extracellular microelectrode that is subsequently band-pass filtered to remove slower (<10 Hz) and faster signal fluctuations (>300 Hz) indicative of sleep-related slow oscillations and neuronal spiking (action potential) activity, respectively.

Cross-References

► Magnetic Resonance Imaging (Functional)

Locomotor Activity

► Motor Activity and Stereotypy

Lofepramine

► Antidepressants
► Tricyclic Antidepressants

Lofexidine

Definition

Lofexidine is as an agonist at α2 adrenoceptors and acts presynaptically to decrease adrenergic neurotransmission in the central nervous system, notably activity of the locus coeruleus. Through this mechanism, it decreases many of the autonomic symptoms of opioid withdrawal in humans and in animal models. It is under investigation for managing withdrawal from heroin or ► methadone and has been found more effective than placebo. Its efficacy appears similar to that of clonidine, another α2 agonist, but it has lesser adverse effects.

Cross-References

► Opioid Dependence and Its Treatment

Long QT Syndrome

Synonyms
LQTS

Definition
A cardiac arrhythmia where the QT interval on the ECG is prolonged; it can be inherited or acquired. The acquired form is due to disturbances in blood electrolytes or to various drugs. It is a condition with delayed repolarization following depolarization (excitation) of the heart, associated with syncope (fainting) due to ventricular arrhythmias, which can deteriorate into ventricular fibrillation and ultimately sudden death.

Cross-References
► Opioid Dependence and Its Treatment
► Sex Differences in Drug Effects

Long-Delay Learning

Definition
Long-delay learning refers to the phenomenon whereby an association of two temporally related stimuli can be made when there is an extended period of time between their presentations. Traditional learning theory suggests that as the temporal delay between the presentations of two stimuli increases, there is a graded reduction in the strength of the association between the two. When long-delay learning occurs, the association of the two stimuli occurs over longer intervals than seen under traditional learning conditions. Such learning is usually suggested to be evolutionarily important.

Cross-References
► Conditioned Taste Aversions

Longitudinal Aspect

Definition
Concerning the long-term course of a disorder with its specific patterns and characteristics.

Long-Lasting Synaptic Depression

► Long-Term Depression and Memory

Long-Term Depression

► Long-Term Depression and Memory
► Synaptic Plasticity

Long-Term Depression and Memory

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Definition

Memory
► Memory describes the storage of information acquired during learning in a form that can be accessed and retrieved. It encompasses the conscious memory of factual information as well as the unconscious use of procedural information.

The acquisition, storage, and retrieval of information are arguably the most complex and fascinating functions of the nervous system, and undoubtedly involve many brain regions. Following pioneering studies in the twentieth century, a convenient working model of learning and memory emerged whereby different brain regions are deemed responsible for storing different types of learned information (Table 1). The famous case of patient H.M. who suffered specific memory deficits following bilateral removal of the medial temporal lobe (reviewed by Squire and Zola-Morgan 1988) was pivotal in highlighting the separation of brain systems concerned with ► declarative memory (conscious recollection of episodic or semantic information) vs. nondeclarative memory (unconscious use of learned information). Whether or not the different forms of memory stored in different brain regions involve common mechanisms, such as alterations in synaptic strength (e.g., long-term depression), remains controversial.

Long-Term Depression
Long-term depression (LTD) is the weakening of neuronal synaptic connections, typically following a specific pattern of neuronal activity. The reduction in synaptic strength (a form of ► synaptic plasticity) lasts from hours to days. It can be ► homosynaptic (specific to the synapses

Long-Term Depression and Memory. Table 1. Classification of memory. (Reviewed by Squire and Zola-Morgan 1988.)

	Declarative	Nondeclarative
Synonyms	Explicit	Implicit
Definition	Conscious recollection of specific information	Unconscious use of learned information
Brain regions	Hippocampus	Basal ganglia
	Perirhinal cortex	Amygdala
	Prefrontal cortex	Cerebellum
Examples	Episodic memory – the features of an event, e.g., *what, where, who*	Procedural learning of skills and habits
	Semantic memory of factual information	Operant conditioning
	Recognition memory	Classical Pavlovian conditioning, e.g., emotional conditioning; motor conditioning (e.g., eye-blink)
	Working (short-term) memory	

that are subject to the inducing pattern of activity) or ► heterosynaptic (spreading to nonstimulated synapses).

LTD is widely expressed throughout the central nervous system (CNS) and is elicited at excitatory and inhibitory synapses via a diverse number of mechanisms (Table 2). Evidence suggests that mechanisms of LTD contribute to experience-dependent development and forms of learning and memory, as well as being implicated in neurological disorders, including mental retardation, ► Alzheimer's disease, and drug addiction. For the purpose of simplicity, we have chosen to focus on LTD at excitatory synapses in two brain regions: the hippocampal CA1 area, where the classical form of LTD is expressed, best understood mechanistically, and a potential target site for cognition-enhancing drugs (► cognitive enhancers), and the ► ventral tegmental area (VTA) of the midbrain, where LTD is targeted by ► drugs of abuse and is therefore of particular psychopharmacological interest.

LTD and Memory in the Hippocampal CA1 Region

The ► hippocampus forms part of the temporal lobe learning and memory system concerned with declarative memory of episodic and semantic information (Table 1). Three forms of ► glutamate receptor-dependent LTD have been described in the hippocampal CA1 region (reviewed by Malenka and Bear 2004); each form is summarized in Table 3. The first description of LTD in the hippocampus was Homosynaptic NMDAR-Dependent LTD at Schaffer collateral synapses onto pyramidal cell dendrites in the CA1 region of hippocampal slices (Fig. 1). Postsynaptic NMDA glutamate receptors permit Ca^{2+} entry into the neuron and it is generally well accepted that this Ca^{2+} influx triggers activation of ► postsynaptic proteins including the protein phosphatases, calcineurin, and protein phosphatase 1 (PP1). Expression of NMDA receptor-dependent LTD depends on modification of AMPA glutamate receptor phosphorylation states in addition to physical loss of ► AMPA receptors from the synapse (► receptor trafficking). ► Protein synthesis and degradation of postsynaptic density 95 (PSD-95) are required for the expression of this form of LTD.

Hippocampal mGluR-dependent LTD was first described in the CA1 region of hippocampal slices (reviewed by Malenka and Bear 2004) and requires mGluR5 receptor activation for its induction. This form of LTD can be induced chemically, via application of the selective group I mGluR agonists, or electrically via synaptic stimulation (Table 3). mGluR-dependent LTD, like NMDA receptor-dependent LTD, is expressed via mechanisms involving protein synthesis and the loss of postsynaptic AMPARs.

A distinct form of mGluR-dependent LTD exists in young rats that is induced by the group 1 mGluR agonist, DHPG, and synaptic stimulation but is expressed presynaptically. A retrograde messenger released from the postsynaptic cell is required, and likely candidates include ► endocannabinoids and 12-lipoxygenase metabolites of arachidonic acid, including 12-(S)-HPETE, recently shown to be the endogenous mediator of mGluR-dependent LTD at excitatory synapses onto CA1 stratum radiatum interneurons (Gibson et al. 2008). This heterosynaptic form of LTD (*TRPV1-dependent LTD*) occurs in response to high-frequency stimulation and release of

Long-Term Depression and Memory. Table 2. Examples of LTD in different brain regions.

Brain region	LTD expressing synapses	Drugs affecting LTD	Implications in memory
Hippocampus	*SC–CA1* pyramidal neurons	*NMDAR* and Ca^{2+} channel antagonists	Declarative learning and memory
	SC and *AC* input to *CA1* and *CA3* pyramidal neurons	mGluR antagonists	e.g., semantic and spatial memory, novelty and learned recognition of environment, stress-induced memory recall
	PP to dentate gyrus interneurons	mGluR antagonists	
	SC–CA1 interneurons	Rimonabant (SR141716A), *CB*1 and TRPV1 receptor antagonists, mGluR antagonists	Clinical relevance: amnesia and cognitive impairment
	Interneuron to *CA1* pyramidal neurons	Δ^9-THC	
Ventral tegmental area	*EPSC*s onto dopamine neurons *IPSC*s onto dopamine neurons	Amphetamine, D2 receptor agonists, Opioids	Nondeclarative forms of learning and memory
Caudate/ putamen	Cortical inputs to medium spiny neurons	NOS and soluble guanylyl cyclase inhibitors, mGluR, D2 and *CB1* receptor antagonists	Adaptive learning of motivated actions in response to salient stimuli; development of habits
Nucleus accumbens	Cortical inputs to medium spiny neurons	Δ^9-THC, *CB1* and TRPV1 receptor antagonists, mGluR antagonists	Clinical relevance: development of "unhealthy" habits, e.g., drug addiction
Perirhinal cortex	Cortical inputs from entorhinal cortex to layer II/III pyramidal neurons	Quinpirole, NMDA, and kainate receptor antagonists	Recognition memory
Prefrontal cortex	Layer II/III fibers to layer V/VI pyramidal neurons	5-HT2A/C antagonists, Group I mGluR antagonists, *CB1*R antagonists, MAPK inhibitors	Executive memory functions e.g., working memory, organization of voluntary movements, emotion
Visual cortex	Thalamocortical input to layer V pyramidal neurons	Group II mGluR antagonists, *NMDAR* antagonists, cocaine	Development of visual circuitry
	White matter to layer II–IV neurons	mGluR antagonists	
Cerebellum	Parallel fiber input to Purkinje neurons	NOS and soluble guanylyl cyclase inhibitors, mGluR, D2 and *CB1* receptor antagonists	Procedural (motor) learning

CB1 cannabinoid type 1 receptor; *EPSC* excitatory postsynaptic currents; 5-HT, serotonin; *IPSC* inhibitory postsynaptic currents; *MAPK* mitogen-activated protein kinase; *mGluR* metabotropic glutamate receptor; *NMDAR* ▶ *N*-methyl-D-aspartate glutamate receptor; *NOS* nitric oxide synthase; Δ^9-THC, delta 9-tetrahydrocannabinol; *TRPV1* transient receptor potential vanilloid 1; *SC* Schaffer collateral; *AC* associational commissural; *PP* perforant path.

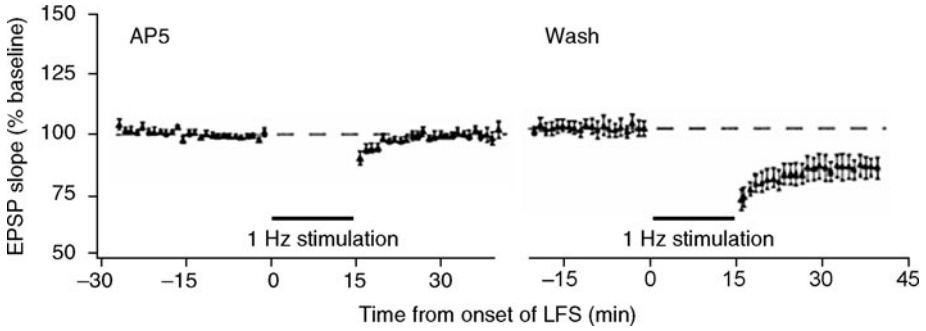
endocannabinoid-like molecules known as endovanilloids that act on presynaptic TRPV1 (transient receptor potential vanilloid 1) receptors.

The question of whether or not experimental models and mechanisms of LTD in the hippocampus underlie memory (reviewed by Massey and Bashir 2007) remains controversial. In principle, one would determine whether or not LTD is induced in the hippocampus coincidentally with learning and memory and then block LTD, producing correlating impairments in memory acquisition and storage. In practice, the difficulties of "measuring" learning and memory make definitive, conclusive experiments of this kind challenging. CA1-restricted *NMDAR1* gene knockout mice lack NMDA receptor-dependent LTD at CA1 synapses and exhibit impaired spatial memory during a hippocampal-dependent task, while learned

Long-Term Depression and Memory. Table 3. Different forms of LTD in the hippocampal CA1 region.

	NMDAR-dependent LTD	mGluR-dependent LTD	Endocannabinoid/Endovanilloid-mediated LTD
Synapses expressing	*SC–CA1* pyramidal neuron	*SC–CA1* pyramidal neuron, *SC–CA1* s. radiatum interneuron	*SC–CA1* pyramidal neuron, *SC–CA1* s.radiatum interneuron
Induction protocol	Low-frequency stimulation (*LFS*), 0.5–3.0 Hz, typically 1 Hz for 15 mins	Paired-pulse low-frequency stimulation (*PP–LFS*), typically 1 Hz for 15 min; Application of *DHPG*	*PP–LFS*, typically 1 Hz for 15 mins; application of *DHPG;* high-frequency stimulation (*HFS*); e.g., 100 Hz (× 2, 20 s inter-train interval)
Mechanism of induction	*Postsynaptic:* NMDAR activation; Ca^{2+} influx and release from intracellular stores	*Postsynaptic*: Group 1 mGluR activation; Ca^{2+} influx	*Postsynaptic:* Group 1 mGluR activation; Ca^{2+} influx; phosphoinositide hydrolysis; release of retrograde messengers
Mechanism of expression	*Postsynaptic*: Activation of protein phosphatase, calcineurin, *PP1*; *PSD-95* degradation; modification and internalization of *AMPARs*; protein synthesis	*Postsynaptic*: Activation of protein tyrosine phosphatase, p38 mitogen activated protein kinase cascade, *PI3K* and Ras-activated *ERK*; *AMPAR* internalization; protein synthesis	*Presynaptic*: Activation of presynaptic receptors e.g., *CB1* and *TRPV1* by retrograde messengers; decreased presynaptic neurotransmitter release

AMPAR α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate acid glutamate receptor; *CB1* cannabinoid type 1 receptor; *DHPG* Dihydroxyphenylglycine; *HFS* high-frequency stimulation; *hertz* (Hz); *mGluR* metabotropic glutamate receptor; *NMDAR* N-methyl-D-aspartate glutamate receptor; *PI3K* phosphoinositide-3 kinase; *PP1* protein phosphatase; *PP-LFS* paired-pulse low-frequency stimulation *PSD-95* postsynaptic density-95;*TRPV1* transient receptor potential vanilloid 1;*SC* Schaffer collateral



Long-Term Depression and Memory. Fig. 1. Original experimental data of Dudek and Bear (1992) showing NMDA receptor-dependent LTD in the hippocampus. In the presence of the NMDA receptor antagonist AP5, low-frequency synaptic stimulation (1 Hz for 15 min) produces no change in the synaptic response. When AP5 is washed off, the same low-frequency synaptic stimulation now produces a decrease in synaptic responses: LTD. (Reproduced from Dudek S, Bear M (1992) Homosynaptic long-term depression in area CA1 of hippocampus and effects of *N*-methyl-D-aspartate receptor blockade. Proc Natl Acad Sci USA 89: 4363–4367 with permission.)

recognition of a novel environment in rats correlates well with the facilitation of homosynaptic NMDAR-dependent CA1 LTD. Hippocampal LTD is also enhanced by stress, which may be significant in stress-induced cognitive impairment. Overall, evidence suggests that LTD in the hippocampus is associated with at least certain forms of learning and memory (Massey and Bashir 2007).

LTD in the Ventral Tegmental Area (VTA)

The VTA is a midbrain nucleus containing dopaminergic neurons that project to the ventral striatum and the prefrontal cortex, along with nondopaminergic projection and local circuit neurons, some of which are GABAergic. Ascending mesocorticolimbic dopaminergic pathways along with nigrostriatal pathways play a role in internally

generated movements, motivation and reward processing, learning, and cognitive functions, including nondeclarative forms of learning and memory. From a psychopharmacological perspective, these pathways are interesting because they are targets for drugs of abuse and are likely target sites for ▶ anti-psychotic drugs.

A substantial body of literature suggests that glutamatergic synaptic plasticity in dopaminergic pathways may contribute to reward-related learning and the neuronal plasticity mechanisms underlying drug ▶ addiction (reviewed by Kauer and Malenka 2007; Wolf et al. 2004). Persistent forms of synaptic plasticity have been described in dopaminergic pathways (reviewed by Kauer 2004; Kauer and Malenka 2007; Wolf et al. 2004). A form of LTD at glutamatergic synapses was first described in VTA dopaminergic neurons in 2000. This form of VTA LTD was not dependent on either NMDARs or mGluRs, but did require an increase in intracellular Ca^{2+}, most likely via influx through voltage-gated Ca^{2+} channels, subsequent activation of a novel signaling mechanism utilizing protein kinase A, and downregulation of AMPARs. A second form of mGluR-dependent LTD is also expressed in VTA (Bellone and Lüscher 2006).

VTA LTD has been proposed as a potential "brake" on dopaminergic neuron excitability (Kauer 2004), as weakening excitatory synaptic strength would limit the tonic and phasic excitatory drive to these neurons from cortical and brainstem regions, potentially minimizing opportunities for synaptic strengthening such as ▶ long-term potentiation. Removal of this "braking" mechanism is a plausible route for psychoactive drugs to manipulate synaptic plasticity in dopaminergic pathways and drive forms of learning that may be dysfunctional, such as habit learning in drug addiction.

Impact of Psychoactive Drugs

Hippocampal LTD, Cognitive Dysfunction, and Cognition-Enhancing Drugs

Evidence supports the idea that LTD may contribute to cognitive dysfunction. For example, soluble ▶ amyloid-beta protein (Aβ) extracted from the brains of ▶ Alzheimer's disease patients enhances hippocampal mGluR-dependent LTD and disrupts the memory of learned behavior in rats (Shankar et al. 2008). Mouse models of ▶ Huntington's disease, a neurological disorder involving cognitive dysfunction, exhibit impairments in CA1 hippocampal LTD as well as behavioral deficits in hippocampal ▶ spatial learning tasks (e.g., Murphy et al. 2000). NMDAR-dependent hippocampal LTD is both necessary and sufficient to cause an acute ▶ stress-induced impairment of ▶ spatial memory retrieval and may be involved in mediating some of the cognitive deficits that occur in disorders whose symptoms are aggravated by stress (reviewed by Massey and Bashir 2007). Taken together, these data suggest an underlying role for the mechanisms of hippocampal LTD in some aspects of cognitive dysfunction associated with specific neurological disorders.

Mechanisms underlying hippocampal LTD serve as possible drug targets for the treatment of cognitive dysfunction. For example, 17beta-estradiol ameliorates cognitive and memory dysfunction in postmenopausal women in addition to minimally suppressing hippocampal LTD in adult rats, suggesting that estrogen may act to improve memory by suppressing forgetfulness via a synaptic mechanism such as LTD (Vouimba et al. 2000). The NMDAR co-agonist D-serine enhances ▶ NR2B-dependent hippocampal LTD and reversal learning in the ▶ Morris water maze, supporting a role for NMDAR-dependent LTD in spatial learning, and highlighting molecular components of the LTD mechanism as targets for cognition-enhancing drugs.

VTA LTD and Psychoactive Drugs

VTA LTD is blocked by dopamine D2 (but not D1) receptor agonists (reviewed by Wolf et al. 2004), and therefore may be targeted by drugs of abuse that cause an increase in extracellular dopamine levels in the VTA. This has been shown for ▶ amphetamine, which blocks and reverses the somatodendritic ▶ dopamine transporter, thus causing release of dopamine within the VTA. One might expect that D2 receptor antagonists, such as many of the anti-psychotic drugs used to treat ▶ schizophrenia, could potentially enhance VTA LTD. However, comprehensive testing of the antipsychotic drugs used in clinical practice against VTA LTD has not been carried out.

If VTA LTD acts as a "brake" on the excitability of dopaminergic neurons (Kauer 2004), inhibiting LTD may provide a window of opportunity for synaptic strengthening. This ▶ synaptic plasticity would be associated with the salient event that caused elevated levels of extracellular dopamine in the VTA – for example, acquisition of novel reward information, or the presence of a drug of abuse. Such associations may contribute to the learning of procedural information with respect to drug-seeking and drug-taking behaviors that are, one might argue, maladaptive forms of memory. Conversely, induction of VTA mGluR-LTD reverses the ▶ cocaine-induced

strengthening of glutamatergic synapses in dopaminergic neurons, and is a putative mechanism for reversing the neuronal plasticity induced by cocaine (Bellone and Lüscher 2006).

Cross-References

- ► Addictive Disorders
- ► Antipsychotic Drugs
- ► Classical Pavlovian Conditioning
- ► Cocaine
- ► Cognitive Enhancers
- ► Declarative Memory
- ► Endogenous Cannabinoids
- ► Excitatory Amino Acid
- ► Long-Term Potentiation
- ► Memory
- ► Operant (Behavior)
- ► Spatial Memory
- ► Stress
- ► Synaptic Plasticity
- ► Working (Short-Term) Memory

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Long-Term Memory

Definition

A protein synthesis-dependent type of memory in charge of maintaining acquired information in a long-lasting manner.

Cross-References

- ► Protein Synthesis as a Mechanism of Memory

Long-Term Potentiation

Synonyms

LTP

Definition

The process by which simultaneous stimulation of two or more neurons induces a long-lasting improvement in the efficacy of the communication between them. A brief and rapid series of stimulation of axons can lead to a long-lasting potentiation of the response of the postsynaptic neurons to a new input. The duration of the potentiation varies from minutes or hours in brain slices and (more rarely) up to weeks in intact animals. It is especially associated with glutamatergic synapses that lasts many hours.

Cross-References

- ► Long-Term Potentiation and Memory
- ► Synaptic Plasticity

Long-Term Potentiation and Memory

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Definition

Memory is central to our understanding about ourselves with a personal history, and consequently memory loss has a devastating impact on both the individual concerned and their carers. Thus, one of the major goals in neuroscience is to understand the neural mechanisms that underlie the formation of memory within different brain

regions. ►Long-term potentiation (LTP), which is the long-lasting increase in synaptic strength produced by trains of stimuli, has been proposed to provide a suitable cellular model of information storage in the brain. This argument is based on the defining characteristics of LTP (i.e., specificity, associativity, and persistence) and the demonstration that psychoactive drugs that block LTP have been shown to impair memory. This chapter presents the evidence that the mechanisms that underlie LTP may be the same as those that are responsible for the formation of memory, with a focus on the impact of specific pharmacological manipulations. Memory formation clearly relies on fast, long-lasting changes in the connections between neurons; however, whether LTP, as per current studies, underlies learning and memory is still unproven and consequently a matter for ongoing debate.

Impact of Psychoactive Drugs

Any neural mechanism underlying learning and memory must involve processes that enable rapid but lasting changes in the efficacy of synaptic connections in the brain. Hebb (1949) famously proposed that memories may be stored in the brain through changes in the strength of communication between neurons. He postulated that "When an axon of cell A is near enough to excite a cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased." In 1973, Bliss and Lømo showed that the repeated application of high-frequency stimulation (a tetanus) to the perforant pathway in the ►hippocampus produced a long-lasting increase in the synaptic response to a subsequent single-pulse stimulus. This long-lasting increase in synaptic strength is termed long-term potentiation (LTP).

The Induction of LTP

LTP has been most extensively studied in the CA1 region of the hippocampus, a region significant because damage here results in severe memory impairments in both humans (specifically, impairments in episodic memory) and in animals (spatial and associative memory). At excitatory synapses in this region, there are two subtypes of ionotropic ►glutamate receptor, the ►AMPA and ►NMDA receptor. LTP is known to depend on the activation of ►NMDA receptors, which are not involved in normal synaptic transmission owing to the presence of magnesium in the ion channel pore of the receptor. However, sustained release of glutamate, which occurs during high-frequency stimulation, causes the post-synaptic cell to depolarize, which removes the magnesium ions from the pore of the NMDA receptor, thus enabling the NMDA receptor to become activated. The NMDA receptor is therefore in a position to detect the co-activation of the presynaptic and postsynaptic cells and can act as what has been described as a "coincidence detector" (Collingridge 2004). Following activation of the NMDA receptor, there is an influx of calcium into the postsynaptic cell, which triggers a range of intracellular second messenger systems, the effect of which is to produce an increase in synaptic strength (LTP). Thus, in most synapses that show LTP, the increase in calcium and thus the induction of LTP depend on the activation of NMDA receptors, but note that there are other forms of LTP, for example in the mossy-fiber-CA3 synapses, that do not depend on NMDA receptors (described as NMDA receptor-independent LTP).

LTP, A Cellular Basis for Memory

It has been argued that LTP displays properties that are consistent with the premise that it is a cellular mechanism underlying memory storage (see Collingridge 2004). These properties include the demonstration that LTP is (1) input-specific, (2) associative or cooperative, and (3) persistent. Input specificity refers to the demonstration that only the afferents that have received stimulation show potentiation. Associativity or cooperative refers to the demonstration that if stimulation of one pathway is insufficient for the induction of LTP, simultaneous strong stimulation of another pathway will induce LTP at both pathways. If LTP is to be considered as a model mechanism for the storage of information, it needs to fulfil other criteria; for example, it must be relatively long lasting, although how long it is required to last is still unclear. Further, LTP must be demonstrated in regions of the brain other than the hippocampus, and indeed there is now accumulated evidence that LTP may be induced in brain areas associated with memory including cortex, striatum, thalamus, cerebellum, and amygdala (see Lynch 2004).

One strategy to investigate the link between memory and LTP has been to investigate whether learning produces LTP-like changes. A number of studies have reported that exposure to stimulus-enriched environment or training on learning tasks such as eye-blink conditioning or radial arm maze can result in increases in synaptic strength within the hippocampal formation (see Martin and Morris 2002). In addition, there is increasing interest in the relationship between LTP in the amygdala and a specific form of learning and memory process known as ►fear conditioning. Fear conditioning is a simple Pavlovian conditioning paradigm, which involves pairing a neutral stimulus, for example a tone (the conditioned stimulus, CS) with an aversive stimulus, for example a mild footshock (the

unconditioned stimulus, US). This form of memory is rapidly acquired, the memory is long-lasting, and the paradigm presents an attractive model for investigation of the neural basis of memory as it is relatively simple when compared with the memory paradigms associated with the hippocampus.

There are several lines of evidence to suggest that LTP in the amygdala underlies the formation of fear conditioning memory. For example, first, LTP may be induced in the same sensory afferents to the amygdala, which show enhanced synaptic transmission during fear conditioning, and second, pharmacological and molecular manipulations that block LTP have also been shown to block the acquisition of fear conditioning (see below). It has also been demonstrated that both LTP and fear conditioning are dependent on the reliability of the CS to predict the US (known as CS–US contingency). Thus, in fear conditioning paradigms, it is well reported that if the CS does not accurately predict the US, or if there is a better predictor, for example other environmental cues, then the memory will be weaker. Similarly, in electrophysiological experiments, it has been shown that when a train of high-frequency stimuli applied to the afferents of the amygdala, were paired with a series of depolarizing current pulses to the postsynaptic cell in the lateral amygdala, robust LTP was produced. However, if a further, unpaired, depolarization was added 10 s after the pairing, no LTP occurred (see Martin and Morris 2002).

Different Forms of LTP may Subserve Different Memory Processes

Further evidence to support the link between LTP and memory is provided by the demonstration that neither LTP nor indeed the formation of a memory is a single process. Different forms of LTP have been described, depending on how long the increase in synaptic efficacy lasts and the degree to which each form of LTP is sensitive to receptor antagonism, dependent on protein synthesis and/or ▶ gene transcription. Broadly, LTP has been divided into two sub-categories: early LTP (E-LTP) and late LTP (L-LTP), where L-LTP lasts for hours in vitro and weeks in vivo. E-LTP (also described as LTP1) decays rapidly, is insensitive to protein synthesis inhibitors, and therefore does not depend on the formation of new proteins in the cell. L-LTP has been further subdivided into LTP2 and LTP3. LTP2 last for an intermediate length of time and depends on new protein synthesis, but not on gene transcription, LTP3 is the long-lasting and most stable component of LTP, which depends on both new protein synthesis and gene transcription (Raymond 2007).

In light of this dissociation between different forms of LTP, mediated by distinct cellular processes, it has been suggested that each may subserve different mnemonic processes. Thus, LTP1 may underlie short-term memory, LTP2 intermediate memory, i.e., memory that lasts up to 3 h, and LTP3 may underlie long-term memory, i.e. memory retained for longer than 3 h (see Blockland and Boess 2008).

The Effects of Pharmacological Agents on LTP and Memory

There is now a vast body of experimental evidence, which has identified pharmacological agents that block both LTP and memory or indeed enhance LTP and memory; hence, a comprehensive review of all such treatments is beyond the scope of this chapter and the reader is referred to the references provided.

Glutamate

NMDA Receptors

One of the first pieces of evidence to suggest that LTP might be required for memory formation in vivo was provided by the demonstration that blockade of ▶ NMDA receptors, by the NMDA receptor antagonist AP5, in the hippocampus, blocks both the induction of LTP and produces an impairment in ▶ spatial learning but not in visual discrimination learning in the rat (see Martin and Morris 2002). Since that initial demonstration, NMDA receptor blockade has been shown to impair a range of hippocampal-dependent memory tasks including T-maze alternation, ▶ contextual fear conditioning, and non-hippocampal-dependent tasks such as fear conditioning. Interestingly, while blockade of NMDAR have been shown to impair both the ▶ encoding and early ▶ consolidation of memory information, and the induction of LTP, blockade of these receptors, has been shown to have no effect on memory ▶ retrieval or on pre-established LTP (Collingridge 2004; Martin and Morris 2002).

▶ Metabotropic Glutamate Receptors

There has been disagreement over the role that metabotropic glutamate receptors (mGluRs) play in LTP. LY341495, an mGluR antagonist, which at certain concentrations antagonizes all known mGlu receptors, has been shown to have no effect on LTP at hippocampal CA1 synapses. In contrast, antagonism of group 1 MGlu receptors has been shown in some studies to block the induction of LTP and blockade of group 1 mGLURs has also been shown to impair a range of behaviors including spatial learning, contextual fear conditioning, and inhibitory avoidance learning (see Lynch 2004).

AMPA Receptors

► Ampakines are a class of compounds, which bind to AMPA receptors but do not show either agonist or antagonist effects. These compounds act to keep the channel open once glutamate has bound, thus prolonging current flow through the receptor. Ampakines have been shown to lower the threshold for the induction of LTP and increase the magnitude of LTP. Behavioral studies have revealed that these compounds improve retention in the ► radial arm maze and improve ► short-term memory (Lynch and Gall 2006).

► Acetylcholine

► Muscarinic Receptors

Acetylcholine muscarinic receptors (mAChRs) are ► G-protein coupled receptors of which there are five subtypes (M_1–M_5). mAChRs have long been implicated in a variety of memory functions, for example ► scopolamine a non-selective mAChR antagonist has been shown to produce significant behavioral impairments in tasks including the water maze, fear conditioning, and ► object recognition. Consequently, the roles of the mAChRs in LTP at many areas of the central nervous system have been extensively studied. Activation of mAChRs has been shown to facilitate the induction of LTP and application of the muscarinic agonist carbacol has been shown to enhance LTP and to improve memory performance (see Blockland and Boess 2008; Shinoe et al. 2005). However, in contrast to such reports, administration of the nonselective mAChR antagonist atropine was found to have no effect on the induction of LTP, although it did significantly reduce the magnitude of the LTP, and scopolamine has been shown to have no effect on the induction of LTP in the perirhinal cortex.

► Nicotinic Receptors

Neuronal acetylcholine nicotinic receptors (nAChRs) are ligand-gated ion channels comprising either α subunits or a combination of α and β subunits, with α7 and α4 β2 being the two main subtypes in the central nervous system. Studies have shown that application of ► nicotine can both induce LTP and enhance LTP produced by sub-threshold levels of stimulation, an effect dependent on both α7 and non- α7 nAChRs. In memory tasks, acute intrahippocampal administration of nicotine after training has been shown to enhance hippocampal-dependent memory, and chronic administration of nicotine has been shown to improve spatial working memory in the radial arm maze however other studies using different doses, dosing methods, and regimes have found conflicting results (see Kenney and Gould 2008).

► Dopamine and Noradrenaline

The neuromodulators dopamine and noradrenaline have been implicated in both LTP and memory. Thus, pharmacological blockade of dopamine D1/D5 receptors has been shown to impair L-LTP in the CA1 region of the hippocampus and to impair long-term but not short-term spatial memory in the water maze while blockade of beta-adrenergic receptors modulates E-LTP (see Martin and Clark 2007). LTP has been produced in the mesolimbic dopamine system, which comprises the ► ventral tegmental area and ► nucleus accumbens and in view of the key role this neural system plays in the behavioral effects of drugs of abuse, there is increasing research into the role of LTP, and other forms of ► synaptic plasticity in the development of addiction (see Saal and Malenka 2005).

Conclusions

There is now a huge body of research attempting to evaluate the hypothesis that LTP is a cellular substrate for learning and memory, and clearly much of this evidence has been obtained from pharmacological studies like those described above. However, such evidence is correlative, and although both LTP and memory may be disrupted by the same interventions, this does not prove that both processes are mediated by the same underlying mechanisms. For example, it has been argued by some investigators that the observed impairments in the water maze following NMDA or muscarinic receptor blockade might be accounted for by impairments in sensorimotor processes, or that LTP might play a role in cognitive processes other than memory, for example attention, that contribute to performance in behavioral tasks (see Martin and Morris 2002). Further, LTP is often studied in vitro, using highly artificial stimulation protocols; so, while the processes that produce LTP in the laboratory may provide valuable insights into synaptic physiology, it must be remembered that they do not represent the actual mechanism for the storage of information in vivo.

Thus, while the acquisition and consolidation of memory must require quick and long-lasting changes in neural circuitry, a definitive link between LTP and the engram has not yet been provided.

Cross-References

► Excitatory Amino Acids and Their Antagonists
► Muscarinic Agonists and Antagonists
► Nicotinic Agonists and Antagonists

► Spatial Learning in Animals
► Synaptic Plasticity

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Long-Term Treatments for Bipolar Disorder

► Mood Stabilizers

Loprazolam

Definition

Loprazolam is a high-potency medium-acting benzodiazepine medication used in the treatment of sleep disorders. It has some antispasmodic and anticonvulsant effects. It is not antidepressant. Unwanted effects include sedation, headaches, paradoxical excitement, confusion, cognitive and psychomotor impairment, and confusion in the elderly. Long-term use may induce dependence with withdrawal reactions. Recreational use and abuse can occur: loprazolam is a scheduled substance.

Cross-References

► Benzodiazepines
► Insomnias
► Minor Tranquilizers

Lorazepam

Definition

Lorazepam is a ► benzodiazepine that has anxiolytic, sedative, and anticonvulsant properties. Its duration of action is of intermediate length relative to other benzodiazepines (i.e., its ► elimination half-life is 10–18 h) and it does not have active (i.e., benzodiazepine) metabolites. Lorazepam is used primarily to treat anxiety, including panic. Like most similar compounds, it is subject to tolerance, dependence, and abuse.

Cross-References

► Anxiolytics
► Benzodiazepines

Lormetazepam

Synonyms

Methyl-lorazepam

Definition

Lormetazepam is a benzodiazepine medication that has anxiolytic, sedative, and anticonvulsant properties. Its duration of action is of intermediate length relative to other benzodiazepines (i.e., ► elimination half-life 10–12 h) and it does not have active (i.e., benzodiazepine) metabolites. It has been used clinically as a hypnotic. Like most similar compounds, lormetazepam is subject to tolerance, dependence, and abuse.

Cross-References

► Anxiolytics
► Benzodiazepines
► Hypnotics

Love Drug

► Methylenedioxymethamphetamine (MDMA)
► Oxytocin

Love Hormone

- ▶ Methylenedioxymethamphetamine (MDMA)
- ▶ Oxytocin

LQTS

- ▶ Long QT Syndrome

LSD

- ▶ Hallucinogen Abuse and Dependence
- ▶ Hallucinogens

LTD

- ▶ Long-Term Depression and Memory

LTP

- ▶ Long-Term Potentiation

LY127809

- ▶ Pergolide

LY139603

- ▶ Atomoxetine

Lysergic and Diethylamide

- ▶ Hallucinogen Abuse and Dependence
- ▶ Hallucinogens

M

μ-Receptor

Definition

The term μ-opioid (μ from *m*orphine) peptide receptor represents the ▶ G-protein-coupled receptor that responds selectively to the majority of clinically useful ▶ opioid drugs. It is usually named the μ-receptor or MOR. It is expressed in areas of the nervous system that mediate therapeutic and adverse effects of most opioid drugs. The MOR receptor protein is produced by a single gene. Several mRNA splice variants are known to exist and produce receptor proteins that display different properties when expressed in cells. When activated, the MOR receptor predominantly transduces actions via inhibitory G-proteins. The direct electrophysiological consequences of MOR receptor activation are usually inhibitory.

μPET

Definition

A μPET machine is a relatively high-resolution positron emission tomography imaging device for the noninvasive assessment of small animals, for example, to study receptor occupancy (with specific radioligands) or functional activity (with radiolabeled deoxyglucose) of the brain, to evaluate animal models of psychiatric or neurological disorders, or to develop novel radiotracers for use in man.

Cross-References

▶ Deoxyglucose
▶ Positron Emission Tomography

mAChR

▶ Muscarinic Receptors

Magnesium Pemoline

▶ Pemoline

Magnetic Resonance

▶ Nuclear Magnetic Resonance

Magnetic Resonance Imaging (Functional)

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Synonyms

fMRI; Functional magnetic resonance imaging

Definition

Functional magnetic resonance imaging (fMRI) is a specialized form of MRI and a modern ▶ neuroimaging technique that is typically used for investigating brain activity in animals and humans. Most fMRI experiments measure blood-oxygenation-level dependent (▶ BOLD) contrast – an endogenous hemodynamic signal that reflects blood oxygenation changes linked to neuronal activity. BOLD fMRI is thus an *indirect* or surrogate measure of neuronal function. Because intracranial recordings of ▶ local field potentials better predict changes in BOLD signal amplitude than ▶ multiunit activity, it is generally considered to reflect synaptic input and local processing in neuronal ensembles as opposed to neuronal spiking activity per se. In conventional applications, BOLD fMRI has a temporal resolution in the order of seconds (1–3 s) and a spatial resolution in the order of millimeters (cubes of tissue 3–5 mm on each side) when covering the whole

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brain. Largely due to its noninvasive nature and good spatiotemporal resolution, but also through growing understanding of the biophysical basis of the BOLD signal, as well as advances in the acquisition, design, and statistical analysis of brain mapping experiments, BOLD fMRI has become a principal research tool in human ▶ cognitive neuroscience since the mid-1990s.

Principles and Role in Psychopharmacology

Blood circulation and energy metabolism are closely linked to neuronal synaptic activity in the brain – an observation first suggested by nineteenth century researchers. fMRI, and specifically BOLD contrast fMRI (BOLD fMRI), is a modern neuroimaging technique that exploits the fact that such processes, particularly blood flow and blood oxygenation, are regionally coupled to changes in neuronal activity levels.

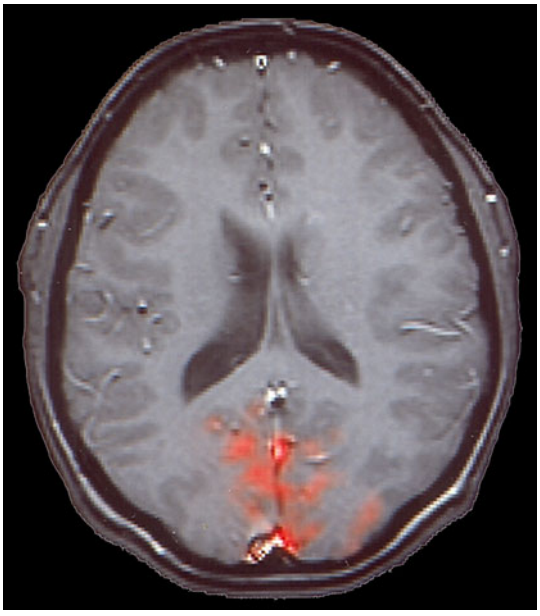
Background Principles

Active neurons consume oxygen that is carried by hemoglobin in capillary red blood cells. Under periods of increased neuronal demand for oxygen (⇑ oxygen utilization), there is an accompanying increase in cerebral blood flow (CBF) to active brain areas, or functional hyperemia. Central to understanding BOLD fMRI is that, during this period of increased blood flow, blood oxygenation increases more than what is required to satisfy the increased neuronal demand for oxygen, leading to local changes in the relative concentration of oxygenated and deoxygenated blood, as well as local cerebral blood volume.

Magnetic resonance imaging (MRI), extending the principle of ▶ nuclear magnetic resonance (NMR), has the capacity to measure physiological changes associated with increased (or decreased) neuronal activity, such as measurements of tissue perfusion, blood volume, and blood oxygenation. To understand these measurements, it is necessary to have basic knowledge of the physical, biophysical, and engineering principles of MRI and its functional variants such as BOLD fMRI. For this, several comprehensive introductory texts are available (inc. Buxton 2002; Huettel et al. 2004; Jezzard et al. 2003).

Two early discoveries of special relevance to BOLD fMRI are (1) that deoxygenated hemoglobin is ▶ paramagnetic and (2) that there is an oxygenation dependence of the transverse relaxation time of water protons in whole blood at high magnetic field strengths (1.5 or greater). This led Ogawa et al. (1990) to investigate whether altering blood oxygenation levels would influence the visibility of blood vessels on T_2^*-weighted MR images. When increasing the relative concentration of deoxygenated hemoglobin in blood, they observed reduced T_2^*-weighted signal intensity in local vasculature on ▶ gradient-echo images (GE). Ogawa and colleagues went on to suggest that their observation of "BOLD contrast" could potentially be used to investigate neuronal activity, albeit indirectly, through changes in blood flow and tissue oxygenation.

The first BOLD fMRI studies of the brain in humans were reported in 1992 and involved sensory related activation of the visual and motor cortices (Fig. 1). This work confirmed that MRI could be used to investigate regional changes in brain activity, similar to functional brain mapping studies undertaken at the time with ▶ PET imaging. Since these initial studies, the growth of BOLD fMRI in neuroscience applications has been extraordinary. While BOLD fMRI initially provided a noninvasive and improved brain mapping alternative to PET imaging, it has since taken on its own unique role in cognitive neuroscience research, as well as having a variety of



Magnetic Resonance Imaging (Functional). Fig. 1. An early blood-oxygenation-level dependent (BOLD) fMRI study of visual cortex activation in a single human subject. This study was performed in October 1992 at the Magnetic Resonance Centre of Pedralbes in Barcelona, Spain (gradient-echo sequence at 1.5 T, GE Signa), single-slice acquisition, 96 × 64 pixel matrix; round surface coil; TR=7 s. The subject was stimulated with an 8 Hz visual flicker in a blocked-design experiment that compared four blocks of visual stimulation alternating with four blocks of darkness. Eight images were acquired per block. (Image courtesy of J. Pujol.)

clinical and commercial applications. According to a recent estimate, over 19,000 peer-reviewed articles are returned from an ISI/Web of Science search with the keyword terms "fMRI" or "functional MRI" or "functional magnetic resonance imaging," and where the rate of fMRI-related publications has risen from a total of four papers in 1992 to eight papers per day by 2007 (Logothetis 2008). Of the total number of reports, approximately 43% investigated functional localization and/or anatomy associated with specific stimuli or tasks (sensory, cognitive, and emotional); 22% were "region of interest" (ROI) studies examining the physiological properties of distinct brain regions; 8% were related to neuropsychology; 5% were on the properties of the fMRI signal; and the remaining work was related to various topics including plasticity, drug action, experimental design, and analysis methods. For a specific overview of fMRI applications in clinical neuroscience, including ▶ pharmacological fMRI (ph-fMRI), see Matthews et al. (2006).

Spatial and Temporal Resolution

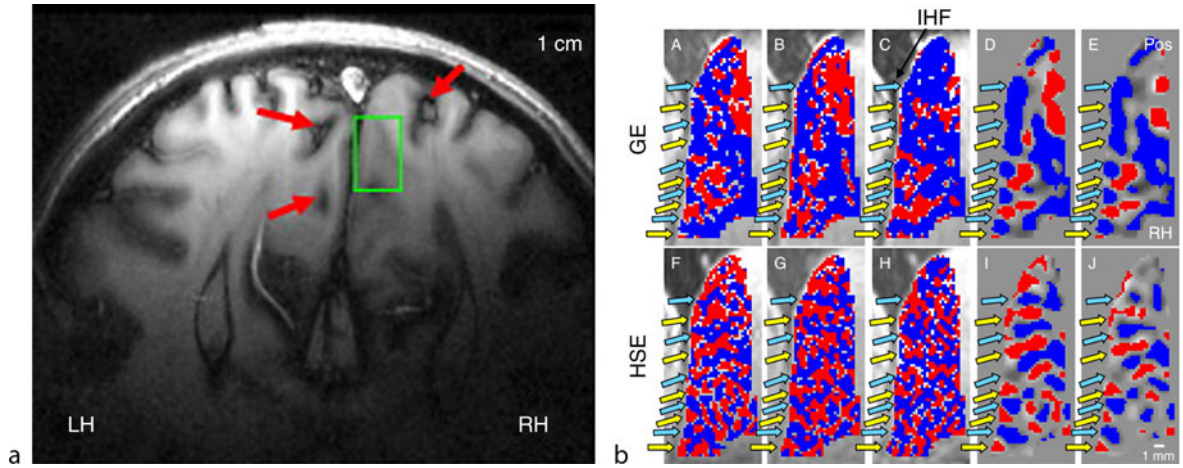
Spatial resolution in fMRI experiments is defined by voxel size – 3D rectangular prisms (volume elements) that form the basic unit of measurement in MR images. In whole brain fMRI studies, voxels will typically have a resolution of 3–5 mm (on a side), which is determined by the field of view, matrix size, and slice thickness of the imaged volume. Reducing the size of voxels generally comes at the risk of decreasing signal-to-noise (given the various noise sources in BOLD fMRI; see below) and increasing acquisition times, especially in whole brain studies. Larger voxels, on the other hand, may contain to a larger extent signal contributions from distinct tissue types or regions, known as "partial volume effects." Determining appropriate voxel size is therefore a trade-off with respect to spatial coverage, resolution, and acquisition time in fMRI studies.

Ultimately, the spatial resolution of BOLD fMRI is constrained by the specificity of the brain's vascular system, which can be said to define the technique's *functional resolution*. This refers to the anatomical coincidence between hemodynamic and neuronal activities, which varies in the brain depending on characteristics of the local microvasculature (e.g., density and architecture). BOLD fMRI is sensitive to signal changes in the capillary bed ($<$10 μm in diameter) and the venous side of the circulation, including venules and larger draining veins (100 μm to mm in diameter), since arteries and arterioles are close to full saturation and contain no deoxygenated blood. In the case of large vessels, signal changes can be displaced up to several millimeters from the activated site and may obscure the localization of smaller magnitude changes, such as those in the capillary bed supplying active neurons. Higher spatial specificity is therefore advantageous in BOLD fMRI experiments. To this end, advanced acquisition sequences have been developed to emphasize or de-emphasize vascular components of the BOLD signal that are distant from neuronal activity, while fMRI experiments can also be designed to better localize hemodynamic responses to specific regions of interest (see example in Fig. 2). The experiments that have compared BOLD fMRI and intracranial microelectrode recordings has shown that the BOLD signal is a robust (linear) predictor of neuronal activity only when considered at the supra-millimeter scale (3–6 mm^2).

Temporal resolution in BOLD fMRI experiments is usually defined by repetition time (TR), or the time taken to acquire one image of the brain or specified volume (number of slices) of interest. In conventional experiments, TR may range from 1 to 3 s, giving such measurements an intermediate level of temporal resolution in-between electrophysiological (ms) and positron emission tomography (PET) imaging (tens of seconds) techniques. Like its spatial resolution, temporal resolution in BOLD fMRI is constrained by technical and physiological factors. In the former case, a major contribution to its current success has been the development of novel acquisition schemes, notably ▶ echo-planar imaging (EPI), that permit rapid functional imaging of T_2^*-weighted images of the whole-brain. Currently, BOLD fMRI with segmented GE-EPI can acquire single slices at a sampling rate of less than 100 ms. Depending on the experimental design, reducing TR (⇑ temporal resolution), will improve the statistical estimation of the BOLD hemodynamic response to a certain extent, although this presents a trade-off between image quality and spatial coverage. Ultimately, temporal resolution in BOLD fMRI is constrained by the slower nature of the hemodynamic response to neuronal activity, whose onset lags behind the timing of actual neuronal events by 4–6 s (see below). Despite these absolute timing differences, well-designed experiments have been able to discriminate the *relative timing* of BOLD signals between different stimuli or brain regions within a few hundred milliseconds (reviewed in Chapter 8, Huettel et al. 2004).

Characteristics and Generation of the BOLD Response

As introduced above, BOLD signal is inversely proportional to the concentration of deoxygenated hemoglobin, which is influenced by local changes in three physiological parameters: cerebral blood volume (CBV), CBF,



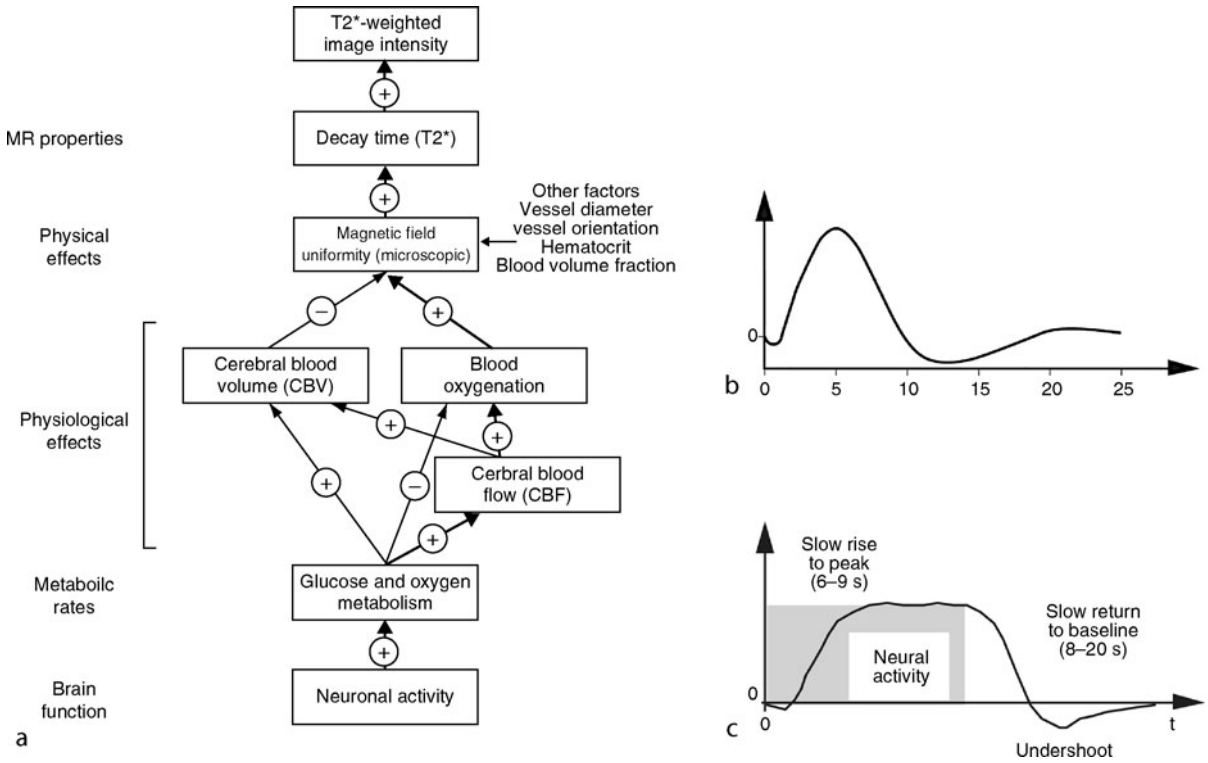
Magnetic Resonance Imaging (Functional). Fig. 2. BOLD fMRI of ocular dominance (OD) columns in the human visual cortex: vertical neuronal columns that respond preferentially to visual stimuli presented to one eye rather than to stimuli presented to the other eye. fMRI studies of OD are often presented to showcase the level of spatial specificity that can be achieved with advanced fMRI techniques. In humans, OD columns are separated by approximately 1 mm. *Left panel* **a**: The imaging slice from a single subject selected in a study by Yacoub et al. (2007) that permitted a resolution of 0.25×0.25 mm^2 in-plane for a slice thickness of 3 mm. *Right panel* **b**: Differential functional OD maps depicting increased activity for left eye stimulation (blue) and right eye stimulation (red) for this subject across distinct sessions (A, B, C & F, G, H) and different filtered averages (D, E and I, J). The upper and lower rows show maps obtained using gradient-echo (GE) and hahn spin-echo (HSE) fMRI, respectively. Both approaches reproduced the expected OD columns, although with increased specificity seen with the HSE method due to its enhanced ability to suppress the influence of large vessels. *Pos* posterior; *RH* right hemisphere; *IHF* inter-hemispheric fissure. (Reproduced with permission from Yacoub et al. 2007 © 2007 Elsevier Inc.)

and the cerebral metabolic rate of oxygen consumption (CMRO2). Signal increases reported in BOLD fMRI experiments are related to the fact that neuronal activity increases regional CBF and glucose utilization (CMRglu) to a larger extent than CMRO2. The net effect of neuronal excitation is therefore to decrease the concentration of deoxygenated hemoglobin ("deoxyhemoglobin washout"; Brown et al 2007), which in turn increases BOLD signal strength. It is now understood that the characteristic BOLD signal changes observed in fMRI studies reflects the summation of these competing events (CBF, CMRO2, and CBV), resulting in a complex response function that is controlled by several parameters (Buxton 2002). In other words, the BOLD signal does not reflect a single physiological process, but rather represents the combined effects of CBF, CBV, and CMRO2 (Fig. 3).

The BOLD response to a short duration event or single stimulus has a canonical hemodynamic waveform shape, which is often described as consisting of (1) a fast response lasting 1–2 s ("initial dip") in which there is a small decrease in BOLD signal amplitude, (2) a larger amplitude hyperemia associated with the inflow of oxygenated blood, which peaks at approximately 4–6 s after stimulus presentation, and (3) a refractory period lasting 6–12 s where the signal undershoots the baseline due to the combination of reduced regional CBF and increased CBV ("post-stimulus undershoot"). The second phase of hyperemia (or hyperoxic phase) is the common focus for detecting increases in brain activity measured by BOLD fMRI. The so-called "initial dip" is suspected to result from early oxygenation changes (oxygen extraction) localized to capillaries, and has been argued as more closely related to neuronal activity than the ensuing hyperemia. However, this observation remains controversial and is not reliably detected in BOLD fMRI studies. Like the BOLD response to a single event, multiple repetitions of the same stimuli in blocks (see below), will see the BOLD response rise to a steady plateau and decline once the block ends, although there are variations to this rule, such as an initial overshoot, slow increasing and decreasing ramps, or an undershoot at the end of the stimulus.

Neurovascular Coupling and Neuronal Correlates of BOLD

The process by which neural activity influences the hemodynamic properties of the surrounding vasculature (principally arterioles) is referred to as neurovascular coupling,



Magnetic Resonance Imaging (Functional). Fig. 3. *Left panel* **a**: Measuring signal changes in fMRI experiments depicted as a complex multistage process, beginning with neuronal activity and ending with BOLD signal measurement as a property of the MRI scanner and pulse sequence. This figure presents a schematic illustration of interactions in the formation of the BOLD signal. Positive/negative arrows indicate positive/negative correlations between the parameters. The right pathway (bold arrows) is the most significant effect in most BOLD fMRI. *Right panels* **b** *and* **c**: Simplified schematic representation of the BOLD hemodynamic response waveform to a short duration stimulus (**b**), and to a block of multiple consecutive stimuli (**c**). (Parts of this figure reproduced with permission from http://www.eecs.umich.edu/~dnoll.)

although the mechanism(s) responsible for this is not fully understood. One hypothesis regarding a principal signaling route is that a feedforward pathway involving neuronal-glial interactions after neurotransmitter release stimulates regional CBF. Astrocytes play a crucial role in neurotransmitter recycling, using energy reliant on glycolysis (nonoxidative glucose metabolism) to clear extracellular glutamate and convert it to glutamine after neuronal firing. Increased glycolysis in astrocytes is suspected to trigger intracellular events that couple glutamate cycling rate to the production of vasoactive agents, including nitric oxide and eicosanoids. Therefore, according to this view, neurovascular coupling is mediated by neuronal signaling mechanisms via glial pathways, as opposed to signaling mechanisms of an energy deficit in neurons per se. This view supports, in part, the notion that glycolysis is relevant to the detection of BOLD activity changes and in explaining the apparent mismatch between CBF, CMRglu, and CMRO2 during evoked brain activity (Raichle and Mintun 2006).

Detailed biophysical models have also been proposed to explain the complex shape of the hemodynamic response observed in BOLD fMRI studies, accounting for the changes in CBF, CBV, and CMRO2 that accompany increased neuronal activity. Most prominent is the "balloon model" of Buxton and colleagues. According to this work, the apparent discrepancy between CBF and CMRO2 results from how oxygen is supplied to neurons related to its poor diffusion in brain tissue. That is, blood flow must increase more than oxygen consumption to maintain tissue–oxygen gradients supporting oxygen delivery to tissue because its extraction (by passive diffusion) from blood is less efficient at higher flow rates (Buxton 2002). Evidence favoring this model versus the former hypothesis (and vice versa) can be found in expanded form in Buxton et al. (2004) and Raichle and Mintun (2006), respectively.

Regardless of the precise cause(s) of the physiological changes that give rise to the BOLD signal, evidence has been marshaled in support of a close relationship between evoked hemodynamic and neuronal activity changes. Notably, in the work of Logothetis et al. (2001), which compared BOLD fMRI and intracranial electrophysiological measurements recorded simultaneously in monkeys, BOLD signal was found to be spatially well localized and scaled with neuronal activity. Specifically, these authors reported that the amplitude of the BOLD signal was better correlated with recordings of local field potentials rather than multiunit activity (Logothetis et al. 2001). That is, BOLD signal better reflects the weighted average of synchronized activity of the input signals into a neuronal ensemble than their spiking (action potential) activities. This suggests that BOLD signal changes, primarily reflect input and integrative processes rather than output (communicative) activity. However, there remains some debate about the contributions of different types of neuronal activity to the BOLD signal (local field potentials vs. spiking activity), as the former will be correlated with the latter in many instances (Raichle and Mintun 2006).

Experimental Design

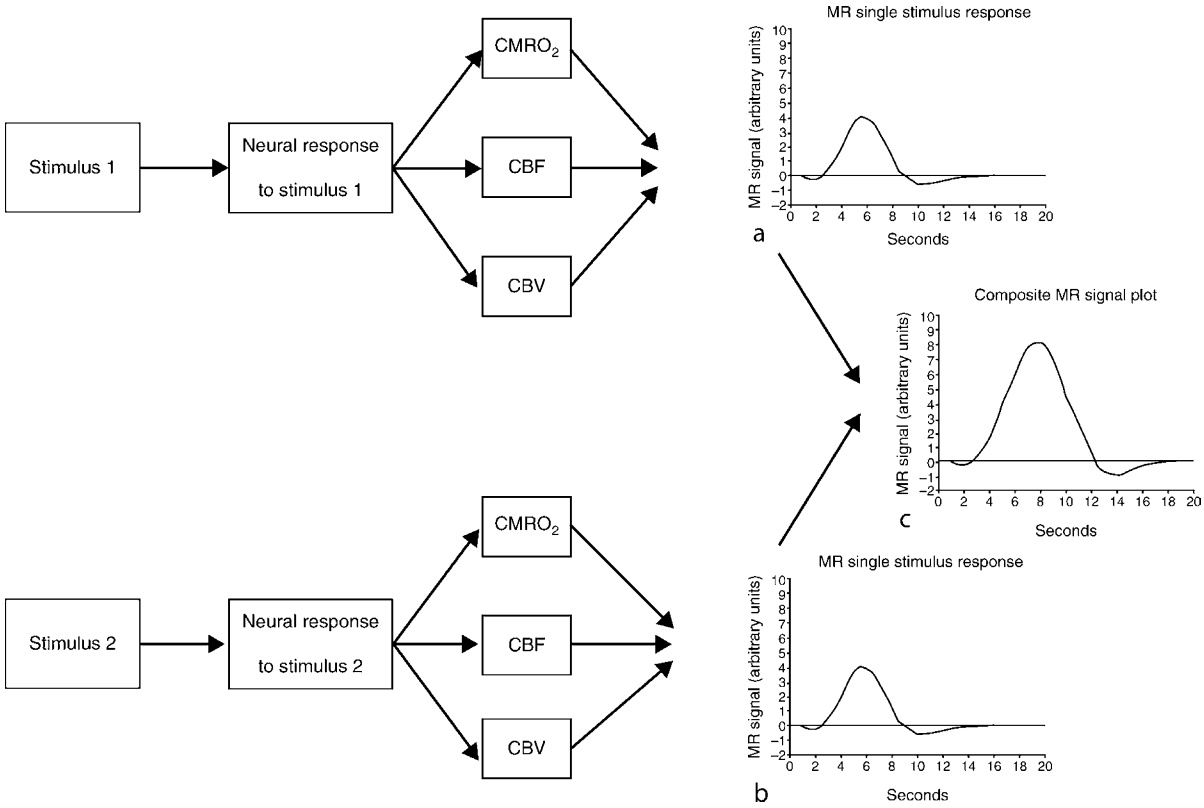
In a conventional fMRI experiment, ▶ time-series of T_2*-weighted images are acquired while subjects are exposed to a specific stimulus or set of stimuli ("task-on") that is systematically varied with respect to a "control-off" condition, typically in the context of a serial or ▶ cognitive subtraction or factorial design. The goal of this approach is to evoke significant changes in blood flow and oxygenation within a given region or network associated with the "task-on" state that will modulate BOLD signal intensity about its mean value. The duration of these stimulus presentations or epochs must be tailored to the dynamics of the hemodynamic response, and will be repeated multiple times to establish sufficient contrast and functional signal to noise ratios for the mapping of "activation" responses. In practice, the magnitude of task-related changes in fMRI studies is small (up to $\pm$5% but usually less) in comparison to the total image intensity and variability across time due to various sources of physical (MR system) and physiological noise. Careful experimental design and the use of post-processing methods for maximizing the detection of activation in the BOLD time series is therefore a critical feature of fMRI studies (Chapter 8–13, Huettel et al. 2004).

One common approach is to take advantage of the summed signal as a way of minimizing the influence of noise in fMRI experiments (Fig. 4). The idea here is that the BOLD response summed over several trials will reduce the influence of random noise sources as a result of averaging (Brown et al 2007). Blocked designs that present the same class of stimuli on multiple occasions seek to capitalize on this strategy. In turn, this involves selecting the correct number and timing of stimuli to occur within a block, the duration of the block itself and its number of repetitions, as well as the number of different block types to be included in a single acquisition for later comparison. Overall, block designs are powerful in terms of detecting significant sustained (steady-state) activation in fMRI studies but are generally poor estimators of the time course of the regional hemodynamic response to neuronal events because of their reliance on linear summation of individual responses.

Event-related designs are a second common approach in fMRI experiments and involve the presentation of specific stimuli as short duration events in order to detect transient associated changes in neuronal activity. With this approach, each event is separated temporally by an interval ranging from a few to tens of seconds and typically in a random order of predefined range. Investigators typically assume a canonical shape to the hemodynamic response to each stimulus presented and model it as a weighted sum to consecutive stimuli – although this linearity assumption may not hold, especially for the early phase of the hemodynamic response. Compared to blocked designs, event-related designs are superior in investigating the shape of regional hemodynamic responses and to compare features such as amplitude or relative timing differences between events. Event-related designs also allow for the investigation of BOLD responses sorted by response types, for instance comparing correct versus incorrect or fast versus slow responses. By comparison, their detection power is relatively poor with respect to blocked designs due to the fewer number of events that can be presented and averaged in a single experimental run.

Analysis of BOLD fMRI

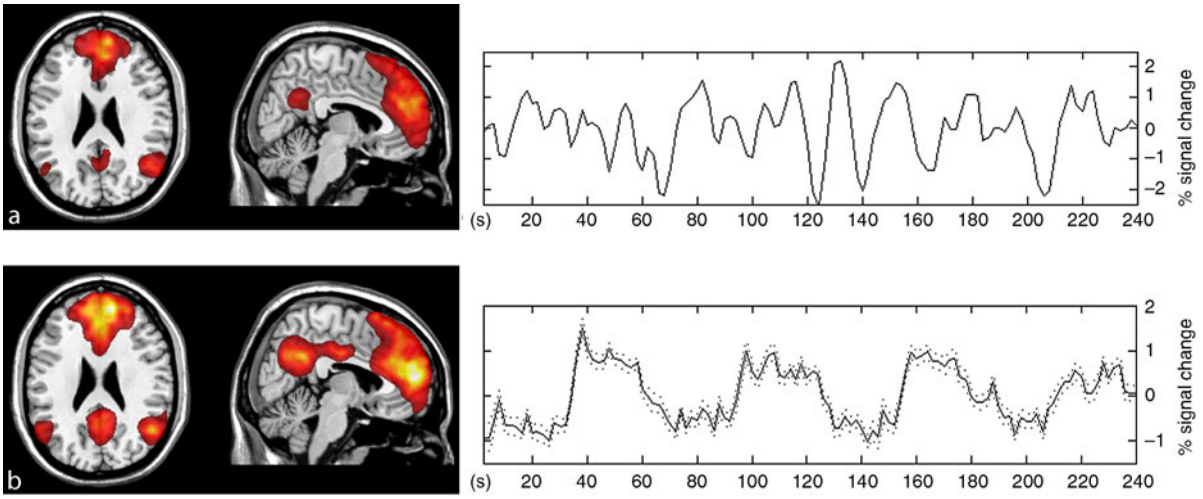
It was previously stated that the BOLD fMRI time series is influenced by a number of sources of physical and physiological noise. In the former case, this includes system noise that causes fluctuations in MR signal (e.g., signal drift) due to magnetic field inhomogeneities and other factors. In the latter case, this includes gross head motion artifacts, motion related to the cardiac (beat-to-beat) and respiratory (breath-to-breath) cycles, as well as slow variations in respiratory rate and volume, which change the pressure of arterial CO_2 – a potent vasodilator. Awareness of these various noise sources in BOLD fMRI studies has led to a range of methods to reduce or mitigate their influence, which continue to be improved upon and refined.



Magnetic Resonance Imaging (Functional). Fig. 4. Linearity of the hemodynamic response: events leading from the presentation of two stimuli to the generation of a summed BOLD signal. To a certain degree, the BOLD response to successive neural events can be predicted from the summed responses (superposition) to single neural events given an appropriate time delay between them. The figure assumes that stimulus 1 is presented 1 s before stimulus 2 and each stimulus evokes a response that alters CMRO2, cerebral blood flow, and CBV. The net effect of these physiological changes leads to the BOLD response for individual stimuli (**a** and **b**). The observed BOLD response (**c**) is a composite of the unobserved BOLD responses to the single stimuli. (Reproduced with permission from Brown et al. 2007. © 2007 Springer Netherlands.)

Pre-processing of the raw fMRI time-series, prior to statistical analysis, generally has two main goals: firstly, to reduce unwanted or uninteresting variability from data and; secondly, to prepare data for statistical analysis and inference given that many statistical tests applied in fMRI studies make assumptions that are met through such preprocessing steps. In practice, this involves modifying the raw data in a series of steps often including *image realignment* – to correct and to diagnose head motion artifact in a time series, *image normalization* – to transform data from different subjects into a common neuroanatomical space, *spatial smoothing* – to filter (or blur) the data to reduce spatial noise and to improve its normality for statistical parametric tests, and *temporal smoothing* – to remove low or high frequency noise sources, such as mentioned above.

There are a growing number of ways to perform statistical analysis in BOLD fMRI experiments. This has been assisted greatly by the development of publicly available neuroimaging analysis software packages, such as Statistical Parametric Mapping (http://www.fil.ion.ucl.ac.uk/spm/), FMRIB Software Library (http://www.fmrib.ox.ac.uk/fsl/FSL), Analysis of Functional Neuro Images (http://afni.nimh.nih.gov/). The majority of fMRI studies to date have adopted a conventional voxel-based mapping approach based on extensions of the general linear model for time-series analysis. The basic premise behind such approaches is that the observed fMRI data can be accounted for by a combination of several experimental (or model) parameters and uncorrelated (or independently distributed) noise. Given the high number of statistical tests performed (voxel by voxel) some correction factor for multiple



Magnetic Resonance Imaging (Functional). Fig. 5. Global functional connectivity of a large-scale and distributed brain network characterized from two distinct task states using independent component analysis (ICA). *Top panel* **a**: Correlated fluctuations of the BOLD signal among regions of the so-called "default-mode network" in a group of healthy subjects scanned at rest (NB: time-course plot is of a single subject). *Bottom panel* **b**: Correlated fluctuations of the BOLD signal among "default mode network" regions in the same group of subjects performing a moral dilemma task (NB: time course plot is of the group mean). The task consisted of four alternating 30 s control (C) and moral dilemma (D) condition blocks (CDCDCDCD). (Modified from Harrison et al. (2008) Proc Natl Acad Sci USA 105:9781–9789. © 2008 by the National Academy of Sciences of the USA.)

comparisons will generally be applied, leading to the generation of statistically thresholded "activation" maps related to the experiment at hand. This may be performed for the whole brain or specific regions of interest.

Other techniques, based on multivariate analysis techniques can also be used to investigate which brain areas are "activated" by a task or a stimulus in fMRI studies. These techniques, as opposed to the general linear model approach, are data driven and therefore do not require the specification of experimental models *a priori*. Another important distinction between this class of statistical tests and the former is that they are sensitive for testing not only "where" activation occurs in a given experimental context but also how different regions or networks of regions may interact or show interdependence in their activities over time (Fig. 5). Such relationships have been characterized as representing distinct forms of brain-functional connectivity, which has become a topic of specific interest with BOLD fMRI in recent years.

Major Strengths of the Method

- Is a safe, noninvasive, highly repeatable and widely available technique for measuring changes in brain activity in vivo.
- Has superior spatial resolution compared to other human neuroimaging techniques.
- Affords high flexibility in experimental design and data modeling.

Major Limitations of the Method

- Measures neuronal activity indirectly via changes in blood oxygenation levels.
- Has a temporal resolution in the order of seconds due to the nature of the hemodynamic response.
- Is susceptible to influences of non-neural changes in the body.

Cross-References

▶ Cognitive Neuroscience
▶ Cognitive Subtraction
▶ Echo-Planar Imaging
▶ Gradient-Echo Images
▶ Local Field Potentials
▶ Magnetic Resonance Imaging
▶ Multi-Unit Activity
▶ Neuroimaging
▶ Nuclear Magnetic Resonance

► Structural and Functional Magnetic Resonance Imaging
► Time-Series

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Magnetic Resonance Imaging

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Definition

Structural and functional magnetic resonance imaging (structural MRI and fMRI, respectively) are medical imaging techniques widely used in radiology and neuroradiology. While structural MRI allows acquiring three-dimensional images of neuroanatomy with high spatial resolution and excellent soft tissue contrast, fMRI is applied to assess brain activity. fMRI provides information on current status and on neuropharmacological modulation of neuronal activity across the entire brain in a spatially and temporally resolved manner. Structural MRI and fMRI methods are readily translatable to clinical systems as they are inherently noninvasive and can therefore be applied in human subjects without exposure to radiation such as in nuclear imaging techniques. However, methodological constraints and limitations require careful interpretation of fMRI data. Today, both structural MRI and fMRI have emerged as powerful tools for neuropharmacological research and hold great potential for clinical applications.

Principles and Role in Psychopharmacology

MRI is a biomedical imaging technique applied in both research laboratories and radiology to visualize the structure and function of the body. MR images represent a weighted distribution of hydrogen atoms (protons) in living tissue, the major contribution being due to water constituting approximately 60–80% of tissue mass (Vlaardingerbroek and den Boer 1999). Hydrogen atoms possess an intrinsic magnetic moment. From a technical point of view, three key components are required to generate the MR signals allowing the formation of an image: the static magnetic field aligning the protons in the direction of the field, the radiofrequency (RF) coil(s) for excitation and reception of the MR signal, and the magnetic gradient field coils for spatial encoding of the MR signal. MRI systems measure the magnetic properties of the protons, which are influenced by electrical and magnetic characteristics of their environment. The local environment varies between tissues or the structures in which the protons are embedded in and are furthermore influenced by physiological processes such as diffusion, perfusion, or blood flow. Consequently, image contrast is governed by a number of MR parameters (Table 1), such as intrinsic relaxation rates (R_1, R_2, R_2^*), incoherent motion of water, such as diffusion or perfusion, coherent blood flow in major vessels and water exchange processes between cellular/interstitial fluid and water bound to macromolecules. MRI acquisition parameters can be adapted to emphasize the specific contrast optimal for the structure or the process of interest. In addition, tissue relaxation rates can be altered using exogenous contrast agents based on paramagnetic compounds, such as gadolinium chelates or iron oxide nanoparticles. The strong effect of contrast agents on relaxation rates is due to unpaired electron(s) contained in their electron shell, the magnetic moment of which is approximately 650 times higher than that of protons.

Structural MRI

Three-dimensional imaging, excellent spatial resolution, and superior soft tissue contrast render MRI the method

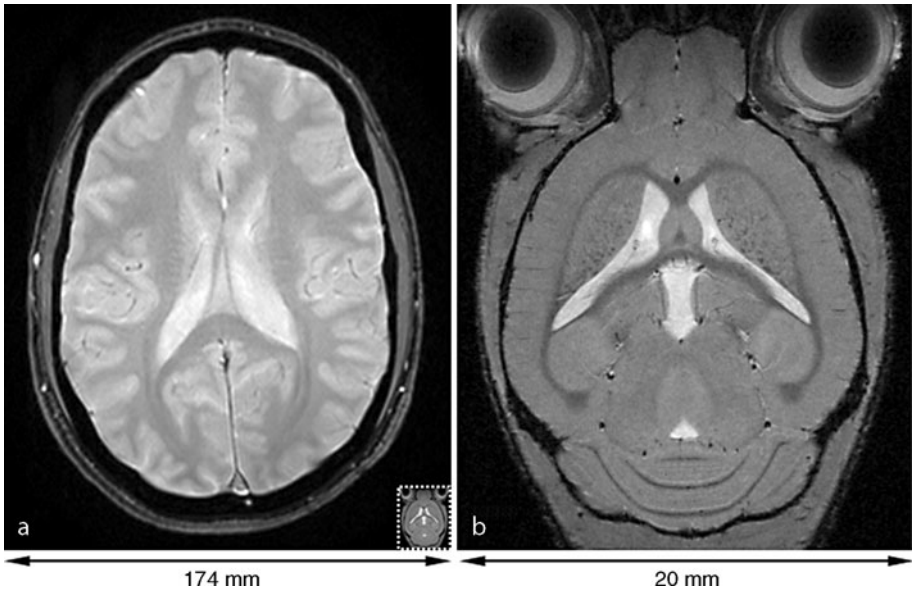
Magnetic Resonance Imaging. Table 1. Intrinsic MR contrast parameter and biological information derived.

Contrast-generating process	MRI parameter	Information derived
Longitudinal relaxation: return to magnetic equilibrium state	R_1 (=1/T_1)	Basic structural information: e.g., gray vs. white matter differentiation enhancement following contrast agent administration: e.g., blood–brain barrier integrity or retrograde axonal tracing
Transverse relaxation: Loss of phase coherence due to stochastic processes	R_2 (=1/T_2)	Basic structural information: sensitive to tissue water content edema formation, inflammation
Magnetic susceptibility: Loss of phase coherence due to magnetic field differences	R_2* (=1/T_2*)	Basic structural information: gray vs. white matter contrast, hemorrhages
		CBF and volume (using intravascular contrast agent) BOLD contrast
Incoherent motion, diffusion: Loss of phase coherence due to molecular diffusion	ADC FA	ADC: cellularity (intracelluar vs. extracellular volume fraction) FA: restricted anisotropic diffusion
Incoherent motion, perfusion: Loss of phase coherence due to flow in capillaries	F	Local tissue perfusion
Water exchange: Water exchange between two states of different water mobility	MTR	Macromolecule content: e.g., degree and integrity of myelination

ADC apparent diffusion coefficient (mm^2/s)
BOLD blood oxygen-level dependent (contrast)
f tissue perfusion (in ml/s/g tissue or ml/min/100 g tissue)
FA fractional anisotropy
MTR magnetization transfer ratio is the ratio between the equilibrium magnetization and the steady-state magnetization under saturation conditions
R_i relaxation rate (s^{-1})
T_i relaxation time (s)

of choice for structural neuroimaging. A weak point of the method is its inherent low sensitivity, which has a negative impact on spatial resolution. Correspondingly, identifying small brain structures or assessing subtle/minor pathological alterations, putting high demands on spatial resolution, is challenging. Substantial efforts have been made in recent years to increase MR sensitivity by either moving to higher static magnetic field strengths or by refining RF detection devices, such as the cryogenic detection technology. State-of-the-art MR systems for routine clinical neuroimaging (Konarski et al. 2007) operate at 3 T allowing for spatial resolutions in the order of 1 mm^3 (Fig. 1a), while clinical research systems up to 7.0 T have been constructed. In contrast, the high spatial resolution required in rodent brain imaging led to the development of MR systems operating at up to 17.6 T. For example, the combination of high magnetic field strength (9.4 T) with cryogenic RF detection devices enabled the routine recording of high-resolution ($52 \times 52 \times 170$ m^3) mouse brain images (Fig. 1b) in a measurement time of 10 min (Baltes et al. 2009).

In structural MRI, usually morphometric comparisons between groups are performed using hypothesis-based selection of regions of interest (ROIs), which is a lengthy process and prone to evaluation errors. More recently, voxel-based morphometry (VBM) has been developed as a fully automated comparison of whole brains on a voxel-by-voxel basis. After spatial normalization of the brains to a stereotactic standard space, brain regions are compared with respect to differences in residual tissue concentrations rather than differences in shape. Clinical application of structural readouts using MRI cover a broad range of disorders from neurodegenerative (i.e., stroke and dementia) to neuropsychiatric diseases (American Psychiatric Association (APA) 2000) (e.g., ▶ schizophrenia, ▶ posttraumatic stress disorder (PTSD), or mood disorders, such as ▶ bipolar affective disorders). For example, VBM studies in schizophrenia generally confirmed and



Magnetic Resonance Imaging. Fig. 1. Visualization of neuroanatomical structures in the human (**a**) and in the mouse brain (**b**) put different demands on spatial resolution. While an in-plane resolution of 0.9 × 0.9 mm^2 in human subjects is sufficient for gray vs. white matter discrimination, a resolution of 52 × 52 m^2 is required in mouse brain to depict cortical structures, such as subfields of the hippocampus. For comparison of the dimensions, the mouse brain image (**b**) is depicted as inset in the human brain image (**a**) using the same scale. (Courtesy of R. Luechinger, PhD, University and ETH Zurich, Switzerland.)

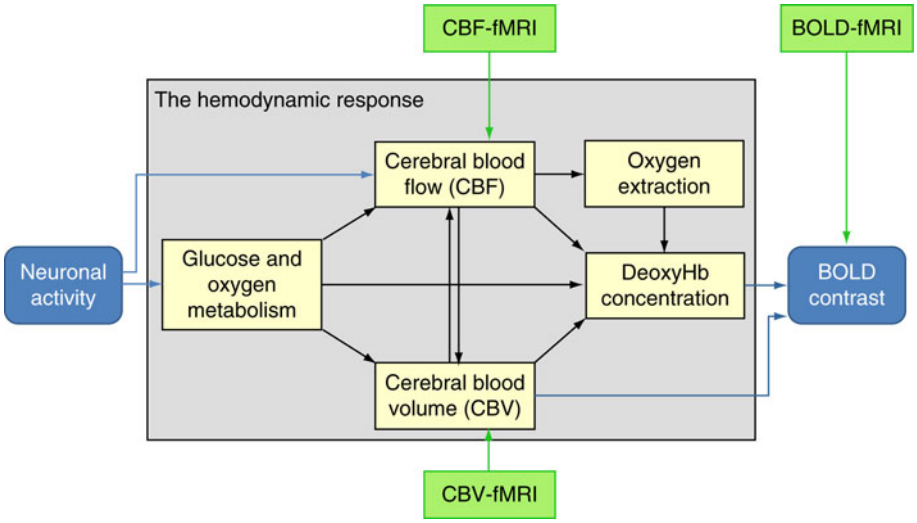
extended ROI-based studies showing less gray matter concentration in multiple cortical and subcortical regions (Pearlson and Calhoun 2007). In patients suffering, e.g., from bipolar disorders, structural MRI has been applied to assess neuroanatomical abnormalities between healthy subjects and patients. While overall brain volumes appeared to be normal, regional differences have been observed in prefrontal cortex, and subcortical and medial temporal structures involved in the behavioral network, which is known to be affected in bipolar disorders (Strakowski et al. 2005). Similarly, in preclinical MRI, morphometric readouts hold promise to phenotype rodent models of central nervous system (CNS) diseases with applications in mouse models of neurological disorders such as ► Alzheimer's disease (AD) or ► Huntington's disease or in rat models of schizophrenia. Its value for detection of subtle or diffuse morphometric abnormalities, i.e., in neuropsychiatric models that are predictive for disease progression or can serve as surrogate markers for end-stage disease status has to be further validated in carefully planned and analyzed longitudinal studies.

While structural MRI provides information on neuroanatomical alterations preceding or accompanying psychiatric diseases, fMRI allows assessing changes in neuronal activation patterns between healthy subjects and patients, which might be more closely related to the disease progression or effects of drug administration.

Functional MRI

Underlying Biological Processes

fMRI is widely applied in clinical and preclinical studies to assess brain function, keeping in mind that the MR method is sensitive to hemodynamic changes prompted by neuronal activity rather than the neuronal activation itself. Local neuronal activity leads to an increased consumption of oxygen and nutrients triggering an increase in local perfusion, i.e., regional cerebral blood flow (CBF) and cerebral blood volume (CBV) (Fig. 2). As the efficiency of oxygen extraction decreases with increasing flow rates, the venous blood contains more oxygenated hemoglobin in the activated state when compared with the resting state. The higher concentration of oxyhemoglobin, and correspondingly the lower concentration of paramagnetic deoxyhemoglobin during activation leads to a decrease in R_2^* relaxation rates, thus an increase in the MR signal. This mechanism, called blood oxygenation level dependent (► BOLD) contrast, has found widespread use in the neuroscience community to study brain function under physiological and pathological conditions. It is



Magnetic Resonance Imaging. Fig. 2. Schematic representation of the relationship between neuronal activity and the hemodynamic response function. fMRI allows to assess various processes involved such as changes in CBF, CBV, and changes in BOLD contrast. (Adapted from Martin and Sibson 2008.)

important to note that an intact neurovascular coupling is essential for the reliability of functional MRI signals.

To elucidate the complex mechanism of neurovascular coupling, further fMRI methods have been developed directly assessing the vascular response to neuronal activation such as CBF and CBV changes. Recently, MR arterial spin labeling (ASL) techniques have been described to measure regional CBF. For this purpose, the arterial blood flowing into the brain is magnetically labeled at the level of the common carotid artery. In this way, arterial blood can be used as endogenous contrast agent. Regional CBF values can be estimated from the difference of the MR signal intensities before and during labeling of the inflowing arterial spins taking the finite lifetime of the magnetically labeled state into consideration. ASL is independent of contrast agent administration and allows therefore continuous CBF monitoring. As CBF changes are supposed to be proportional to neuronal activity, ASL presents itself an attractive method for providing a more direct readout of neuronal activity than BOLD and CBV measurements, which are highly nonlinear. Furthermore, CBF measurements are less susceptible to magnetic field variations than BOLD fMRI based on fast-gradient echo sequences.

For the assessment of local CBV values, MRI methods have been developed using exogenous contrast agents with a long plasma half-life such as iron oxide nanoparticles leading to an increase in the R_2 and R_2^* relaxation rates. A few minutes after intravenous administration of the contrast agent, a steady-state concentration is reached. The relative change in local relaxation rates R_2 and R_2^* is proportional to the amount of contrast agent in the tissue and thus proportional to the local CBV. Subsequently, neuronal activity prompting local CBV changes can be detected by measuring relative changes in local relaxation rates R_2^*. As oxygen extraction decreases for increasing flow rates and the ► BOLD Contrast decreases at lower magnetic field strength, CBV measurements are more sensitive than fMRI based on the BOLD contrast.

Stimulation Paradigms

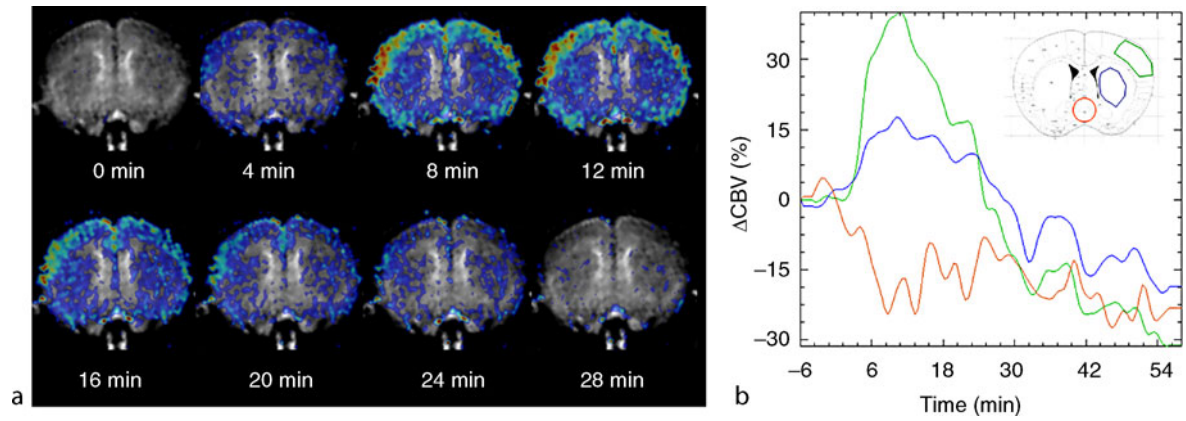
A key component of fMRI experiments is the ► Stimulation Paradigm applied to evoke brain activity. A variety of different stimuli ranging from no stimulation (resting-state fMRI) over thermal, sensory, mechanical, visual, or auditory to pharmacological stimuli have been used during fMRI studies. The rationale behind resting state fMRI is to investigate activation differences between a healthy control group and patients suffering, e.g., from schizophrenia (Pearlson and Calhoun 2007) as these experiments do not rely on the ability of the patient to perform certain tasks. Aside from resting state fMRI, which analyzes spontaneous activity/hemodynamic changes in the brain, fMRI studies always rely on at least two measurements comparing state A (e.g., the resting state) with state B (e.g., during stimulus-induced activation). When designing fMRI studies, it is important to consider the dynamics of the hemodynamic response to neuronal activity, which determines the time resolution that can be achieved in the experiment.

In ► Pharmacological fMRI (► phMRI), the functional response to ligand-induced receptor stimulation or

inhibition after drug administration is assessed throughout the brain using the above-described fMRI methods. Consequently, phMRI, like all fMRI methods, relies on intact neurovascular coupling and assesses the functional response induced by drug administration. In humans, phMRI involves BOLD signal acquisition before, during, and after the administration of a drug, while in animals CBF and CBV measurements are also widely established. phMRI studies in the rat measuring BOLD or CBV changes confirmed sufficient sensitivity to detect dose-dependent effects of systemically administered receptor ligands. Assessment of alterations in magnitude and spatial extend of neuronal activity induced by pharmacological targeting has been successfully demonstrated for various neurotransmitter systems such as the dopaminergic, ▶ opioid, ▶ GABAergic, glutamatergic, or cannabinoid system. Figure 3 shows an example of phMRI in the mouse. Acute administration of the $GABA_A$ receptor antagonist bicuculline led to region-specific CBV changes. The impact and potential of phMRI in the area of psychopharmacology will be discussed in the following for the example of mood and anxiety disorders. Investigations using in vivo neuroimaging techniques within the field of major (clinical) depression and anxiety disorders are largely dominated by measuring serotonergic (5-hydroxytryptamine; 5-HT) neurotransmission and receptor level and their response to medication treatment as alterations in serotonin neurotransmitter system have been clearly implicated in the pathophysiology of these two ▶ neuropsychiatric disorders. Based on the availability of radiolabeled 5-HT receptor ligands, distinct ▶ serotonin receptor populations have been imaged using positron emission tomography (PET) and single positron emission tomography (SPECT). On the other hand, the nature of serotonergic neurocircuitries can be investigated using phMRI by modifying endogenous neurotransmitter levels or manipulating their receptor activity by specific ligands. Most phMRI studies investigated the $5\text{-}HT_{2C}$ receptor system as one of the main targets for novel anxiolytic drugs. Among the different ligands used, meta-chlorophenylpiperazine (m-CPP), a mixed $5\text{-}HT_{1B/2C}$ receptor agonist, has been advanced as a useful pharmacological substance for fMRI studies of regional activation in rats and in human beings. Furthermore, the acute and chronic effect of SSRI on region-specific neuronal activation measured by BOLD-fMRI in human beings has been examined using citalopram or in the rats using ▶ fluoxetine. The literature on phMRI investigating specifically the $5\text{-}HT_{1A}$ receptor is rather sparse, but represents an attractive field of research given that $5\text{-}HT_{1A}$ autoreceptor desensitization is one of the suggested mechanisms of action of chronic antidepressants (i.e., ▶ selective serotonin re-uptake inhibitors, SSRIs) and might be responsible for the delayed onset of antidepressants under clinical conditions. Using CBV-fMRI, decreased activity across several brain areas of the rats was mapped with the strongest effects in ▶ hippocampus and septum after acute administration of the $5\text{-}HT_{1A}$ receptor agonist 8-OH-DPAT.

Data Analysis and Interpretation

The analysis of fMRI data turns out to be especially challenging because of the complex relationship between the physiological processes involved (Fig. 2) and,



Magnetic Resonance Imaging. Fig. 3. Example of phMRI in the mouse. CBV changes in the mouse brain during infusion of the $GABA_A$ receptor antagonist bicuculline. (**a**) Percentage ΔCBV activity maps of brain section +0.74 mm relative to the Bregma showing the highest activity in cortical areas. (**b**) Temporal profile for three different ROIs (see brain atlas inlet: green=cortex, blue=striatum, orange = control ROI) highlighting the region specificity of the induced CBV changes.

furthermore, the small signal changes detected in fMRI, e.g., BOLD signal changes in humans are in the order of 1–5%. For this reason, the fMRI analysis is often simplified by fitting a general linear model (GLM) based on a priori information of the stimulation paradigm convolved with an assumed hemodynamic response function. More sophisticated approaches incorporate the various processes associated with the hemodynamic response to form a biophysically plausible framework such as the balloon model (Buxton et al. 1998). However, phMRI aims at resolving neuronal networks and connectivities throughout the brain. As the functional relationship and the causal dependencies between different brain areas are a priori unknown, hypothesis-driven methods, such as GLM, might lead to false results or to a loss in sensitivity in activated areas. In this case, data-driven or exploratory approaches are assumed to be superior: these include independent component analysis (ICA) or methods detecting temporal or spatial correlations. For example, in wavelet-based cluster analysis (WCA), activated pixels are grouped according to their own activity pattern avoiding assumptions derived from the experimental design.

As phMRI methods monitor neuronal activity via neurometabolic or neurovascular coupling processes, careful interpretation of phMRI data is indicated taking various processes influencing the phMRI signal into account. Direct systemic effects of the drug administered or influences of the pathology on the vascular tone might lead to changes of the functional response measured by phMRI, which do not necessarily reflect changes in neuronal activity (Mueggler et al. 2002). Furthermore, one needs to keep in mind that phMRI detects brain regions showing hemodynamic changes, which usually exceed local regions of neuronal activity, thus overestimating the region involved, or neurons even project to distant brain regions, which do not reflect the underlying receptor distribution. In small rodents, phMRI is commonly carried out in anesthetized animals, in which the anesthetic might potentially interfere with the ligand–receptor interaction of interest.

The remaining topics with respect to fMRI data analysis and interpretation are the understanding of the functional signal changes acquired and their link to neuronal activity even in healthy subjects. The missing clear understanding of the fundamental process makes the interpretation of fMRI under pathological conditions even more complex. Furthermore, fMRI data analysis and interpretation is carried out on groups of healthy or diseased subjects. As described above, normalization of all brains of a group to a standard space reduces within-group difference, thus enhancing between-group difference and accordingly statistical significance of the differences (Konarski et al. 2007). The biological variability and the slightness of the signal changes hamper subject-specific interpretation or diagnosis of fMRI examinations.

Advantages and Limitations with Respect to Alternative Neuroimaging Modalities

The neuroimaging technique to be applied depends on the biomedical question to be addressed. Assessing structural information commonly requires high spatial resolution and adequate contrast for the structure of interest, while image acquisition time, typically in the order of several minutes, is not an issue because the anatomical structures can be assumed to be static during the data collection period. As alternative imaging modality, computerized tomography (CT) can be applied measuring X-ray attenuation by tissue. Both structural MRI and CT provide three-dimensional information with excellent spatial resolution and the accessibility to deep brain structures allowing to quantitatively document volumetric and morphological changes (Konarski et al. 2007). However, the advantage of structural MRI is completely noninvasiveness, thus enabling repeated measurements in longitudinal studies to monitor disease progression or therapeutic effects and superior soft tissue contrast.

In contrast, imaging of dynamic processes, such as brain perfusion, requires not only sufficient sensitivity to detect, but also sufficient temporal resolution to resolve the physiological changes under investigation. The time available for imaging is determined by the physiological process of interest, which has an impact on the fMRI method that can be applied and the spatial resolution that can be achieved. Alternative imaging modalities to fMRI are ► SPECT or ► PET. Both modalities are using exogenous contrast agents labeled with radionuclides, such as fluorine-18 for PET and iodine-123 for SPECT (Rudin 2005). Although PET is relatively expensive when compared with SPECT, it is superior in terms of sensitivity and spatial resolution, and provides inherently quantitative data. PET provides information on physiological (perfusion) and biochemical processes, such as neuronal glucose metabolism. With respect to SPECT and PET, fMRI is less sensitive, but provides information on functional consequences of drug administration in a spatially highly resolved manner. Due to their noninvasiveness, fMRI and nuclear imaging methods developed in small rodents are readily translatable to clinical applications.

The dimensions of small rodents further allow the use of fluorescent molecular tomography (FMT) as alternative neuroimaging method. In this method, a compound labeled with a fluorescent dye is administered. After specific binding of this reporter to the target and after clearance

of the unbound fraction, the fluorophor is excited using laser light in the near-infrared range (Rudin 2005). FMT is superior to MRI in terms of sensitivity, lower detection limits are in the nanomolar range, but provides relatively poor spatial resolution. However, in human subjects deep brain areas are not accessible due to the small penetration depth of light in the near-infrared range.

Future Directions

Noninvasive neuroimaging has been rapidly developing in the past decade, as various imaging modalities provide an overwhelming amount of information on functional neuroanatomy, neuronal activity, and neuronal networks. However, technical limitations such as low sensitivity in fMRI or poor localization in EEG prevented the assessment of an integrated view of the brain function. These issues have prompted the development of data fusion methods aiming to combine complementary information from different imaging modalities. For example, EEG data have been constrained using fMRI activation maps (Pearlson and Calhoun 2007). Although these methods hold great potential to improve data interpretation, one has to avoid unrealistic assumptions. Alternative approaches under development are trying to combine the strengths of two modalities such as the high sensitivity of molecular imaging with the high spatial resolution and localization of CT and MRI. Substantial efforts have been made to bring forward such hybrid imaging systems combining, e.g., CT-PET or MRI-PET for clinical applications. In small animal imaging, CT-FMT or MRI-PET solutions are also pursued.

Cross-References

- ▶ BOLD Contrast
- ▶ Cerebral Perfusion
- ▶ Functional MRI
- ▶ MR Image Analysis
- ▶ Neuropsychiatric Disorders
- ▶ Pharmacological fMRI
- ▶ Stimulation Paradigm
- ▶ Structural and Functional Magnetic Resonance Imaging
- ▶ Translational Neuroimaging

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Major and Minor and Mixed Anxiety-Depressive Disorders

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Synonyms

Clinical depression; Depression; Unipolar depression

Definition

The depressive disorders comprise a spectrum of clinical syndromes characterized by persistent depressed mood or sadness, loss of interest (apathy), or loss of pleasure (anhedonia). These symptoms are to be distinguished from the transient feelings of unhappiness or sadness that constitute normal reactions to the disappointments or losses experienced in everyday life. The symptoms of depressive disorders cause clinically significant distress or impairment in social, occupational, or other important areas of functioning, and are not due to the direct physiological effects of a substance or a general medical condition. Depression is generally differentiated from bereavement, the expectable constellation of depressive symptoms

following the loss of a loved one, although depression may be diagnosed if such symptoms are unusually prolonged (e.g., more than 2 months) or are not characteristic of a "normal" grief reaction in the individual's culture. The depressive disorders are also to be distinguished from depressive *episodes* of ▶ bipolar disorder, which is diagnosed if the individual has ever had a manic, mixed, or hypomanic episode.

Role of Pharmacotherapy

Clinical Features, Etiology, and Pathogenesis

Recognition of depression as a distinct disease dates back at least as far as the Hippocratic writings of the fifth and fourth centuries B.C. Lifetime prevalence varies among diagnostic categories and according to the specific diagnostic criteria used, with risks for major depression ranging from 10 to 25% in women and 5 to 12% in men. Prevalence rates are unrelated to income, education, marital status, or ethnicity. Depressive disorders may have their onset at any age, but the average is in the mid- 20s. At least 60% of individuals with a single episode of major depression will have subsequent episodes. Major depression is associated with significantly increased mortality; up to 15% of individuals with severe illness die by ▶ suicide.

The etiology of depressive disorders is unknown. There is a familial pattern, with major depression 1.5–3 times more common in individuals with an affected first-degree biological relative; ▶ heritability based on twin studies is 40–50%. However, no single major gene locus has been shown to cause depression. Rather, genetic risk appears to involve multigenic and/or gene-environment interactions. The short allele of the serotonin transporter-linked polymorphic region (5-HTTLPR), in particular, has been most strongly implicated in gene-environment interactions leading to depression. Environmental risk factors include early-life abuse and neglect and major life stress.

The predominant theories of pathogenesis in depression have focused on monoamine neurotransmission and ▶ hypothalamic-pituitary-adrenal (HPA) axis dysfunction. Early monoamine theories posited simple deficiencies in ▶ serotonin or ▶ norepinephrine function, but such hypotheses have been superseded by complex formulations involving a wide array of intracellular and trans-synaptic signaling pathways. Similarly, while early HPA axis theories emphasized hyperactivity, more recent work suggests that derangements in this neuroendocrine system are more variable, and may be linked to abnormalities in neurotrophins (such as ▶ brain-derived neurotrophic factor (BDNF)) and ▶ neurogenesis. Other theories of pathogenesis have explored the role of reduced neurotransmission in the ▶ dopamine and ▶ GABA systems, altered glutamatergic neurotransmission, impaired ▶ endogenous opioid function, abnormal ▶ circadian rhythms, hypothalamic-pituitary-thyroid (HPT) axis dysfunction, monoamine–acetylcholine imbalances, cytokine-mediated neuroimmune abnormalities, deficient ▶ neurosteroids synthesis, and dysfunction of specific brain structures and circuits.

Diagnostic Categories

Major Depressive Disorder (Major Depression)

The diagnosis of major depression requires the presence of at least five of nine key symptoms during the same 2-week period, with at least one of the symptoms being either (1) depressed mood, or (2) loss of interest or pleasure. In addition to these, the other key symptoms are (3) significantly decreased or increased weight or appetite, (4) insomnia or hypersomnia, (5) psychomotor agitation or retardation, (6) fatigue or loss of energy (anergia), (7) feelings of worthlessness or guilt, (8) diminished concentration or indecisiveness, and (9) recurrent thoughts of death, suicidal ideation, or suicidal behavior.

Between 50 and 70% of individuals show clinically significant improvement with a given antidepressant. There is no compelling evidence of differential efficacy between drugs in unselected patients, and drug selection is usually based on a consideration of side-effect profiles. Selective serotonin reuptake inhibitors (▶ SSRIs) are the most frequently used first-line drugs for major depression. This group includes ▶ fluoxetine, ▶ paroxetine, ▶ sertraline, ▶ fluvoxamine, ▶ citalopram, and ▶ escitalopram. Common side effects of these drugs are constipation, diarrhea, dizziness, headache, insomnia, nausea, somnolence, and sexual dysfunction. Other frequently used classes of ▶ antidepressants are the serotonin-norepinephrine reuptake inhibitors (▶ SNRIs) and the norepinephrine reuptake inhibitors (▶ NARIs). The SNRIs include ▶ venlafaxine, desvenlafaxine, ▶ milnacipran, and ▶ duloxetine, which have side-effect profiles generally similar to the SSRIs. The NARIs include ▶ bupropion and ▶ reboxetine, with side effects that include dry mouth, insomnia, headache, nausea, constipation, tremor, and tachycardia; bupropion is less likely to cause sexual dysfunction than the SSRIs or SNRIs, but lowers the seizure threshold at high doses. The ▶ tricyclic antidepressants (TCAs) include ▶ amitriptyline, ▶ imipramine, ▶ clomipramine, ▶ nortriptyline, desipramine, protriptyline,

► trimipramine, amoxapine, and dothiepin. While the TCAs were the first class of drugs used to treat depression, they have largely been supplanted in that role by newer drugs because of their unfavorable side-effect profile (► anticholinergic effects, cardiovascular effects, somnolence, and tremor) and their high degree of lethality in overdose. Tetracyclic antidepressants, which include maprotiline, ► mirtazapine, and ► mianserin, constitute another group of less commonly used agents; maprotiline has side effects similar to the TCAs, whereas mirtazapine and mianserin are notable for causing somnolence, dry mouth, and substantial weight gain. The nonselective ► monoamine oxidase inhibitors (MAOIs), which include ► phenelzine, ► tranylcypromine, and ► isocarboxazid, are generally considered third- or later-line drugs, as they can cause life-threatening hypertensive or hyperpyrexic reactions when inadvertently combined with foods or drugs that enhance noradrenergic or serotonergic activity. More selective MAOIs, such as the reversible inhibitor of monoamine oxidase A (RIMA) ► moclobemide or the transdermal formulation of the MAO-B selective ► selegiline, are far less likely to cause such reactions. The triazolopyridine antidepressants, ► trazodone and its congener nefazodone, are now infrequently used as primary treatments for depression; trazodone can cause severe priapism, while nefazodone has been associated with rare fatal hepatic necrosis, and both drugs cause significant somnolence.

Major depression of mild to moderate severity may be treated with psychotherapy, with or without medication; ► cognitive-behavioral therapy and ► interpersonal psychotherapy, in particular, have been supported in controlled clinical trials. Milder cases of depression may also respond to complementary and alternative medical approaches, such as light (phototherapy), exercise, and herbal or dietary supplements (e.g., St. John's wort (*Hypericum perforatum*), omega-3 fatty acids, S-adenosine-L-methionine (SAMe)). Severe and treatment-resistant cases of depression are often managed with combinations of drugs or with ► electroconvulsive therapy. Rarely, stereotactic ablative neurosurgery, generally involving lesions in frontolimbic circuitry, is used in intractable cases. The role of newer neuromodulatory approaches, such as ► transcranial magnetic stimulation, ► vagus nerve stimulation, and ► deep brain stimulation, is currently under investigation.

Major Depressive Disorder with Psychotic Features (Psychotic Depression)

This form of depression is defined by the presence of either ► delusions or ► hallucinations, and is invariably severe; inpatient treatment is usually necessary because of profound functional impairment or intense suicidality. Psychotic features whose content reflects the typical depressive themes of personal inadequacy, guilt, disease, death, nihilism, or deserved punishment are considered mood-congruent; mood-incongruent psychotic features generally involve non-depressive persecutory delusions, thought insertion, thought broadcasting, or delusions of control. Pharmacotherapy usually involves the use of an ► antipsychotic in combination with an antidepressant. However, ECT is often required.

Major Depressive Disorder with Catatonic Features

Catatonia is diagnosed when at least two of five key symptoms are present, including (1) motoric immobility, such as catalepsy or stupor, (2) excessive purposeless motor activity (catatonic excitement), (3) extreme negativism (motiveless resistance to instructions or maintenance of a rigid posture against attempts to be moved) or mutism, (4) bizarre posturing, stereotypies, mannerisms, or grimacing, and (5) ► echolalia or ► echopraxia. Catatonic symptoms often respond acutely to ► benzodiazepines. However, since this syndrome generally occurs in the context of psychotic depression, treatment with an antipsychotic/antidepressant combination or ECT is usually necessary for sustained improvement.

Major Depressive Disorder with Melancholic Features (Melancholia)

The critical feature of this syndrome is profound anhedonia or lack of reactivity (not even transient mood improvement in response to positive events). In addition, at least three of six key symptoms are present, including (1) distinct quality of mood (different from usual feelings of sadness or loss), (2) morning worsening of mood (diurnal variation), (3) early morning awakening, (4) marked psychomotor retardation or agitation, (5) significant anorexia or weight loss, and (6) excessive guilt. Episodes of melancholia are usually severe, and patients with psychotic depression are usually melancholic. As the successor to the historical syndrome of endogenous depression, melancholia was originally defined in an attempt to identify those patients who would have a better response to somatic treatment than other patients. Subsequent research has failed to establish this preferential response, but has shown that melancholic patients are less likely than other patients to respond to placebo. Pharmacotherapy involves standard antidepressant drugs. Some authorities believe that first-generation drugs (i.e., TCAs and MAOIs) are more effective. Severe cases may require ECT.

Major Depressive Disorder with Atypical Features (Atypical Depression)

This syndrome is defined by the presence of mood reactivity (mood brightening in response to positive events) in conjunction with at least two of four key symptoms, including (1) significant weight gain or appetite increase, (2) hypersomnia, (3) leaden paralysis (heavy feelings in the limbs), and (4) a long-standing pattern of interpersonal rejection sensitivity. The diagnostic criteria for atypical depression reflect early efforts to identify a group of patients who would preferentially respond to MAOIs rather than TCAs. The importance of this distinction has receded as other, safer agents have supplanted the MAOIs, and treatment of atypical depression is now usually initiated with SSRIs or other second-generation antidepressants. However, ongoing research has generally supported the existence of meaningful neurobiological differences between atypical depression and melancholia (e.g., HPA axis hypoactivity in atypical depression vs. hyperactivity in melancholia).

Major Depressive Disorder with Postpartum Onset (Postpartum Depression)

Episodes of major depression whose onset is within 4 weeks of delivery are considered postpartum (as are similarly timed manic or mixed episodes). Diagnostic criteria are otherwise the same as for other depressive syndromes, although postpartum episodes are usually distinguished by symptom content that is focused on the infant. The mother may express excessive concern for the infant's well-being, feelings of being overwhelmed, fear of being responsible for the infant, hostility, or apathy. Psychotic symptoms may develop, in which case there may be a risk of infanticide. Postpartum depression must be distinguished from the transient mood lability ("baby blues") occurring in the first 10 days postpartum in up to 70% of women, which resolves on its own. Pharmacotherapy for postpartum depression involves standard antidepressant drugs, with antipsychotics if psychotic symptoms are present. All antidepressants are secreted in breast milk, but few specific adverse events have been reported, so benefits and risks of breastfeeding must be addressed.

Major Depressive Disorder with Seasonal Pattern (Seasonal Depression, Seasonal Affective Disorder)

Episodes of major depression are considered seasonal (as are manic or mixed episodes) if (1) there has been a regular temporal relationship between the onset of the episode and a particular time of year (for depression, usually fall or winter), (2) full remissions also occur at a characteristic time of year (usually spring), (3) in the last 2 years two episodes have occurred with the seasonal pattern, but no nonseasonal episodes have occurred, and (4) seasonal episodes substantially outnumber nonseasonal episodes over the individual's lifetime. The diagnosis is not made if seasonal psychosocial stressors (e.g., school or work) better account for the seasonal pattern. Seasonal depression is more common at higher latitudes and in younger individuals. Pharmacotherapy usually involves SSRIs or NARIs, although light therapy appears to be equally effective and is often used.

Minor Depressive Disorder (Minor Depression)

The diagnostic criteria for this syndrome are the same as those for major depression, but fewer symptoms are required. Thus, at least two, but less than five, of the nine key symptoms must be present during the same 2-week period, again with at least one of the symptoms being either depressed mood or loss of interest or pleasure. At present, these diagnostic criteria are considered investigational, and the nosological status of this syndrome is not established. There is only limited support for using pharmacotherapy in the management of minor depression, and while some studies suggest SSRIs may be of benefit, an especially careful assessment of risks and benefits should be undertaken.

Mixed Anxiety-Depressive Disorder (Mixed Anxiety-Depression)

This syndrome is defined by persistent or dysphoric mood lasting at least 1 month, accompanied by at least four of ten key symptoms lasting at least 1 month, including (1) difficulty in concentrating, (2) sleep disturbance, (3) fatigue, (4) irritability, (5) worry, (6) tearfulness, (7) hypervigilance, (8) anticipating the worst, (9) hopelessness, and (10) low self-esteem. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning, and are not due to the direct physiological effects of a substance or a general medical condition. In addition, criteria have never been met for major depression, ► dysthymic disorder, ► panic disorder, or ► generalized anxiety disorder, and criteria are not currently met for any other anxiety or mood disorder. As in the case of minor depression, mixed anxiety–depression is still considered an investigational diagnosis, and is not recognized in the official nomenclature. However, the greater symptom burden in mixed anxiety–depression supports a more prominent role for pharmacotherapy. SSRIs and SNRIs are preferred, as NARIs may lack efficacy and the side-effect profiles of other antidepressants are often

poorly tolerated in this population. Benzodiazepines are frequently used adjunctively, especially early in treatment.

Cross-References

- ▶ Antidepressants
- ▶ Antipsychotic Drugs
- ▶ Benzodiazepines
- ▶ Bipolar Disorder
- ▶ Monoamine Oxidase Inhibitors
- ▶ NARIs
- ▶ Neurogenesis
- ▶ Neurosteroids
- ▶ SNRIs
- ▶ SSRI
- ▶ Suicide

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Major Tranquilizer

Synonyms

Antipsychotic; Neuroleptics

Definition

A medication used in the treatment of psychotic disorders of any type with a particular emphasis on inducing sedation. The term is less used than its synonyms and is poorly characterized in pharmacological terms. It tends to be used less by psychiatrists than by nonspecialists.

Cross-References

- ▶ Antipsychotic Drugs
- ▶ First-Generation Antipsychotics
- ▶ Second and Third Generation Antipsychotics

MALDI

- ▶ Matrix-Assisted Laser Desorption Ionization

Malleability

- ▶ Elasticity

Malonylurea

- ▶ Barbiturates

Manerix

- ▶ Moclobemide

Mania

Definition

A state in which the individual experiences euphoria, irritability, lack of sleep, and increased drives, often to the point of poor judgment.

Manic-Depressive Illness

- ▶ Bipolar Disorder
- ▶ Bipolar Disorder in Children

MAO-B Inhibitor

Definition

A drug that blocks the action of monoamine oxidase type B.

Marijuana Abuse

► Cannabis Abuse and Dependence

Marijuana Addiction

► Cannabis Abuse and Dependence

Marijuana Dependence

► Cannabis Abuse and Dependence

Marplan

► Isocarboxazid

Mass Spectrometry

Synonyms

Mass spectroscopy

Definition

Mass spectrometry is an analysis technique that measures the molecular mass of an analyte. A mass spectrometer typically consists of three modules: (1) an ion source in which the convert sample is vaporized and ionized to make it analyzable; (2) a mass analyzer, which separates the sample components on the basis of their mass (more precisely their mass/charge ratios); (3) and a detector, which provides data for calculating the abundances of each ion present.

Cross-References

► Electrospray Ionization (ESI)
► Imaging Mass Spectrometry (IMS)
► Matrix-Assisted Laser Desorption Ionization (MALDI)
► Metabolomics
► Neuropeptidomics
► Post-Translational Modification
► Proteomics
► Two-Dimensional Gel Electrophoresis

Mass Spectrometry Imaging

► Mass Spectrometry

Mass Spectroscopy

► Mass Spectrometry

Matching Law

Definition

A behavioral allocation function that relates the rate of operant performance to the rate of reward delivery. The generalized matching law incorporates additional independent variables, such as the strength, amount, imminence, and likelihood of reward.

Maternal Deprivation Model

Definition

An animal model in which young rats are separated from their mother for a single period of 24 h. The most optimal day for separation is postnatal day 9. These animals develop a large number of schizophrenia-like phenomena in adulthood. Interestingly, most of these phenomena occur after puberty in accordance with the clinical literature on schizophrenia.

Cross-References

► Schizophrenia: Animal Models
► Simulation Model

Mating Behavior

► Sexual Behavior

MATRICS

Synonyms

Measurement and treatment research to improve cognition in schizophrenia

Definition
This is an initiative of the National Institutes of Health in the USA to enhance the methodology of assessing cognitive impairment in ► schizophrenia, using neuropsychological tests, for the purpose of clinical trials. This initiative has also boosted interest in cognitive assessment in experimental animals in order to evaluate putative cognitive enhancing compounds.

Matrix-Assisted Laser Desorption Ionization

Synonyms
Laser desorption ionization; MALDI

Definition
Formation of gas-phase ions from molecules that are present in a solid or liquid matrix that is irradiated with a pulsed laser.

Cross-References
► Imaging Mass Spectrometry (IMS)
► Mass Spectrometry (MS)
► Metabolomics
► Neuropeptidomics
► Proteomics
► Two-dimensional Gel Electrophoresis

MDAS

► Memorial Delirium Assessment Scale

MDMA

► Methylenedioxymethamphetamine (MDMA)

MEA

► Glutamate Microelectrode Arrays
► Microelectrode Arrays

Measures

► Rating Scales and Diagnostic Schemata

Measure of Drug Activity

► Potency

Measurement and Treatment Research to Improve Cognition in Schizophrenia

► MATRICS

Measurement of Biological Effect Resulting from Interaction with the Receptor

► Receptors: Functional Assays

Measurement of Neuronal Activity

► Extracellular Recording

Measurement of Receptor Signaling

► Receptors: Functional Assays

Mecamylamine

Definition
A nicotinic antagonist that is well absorbed from the gastrointestinal tract and crosses the ► blood–brain barrier.

Medazepam

Definition
Medazepam is a benzodiazepine that has anxiolytic, sedative, and anticonvulsant properties. It has a very long duration of action, mainly due to a long ► elimination half-life (36–200 h) and conversion to active metabolites including the benzodiazepines ► diazepam and

N-desmethyl-medazepam, both of which also are long-acting and also have long-acting metabolites. Like most similar compounds, medazepam is subject to ► tolerance, ► dependence, and ► abuse.

Cross-References
► Anxiolytics
► Benzodiazepines

Medial Forebrain Bundle

Definition
The MFB is a complex bundle of axons coming from the basal olfactory regions, the periamygdaloid region, and the septal nuclei, and passing to the lateral hypothalamus with some carrying on into the tegmentum. It contains both ascending and descending fibers. It is commonly accepted that the MFB is part of the reward system involved in the integration of reward and pleasure. Electrical stimulation of the MFB is believed to cause sensations of pleasure.

Medial Prefrontal Cortex

Synonyms
mPFC

Definition
A brain structure located in ► prefrontal cortex that receives dopamine input from the midbrain. It has been implicated in drug reward, behavioral inhibition, and stress reactivity.

Medical Herbalism

► Herbal Remedies

Medically Unexplained Symptoms

► Somatoform and Body Dysmorphic Disorders

Medicine

Synonyms
Drug; Human medicinal product

Definition
Any substance or combination of substances that may be used in or administered to human beings either with a view to restoring, correcting, or modifying physiological functions by exerting a pharmacological, immunological, or metabolic action, or to making a medical diagnosis.

Medicines Control

► Licensing and Regulation of Medicines

Medicines Regulation

► Licensing and Regulation of Medicines

Megakaryocytes

Definition
The megakaryocyte is a nucleated cell originating from the bone marrow and responsible for the production of platelets (thrombocytes), which are necessary for the process of hemostasis. The cytoplasm, exactly as platelets that bud off from it, contains alpha-granules and dense bodies.

Megalomania

► Delusional Disorder

Melanin-Concentrating Hormone

Definition
Lateral hypothalamic peptide involved in the regulation of feeding motivated behaviors including food intake. Like ► hypocretin/orexin, cells producing this peptide are located in the lateral hypothalamic region, but melanin-concentrating hormone (MCH)-producing cells do not co-express hypocretin/orexin.

α-Melanocyte-Stimulating Hormone

Definition
Cleaved product of the proopiomelanocortin pre-pro peptide. In the brain, this peptide is critical for the regulation of energy balance and genetic alterations that inactivate this peptide are associated with morbid obesity and insulin resistance.

Melatonin

Definition
Melatonin is a neurotransmitter that participates in the regulation of the sleep/wake cycle. It is produced endogenously and also available over-the-counter as an effective hypnotic for sleep onset.

Memantine

Definition
Memantine is used as an anti-dementia drug with some efficacy in the treatment of moderate to severe ► Alzheimer's disease. It reduces glutamatergic neurotransmission by acting as a low-affinity ► NMDA-receptor antagonist and this action is thought to underlie its protective effects against neuronal excitotoxicity. In addition to its anti-glutamate action, memantine also acts as a noncompetitive antagonist at serotonin 5-HT_3 and nicotinic acetylcholine receptors, and as an agonist at the dopamine D2 receptor; the role of these actions in the anti-dementia properties of the drug is unknown. Adverse side effects include confusion, dizziness, drowsiness, headache, insomnia or sleepiness, agitation, and hallucinations. In addition to Alzheimer's disease, memantine is currently being tested as a potential treatment for a number of other disorders. Preclinical studies as well as the clinical absence of withdrawal symptoms suggest that this drug has a low abuse potential.

Membrane Potential

Synonyms
Membrane voltage

Definition
A cell's membrane potential is the voltage difference across the plasma membrane that is present in all living cells.

Cross-References
► Intracellular Recording

Membrane Potential Recording

► Current Clamp

Membrane Voltage

► Membrane Potential

Memorial Delirium Assessment Scale

Synonyms
MDAS

Definition
The memorial delirium assessment scale (MDAS) is a 10-item, 4-point clinician-rated scale (possible range: 0 to 30) designed to quantify the severity of ► delirium, validated among hospitalized patients with advanced cancer and AIDS. Items included in the MDAS reflect the diagnostic criteria for delirium in the ► DSM-IV, as well as symptoms of delirium from earlier or alternative classification systems (e.g., DSM-III, DSM-III-R, ICD-9). The MDAS is both a good delirium diagnostic screening tool as well as a reliable tool for assessing delirium severity among patients with advanced disease. Scale items assess disturbances in arousal and level of consciousness, as well as in several areas of cognitive functioning (memory, attention, orientation, disturbances in thinking) and psychomotor activity. A cutoff score of 13 is diagnostic of delirium. The MDAS is designed to be administered repeatedly within the same day, in order to allow for objective measurement of changes in delirium severity in response to medical changes or clinical interventions. The MDAS has advantages over other delirium tools in that it is both a diagnostic as well as a severity measure that is ideal for repeated assessments and for use in treatment intervention trials.

Memory

Definition

Memory refers to the ability to recover information about past events or knowledge, the process of recovering information about past events or knowledge, as well as cognitive reconstruction. The brain engages in a remarkable reshuffling process in an attempt to extract what is general and what is particular about each passing moment.

Memory may be divided into short-term (also known as working or recent memory) and long-term memory. Short-term memory recovers memories of recent events, while long-term memory is concerned with recalling the more distant past.

Cross-References

- ▶ Long-Term Memory
- ▶ Short-Term and Working Memory in Animals
- ▶ Short-Term and Working Memory in Humans

Memory Consolidation

- ▶ Consolidation
- ▶ Protein Synthesis and Memory

Mental Deficiency

- ▶ Autism Spectrum Disorders and Mental Retardation

Memory Dysfunction

- ▶ Dementias and Other Amnestic Disorders

Memory-Impairing Drugs

- ▶ Inhibition of Memory

Memory Impairment

- ▶ Dementias and Other Amnestic Disorders

Memory: Information Storage, Learning and Memory

- ▶ Long-Term Depression and Memory

Memory Persistence

- ▶ Protein Synthesis and Memory

Memory Restabilization

- ▶ Consolidation and Reconsolidation

Memory Stabilization

- ▶ Consolidation and Reconsolidation

Memory Storage

- ▶ Consolidation
- ▶ Protein Synthesis and Memory

Memory-Storage Effect

Definition

Memory-storage effect refers to the gradual effect of a drug to alter the long-term memory of the estimated duration that is dependent on the translation of the clock reading into memory. In the ▶ Peak Internal (PI) procedure, a memory effect is observed as a gradual horizontal shift in the response function in PI trials following drug administration that is proportional to the estimated duration (see Meck, 1996).

Cross-References

- ▶ Timing Behavior

Mental Disorders

- ▶ Neuropsychiatric Disorders

Mental Retardation

► Autism Spectrum Disorders and Mental Retardation

MEOS

► Microsomal Ethanol-Oxidizing System

Meperidine

► Opioids
► Pethidine

Meprobamate

Synonyms
Miltown

Definition
Meprobamate is a sedative with a medium duration of action and is generally akin to the barbiturates used in the treatment of ► anxiety. It has largely been replaced by the benzodiazepines. Unwanted effects include sedation, headaches, paradoxical excitement, confusion, cognitive and psychomotor impairment, and confusion in the elderly. Interaction with ► alcohol can be hazardous. It depresses respiration and is toxic in overdose. Long-term use can induce ► dependence with severe withdrawal reactions. Recreational use and abuse can occur: it is a scheduled substance.

Cross-References
► Barbiturates
► Minor Tranquilizers

Meptazinol

Definition
Meptazinol is an opioid analgesic for use in moderate to severe pain. It is most commonly used to treat pain in obstetrics (childbirth). As a partial μ-opioid receptor agonist, its mixed agonist/antagonist activity results in a lower risk of dependence and abuse in comparison to full μ-agonists such as ► morphine. Meptazinol exhibits not only a short onset of action, but also a shorter duration of action relative to other opioids.

Cross-References
► Addiction
► Analgesics
► Dependence
► Opioids
► Pain
► Tolerance

Merital®

► Nomifensine

Mesolimbic System

Definition
Brain pathway that is dominated by dopamine projections branching to the subcortical ventral striatum (► nucleus accumbens) and to the ► prefrontal cortex.

Mesotelencephalic Dopamine Reward Systems

Synonyms
Brain reward systems; Dopamine reward systems

Definition
The mesotelencephalic dopamine system has three components, the nigrostriatal, mesolimbic, and mesocortical pathways consisting of cell bodies in the substantia nigra and ► ventral tegmental area that project to a number of regions including the ► nucleus accumbens, ► amygdala, striatum, and ► prefrontal cortex. These areas of the brain are strongly implicated in reward-related learning.

Meta-Analysis

Definition
A statistical technique for combining data from independent but methodologically similar studies to answer

related hypotheses and to estimate an overall effect across all the studies. Examples of its use include clinical trials and studies of behavioral and psychiatric genetics.

Metabolic Encephalopathy

► Delirium

Metabolic Toxins

► Neurotoxins

Metabolism

Synonyms
Biotransformation

Definition
Metabolism is the irreversible transformation of drugs into metabolites.

Cross-References
► Absorption
► Distribution
► Excretion
► Liberation
► Pharmacokinetics

Metabolomics

Synonyms
Metabonomics

Definition
Study of the complete set of small-molecule metabolites, such as metabolic intermediates, hormones, and other signaling molecules, and secondary metabolites, found within a biological sample.

Cross-References
► Electrospray Ionization (ESI)
► Imaging Mass Spectrometry (IMS)
► Mass Spectrometry (MS)
► Matrix-Assisted Laser Desorption Ionization (MALDI)
► Neuropeptidomics
► Post-Translational Modification

Metabonomics

► Metabolomics

Metabotropic Glutamate Receptor

Synonyms
mGluRs

Definition
G-protein-coupled receptor for which glutamate is the endogenous ligand.

Metabotropic Glutamate Receptors 2 and 3

► Group II Metabotropic Glutamate Receptor

Meta-Phenylenediamine

Synonyms
m-PD

Definition
All microelectrode arrays sites are electroplated with meta-phenylenediamine (m-PD) by applying a potential of +0.5 V to the Pt sites versus a silver/silver chloride (Ag/AgCl) reference electrode (Bioanalytical Systems, RE-5) in a deoxygenated 0.05 M phosphate buffered saline (PBS, pH 7.1–7.4) with 5.0 mM m-PD. The m-PD forms a size-exclusion layer over the sites, blocking DA, ascorbic acid (AA), DOPAC, and other electroactive compounds.

Meta-Plasticity

Definition
Some forms of ► neuronal plasticity affect LTP and LTD, which are already forms of plasticity. Therefore, the term "meta-plasticity" was introduced.

Metergoline

► Methergoline

Methadone

Definition
Methadone is an opioid racemate drug that acts as an agonist on the μ opiate receptor and is the best-studied substance available for opioid maintenance in terms of clinical effectiveness reducing illicit opioid consumption and reducing high-risk behavior such as needle sharing and increasing rates of treatment retention.

Cross-References
► Opioid Dependence and Its Treatment

Methamphetamine

Synonyms
Desoxyephedrine; Methylamphetamine; N-methylamphetamine

Definition
Methamphetamine is a ► psychostimulant and sympathomimetic drug that has a blood ► half-life of 9–15 h. The primary metabolite of methamphetamine is ► amphetamine, a chemical that itself is a potent psychostimulant. Methamphetamine is clinically available for the treatment of obesity, ► narcolepsy, and in some cases ADHD. Methamphetamine is a highly potent drug of abuse, with its illicit use reaching epidemic proportions in several Western countries including North American, Asian, and Pacific regions. Chronic exposure to methamphetamine can lead to schizophrenia-like psychosis and ► neurotoxic degeneration of dopaminergic neurons.

Cross-References
► Addiction
► Adolescence and Response to Drugs
► Amphetamine
► Attention Deficit Hyperactivity Disorder
► Dependence
► Dopamine
► Half-Life
► Narcolepsy
► Neurotoxicity
► Psychomotor Stimulants
► Sensitization to Drugs

Methergoline

Synonyms
Metergoline

Definition
Methergoline is a synthetic compound that acts as a nonselective ► partial agonist at serotonin (5-hydroxytryptamine) receptors. It is potent at some subtypes of both 5-HT_1 and 5-HT_2 receptors but has little action at 5-HT_3 receptors. It also acts as a dopamine agonist.

Cross-References
► Drug Discrimination

Methotrimeprazine

► Levomepromazine

Methylamphetamine

► Methamphetamine

N-Methylamphetamine

► Methamphetamine

N-Methyl-D-Aspartate Receptor

Synonyms
NMDA receptors

Definition
The N-methyl-D-aspartate receptor (NMDA) receptor is one of several subtypes of glutamate receptor. It is a voltage-sensitive ionotropic receptor (ligand-gated ion channel) that facilitates excitatory transmission of electrical signals between neurons by depolarizing the postsynaptic neuronal membrane. Although it is named after a selective agonist (NMDA), endogenous ligands for the receptor include glutamate or aspartate. Efficient channel

opening also requires binding by the co-agonist glycine and a positive change in transmembrane potential. Activation of NMDA receptors results in the opening of an ion channel that is nonselective to cations, allowing the influx of Na^+ and Ca^{2+} and the efflux of K^+. In addition to facilitating excitatory neurotransmission, NMDA receptors are thought to play a key role in ► synaptic plasticity, thereby having an important role in learning and memory.

Cross-References

► Excitatory Amino Acids and their Antagonists
► Glutamate
► Glycine

Methyl Benzene, Toluol

► Toluene

Methyl (1R,2R,3S,5S)-3-(Benzoyloxy)-8-Methyl-8-Azabicyclo[3.2.1] Octane-2-Carboxylate

► Cocaine

Methylbenzylpropynylamine

► Pargyline

Methyl Chloroform

► Trichloroethane

Methylenedioxymethamphetamine (MDMA)

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Synonyms

E; Eccie; Ecstasy; Hug drug; Love drug; Love hormone; 3,4 Methylenedioxymethamphetamine; XTC

Definition

MDMA is a popular recreational drug that is renowned for its ability to produce euphoria and unique prosocial effects. It is the best known and most commonly used member of the family of phenethylamines (substitutes for ► amphetamines) that are sometimes known as ► entactogens, empathogens, or the MDxx class of drugs. MDMA has multiple neurochemical effects, the most prominent of which is to promote the release of serotonin via an action on the ► serotonin transporter (SERT). The prosocial effects of MDMA have recently been linked to the release of the neuropeptide ► oxytocin. High doses of MDMA can cause long-term depletion of serotonin in the brains of laboratory animals, but whether this also occurs in humans and whether this leads to associated psychopathology such as ► depression and ► cognitive impairment remains unclear.

Pharmacological Properties

History

MDMA was first synthesized in 1912 by the company E. Merck. Although commonly thought to have been designed as an appetite suppressant, the original patent bears no record of this and simply states that MDMA was deemed to contain primary constituents for therapeutically active compounds. The first reported pharmacological study involving MDMA occurred in 1927 although basic toxicology studies were not undertaken until the 1950s. Further studies at the University of Michigan, supported by the US Army, reported LD_{50} values for five different species, with the lowest LD_{50} value found in dogs and the highest in mice.

The first systematic use of MDMA was as an adjunct to insight-oriented psychotherapy, with administration of MDMA producing an easily controllable altered state of consciousness with positive emotional and sensual overtones. The colloquial term for MDMA changed from "Empathy" as was used by therapists in the 1970s to "Ecstasy," emphasizing the drug's euphoric effects. Heavy media attention in 1985 sensationalized Ecstasy's euphoric effects and caused a surge in recreational use.

In 1986, MDMA became a Schedule 1 drug in the United States, deemed to possess no recognized therapeutic value. By the 1990s, ► Ecstasy had become intrinsically linked to the club and rave culture, with its use by groups of young people attending all-night dance parties where

vigorous dancing occurred to highly repetitive and hypnotic "techno" music. The popularity of MDMA has continued to grow to the point where it is now one of the most widely used illicit drugs in the world.

Mechanisms of Action

MDMA is a ring-substituted amphetamine, with a methylenedioxy group attached to the aromatic ring of amphetamine. It has multiple, complex pharmacological actions. The most important property is to potently release ▶ serotonin (5-HT) from axon terminals into the synapse and to inhibit 5-HT reuptake. To a lesser extent, MDMA also releases dopamine, noradrenaline, and acetylcholine. MDMA reverses the action of the SERT causing 5-HT stores from the neuron to be pumped into the synapse. An additional related action is to block the reuptake of 5-HT (▶ uptake), which further increases synaptic 5-HT concentrations. Pretreatment with SERT ligands including ▶ SSRIs (e.g., fluoxetine) prevents MDMA-induced 5-HT release in brain slices and in vivo. In addition to these effects on 5-HT efflux, MDMA-mediated inhibition of ▶ monoamine oxidase prevents the breakdown of 5-HT and other ▶ neurotransmitters such as dopamine, further contributing to elevated monoamine levels. A further effect of MDMA is to inhibit tryptophan hydroxylase (the rate-limiting enzyme for 5-HT synthesis). This effect may contribute to depletion of 5-HT stores in the days following MDMA use.

MDMA possesses two stereoisomers: (−)-MDMA has a higher affinity for postsynaptic 5-HT receptors while (+)-MDMA has a higher affinity for the SERT. The two isomers differ in their behavioral effects in rhesus monkeys and subjective effects in humans. These two isomers also differ in the rate in which they are metabolized across individuals which may result in large inter-individual differences in the overall response to MDMA.

MDMA also binds to various 5-HT receptors with moderate to high affinity. Receptor-binding studies indicate that MDMA possesses a high affinity for the 5-HT_2 family of receptors and a moderate affinity for 5-HT_1-type receptors. Activation of ▶ 5-HT_{1A} receptors largely acts to inhibit serotonergic cell firing although the resultant inhibitory effects on 5-HT release are overridden through MDMA-induced effects at the SERT in forebrain regions.

MDMA acts to increase synaptic ▶ dopamine levels, but these increases are generally smaller than the increases in 5-HT in any given region. MDMA-induced dopamine release may involve both an indirect ▶ 5-HT_{2A}-receptor mechanism as well as a direct action on the ▶ dopamine transporter (DAT). Dopamine levels are also augmented by an action of MDMA on the vesicular monoamine transporter (VMAT2) causing dopamine efflux from vesicular stores via carrier-mediated exchange.

MDMA also causes a significant release of ▶ norepinephrine via an interaction with the ▶ norepinephrine transporter (NET). ▶ Acetylcholine release also occurs in the prefrontal cortex and dorsal hippocampus following MDMA, and there is also the involvement of GABA, glutamate, nitrergic, and sigma ($\sigma 1$) systems. MDMA causes major endocrine changes (▶ neuroendocrine markers for drug action) including an increase in plasma oxytocin, vasopressin, cortisol, and prolactin.

Pharmacokinetics

Human ▶ pharmacokinetic studies show that MDMA's distinctive effects occur at doses of 1 mg/kg or above with peak MDMA serum concentrations observed 2 h post administration, coinciding with peak psychological effects. MDMA has nonlinear pharmacokinetics, with increasing doses resulting in unpredictable blood/body concentrations. Like most other psychoactive drugs, MDMA is primarily metabolized by the liver via the ▶ cytochrome P450 family of enzymes, with the 2D6 isozyme particularly implicated. However, MDMA has a very complex metabolic pathway in comparison to other amphetamine analogs, and this may explain the sometimes complex and unpredictable relationship between Ecstasy tablet intake and acute effects of the drug. The primary metabolites of MDMA in humans, HHMA and HMMA, are readily broken down in the body to ortho-quinones, highly reactive compounds that may lead to ▶ free radical-induced brain injury.

Neurotoxicity

Exposure to relatively high doses of MDMA can cause a long-lasting reduction in brain monoamine levels in a variety of animal species. While rats and primates show a primary reduction in brain 5-HT, mice show primary reductions in brain dopamine. Reductions in SERT density in cortical, limbic, and striatal regions has also been reported in many studies with rats and primates. Given that the SERT protein is primarily located in 5-HT axons, MDMA-induced axotomy has been invoked as the primary reason for this effect and has been confirmed in some histological studies. Abnormal 5-HT axonal immunoreactivity has been seen in primates 7 years post MDMA treatment. However, these pattern of findings do not confirm a neurotoxic effect in the classic sense. Gliosis is not typically observed following MDMA administration; nor is there any damage to serotonergic cell bodies. The widely discussed notion of MDMA-induced ▶ neurotoxicity therefore remains controversial (Baumann et al. 2007).

In addition to global SERT changes, alterations in the density of specific 5-HT receptor subpopulations can be seen following MDMA. Significant reductions in 5-HT_{2A} receptor density in cortical, striatal, thalamic, and hypothalamic regions have been reported in rats months after MDMA treatment, although opposite findings on 5-HT_{2A} receptor density have been reported in some human studies. ▶ 5-HT_{1B} receptor density was reduced in MDMA-treated rats in the globus pallidus, ▶ hippocampus, and medial thalamus but increased in the ▶ nucleus accumbens and lateral septum.

High ambient temperatures at the time of dosing, typical of the dance parties where MDMA is often taken, may exacerbate MDMA-induced 5-HT depletion. A ▶ neuroprotective effect of coadministered drugs (e.g., haloperidol, ketanserin, pentobarbitone, and various antioxidants) may result from an induction of hypothermia or by preventing the hyperthermic effects of MDMA. However, some drugs (e.g., ▶ cannabinoids) are protective independently of their body temperature effects.

Some human studies have found that Ecstasy users differ from controls on a range of measures related to 5-HT, including a reduction of cerebrospinal 5-HIAA levels and a blunted ▶ neuroendocrine responses to serotonergic ligands. Decreased global and regional SERT density in Ecstasy users have been reported in some ▶ PET imaging and ▶ SPECT imaging studies although these are generally modest effects and may recover with abstinence from the drug.

Positive Effects in Humans

MDMA induces a positive mood state in humans along with increased energy and euphoria, typical of amphetamine and its derivatives. However, MDMA users also report a unique sense of intimacy and empathy coupled with an increased feeling of closeness to others (▶ entactogen) that is not always typical of amphetamine (▶ social behavior). In addition, MDMA users also report mild ▶ hallucinogen-like enhancement of perceptions and sensations with augmented responses to touch and music. Unlike amphetamines, MDMA appears to have relatively low ▶ abuse potential in humans, perhaps due to rapid ▶ tolerance developing to the positive effects with repeated use.

SSRIs attenuate many of the acute psychological effects of MDMA in humans, consistent with a primary action of MDMA on SERT. SSRIs also reduce MDMA-induced heart-rate changes. Other studies showed that MDMA-induced perceptual changes and emotional excitation are partially mediated by post-synaptic 5-HT_{2A} receptors since these effects can be attenuated by ketanserin (Liechti and Vollenweider 2001).

The positive acute effects of MDMA in humans may involve other neurochemical systems. Thus, the ▶ antipsychotic drug ▶ haloperidol partially antagonized the positive and mania-like mood states induced by MDMA. In a recent laboratory study, the increased feeling of sociability after MDMA was associated with increased plasma levels of oxytocin in human subjects (Dumont et al. 2009).

Effects in Laboratory Animals

The acute effects of MDMA have been investigated in a diverse range of laboratory animal species. A key consideration in utilizing animal models is in establishing appropriate species-equivalent dosing levels to model human MDMA use (Green et al. 2009). This issue is still far from resolved with many animal studies using MDMA dose regimes that are in the extreme range. Species-specific ▶ pharmacokinetics also complicate the picture.

MDMA has amphetamine-like sympathomimetic effects, increasing blood pressure and heart rate. It exerts a powerful influence on body temperature, with the direction of change (hyperthermia or ▶ hypothermia) dependent upon the ambient temperature of the environment (Green et al. 2003). The hyperthermic response to MDMA appears in part to be reliant upon the mitochondrial uncoupling protein 3 (UCP-3) acting in striated myocytes. MDMA also produces peripheral vasoconstriction, further preventing heat loss.

Behaviorally, MDMA causes amphetamine-like ▶ hyperactivity and locomotor ▶ sensitization in rodent species. ▶ Intravenous self-administration of MDMA is seen in mice, rats, and nonhuman primates although rates are significantly less than that of other abused drugs such as the ▶ psychostimulants cocaine and methamphetamine. Self-administration of MDMA in rats is increased at high ambient temperatures, and this may be in part due to augmentation of MDMA-stimulated increases in dopamine and neuronal activation in reward-relevant brain regions. Rats will also show a ▶ conditioned place preference to MDMA, an effect that involves dopamine, ▶ opioid, and ▶ endocannabinoid systems.

In line with its characteristic prosocial effects in humans, MDMA reduces aggression and increases social interaction in rodents. In the ▶ social interaction test, rats spend increased times in adjacent contact following acute MDMA treatment, and this effect is also augmented at high ambient temperatures. This prosocial effect of MDMA is

reduced by oxytocin antagonists and is minimicked by the ► 5-HT_{1A} agonist 8-OH-DPAT (McGregor et al. 2008).

MDMA-Associated Hazards and Psychopathology

Hyperthermia and other components of the ► serotonin syndrome are the main acute hazards facing human MDMA users, particularly when the drug is taken in high doses and in hot environments. Despite considerable media attention, lethal effects of MDMA (taken alone) appear comparatively rare. However, combining MDMA with other serotonergic drugs (e.g., ► monoamine oxidase inhibitors) can be extremely dangerous due to the possibility of ► serotonin syndrome. Other problems for users relate to the fact that Ecstasy tablets do not always contain MDMA, with a wide range of adulterants reported in analytical studies.

Acute adverse psychological effects are occasionally reported with MDMA, most commonly ► anxiety and paranoia. A greater research focus, however, has been on possible lasting adverse psychological effects of MDMA use, effects that might be associated with serotonin depletion. In various studies, Ecstasy use has been linked to ► anxiety, ► depression, and ► mild cognitive impairment. However, many of these studies have inherent methodological problems. For example, Ecstasy users typically use other substances and coincident heavy cannabis use is a particularly troublesome confound in studies probing cognitive impairment after MDMA. There is also evidence that people with a preexisting childhood tendency toward anxiety and depression are more likely to become Ecstasy users, providing an additional confound. There is therefore a need for prospective longitudinal studies to control for premorbid psychiatric and cognitive problems in assessing MDMA-related harms. An example of this is the recent Netherlands XTC Toxicity (NeXT) study. This has uncovered subtle abnormalities in brain function in a sample of young persons taking MDMA for the first few times (de Win et al. 2008).

Preclinical studies are also important in addressing the issue of whether MDMA exposure has lasting adverse consequences. Consistent, lasting adverse effects have been reported in a number of behavioral tests in rodents pretreated with MDMA. These include increased anxiety as assessed in the emergence test and the ► elevated plus maze, increased depressive-like symptoms in the Porsolt test (► Depression: Animal Models), and impaired ► novel object recognition and ► spatial memory. The ► social interaction test has been found to be particularly sensitive to detecting lasting adverse effects of MDMA in rodents, with decreased social behavior detected even months after low-dose MDMA exposure. Many of the above long-term effects are seen with low-dose regimes of MDMA that do not deplete brain 5-HT. As yet, unspecified neuroadaptations in nonserotonergic brain systems may therefore underlie these lasting adverse effects (McGregor et al. 2008).

Therapeutic Uses

Despite concerns relating to the neurotoxicity and possible psychopathology associated with MDMA use, a number of reputable scientists have called for further study of the use of MDMA as a therapeutic for anxiety and depression and relationship issues. This marks something of a return to the original use of MDMA as a tool for assisting ► interpersonal psychotherapy in the 1970s and 1980s. The Multidisciplinary Association for Psychedelic Studies (MAPS) (http://www.maps.org/mdma/) is currently sponsoring small clinical trials of MDMA in several countries for the treatment of ► traumatic stress disorder, and are also sponsoring a study of MDMA for alleviation of anxiety linked to terminal cancer.

Conclusions

MDMA is a controversial drug with a unique and complex pharmacology. No other drug, with the possible exception of GHB (► sodium oxybate), has the capacity to produce such marked facilitatory effects on ► social behavior in humans and other animal species. It is therefore encouraging to see that recent psychopharmacological studies of MDMA have started to focus on the positive prosocial effects of the drug in humans (Bedi et al. 2009; Dumont et al. 2009), and not just on its possible adverse effects and neurotoxicity.

Despite a plethora of human and animal studies spanning more than two decades, experts cannot appear to reach a consensus on the relative harms associated with MDMA use: some claim MDMA is largely innocuous (Nutt 2009) while others proclaim its dangers (Parrott 2002). Fortunately, our overall knowledge of MDMA psychopharmacology continues to grow, as research studies involving both human Ecstasy users and laboratory animals given MDMA evolve in their sophistication, scope, and power. Perhaps given another decade of research, a greater consensus will emerge, and we will understand not only how MDMA acts in the brain to produce "chemical love" but also whether this is a good or a bad thing for the health of the individual.

Cross-References

► Amphetamine
► Anxiety: Animal Models

- ▶ Depression
- ▶ Dopamine Transporter
- ▶ Hypothermia
- ▶ Neurotoxicity
- ▶ Serotonin Syndrome
- ▶ Serotonin Transporter
- ▶ Social Behavior
- ▶ Transporters
- ▶ Traumatic Stress Disorder

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3,4 Methylenedioxymethamphetamine

▶ Methylenedioxymethamphetamine (MDMA)

Methyl-Lorazepam

▶ Lormetazepam

(3R)-*N*-Methyl-3-(2-Methylphenoxy)-3-Phenyl-Propan-1-Amine

▶ Atomoxetine

Methylmorphine

▶ Codeine

Methylphenidate

Synonyms

Dexmethylphenidate; Ritalin; Vitamin R

Definition

Methylphenidate (MPH) is the most commonly prescribed psychostimulant for the treatment of attention-deficit hyperactivity disorder (juvenile and adult forms), although it has also been used in the treatment of narcolepsy and postural orthostatic tachycardia syndrome. It was first synthesized in 1944 and is chemically related to cocaine; it was originally formulated as a mixture of two racemates, 80% (±)-erythro and 20% (±)-threo, though its efficacy was later realized to derive from the threo isomer. Like most psychomotor stimulants, it acts to enhance ▶ dopamine release and block reuptake with additional effects on ▶ noradrenaline reuptake; it is not thought to affect central serotonin directly, unlike the prototypical psychomotor stimulant ▶ amphetamine, or ▶ cocaine. Its main cognitive effects are to reduce ▶ fatigue, enhance ▶ attention, and reduce ▶ impulsivity. Experimental studies in non-sleep-deprived healthy humans have indicated beneficial effects on ▶ working memory, leading to its current reputation as a "▶ cognition enhancer." Its mode of action on cognition is probably in fronto-striatal circuits as shown from human imaging and animal studies. Its relatively slow onset of action when taken orally may well contribute to its relative lack of abuse potential in the conventional sense, although it has recently been shown to be a popular "cognition enhancer" in college students where it is sometimes called "Vitamin R." Adverse effects of methylphenidate include slight growth retardation, appetite suppression, and, occasionally, motor tics. Long-term effects are largely unknown, although it has been suggested to "protect" ADHD juveniles from future drug abuse.

Cross-References

► Attention Deficit and Disruptive Behavior Disorders
► Attention Deficit Hyperactivity Disorders: Animal Models
► Cognitive Enhancers
► Hypersomnia
► Impulse Control Disorders
► Impulsivity
► Methylphenidate and Related Compounds
► Pemoline
► Psychomotor Performance
► Psychomotor Stimulants

Methylphenidate and Related Compounds

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Synonyms

Ritalin

Pharmacological Properties

Several newspapers in the US recently reported the contention that healthy people should have the right to boost their brains with psychoactive drugs, drugs that are normally described for disorders such as attention deficit disorder (ADD), ► attention deficit/hyperactivity disorder (ADHD), ► narcolepsy, and memory-impairment in older individuals (► dementia). College students are already taking Ritalin as a ► cognitive enhancer before exams to help them study better, and some students contend that "We should welcome new methods of improving our brain function" and that doing it with pills is no more morally objectionable than eating right or getting a good night sleep (Houston Chronicle, December 8, 2008). But what do we know about this psychoactive drug?

Psychoactive drug use is a practice that dates back to prehistoric times. A psychoactive drug is a central nervous system (CNS) stimulant that modulates consciousness, perception, mood, and behavior. There is archeological evidence of the use of psychoactive drugs as far back as several thousand years ago. These drugs were used therapeutically as medication, for ritual and spiritual purposes, as well as recreationally to alter one's mood and to get "high." Because psychoactive drugs elicit changes in consciousness and mood, the user feels alert, joyful, pleasant, and becomes euphoric. Many psychoactive drugs are abused despite the risks of negative consequences, that is, ► dependence. Methylphenidate belongs to this family of drugs.

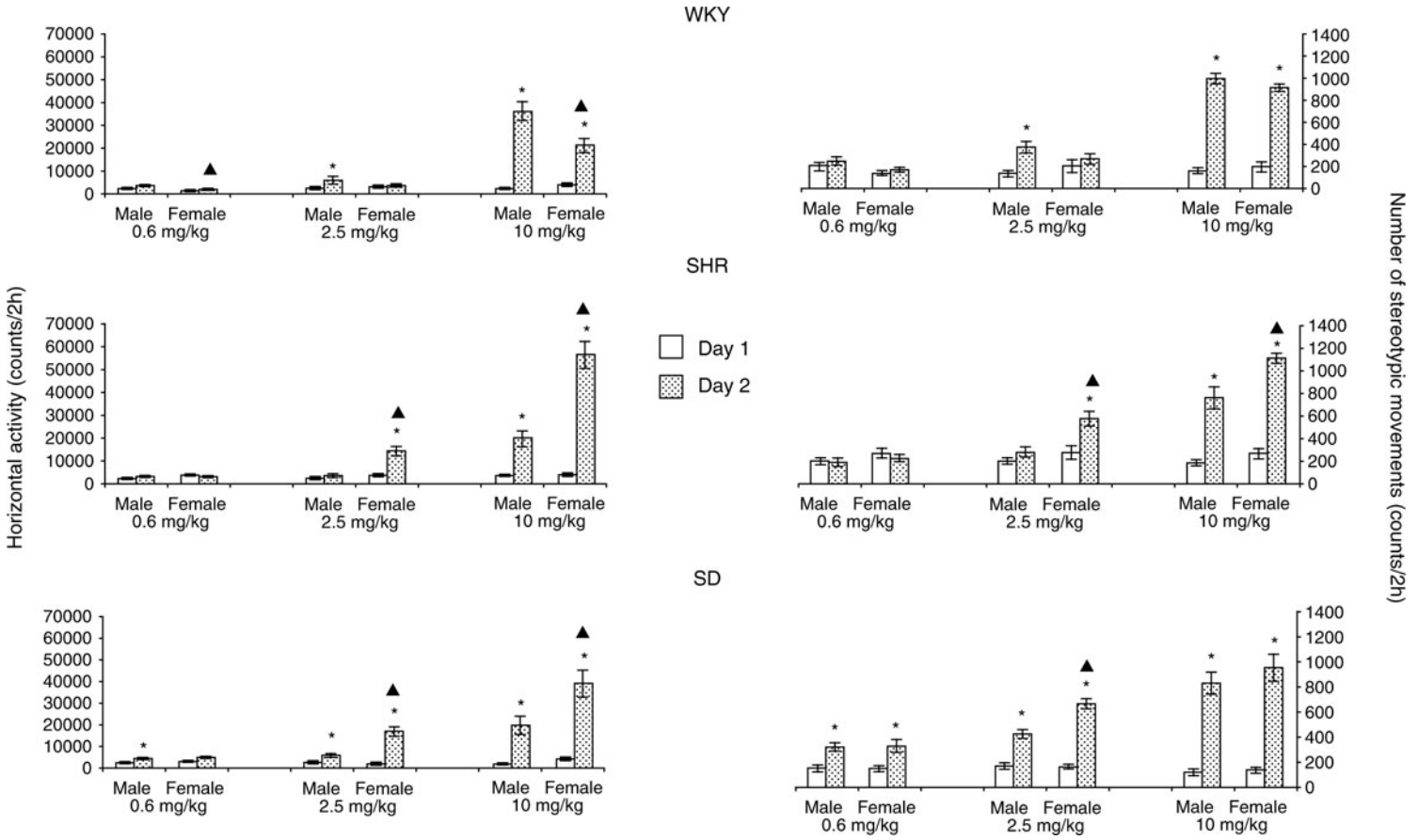
What is methylphenidate? MPD is one of the most prescribed psychostimulants for the treatment of children and adults with ADHD. ADHD is characterized by a persistent pattern of inattention and/or hyperactivity, with impulsivity more often displayed and more severe than is typical for individuals at a comparable level of development. ADHD is a developmental disorder that affects as much as 5–15% of school-aged children in the US (Kollins et al. 2001). Methylphenidate is a CNS stimulant that is structurally closely related to ► amphetamine. The neuropharmacological profile of methylphenidate is also similar to that of ► cocaine (Volkow et al. 1999). The drug was first synthesized in 1944 and was used initially as an analeptic for several types of barbiturate-induced coma. It was later used as a drug to improve memory in elderly patients. Since then, its usage has been extended to improve alertness and attention in children and adults with emotional, behavioral, and learning difficulties. Methylphenidate is highly effective in treating ADHD. Methylphenidate may also be useful in providing relief from intractable pain in narcolepsy and chronic fatigue. When methylphenidate is given orally, it is absorbed from the intestinal tract and has a half-life time of about 1 h with equally short duration and efficacy (Solanto 2000). Its peak level following injection (systemic) is faster and is reached in 8–20 min post injection (Kuczenski and Segal 1997), a pattern that is similar to systemic cocaine and amphetamine administration (Volkow et al. 1999). When methylphenidate is given systematically, it binds with similar affinity to the ► dopamine transporter (DAT) and has a potency (K_i=200) similar to cocaine (K_i=224) (Kuczenski and Segal 1997). The relationship between drug doses (milligrams of hydrochloride salt/kilogram of body weight) and percentage occupancy of DAT is identical for cocaine and methylphenidate in rodents and humans (Gatley et al. 1999). The dose and route of administration are important because the features of the behavioral and neurochemical responses to the drug are dependent on the speed of the drug to reach the peak level, that is, the rise time of drug concentration (Kuczenski and Segal 1997). Peak levels of methylphenidate following intravenous (i.v.), intraperitoneal (i.p.), and oral administrations were 8–20 min, 15–28 min, and 60–90 min, respectively (Gerasimov et al. 2000). Similar peak levels of i.v., i.p., and oral administrations were obtained following amphetamine and cocaine (Gerasimov et al. 2000). The ability to reach the peak level in a short time (i.v., 8–30 min) is one of the main

factors in eliciting adverse effects such as its euphoria, ▶ tolerance, and ▶ sensitization. Stimulants have been abused for both "performance enhancement" and for recreational purposes. For the former, they suppress appetite, facilitate weight loss, increase wakefulness, and increase focus and attention. Their euphoric effects usually occur when the stimulants are crushed and inhaled through the nose or injected. Methylphenidate is absorbed and metabolized via de-esterification to ritalinic acid and released into urine within 48 h. Brain concentrations of methylphenidate exceed that of plasma, since the psychostimulant is concentrated in catecholamine systems with free passage across the ▶ blood-brain barrier. Methylphenidate has a rapid uptake in the brain similar to amphetamine and cocaine, but differs from amphetamine and cocaine in that the rate of clearance from the brain is much slower. Intravenous (i.v.) or intranasal administration of methylphenidate is associated with a higher mortality rate than cocaine or amphetamine use, and every year more adolescents and young adults use (or misuse) the drug in these routes of administration. The outcome of methylphenidate treatment results primarily in dopamine (DA) release and inhibits the reuptake of DA, norepinephrine (NE), and serotonin (5-HT) (Kuczenski and Segal 1997). Like cocaine, methylphenidate is an indirect catecholamine agonist, since it does not stimulate the catecholamine receptors directly but rather facilitates the action of the catecholamine (Volkow et al. 1999). The therapeutic effects of methylphenidate in the treatment of ADHD has been attributed to its ability to increase the efflux of these neurotransmitters (Askenasy et al. 2007; Dafny and Yang 2006) by binding to their transporters and blocking the reuptake of these neurotransmitters. This causes increases in extracellular DA, NE, and 5-HT levels (Kuczenski and Segal 1997), which has an effect that has been linked to its reinforcing properties (Solanto 2000; Volkow et al. 1999). Methylphenidate has moderate effects on the peripheral circulatory system. In rats, methylphenidate administration in low doses (2.0–5.0 mg/kg) stimulates locomotor activity (Fig. 1) and elicits behavioral sensitization (Fig. 2.). In higher doses (10.0 mg/kg and higher), it stimulates stereotypical behavior and tolerance (Dafny and Yang 2006). The therapeutic effects of stimulants such as methylphenidate and amphetamine are achieved by slow and steady increases of DA, NE, and 5-HT which are similar to natural production by the brain. The most commonly prescribed medication for ADHD patients include amphetamine (e.g., Adderall, a mixture of amphetamine salts), methylphenidate (i.e., Ritalin, which is short acting), and formulations such as Concerta that release methylphenidate over a longer period of time.

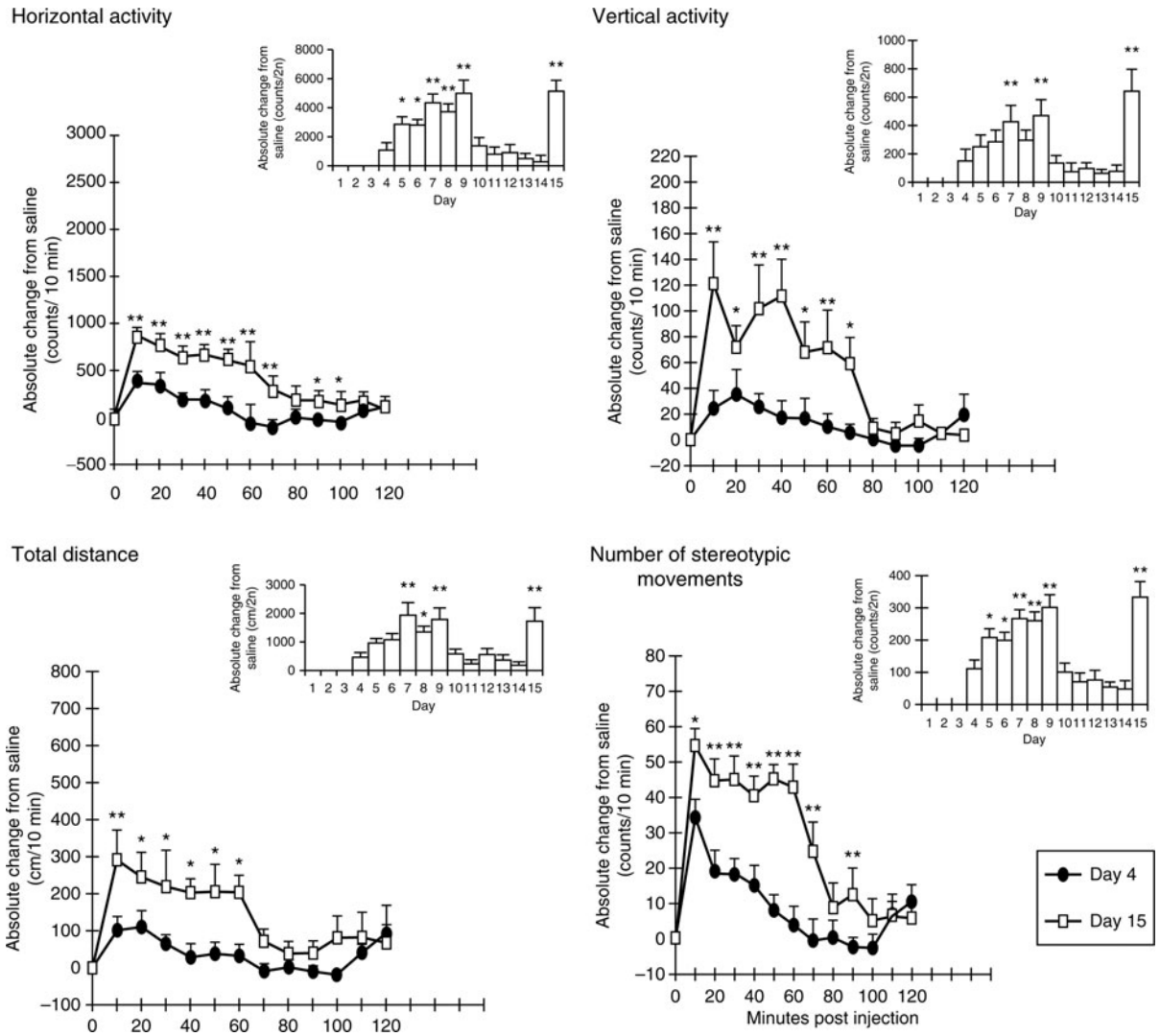
Domestic sales of methylphenidate in the US showed an increase of almost 500% in the last decade. The therapeutic benefits of methylphenidate treatment for ADHD are clear. Moreover, concerns exist that during adolescent years, crucial neurodevelopment occurs with the production and elimination of numerous neuronal synaptic connections, that is, synaptic pruning. Children with ADHD who are going through neurodevelopmental processes are treated with methylphenidate for extended periods of time. Chronic treatment with psychostimulants such as methylphenidate and amphetamine can modulate these neurodevelopmental processes critically, which in turn may alter the body's homeostasis. Any modulation produced by such psychopharmacological intervention in a still-developing brain should generate significant public health concerns. Additional concerns are raised that psychostimulant therapy given to adolescents and young adults may result in an increased risk for behavioral disorders (Robinson and Berridge 1993), while other reports have shown that psychostimulant treatment in adolescents with ADHD protects them from later substance use. These contradictory reports call for basic in-depth studies to resolve this critical issue. Animal models using behavior and neuronal recordings following acute and chronic methylphenidate treatment can be used to clarify this contradiction.

Animal Models for Studies of Methylphenidate

Methylphenidate is the drug most often used for treating children and adults with ADHD, for many years. It is expected that these patients would be used to study the prolonged effects of methylphenidate on their physiological and behavioral properties. However, there are ethical, methodological, and economic factors that limit research on children and adults exhibiting ADHD and on the therapeutic effects of methylphenidate. Therefore, research uses animal models for the understanding of the disorders. Researchers deal with a simpler system, which yields data that may be easier to interpret than that of a clinical case. In addition, animal models offer the possibility of understanding neurobiological processes that cannot be readily studied in humans. The question is which animal, and if a rat is selected, which strain? It has been argued that the most adequate model to study the physiological properties of methylphenidate is the one that best mimics a clinical case of ADHD and is able to predict aspects of ADHD behavior. There are differences between different strains of rats in the susceptibility to psychostimulants and their chronic effects such as tolerance or sensitization. Each strain of rats comprises a different gene pool. This results in different susceptibilities to



Methylphenidate and Related Compounds. Fig. 1. The figure summarizes the dose-response of acute methylphenidate injection on the horizontal activity and the number of stereotypic activities of female and male WKY, SHR, and SD rats, using the open field assay. Each group consists of $N=8$ and was given saline on experimental day 1 and methylphenidate on experimental day 2. The 0.6 mg/kg methylphenidate failed to elicit any changes in the horizontal activity of female and male WKY and SHR groups, while this low dose of methylphenidate significantly increased the horizontal activity of male SD rats (Fig. 1 – *left column*). The 2.5 mg/kg methylphenidate given i.p., increased significantly (*$P<0.05$) only the horizontal activity of male WKY and SD rats and female SHR and SD rats (Fig. 1 – *middle column*), as compared to that of the saline control group. Female SHR and SD exhibited significantly (Δ $P<0.05$) greater increase in activity compared to their male counterparts. The highest methylphenidate dose (10.0 mg/kg) induced robust increase in locomotor activity when compared to baseline. * – indicates significant ($P<0.05$) difference when comparing the animal group to its control day, that is, experimental day 2 to experimental day 1. Δ indicates significant ($P<0.05$) difference between the sexes of each rat strain.



Methylphenidate and Related Compounds. Fig. 2. This figure demonstrates behavioral sensitization. The embedded histograms in the upper right corner depict the total change from the baseline activity in the initial 2-h following injection at all administration times. The numbers indicate the experimental days. The figure summarizes 15 consecutive recordings ($N=8$) of four different locomotor activity indices. The locomotor recording of three control days (baseline) was set arbitrarily as 0. Following the control days, six single daily injections of 2.5 mg/kg methylphenidate (i.p.) were given at 07:00, and followed by 5 days of washout. Finally, a re-challenge injection of 2.5 mg/kg methylphenidate (i.p) was administered on experimental day 15. In all the four locomotor indices, the activity on experimental day 15 was significantly elevated as compared to the recording on experimental day 4 (1st day of methylphenidate injection). In the temporal graphs, the filled circles are the recordings after saline injection, while the squares denote the locomotor activity after 2.5 mg/kg methylphenidate.

psychostimulants by different strains, and the long-term effects of the drug (sensitization or tolerance) can also be different in each strain.

Since no biological marker for ADHD has yet been identified, diagnosis of ADHD is presently based only on behavioral symptoms. Many suggested ► animal models of ADHD exist, including rats selected from a general population, rats reared in social isolation, rats exposed to environmental pollutants, rats that have undergone neonatal anoxia, rats that have undergone hippocampal X-irradiation in infancy, rats that have undergone neurotoxic brain lesions, Naples High/Low excitability rats,

and knockout mice. There are also genetic models, including the spontaneously hypertensive/hyperactive rat (SHR) strain, which was bred from progenitor Wistar Kyoto (WKY) rats (Dafny and Yang 2006). The SHR is a rat strain hyperactive in a variety of behavioral characteristics that are comparable to the behavior of children with ADHD, including motor and cognitive impulsiveness, impaired sustained attention, hyperactivity, and reduced DA function. Therefore, the SHR strain is used most often in ADHD/methylphenidate studies. Most investigators who study the properties of drugs on animals do so in the belief that their work will ultimately be relevant to people.

Behavioral Models for Drug Dependence and Abuse

The concept of drug ► abuse liability is related operationally to the ability of a drug to support ► self-administration. There are only two studies that investigated the self-administration behavior of methylphenidate (Askenasy et al. 2007) and they reported that methylphenidate supported self-administration behavior. They conclude that the reinforcing effects of methylphenidate were similar to those of amphetamine and cocaine. The ► conditioned place preference paradigm is an experimental procedure in which, after training, an animal develops a preference for certain environment by virtue of its association with the rewarding state induced by a drug. The procedure consists of a box that is divided into two compartments that are qualitatively different from each other, for example in texture, color, smell, and connected to each other via a chamber that acts as a gateway between the compartments. The studies paired the drug (methylphenidate) with the less preferred compartment and they demonstrated that methylphenidate induced CPP in drug naïve rats (Askenasy et al. 2007).

Age differences in methylphenidate effects: The response to psychostimulants was reported to vary with age (Dafny and Yang 2006). During normal development, overproduction of synaptic connections and receptors occurs and follows by their pruning or competitive elimination. The marked overproduction and elimination of synapses and receptors during adolescence may serve as a permissive factor for a number of behavioral/psychiatric disorders, including ADHD (Andersen and Teicher 2000). Between 5 and 15 years of age, in humans, synaptic density in the frontal cortex decreases by approximately 40%. The time course and nature of ADHD parallel the pattern of overproduction and regressive synaptic elimination described earlier. Some adverse consequences of neuronal development in children were reported. Adolescent rats are affected differently by catecholaminergic agonists when compared with adult rats. It was reported that adolescent rats exhibited an attenuated behavioral response, while adult rats exhibited an increase in behavioral response to psychostimulants (Laviola et al. 1995). Rats exposed to methylphenidate during the period equivalent to human adolescence experienced behavioral changes that endured into adulthood, which suggests that methylphenidate does have a neurobiological effect in adolescents that modulates the "normal" development to adulthood (Dafny and Yang 2006). Studies of cocaine-induced behavioral ► sensitization in developing animals have yielded conflicting results, depending upon the age tested, the drug maintenance dose, the intervals between the repetitive drug treatment, and the challenge dose. Adolescent rats showed behavioral sensitization to the locomotor activating effects of cocaine, whereas different locomotor sensitization profiles were found in adult rats (Laviola et al. 1995). However, others have reported that younger animals treated chronically with stimulants rarely exhibited behavioral sensitization and that when sensitization occurred, it persisted for a shorter period of time.

When adolescent and adult rats were compared to their responses following chronic stimulant, adolescent rats showed alterations in psychopharmacological sensitivity which apparently did not rely on age-specific decreases in brain drug availability, but rather appeared to be related to alterations in CNS sensitivity (Laviola et al. 1995). It was also reported that adult rats repeatedly exposed to methylphenidate during adolescence were significantly more vulnerable to cocaine, as determined by increased self-infusion of psychostimulants and increased motor activity. This suggests that adult responses to cocaine are altered following childhood methylphenidate exposure. The ontogeny of brain/behavior relationship during the period between preadolescence, adolescence, and attained sexual maturity needs to receive more attention.

Sex Differences in Methylphenidate Effects

Biomedical investigation has been conducted almost exclusively on male subjects. The reason for excluding females as subjects in the research is that they have greater biological complexity than males due to their reproductive cycle. It has only recently become evident that the gonadal steroid hormones have multiple functions. Furthermore, sex-related differences are often controversial and not documented. Differences in the response to cocaine and amphetamine are reported to be sex-dependent. Observations of ► sex differences in response to drug treatment may be due to drug ► pharmacokinetics, particularly drug metabolism. The neural systems mediating the behavioral response to psychomotor stimulants are sexually dimorphic and are modulated by genes

and pituitary and gonadal hormones. For example, estrogen enhances the acute behavioral and neurochemical responses to dopamine (DA), amphetamine, and cocaine in female rats. The effects of gonadal hormones are postulated to have important implications for gender differences in the acute and chronic responses and in the susceptibility of addiction to psychomotor stimulants. There are also remarkable gender differences in the behavioral expression of ADHD patients (Andersen and Teicher 2000). For example, ADHD is more often diagnosed in males than in females and is 2–9-fold more prevalent in males. Females with ADHD may be more severely affected than males, as female ADHD subjects tend to have a higher genetic loading for the disorder. It was hypothesized that there is an extensive overproduction of DA receptors in the male striatum and NAc during prepubertal development, which may help to explain why males are often afflicted with ADHD because dopaminergic activity increases in these regions can produce hyperactivity and stereotypical behavior. Sex differences in ADHD may also be attributed to sex differences in DA receptor density. Striatal D_2 receptor density in males increases to $144 \pm 26\%$ in between 35 and 40 days, while that in females increases only to $31 \pm 7\%$. The rise in striatal DA receptors in males parallels early development of ADHD motor symptoms (Dafny and Yang 2006).

In general, females were more sensitive than males to methylphenidate, cocaine, and amphetamine. The development of behavioral sensitization to these drugs was a function of sex-specific alterations in the sensitivity to psychostimulants. In addition, accumulating evidence indicates that the antecedents, consequences, and mechanisms of drug abuse and addiction are different in females and males. It was reported that adult female rats were more seriously addicted to psychostimulants and express a more rapid behavioral sensitivity to chronic exposure of these drugs compared to their male counterparts. This sexual dimorphism was only observed in adult rats, suggesting that gonadal hormones secreted in adulthood may modulate the responsiveness to psychostimulants (Dafny and Yang 2006).

Cross-References

► ADHD
► Psychostimulants

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Methylphenoxy-Benzene Propanamine

► Atomoxetine

N-Methyl-N-2-Propynylbenzylamine

► Pargyline

(–)-1-Methyl-2-(3-Pyridyl)Pyrrolidine

► Nicotine

8 β[(Methylthio)Methyl]-6-Propylergoline Monomethanesulfonate

► Pergolide

Mexazolam

Definition
Mexazolam is a benzodiazepine derivative that has anxiolytic, anticonvulsant, hypnotic, sedative, amnesic, and muscle-relaxant properties.

Cross-References
► Anxiolytic
► Benzodiazepine

mGluRs

► Metabotropic Glutamate Receptor

Mianserin

Definition
Mianserin is a tetracyclic second-generation ► antidepressant with combined serotonergic–noradrenergic mechanism of action. It increases serotonergic (5HT) and noradrenergic (NA) neurotransmission by acting as an antagonist mainly at 5-HT_2 and α2 presynaptic and somatodendritic auto- and hetero-receptors. This drug also has a strong antihistaminic effect but, unlike the ► tricyclic antidepressants, it has almost no anticholinergic and cardiotoxic properties. In addition to its antidepressant effects, mianserin also has anxiolytic, sedative-hypnotic, antiemetic, and appetite-enhancing effects. Clinical effects of mianserin usually become noticeable after 1–3 weeks of treatment. Common side effects include dizziness, blurred vision, drowsiness, weight gain, dry mouth, and constipation while more serious adverse reactions may include hypomania, fainting, seizures, and hematological problems. As with other antidepressants, abrupt or rapid discontinuation of mianserin therapy may induce withdrawal effects, such as rebound depression, anxiety, panic attacks, anorexia, and insomnia.

Cross-References
► SNRI Antidepressants

Michael Kohlhaas' Syndrome

► Delusional Disorder

Microamines

► Trace Amines

Microdialysis

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Synonyms
Brain microdialysis; Intracerebral microdialysis

Definition
Brain microdialysis is a sampling technique developed to study the concentration of chemical solutes (mainly neurotransmitters) in the extracellular compartment of the brain by means of implanting a tubing of dialysis membrane. During the last decades, the necessity to measure the release of neurotransmitters in vivo in the central nervous system (CNS) has prompted the development of innovative techniques for sampling the extracellular fluid in the brain of experimental animals. Historically, one of the methods that evolved for this purpose was the push–pull perfusion which involved the stereotaxic insertion of a push–pull cannula into a selected area of the brain. Being an open flow system, push–pull perfusion allowed a direct contact of perfusion fluid with brain tissue, which often caused tissue damage, microbial and blood contamination, etc. To circumvent such drawbacks, a semipermeable membrane was attached to the cannula tip and this device was called dialysis bag or dialytrode. This was soon replaced by a more straightforward approach, the intracerebral dialysis, in which the dialysis bag was substituted by a hollow fiber, the dialysis membrane (Ungerstedt 1984).

Principles and Role in Psychopharmacology
The term dialysis refers to the passage of small molecules through a semipermeable membrane, a process driven by a concentration gradient. The endogenous substances diffuse out of the extracellular fluid into the perfusion

medium. On the other hand, exogenous compounds can be infused locally through the dialysis probe and reach the brain compartment through this concentration gradient. Unlike push–pull perfusion, dialysis is based on a closed flow system. Therefore, only a single perfusion pump is needed. The probe is constantly perfused with a physiological solution at a low flow rate (typically <2 µL/min) and perfusate samples are then collected for further analysis. Due to its relative ease of use, microdialysis has become the technique of choice for the in vivo analysis of neurotransmitters in the extracellular compartment of the brain of experimental animals. Its use has been fundamental in the identification of the mechanism of action of numerous psychoactive drugs. In particular, microdialysis has enabled to clarify neuronal elements (neurotransmitters, receptors) and brain networks affected by two of the most important drug classes in psychiatry: ► antidepressants and ► antipsychotics (Artigas and Adell 2007).

The low concentration of endogenous neurotransmitters in the extracellular brain space has been one of the main difficulties associated with the dialysis technique. The development of highly sensitive ► high-performance liquid chromatographic (HPLC) methods has made possible the increasing use of the microdialysis technique for the in vivo analysis of nanomolar concentrations of neurotransmitters and their metabolites (usually at higher concentrations) in brain. Capillary electrophoresis has also been successfully applied to the analysis of amino acids and amines. However, the need to sample for relatively long periods of time (typically >10 min) is one of the main drawbacks of microdialysis, compared with other in vivo techniques assessing brain function, such as electrophysiology and ► electrochemical techniques.

The dialysis membrane constitutes a real barrier between the perfusion fluid and the interstitial brain space, which usually excludes the transport of large molecules that may interfere with the substances of interest in the analytical procedure. Furthermore, enzymes that could cause a breakdown of the neuroactive compounds are also prevented from being picked up by the dialysate. The implant and functioning of microdialysis probes may cause tissue reactions ranging from an excessive washout of neurotransmitters and metabolites if flow rates are too high, to glial reaction surrounding the probe that may act as an actual barrier for the passage of components from the extracellular brain space to the inner part of the microdialysis probe. These aspects need to be examined in detail while establishing the experimental protocols. In particular, the effect of flow rate and duration of experiments need to be carefully assessed.

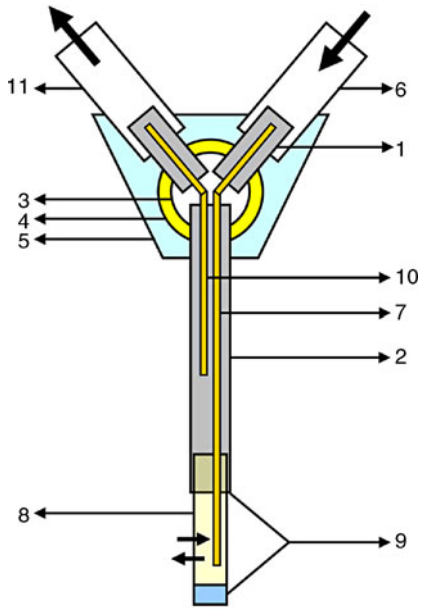
Methodology

Microdialysis probes are implanted stereotaxically in the brain of anesthetized animals. The coordinates for rat or mouse brain are usually taken from the corresponding atlas (Franklin and Paxinos 1997; Paxinos and Watson 2005). This allows a theoretical precision of 0.1 mm in the placement of microdialysis probes, although the actual precision is impaired due to individual variations in the size and shape of brain of experimental animals.

Once the dialysis probe has been positioned in the area of the brain to be studied, flushing with artificial cerebrospinal fluid (CSF) is recommended in order to check the integrity of the membrane. Then, the probe is secured to the skull with anchor screws and dental cement.

Construction of a Dialysis Probe

At present, the type of dialysis probe most commonly used has a concentric structure (Fig. 1). This kind of probe has been used in a wealth of experimental research



Microdialysis. Fig. 1. Schematic representation of a concentric microdialysis probe made up of the following components (see text for details): 27 gauge stainless steel tubing (1), 25 gauge stainless steel tubing (2), epoxy resin (3 and 9), dental cement (4), hot-melt adhesive (5), polyethylene tubings (6 and 11), fused silica capillary tubings (7 and 10), and dialysis membrane (8). Small arrows indicate the interchange process through dialysis membrane. Larger arrows indicate the direction of perfusion fluid.

because it is well suited for reaching deep structures and/or small nuclei of the brain. A detailed description of the materials and suppliers can be found in Adell and Artigas (1998). Briefly, the body of the probe is made up of 20-mm long 25 gauge stainless steel tubing. The inflow and outflow tubes threaded through the 25 gauge tubing consist of fused silica capillary tubing of 0.11 mm OD, 0.04 mm ID. The upper exposed end of fused silica tubings are inserted into a 7-mm piece of 27 gauge (0.41 mm OD, 0.20 mm ID) stainless steel tubing. The junction of the 27 and 25 gauge stainless steel tubings is sealed with epoxy glue and covered with dental cement to harden the assembly. Sampling of monoaminergic neurotransmitters usually requires a dialysis membrane consisting of a regenerated cellulose hollow fiber (0.17 mm OD, 0.15 mm ID), with a molecular weight cutoff of 6,000 Da, which is placed over the protruding lower portion of the inlet fused silica tubing and glued with epoxy resin to the inside surface of the 25 gauge stainless steel tubing. The tip of the hollow fiber is sealed also with epoxy glue. The length of the dialysis membrane exposed to the tissue varies according to the brain area to be examined. Finally, the 27 gauge protective steel tubes are friction-fitted with 20-mm lengths of polyethylene tubing of 0.61 mm OD, 0.28 mm ID to facilitate the connection of the probe to the perfusion pump and outflow line. These polyethylene and steel tubes are secured together with hot-melt glue.

Perfusion Fluids

One of the crucial aspects in microdialysis studies is that the composition of the perfusion medium must be physiological, i.e., isotonic with respect to that of the interstitial space. However, several fluids are being used currently that differ in their electrolytic composition/concentration (reviewed by Benveniste and Hüttemeier 1990). With little variation, the fluids used to perfuse dialysis probes are those derived from Krebs–Ringer solutions or artificial CSF. Typically, the concentration of Ca^{2+} ions in the perfusion fluid may vary from the physiological 1.2 mM–3.3 mM. Since Ca^{2+} ions are essential for the process of exocytosis, some authors have used higher concentrations to stimulate transmitter release. Although the buffering capacity of the extracellular fluid for some cations such as K^+ and Ca^{2+} is high, differences in the ionic composition of the perfusion and interstitial fluids may alter the responsiveness of neurons.

Other perfusing solutions also contain glucose to prevent its depletion from the interstitial space produced by the continuous drainage of dialysate. Glucose addition to the perfusion fluid also provides the essential nutrient for neurons to cope with the cell damage and disruption of the ▶ blood-brain barrier caused by probe implantation. However, the concentration of lactate, pyruvate, aspartate and glutamate in rat cortical dialysates is similar when the perfusion fluid contains 0 or 3 mM glucose, which suggests that the presence of glucose does not play a critical role in neuronal metabolism during microdialysis experiments. In addition, it should be kept in mind that the presence of glucose may favor bacterial growth in the perfusion fluid, thus altering the extraction of neurotransmitters.

One common problem inherent to most microdialysis studies is the very low concentration of neurotransmitters in the dialysate caused by efficient mechanisms of removal from interstitial space, such as reuptake or enzymatic degradation. To circumvent this complication, an uptake blocker or an inhibitor of enzymatic breakdown is included in the perfusion medium. In the absence of such agents, the extracellular concentration of a transmitter (but not of its metabolites) reflects the balance between the processes of release and inactivation. However, in the presence of such agents, the release component is amplified and this has to be taken into consideration while interpreting dialysis results. For example, the use of an uptake blocker may allow to detect changes in the extracellular level of transmitters that otherwise may be overlooked. The most common compounds added to the perfusion fluid are uptake inhibitors such as ▶ citalopram for serotonin, ▶ nomifensine for dopamine, desipramine for norepinephrine, and ▶ physostygmine or neostygmine to block the enzymatic degradation of acetylcholine.

However, the use of such agents can complicate the interpretation of results, as the higher neurotransmitter concentration they induce may result in the activation of terminal autoreceptors in nerve endings, which usually results in a negative feedback affecting neurotransmitter synthesis and release. On the other hand, the addition of ▶ acetylcholinesterase inhibitors, which increase the concentration of acetylcholine in dialysates, has been shown to influence markedly the interaction between cholinergic and dopaminergic brain systems. Therefore, these modified perfusion fluids must be used with caution, as they may alter the function of drugs whose mechanism of action is examined.

The choice of an appropriate flow rate for the perfusion (usually ranging between 0.1 and 2 μL/min) is an important practical point for several reasons. The relative recovery of neurochemical compounds through dialysis membranes declines as the flow rate increases. High flow rates generate a concentration gradient and compounds can be carried away from the extracellular space with the subsequent enrichment of dialysate samples so that the absolute recovery per time unit is greater. However, such

a washing effect may reduce the tone on terminal autoreceptors and, therefore, alter the dynamics of the release process.

For all of the above reasons, low flow rates are preferred in order to approach ideal dialysis conditions and maximize the recovery of transmitter substances from the interstitial space. Flow rates of 0.25–3 μL/min provide a sample volume of 5–60 μL per 20-min fraction, which can be collected in plastic microvials and is easy to handle for further analysis by HPLC procedures.

Quantitative Aspects

Different attempts have been made to calculate the extracellular concentration of neurotransmitters stemming from the level obtained in dialysate samples. The simplest method is to calibrate the probes for in vitro recovery. To this aim, the probes are immersed in a beaker filled with a known concentration of the substances of interest dissolved in the perfusion fluid. The ratio between the concentration of the substance in the probe effluent and in the medium provides the recovery value of such a substance. The term "absolute recovery" refers to the total amount of a compound that passes into the perfusion fluid per unit of time, whereas "relative recovery" describes the concentration of a compound in the dialysate relative to that in the perfusion medium expressed as a percentage value. The flow rate of the perfusion fluid is inversely related to the relative recovery and the magnitude of absolute recovery is limited by perfusion flow rate. It is important to note herein that the absolute recovery is proportional to the concentration of the substance outside the dialysate, whereas the relative recovery is not. In addition, the calibration in vitro of the probes depends on the temperature and physicochemical stability of the compounds to be analyzed. The validity of these calibration procedures is based on the assumption that the conditions in vitro and in vivo are similar. However, the brain interstitial space is a more complex matrix and the tortuosity of the diffusion created by cell membranes and the drainage of endogenous compounds induced by the continuous perfusion are factors that must be taken into consideration.

Several refined mathematical models have been described to determine the actual concentration of transmitters in the extracellular compartment of the brain, yet they are usually too complex to be used routinely in neuropsychopharmacology research. A more practical approach was reported in which the dialysate concentration of a neurotransmitter is measured at different flow rates and extrapolated to a flow rate of zero (Justice 1993). With no net flow, the dialysate is in equilibrium with the extracellular fluid. Therefore, the level found at zero flow should represent the actual in vivo concentration of the transmitter.

Finally, it should be considered that, for many applications, the knowledge of the in vivo concentration of a transmitter is not necessary. Instead, the change with respect to baseline level is what actually matters and is to be related to the mechanism of action of drugs.

Statistical Analysis of Data

The working hypothesis usually tested in microdialysis experiments tests whether a physiological or pharmacological manipulation affects the concentration of a transmitter in dialysate samples. Typically, the experimental approach consists in the collection of several pretreatment samples until stable baseline values are attained. Then, drugs are administered or animals are subjected to certain procedures (e.g., stress, forced motor activity, behavioral manipulation, etc.) and a number of posttreatment samples are collected. These temporal data series are often analyzed by means of analysis of variance (ANOVA) for repeated measures followed by appropriate *post hoc* tests to compare pre- and posttreatment periods. In more complex experiments (e.g., when assessing the effects of different drug doses or in various areas of the brain), the use of two-way ANOVA for repeated measures is better suited, with dose (or region) as the independent factor and time (or treatment) as the dependent variable. AUCs of the posttreatment periods can be also calculated as an integrated estimate of drug action and compared by means of one- or two-way ANOVA.

Neural Origin of Transmitters in Dialysate

In order to determine the neural origin of neurotransmitter efflux measured in dialysis experiments, several specific criteria must be fullfilled. First, basal transmitter release from nerve terminals has to be impulse-dependent. This is usually assessed by the addition of the sodium channel blocker tetrodotoxin, which impairs the release of the transmitter. A second requirement for the neuronal origin of a putative transmitter is its disappearance or decrease from dialysate, when Ca^{2+} is omitted from the perfusion medium. The basis for such an action is that the impulse-dependent release of a transmitter by exocytosis is dependent on the availability of extracellular Ca^{2+} (Augustine et al. 1987). Finally, the ability of elevated concentrations of K^{+} to depolarize neural structures and stimulate the output of transmitters has been taken as an additional criterion for their neural provenance.

Working Practices

As detailed in the preceding sections, microdialysis is only a sampling procedure. The combination with appropriate

analytical techniques has made it possible to monitor changes in the concentration of small molecules in the interstitial space of the CNS. In addition, researchers have devised a number of different experimental approaches to exploit the capabilities of this technique.

Local Administration of Chemicals and Drugs

Due to the ability of the microdialysis membrane to allow the passage of small molecules in both directions, microdialysis probes have been used to deliver chemicals in restricted areas of the brain by reverse dialysis. Ions or pharmaceutical agents known to affect neural function can be dissolved in the perfusion fluid and delivered to the brain structures of interest, provided that the molecular weight cut-off of the membrane is appropriate. Changes in the concentration of transmitters can thus be monitored locally or distally, by means of a second dialysis probe implanted in an area anatomically or functionally related to the brain structure in which the first probe is located (see Section 7.3).

When appropriate amounts of chemical agents or drugs have to be dissolved in the perfusion fluid, it is important to check that they do not alter pH or osmolarity of the fluid. Usually, once stable baseline values are obtained, the standard dialysis fluid is replaced by one containing the compound(s) of interest. This procedure may be particularly useful when examining the effects of substances with a poor penetration into the brain or when assessing regional differences in the effects of drugs.

Quantitative effects of drugs in vivo can be estimated through ► ED_{50} values calculated after local application of drugs. The ED_{50} values obtained in this manner are by no means comparable to those obtained using cell cultures, membranes, synaptosomes, or other in vitro preparations. Several factors account for these differences, including (1) the recovery of the dialysis membrane, usually much lower than 100%; (2) the diffusion of chemicals within the brain once they have crossed the dialysis membrane and the tortuosity of the neural tissue; (3) the continuous drainage of applied drugs by the CSF; and (4) the unspecific binding to cell membranes, particularly of lipophilic molecules. All these factors contribute to reduce the actual concentration of drugs reaching the active sites in the brain, dramatically. In contrast, in vitro drug affinities for receptors/transporters are calculated under almost ideal conditions, i.e., with enriched preparations and unlimited access of the chemicals to their cellular targets, generally at equilibrium and under nondegrading conditions.

Systemic Administration of Drugs

Experiments involving the systemic administration of drugs constitute the vast majority of the applications of microdialysis. In such experiments, however, appropriate controls must be carried out, because the procedure of drug delivery or the vehicle used may change transmitter function due to the associated stress or the sensitivity of some neuronal groups to sensory stimuli. The changes in the concentration of transmitters in an area of the brain after systemic administration of drugs do not necessarily parallel those found after their local application. In general, when drugs are applied locally, larger concentrations are needed to reach effects similar to those obtained after systemic application. This possibly reflects a better distribution of drugs administered systemically through the diffuse network of brain capillaries. Another factor frequently ignored is the fact that the diffusion of a chemical agent delivered by reverse dialysis is limited to a small portion of the brain tissue surrounding the dialysis probe. In contrast, the changes in the extracellular concentration of the transmitter in the same area after systemic administration of a drug results from an integrated response of the whole CNS, i.e., local and transynaptic effects.

Dual Probe Models

Experiments carried out with two or more probes implanted in the same animal present two distinct advantages. First, such an approach allows to reduce the number of animals used in a single experiment and, second, it is ideal to examine functional interactions between different brain areas. This latter asset was first employed for dopamine and serotonin systems to study how the release in terminal areas is regulated by the activity at the level of cell bodies. This was possible because the cell bodies of those neuronal systems are tightly packed in the midbrain substantia nigra, ventral tegmental area, and raphe nuclei. Therefore, the local application of drugs known to interact with receptors or transporters located on these monoaminergic cell bodies induces changes of the release of the transmitter in projection areas. Dual probe microdialysis studies have been extremely helpful for the study of the functional connections between different brain areas and the transmitter/receptors involved (Adell and Artigas 1991; Santiago et al. 1991).

Coupling to Electrical Stimulation

Similar to the experiments described in the previous section, electrical stimulation coupled with microdialysis in distal areas has been used to assess the existence of functional connections between brain areas. This is usually achieved by inserting an electrode in an area containing the cell bodies of a certain transmitter system and a dialysis probe in the corresponding projection areas. For instance, the electrical stimulation of the substantia nigra

or the raphe nuclei results in an enhanced release of dopamine and serotonin, respectively, in projection areas. Similar experimental procedures combining electrical stimulation and microdialysis have been used to study the modulatory role of ► prefrontal cortex on dopaminergic and cholinergic activity in subcortical structures such as the dorsal striatum or the ► nucleus accumbens.

Advantages and Limitations of Microdialysis

Since its first applications, microdialysis has become increasingly popular to study brain function. The use of alternative in vivo procedures such as push–pull perfusion or voltammetry has remained constant or even declined during last years. A comparison between microdialysis and voltammetry reveals that microdialysis is applicable to most types of small molecules whereas the use of voltammetry is limited to easily oxidizable compounds such as catecholamines and serotonin. Moreover, microdialysis appears to be simple to use on a routine basis and can easily be applied to study freely moving animals.

Table 1 summarizes some of the advantages and limitations of microdialysis. Certainly, microdialysis is by no means a definitive method for the assessment of the active transmitter concentrations in the brain. Yet, it has a number of advantages over its predecessor, the push–pull perfusion, which have led to a more widespread use. The main limitations of microdialysis are the size of the probes and the tissue damage caused by their insertion. For certain applications, size may not be a problem (e.g., to assess the effects of drugs in large brain regions). However, the study of physiologically- or pharmacologically-induced changes of transmitters in small nuclei may pose some constraint because a larger proportion of neurones is damaged.

Finally, the low amount of certain neurotransmitters in brain dialysates makes it necessary to collect samples every 20 or 30 min, a time scale which is far from that of neuronal events. This may not be a problem in pharmacological studies because most drugs reach peak levels at a time compatible with the usual periods of sampling of 20 or 30 min. This enables to follow up drug-induced transmitter changes. However, microdialysis may not be suitable for the study of the effects of neuronal stimulation on transmitter release at a physiological time scale. Recent advances in the detection of very low concentration of certain transmitters with capillary electrophoresis have permitted a considerable shortening of the sampling periods. Yet, this is still far from the scale at which neuronal excitation or inhibition is associated to the release of a transmitter. It is hoped that future methodological and technical developments will overcome some of these limitations.

Microdialysis. Table 1. Advantages and limitations of the microdialysis technique.

Advantages	Easy to use routinely Easy manufacture of probes No enzymatic degradation of transmitters in samples Coupling to chemical methods of analysis (HPLC, mass spectrometry, capillary electrophoresis, etc.) Possibility of local administration of drugs Possibility of concurrent determination of drugs after systemic administration Dual probe approaches Possibility of concurrent recording of electrical activity Concurrent study of behavior in freely-moving animals
Limitations	Invasive procedure: causes neuronal death and reactive gliosis Limited spatial resolution Limited temporal resolution Analytical difficulties with some transmitters Low membrane recoveries with high molecular weight compounds

Cross-References

► Antidepressants
► Antipsychotic Drugs

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Microelectrode Arrays

Synonyms
MEA

Definition
Ceramic-based multisite microelectrode arrays (MEAs; 15 μm × 330 μm or 20 μm × 150 μm recording sites) with platinum recording sites and polyimide insulation that have been recently described (Hascup et al., 2007). The triangular design of the microelectrodes yields a microelectrode array ranging in thickness from 37 to 125 μm and an overall length of 8–10 mm. These arrays are wire bonded to printed circuit board holders that adapt MEA's for measures in brain slices and studies in anesthetized and awake mice, rats, and nonhuman primates. More than 20 varieties of geometries ranging from 4 to 16 Pt recording sites have been designed.

Microelectrophoresis

► Microiontophoresis and Related Methods

Microiontophoresis and Related Methods

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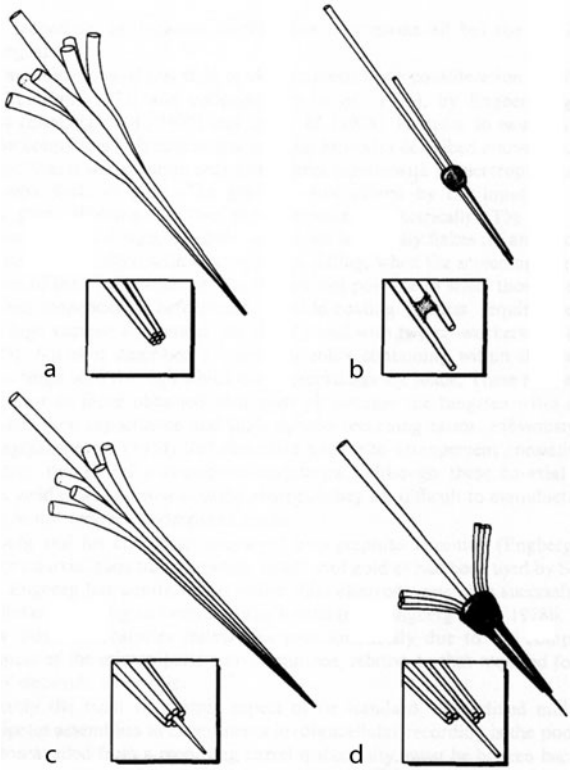
Synonyms
Iontophoresis

Definition
The term microiontophoresis is derived from the ancient Greek term *phoretikos*, which refers to the production or induction of movement. Microiontophoresis is a technique with which drugs and other ionized particles can be ejected in very small amounts from solutions contained in glass micropipettes. This ejection is accomplished by applying a voltage across the micropipette and causing the electrode to become polarized. Ionized particles in solution migrate in the applied field and will be ejected from the tip as they carry the current into the tissue. This technique is widely used to determine the effects of various substances on firing parameters of both central and peripheral neurons and muscles. In investigating the phenomenon of synaptic transmission at the neuromuscular junction, during the 1950s, this technique became very popular. A technique appropriate for the study of synaptic pharmacology was first realized by Nastuk (1953) and was later developed by del Castillo and Katz (1955), and it consisted essentially of the microiontophoretic method, i.e., movement of charged particles produced by an electric current, restricted to a micropipette with a tip diameter of the order of 1 μm. Thus, solutions of ► acetylcholine chloride were used, and by passing a suitable current to this solution, acetylcholine ions could be ejected from the 1 μm orifice onto a correspondingly localized area of subsynaptic membrane at the neuromuscular junction. Later, Curtis and his colleagues adopted this technique for studying the mammalian central nervous system (CNS) (Curtis and Eccles 1958b). The experiments of Curtis and coworkers, however, involved an important modification of the original method, in that this group used ► multibarrel micropipettes. In the production of these, several lengths of tubing are fused together and then pulled so as to produce a single collective tip, but with each barrel having its own orifice. Multibarrel micropipettes are usually composed of five to seven barrels (Fig. 1). Usually, the central barrel is the recording electrode, whereas the other side barrels contain drug solutions (Fig. 1). As the drug molecules would tend to diffuse from solution in the pipette tip into the extracellular environment, it is necessary to apply a small current to reduce that efflux. This is known as a "holding" or "retaining" current (Fig. 2). It is also a usual practice to include a barrel containing sodium chloride solution, which can be used to control the effects of the current itself. This may be done either by periodically passing through the control barrel the same current used for drug ejection or by passing continuously a current adequate to cancel out the instantaneous sum of ► ejecting and ► retaining currents passing through the drug-containing barrels. This is known as "current balancing." The use of microiontophoresis is suitable for any ionized molecule, but nonionized compounds can be ejected by the closely related variant "electro-osmosis," which is attributable to the presence of an electrical "double



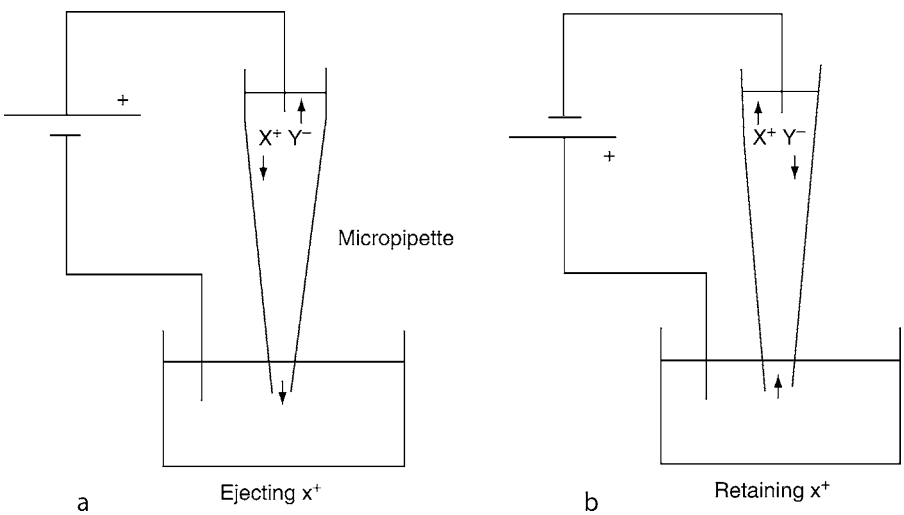
Microiontophoresis and Related Methods. Fig. 1. Examples of different types of multibarrel micropipette assemblies used in microiontophoretic experiments. (**a**) Standard 7-barrel assembly in most common use, introduced first by Curtis. (**b**) Twin, or parallel micropipette. (**c**) Co-axial assembly. (**d**) Staggered tip multibarrel. (From Hicks, 1984.)

layer" within the barrel tip. When an aqueous solution is in contact with glass, negative ions are tightly adsorbed on the glass surface, leaving the bulk of solution carrying a net positive charge. The passage of positive (or outward) current then causes the ejection of a small volume of solution containing the compound of interest (Fig. 2). It should be noted, however, that this mechanism has nothing to do with the osmotic pressure of a solution or the establishment of any osmotic gradient. The term electroosmosis derives simply from the fact that the driving force is the movement of the *solvent,* not the solute, just as the case of osmotic movements across a semipermeable membrane. An alternative method of applying both ionized and nonionized compounds from micropipettes is the use of pressure. A suitable source of pressure, usually a cylinder of compressed gas, is connected to the open end of a micropipette barrel. Pressure usually up to 20 pounds per square inch (p.s.i.) will eject fluid from a 1 µm pipette tip. One advantage of micropressure ejection is that it can be applicable to all compounds; however, it is not devoid of problems and artifacts and is unlikely to replace microiontophoresis as a microapplication method.

Principles and Role in Psychopharmacology

General Principles

Each barrel of a micropipette assembly to be used for drug ejection is filled with a solution of the ionized compound and the solution is connected to the iontophoresis machine by a suitable lead, which is in contact with the drug solutions. The establishment of a potential difference



Microiontophoresis and Related Methods. Fig. 2. Schematic diagram of a micropipette that contains a salt X^+Y^-, showing the direction of current necessary to eject (**a**) and retain (**b**) the ion X^+. (From Hicks, 1984.)

between the drug solution and the medium surrounding the barrel tip will then cause the movement of ions through the solution and out of the pipette tip (Fig. 2). A chief advantage of the microiontophoretic method is that it is possible to examine the effects of drugs on single neurons in vivo without affecting the whole nervous system or other physiological responses, such as those that may occur when drugs are administered systemically (Aghajanian 1972). If a voltage is applied to a solution, ions and charged molecules will migrate toward and away from the source of the imposed electrical field depending on the sign of their net charge. This phenomenon is the fundamental principle of microiontophoresis: the desired charged particles are ejected from the mouth of one barrel of a multipipette assembly by appropriately charging the interior of that barrel (Fig. 2). An outward current will cause the "ejection" of positively charged ions, and an inward current flow, the ejection of negatively charged particles. If the pipette assembly is positioned close to a neuron, so that the recordings of its activity can be made through another electrolyte-filled barrel, drugs may be ejected and their pharmacological effects are inferred by the resulting changes in the rate and/or ► firing pattern.

The Transport Number and the T_{50} Value

An important technical consideration for experiments employing microiontophoresis is the transport number. The transport number is a measure of the amount of drug released from the micropipette by iontophoretic expulsion and it is important, because it helps one to evaluate dose–response relations between different compounds, and it can also provide some indication of the absolute potency of compounds. The transport number varies for individual compounds and is based on the interaction of the following variables: their solubility, the extent of their dissociation in solution, their polarity, and the nature of the external medium into which the drugs are administered. The transport number may be formally described by the following equation:

$n = R_i ZFi^{-1}$, where

n = apparent transport number of the drug ion,

Z = valency,

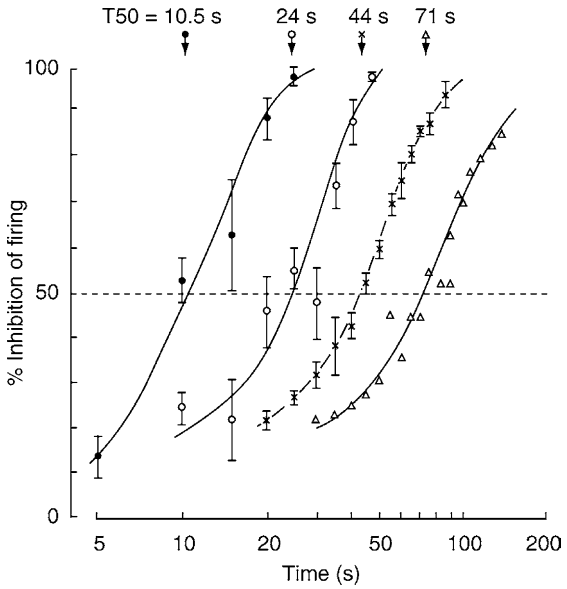
F = Faraday's constant, in Coulombs

i = intensity of ► ejecting current, in nanoamperes, and

R_i = rate of microiontophoretic release (which is equivalent to total release minus the sum of the rate of steady-state spontaneous release and where applicable, the release due to electro-osmosis).

During microiontophoresis, the total number of ions transported is related in a direct manner to the amount of current applied to the solution, according to Faraday's law. However, only a certain proportion of the charge imposed is carried by the ion species of interest. This value, which is "n," the transport number, is not constant for a given material but will vary not only from pipette to pipette, but also, to a lesser extent, between different barrels of the same micropipette assembly containing identical solutions. Despite these inconsistencies, it remains valid that under steady-state conditions, drug release from micropipettes conforms to Faraday's law: the amount of drug released is proportional to the magnitude of current passed (Hicks 1984).

Another important parameter to consider when interpreting microiontophoretic data is the T_{50} value, which is the time taken for a response to reach 50% of its maximum (Fig. 3). The basis for this procedure is the hypothesis that each individual response to an agonist may be considered as a cumulative dose–response relationship



Microiontophoresis and Related Methods. Fig. 3. Time courses of inhibition of neuronal firing following microiontophoretic application of GABA with four different currents, 20 nA (filled circle), 10 nA (o), 5 nA (×), and 2 nA (open triangle). Each curve was obtained from the same neuron at a depth of 957 μm in the middle suprasylvian gyrus of the cat cortex. The neuron was driven by continuous microiontophoretic application of L-glutamate (20 nA). Each of the points for 20, 10, and 5 nA applications of GABA is the mean ± SEM of three values obtained from three separate applications of the same current of GABA. The values of T_{50} shown are the times taken to achieve 50% inhibition of neuronal firing. (From Hill and Simmonds (1973) Br J Pharmacol 48:1–11.)

reflecting the gradual increase in tissue concentration of drug during the ejection period. If a series of such responses are obtained, reaching the same maximum amplitude, they can be readily characterized by the T_{50} value (Fig. 3). Moreover, T_{50} value is easier to measure accurately than a response size. Thus, it can be very difficult to obtain reproducible graded response amplitudes to some very potent compounds such as amino acids. Any changes in ▶ firing rate during a response, which ideally should be of the plateau variety, may further complicate any assessment of the response size, whereas in the determination of T_{50} values, all responses increase to the same maximal level, which may be 100% inhibition or a clear maximal plateau of excitation tending toward overdepolarization.

Microiontophoresis in the Central Nervous System

It is now more than 50 years since Curtis and Eccles (1958a, b) first employed the technique of microiontophoresis in the CNS. Microiontophoresis has provided so far a great contribution in the identification of the central effects of neurotransmitters, including glutamate, aspartate, γ-aminobutyric acid (GABA), noradrenaline, serotonin, dopamine, and a variety of neuropeptides (enkephalins, cholecystokinin, neurotensin, tachykinins). Microiontophoresis also allows the histological confirmation of the sites of electrophysiological recordings, and the neuroanatomical determination of pathways by applying dyes, markers, and materials, which are carried by axonal transport for tracing fiber tracts. Alterations in neuronal sensitivity due to the influence of anesthetic compounds have been monitored when pharmacological agonists have been tested using microiontophoresis.

Applications

The largest number of studies has been concerned with the central nervous system. These studies have yielded information on: (1) the qualitative sensitivity of neurons to putative neurotransmitters and drugs; (2) quantitative estimates of variations and sensitivity in different CNS regions or of different cell types and the following lesions or the administration of drugs; (3) the pharmacology of transmitter receptors; (4) the effects of modifier of putative transmitter effects (antagonistic or enhancing substances) on synaptic transmission; and (5) the mechanisms and ionic conductances underlying transmitters effects.

Excitatory Amino Acids

Some of the earliest iontophoretic studies demonstrated marked excitatory activity of several simple dicarboxylic acids, including L-glutamic and L-aspartic acids (Curtis and Watkins 1960). Responses to some of these amino acids, especially ▶ glutamate and aspartate, terminate rapidly when an ejecting iontophoretic current is switched off. It is unclear to what extent this is due to the kinetics of iontophoresis or reflects the presence of rapid and efficient uptake processes. Some authors have reported long-lasting changes of cortical neuronal firing following iontophoresis of glutamate sufficient to at least double the resting firing rate. The development of a series of potent amino acids analogs with very high agonist potency led to the discovery of NMDA and non-NMDA glutamate receptors. This discovery was strengthened by additional findings that phosphonate analogs of amino acids, such as 2-amino-5-phosphonovaleric acid (AP-5) blocked the effects of NMDA, but not of quisqualic and kainic acids.

Inhibitory Amino Acids

Both glycine and ▶ GABA act as potent inhibitors of neuronal activity in the CNS, usually causing ▶ hyperpolarization associated with increased membrane conductance to chloride. Glycine is selectively antagonized by strychnine, whereas the effects of GABA are blocked by picrotoxin and bicuculline. Microiontophoretic experiments showing potentiation of the inhibitory effects of GABA by ▶ benzodiazepines were among the earlier experimental evidence for the modulatory action of these drugs on ▶ $GABA_A$ receptors (Gallagher 1978).

Acetylcholine

Almost every region of the brain has been examined for its sensitivity to iontophoretically applied cholinergic agents. Most of the earlier work in vivo was concerned primarily with establishing the direction of responses to cholinomimetics and whether the effects involved muscarinic or nicotinic receptors. Many studies examined only cells encountered randomly in a particular brain region, but others have often succeeded in relating the direction of responses to cholinomimetics with some specific function. In the cerebral cortex deep pyramidal tract, cells are excited by ▶ acetylcholine. Several authors have also described an inhibitory action of acetylcholine, largely muscarinic in nature, in more superficial levels of the cortex and an excitatory action, which appears to have a predominant nicotinic pharmacology, in the same superficial layers. Some authors have shown that acetylcholine enhances the stimulus-evoked responses of visually driven cortical units, without affecting the overall excitability of the cell. Thus, orientation and direction specificity of neurons is preserved and increased relative to the non-preferred responses. This phenomenon is reminiscent of the effects of some amines, which can also increase the

signal-to-noise ratio by potentiating evoked activity and suppressing background.

Noradrenaline

Early microiontophoretic studies have shown that ► noradrenaline would cause a depression of neuronal firing in the cat cerebral cortex, and a large number of experiments have revealed similar responses in most areas of the CNS. This inhibition often seems to involve a voltage-dependent hyperpolarization accompanied by an increased membrane resistance, although a decreased membrane resistance was found on neurons of the locus coeruleus in slice preparation in vitro. The biochemical basis of this hyperpolarization has been the subject of much argument. Although it was originally suggested that they may be mediated by an increase in the intracellular concentration of cyclic AMP, some group failed to reproduce these findings. Overt excitatory effects of noradrenaline have also been observed in many areas of the CNS. Neuronal responses to iontophoretic application of noradrenaline, apparently excitatory as well as inhibitory, can be enhanced by antidepressants. However, this potentiation can occur even after the loss of most amine-containing terminals, and it may be restricted to certain layers of the cortex. The pharmacology of responses to iontophoretically applied noradrenaline has been extensively studied. Some authors have postulated that, in the neocortex, excitatory responses to noradrenaline are mediated by α_1-adrenergic receptors, whereas inhibitory responses occur through β-adrenergic receptors. Activation of α_2-adrenergic receptors does also elicit inhibitory responses.

Dopamine

► Dopamine was first tested iontophoretically in the cerebral cortex, where profound suppression of spontaneous cell firing was observed. This action has been confirmed by several authors, although excitatory effects have also been reported. Much attention has been centered on the effects of dopamine in the neostriatum where its action is usually inhibitory in the caudate nucleus. Bunney and Aghajanian (1976) have performed a laminar analysis of amine responses in the rat cerebral cortex. They found that neurons in layers II and III, which receive a dense noradrenergic projection, were more sensitive to noradrenaline than dopamine, whereas the reverse pattern was noted in layers V and VI, which receive a greater dopamine-containing projection. These authors also reported that desipramine, a selective inhibitor of noradrenaline reuptake, would enhance noradrenaline responses in layers II and III, but not in deeper layers, while benztropine enhanced dopamine responses only in layers V and VI. Dopamine receptors are present not only on innervated cells but also on the dopaminergic neurons themselves: the so-called ► autoreceptors. Activation of such receptors by dopamine or apomorphine causes marked inhibition of cell firing, and these effects are blocked by neuroleptic drugs. Microiontophoretic studies of dopamine response pharmacology have mostly proved consistent with behavioral and neurochemical work. Phenothiazines, for example, block dopamine but not noradrenaline responses in the cerebral cortex and the striatum. Iontophoretically applied ► α-flupenthixol can also block the effects of dopamine, although intravenously administered α-flupenthixol or ► pimozide did not modify neuronal responses to iontophoretic dopamine.

Serotonin

There is an extensive scientific literature regarding the effects of microiontophoretically applied ► serotonin on different areas of the central nervous system. Indeed, the microiontophoretic technique contributed substantially to the elucidation of the physiology and pharmacology of the central serotonergic system. Thus, an important factor controlling the activity of central serotonergic neurons is neuronal feedback inhibition. This is thought to be a homeostatic response, which, under physiological conditions, acts to compensate for increases in synaptic availability of serotonin. Thus, as the concentration of serotonin increases in the brain, the activity of central serotonergic neurons correspondingly decreases. The mechanism underlying this feedback regulation is both local or intrinsic to the raphe region (where serotonergic cell bodies are located) and through a feedback loop from postsynaptic target neurons. Serotonin released in the raphe region from dendrites and possibly from axon terminals appears to inhibit serotonergic neurons by activating somatodendritic autoreceptors, which produces hyperpolarization of the cell membrane *via* an increase in potassium conductance. Historically, the first drug reported to exert a preferential action on the 5-HT autoreceptor was LSD (lysergic acid diethylamide) applied microiontophoretically on the dorsal raphe nucleus of rats. Subsequently, several other hallucinogenic indoleamines, notably 5-MeODMT (5-methoxy-*N*,*N*-dimethyltryptamine), were found to share this property with LSD. Since that time, several highly selective 5-HT_{1A} agonist compounds such as 8-OH-DPAT have been synthesized and shown to suppress the firing of serotonergic neurons with potencies comparable with, or even greater than, that of LSD. On the basis of electrophysiological data, the serotonin autoreceptor has been characterized as the 5-HT_{1A} subtype. Microiontophoretic technique also contributed to

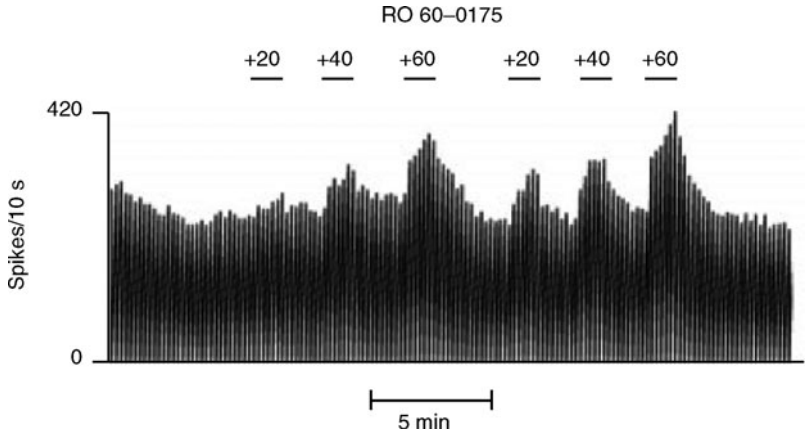
characterize the action of serotonin agonists and antagonists and to elucidate the physiological role of serotonin receptor subtypes such as 5-HT_{1B}, 5-HT_{2A}, and 5-HT_{2C}. As regards the 5-HT_{2C}, it was found that this receptor subtype exerts a tonic inhibitory influence on the activity of dopamine-containing neurons in the substantia nigra pars compacta and the ► ventral tegmental area. Apparently, this inhibitory effect is mediated through the activation of nondopaminergic (presumably GABA-ergic) neurons in the substantia nigra pars reticulata. Thus, it was recently shown that microiontophoretic application of 5-HT_{2C} receptor agonists stimulates the basal activity of nondopaminergic (presumably GABA-ergic) neurons in the substantia nigra pars reticulata (Invernizzi et al. 2007) (Fig. 4). By using microiontophoresis, it was also found that serotonin exerts a tonic inhibitory influence on the activity of noradrenergic neurons in the locus coeruleus.

Opiates and Opioids

Microiontophoresis has proved exceedingly valuable for opiate system studies, since it allows the testing of discrete units activated by noxious or nonnoxious stimuli in the same preparation. In most such studies, the applied opiates have depressed noxious stimulus-evoked activity, although usually in parallel with the effects on spontaneous or chemically induced firing. Microiontophoresis has also been proved as a popular means for comparing qualitatively opiate responses in normal and opiate-tolerant animals. Thus, inhibitory responses to ► morphine were encountered less frequently in the neocortex of morphine-tolerant rats than in controls. It was shown that iontophoretically applied ► naloxone would elicit a large increase of firing in the locus coeruleus noradrenergic neurons in morphine-tolerant rats, presumably as a correlate of the withdrawal phenomenon in such animals. Also, opioid peptides have been tested iontophoretically in many regions of the central nervous system. Opioid peptides were found to excite hippocampal neurons; however, these effects were apparently mediated through an indirect action on transmitter release or to a naloxone-sensitive depression of local inhibitory interneurons.

Peptides

Microiontophoretic or pressure ejection has been used to apply a wide range of endogenous and synthetic peptides to neurons in vivo and in vitro. However, partly because of the lack of selective antagonists, there has been little progress in relating the observed responses to a physiological role, and as a result, attention has been concentrated on the mechanism of the observed responses, and potential interactions with neurotransmitters. ► Substance P, for example, appears to interact selectively with acetylcholine. Microiontophoretic substance P has also been found to enhance the response of spinal cord neurons to noxious stimulation but not innocuous ones, in some cases leading to the occurrence of responses in initially unresponsive units. Some excitatory effects of substance P can be mimicked by capsaicin, also applied iontophoretically. It was also reported that the excitatory effect of substance P on noradrenalin-containing neurons in the locus coeruleus is blocked by the selective antagonist [D-Pro^2, D-$Trp^{7,9}$] substance P. Thyrotropin releasing hormone (TRH) has been found to enhance the excitatory effects of acetylcholine on cortical neurons,



Microiontophoresis and Related Methods. Fig. 4. Representative rate histogram showing the effect of the selective 5-HT_{2C} receptor agonist RO 60-0175 on the basal activity of a nondopaminergic (presumably GABA-ergic neuron) of the rat substantia nigra pars reticulata. Microiontophoretic application of RO 60175 causes excitation of basal neuronal activity, which is proportional to the amount of the ejecting current applied (numbers above each bar in nA). (From Invernizzi et al. 2007.)

with no effects on resting firing rate. ▶ Somatostatin exerts a potent excitatory effect on hippocampal neurons. ▶ Cholecystokinin (CCK) and ▶ neurotensin are also frequently excitatory while angiotensin has excitant properties, which appear to be restricted to the subfornical organ and related structures. However, it is important to point out that peptides present special problems for microiontophoresis. Larger molecules tend to be adsorbed on to charged surfaces, which include the internal wall of a micropipette tip. Some peptides may also undergo denaturation or degradation during iontophoretic experiments. This problem may be exacerbated if very high currents are applied for long periods of time through high resistance tips, in that any change of local temperature may have a major impact on the stability of a peptide.

Advantages and Disadvantages of Microiontophoresis

The original microiontophoretic technique was developed for answering questions concerned with synaptic transmission and the neuromuscular junction. Using this preparation, it is a simple matter to microscopically examine the muscle fiber being studied, to determine the distance of the micropipette from the tissue, and to have ready access to known synaptic inputs. These advantages are not valid for the CNS. Nevertheless, with some further precautions and considerations, the technique has been used successfully in the CNS for about 50 years. It is important to consider other potentially confounding technical factors limiting the utility of microiontophoresis, as it is used in central investigations. Of primary concern is the site of drug administration relative to cell soma, where the strongest depolarizing or hyperpolarizing influences are manifested, and the dendritic field, where synaptic influences are normally expressed and where antagonists of transmitters must accumulate to modify trans-synaptic excitations. Another consideration for central investigations also concerns the spatial distribution of drugs in the CNS. Since the CNS is densely packed with cells, microiontophoretically administered compounds cannot affect single neurons in isolation. This must be kept in mind when interpreting the data.

Conclusions

Microiontophoresis, an experimental technique introduced more than 50 years ago, prompted a great impetus to the study of the physiology and pharmacology of the central nervous system. By mimicking the synaptic function, it provided a crucial step in establishing the physiological role of most neurotransmitters, including amines, amino acids, and neuropeptides. Although it is now considered by some as a "classical" neurophysiologic approach to the study of central nervous system, it is likely that it will still contribute substantially to the progress of neuroscience.

Cross-References

▶ Antidepressants
▶ Excitatory Amino Acids
▶ Extracellular Recording
▶ Hallucinogens
▶ Inhibitory Amino Acids
▶ Intracellular Recording
▶ Neurotensin
▶ Opioids
▶ Somatostatin
▶ Tachykinins

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Microsomal Ethanol-Oxidizing System

Synonyms

MEOS

Definition

Secondary pathway of alcohol metabolism in the liver, which plays a pronounced role during heavy and sustained drinking.

Midazolam

Definition

Midazolam is an ultra short-acting benzodiazepine derivative with potent anxiolytic, amnestic, hypnotic, anticonvulsant, skeletal muscle relaxant, and sedative properties. It is considered an ultra short-acting benzodiazepine, with an ► elimination half-life of about 2 h. It is used in some countries for the short-term treatment of insomnia and in many countries as a premedication before surgery. Intravenous midazolam is indicated for procedural sedation (often in combination with an ► opioid, such as ► fentanyl), for pre-op sedation, for the induction of general anesthesia, and for sedation of ventilated patients in critical care units.

Cross-References

► Benzodiazepines

Mild Cognitive Impairment

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Definition

Mild cognitive impairment (MCI) is a relatively recent term. It is used to describe individuals who have ► cognitive impairments beyond that expected for their age and education, but that do not interfere significantly with their daily activities (Petersen et al. 1999). The criteria for MCI are shown in the next section. It is considered to be a transitional stage between normal aging and various types of ► dementia. Although MCI can present with a variety of symptoms, when memory loss is the predominant symptom it is termed "amnestic MCI" and is frequently seen as a risk factor for Alzheimer's disease (AD) (Morris et al. 2001). Individuals who have impairments in cognitive domains other than memory are classified as nonamnestic single- or multiple-domain MCI. Subtype of MCI may influence rates of progression to dementia and has a major influence on subsequent type of dementia diagnosis (Yaffe et al. 2006).

Studies clearly suggest that MCI patients tend to progress to probable Alzheimer's disease at a significantly higher rate than healthy individuals of the same age. It is important that people with cognitive impairment are diagnosed as early as possible, so that they can benefit from therapeutic interventions.

Criteria for MCI

The criteria for MCI are those previously proposed by Petersen et al. (1999)

- Presence of a subjective memory complaint
- Preserved general intellectual functioning
- Demonstration of a memory impairment by cognitive testing
- Intact ability to perform activities of daily living
- Absence of dementia

The revised MCI criteria are those proposed by the Stockholm Group consensus.

- Presence of a cognitive complaint from either the subject and/or a family member
- Absence of dementia
- Change from normal functioning
- Decline in any area of cognitive functioning
- Preserved overall general functioning but possibly with increasing difficulty in the performance of activities of daily living

Role of Pharmacotherapy

Epidemiology and Risk Factors

People with MCI are more likely to develop Alzheimer's or other dementias than are those without cognitive impairment. In fact, about half the people with MCI will progress to ► Alzheimer's disease within 5 years. In the general population, the prevalence of MCI was estimated to be about 3% (Ritchie et al. 2001). In the same population, a prevalence rate of about 18% was reported for age-associated cognitive decline, which is a similar concept as MCI but is related to normal cognitive aging processes rather than incipient dementia. Most of the studies described an increase in prevalence of MCI with age. A higher prevalence rate of MCI has been found in females.

Vascular diseases were identified as risk factors for MCI in some studies. Patients, particularly in general hospitals, represent a high-risk group for MCI, since risk factors like cardiovascular diseases are quite common (Bickel et al. 2006). MCI is also positively associated with stroke and peripheral arterial obstructive disease.

Depressive symptoms are highly prevalent among elderly MCI subjects and in cognitively normal elderly individuals. These symptoms are associated with an increased risk of developing MCI (Ravaglia et al. 2008).

Depressive symptoms may also increase the conversion rate from MCI to ▶ dementia (Barnes et al. 2006). A synergistic interaction between ▶ apolipoprotein E genotype (epsilon3/epsilon4 or epsilon4/epsilon4) and depression was reported with regard to the incidence of MCI (Geda et al. 2006). Association between MCI and apoE allele 4 status largely depends on MCI subtype. For Alzheimer's disease, the apoE allele 4 status is probably the most established risk factor.

Symptoms

How do the memory difficulties in MCI differ from those of normal aging? Numerous studies have examined the cognitive performance of patients with MCI. In general, information on cognitive performance over time is essential for definition of MCI to substantiate a worsening over time. Neuropsychological examinations have demonstrated that, in general, these patients are impaired on tests of memory compared with age-matched healthy individuals. Forgetting things that are usually remembered may be a first symptom of MCI patients. MCI may encompass deficiencies in any or all of the following categories: language, visuospatial ability, for example, placement of things in time and space becomes more difficult; executive function, for example, decision making becomes more challenging; ▶ episodic memory, for example, what happened yesterday. A general recommendation for individuals concerned about their memory would be to discuss these concerns with their physician.

MCI patients may report distinct difficulties in other areas of cognition, such as naming objects or people and complex planning tasks. These symptoms are comparable, but less severe, than the neuropsychological deficits found for Alzheimer's disease, especially for amnestic MCI. A careful interview may reveal that the MCI patient has mild difficulties with daily activities. These problems should be confirmed by a significant other.

People with MCI may also experience:

- Depression
- Irritability
- Anxiety
- Aggression
- Apathy

Diagnosis

In general, a lot of research has focused upon techniques to try to improve ways of identifying people with MCI. The diagnosis of MCI requires considerable clinical judgment, which consists of a comprehensive clinical assessment, including clinical observation, laboratory examinations, neuropsychological assessment, and neuroimaging. These examinations are also performed to rule out any alternate diagnosis which may lead to cognitive impairment. A similar assessment is usually performed for the diagnosis of Alzheimer's disease or other types of dementia.

As part of physical examination, neurological examination checks for signs of ▶ Parkinson's disease, strokes, tumors, or other medical conditions that can impair memory as well as physical function.

Laboratory Tests

Simple blood tests can rule out physical problems that can affect memory, such as vitamin B-12 deficiency or an underactive thyroid gland.

Neuroimaging

There is emerging evidence that magnetic resonance imaging (MRI) can observe deterioration, including progressive loss of gray matter in the brain, from MCI to Alzheimer disease. MRI-based volumetric measurements of medial temporal lobe structures can discriminate between normal elderly control subjects and patients with Alzheimer's disease. The extent of medial temporal lobe atrophy distinguishes probable Alzheimer's disease and amnestic MCI from healthy subjects. Neuroimaging also helps to monitor disease progression from a diagnosis of MCI to different stages of AD. Furthermore, MRI or CT is necessary to rule out the possibility of a tumor, evidence of stroke, or bleeding which could also cause some of the symptoms seen in MCI patients.

Biomarker

Currently, a lot of research is done with biomarkers in Alzheimer's disease and in MCI patients. A promising area of research for biochemical diagnosis of AD and mixed forms of dementia is the analysis of cerebrospinal fluid (CSF) Biological markers can serve as early diagnostic indicators, and as markers of preclinical pathological change. They are likely to take on an increasingly important role in the diagnosis and monitoring of AD, and probably also in MCI. Some biomarkers are currently in the process of implementation as outcome variables. In a large multicenter study, the CSF biomarkers Aβ42, T-tau, and P-tau could predict with good accuracy which MCI patients will develop AD, which is a finding that was previously found in smaller studies (Mattsson et al. 2009). The sensitivity and specificity and ease of use are the most important factors that ultimately define the usefulness of a biomarker for diagnosis.

Neuropathology

MCI often causes the same types of brain changes seen in Alzheimer's disease or other forms of dementia. The difference between MCI and other types of dementia lies in the extent of these changes. The available data suggests that MCI is associated with the early stages of the neuropathological changes that are found in the lesions of AD; including the accumulation of neuritic ▶ plaques, neurofibrillary tangles, synaptic and neurotransmitter associated deficits, and significant neuronal cell death. There is evidence suggesting that while amnestic, MCI patients may not meet the neuropathologic criteria for Alzheimer's disease, and these patients may be in a transitional stage of evolving Alzheimer's disease.

Treatments and Drugs

In general, there is no cure for MCI. There are several medications as well as many nonmedication approaches that can potentially improve MCI-related symptoms. Treatment of coexisting conditions, such as high blood pressure or depression, may help reduce cognitive problems. As MCI may represent a prodromal state to clinical Alzheimer's disease, treatments proposed for Alzheimer's disease, such as antioxidants and ▶ cholinesterase inhibitors have also been tested for MCI. Patients with MCI are frequently being treated with "off label" cholinesterase inhibitors and ▶ memantine, as well as other possible cognition-enhancing drugs.

Acetylcholinesterase-inhibitors (AChEIs) and Memantine

Randomized, placebo-controlled trials examining the therapeutic value of ▶ acetylcholinesterase-inhibitors (AChEIs) have been performed during the last years. All of them have had a negative outcome with regard of the primary outcome parameter which was to prevent the conversion from MCI to real Alzheimer's disease. Negative results have also been obtained with steroidal or anti-inflammatory compounds or antioxidants. As these compounds are thought to target the early steps in the pathophysiological cascade of dementia, the negative results are disappointing. So far, no disease modifying drugs with a proven efficacy are available for the treatment of MCI patients. As a consequence of these largely negative studies, there is no proven treatment or therapy for MCI. For example, ▶ rivastigmine failed to stop or slow progression to Alzheimer's disease or on cognitive function for individuals with MCI (Feldman et al. 2007). Donepezil showed only minor, short-term benefits. During the first year of a 3-year study, the rate of progression from MCI to Alzheimer's was significantly lower in the people who took ▶ donepezil (Petersen et al. 2005). However, that difference disappeared by the end of the study. A recent study showed that depression is predictive of progression from amnestic MCI to Alzheimer's disease, and treatment with donepezil delayed progression to AD among depressed subjects with amnestic MCI (Lu et al. 2009). Also ▶ galantamine has not changed the conversion rate from MCI to Alzheimer's disease, but may increase the risk of sudden death from heart attacks and strokes when used in people who have MCI (Winblad et al. 2008). However, several clinical trials are in progress to determine if any medications will prevent or delay the rate of progression from MCI to dementia.

High Blood Pressure Drugs

People who have MCI are also more likely to have problems with the blood vessels inside their brains. High blood pressure can worsen these problems and cause memory difficulties. Therefore, antihypertensive drugs are under investigation of whether they can reduce the conversion rate from MCI to dementia. But also because of other medical complications, it is essential to keep blood pressure at normal levels.

▶ Antidepressants

Depression is common in people who have MCI, and depression, itself, can cause memory problems. Treating ▶ depression may help to improve memory. However, the studies to date were of short duration, and it is not clear whether there is a longer-term benefit associated with antidepressant treatment. Further studies are needed to investigate the role of antidepressants in depressed MCI patients, especially whether they can reduce the conversion rate from MCI to dementia.

Antioxidants

The antioxidant vitamin E may help to protect brain cells from the oxidative stress that appears to play a role in dementia, but it works no better than placebo in relieving the symptoms or delaying the progression of MCI. Ginkgo appears to improve memory and concentration in older adults with no major memory problems, but it is still uncertain if ginkgo can reduce the memory problems associated with MCI.

Physical Activity

Observational studies have shown that physical activity reduces the risk of cognitive decline. In a ▶ randomized controlled trial of a 24-week physical activity intervention, participants in the intervention group improved suggesting that a 6-month program of physical activity

provided a modest improvement in cognition over an 18-month follow-up period (Lautenschlager et al. 2008). In general, study results are to a certain extent controversial whether physical activities can prevent or reverse MCI. Nevertheless, physical activity can be part of a healthy lifestyle for older people with or without MCI.

Conclusion

The concept of MCI is currently of high interest. A number of studies have been dealing with different aspects of MCI with regard to diagnosis and therapeutic strategies. Upto now, no drug is licensed for the indication of MCI. However, there is hope that new compounds may be efficacious in the treatment of MCI to reduce the conversion rate from MCI to dementia.

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Milnacipran

Synonyms

Milnacipran hydrochloride

Definition

Milnacipran, under the brand name Ixel, became available in the late 1990s in Europe and several other countries for the treatment of Major Depressive Disorder. It was approved in 2009 for the treatment of fibromyalgia in the USA.

Milnacipran Hydrochloride

► Milnacipran

Miltown

► Meprobamate

Minimal Brain Damage

► Attention Deficit and Disruptive Behavior Disorders

Minimal Cerebral Dysfunction

► Attention Deficit and Disruptive Behavior Disorders

Minipress®

► Prazosin

Minor Cerebral Dysfunction

► Attention Deficit and Disruptive Behavior Disorders

Minor Tranquilizer

Synonyms

Antianxiety medication; Anxiolytic; Sedative; Tranquilizer

Definition

A medication used in the treatment of anxiety disorders and also as a nonspecific sedative. It is a more precise term for the drugs used to lessen anxiety than its synonyms. The distinction from sedative is not a clear one. Minor tranquilizers lie on a continuum from mild antianxiety effects through more pronounced effects and induction of sleep and relaxation to anesthesia of increasing depth.

Cross-References

► Anxiolytics
► Benzodiazepines
► Generalized Anxiety Disorder

Miraa

► Khat

Mirtazapine

Synonyms

Remeron; Zispin

Definition

Mirtazapine is the first atypical antidepressant with noradrenergic and specific serotonergic receptor antagonism (NaSSa), introduced in 1994, with fewer serotonergic, anticholinergic, and antiadrenergic side effects, and comparable effectiveness to ► tricyclic antidepressants. It also has beneficial effects on symptoms of anxiety and sleep disturbances. Its most common side effects are increased appetite and subsequent weight gain, drowsiness, and dizziness.

Cross-References

► Antidepressants

Mismatch Field

► Mismatch Negativity

Mismatch Negativity

Synonyms

Mismatch field; MMN

Definition

Mismatch Negativity (MMN) is similar to the P300 in that it is an event-related potential component seen when subjects are presented with a rare or "deviant" stimulus in a train of frequent or regular stimuli. It can be found using stimuli in a variety of sensory modalities but has been most researched using auditory or visual stimuli. The deviant stimuli can vary from the frequent ones in any way, for example, tone, pitch, loudness. Unlike the P300, subjects do not need to be paying conscious attention to the stimuli. MMN is a negative potential observed over fronto-central scalp with a typical latency of 150–250 ms after the onset of the deviant stimulus.

Cross-References

► Event-Related Potentials

Misoprostol

Synonyms

Cytotec

Definition

Misoprostol is an FDA-approved drug for the prevention of nonsteroidal anti-inflammatory drug-induced gastric ulcers. Misoprostol is also widely used by obstetricians and gynecologists for the induction of labor, therapeutic abortion, and the early termination of pregnancy.

Chemically, misoprostol is a synthetic prostaglandin E1 analogue. The most commonly reported adverse effects of misoprostol are: diarrhea, abdominal pain, nausea, and headache.

Cross-References
► Autism: Animal Models

Mitochondrial Complex Chain

Definition
Mitochondria provide the energy source of cells by synthesis of adenosine triphosphate (ATP). A series of enzymes and cofactors (complexes I – V) in the inner membrane of the mitochondrion oxidize carbohydrates to release electrons that drive the proton pumps necessary to provide the energy for ATP synthesis. A range of drugs and toxins act on these enzyme complexes to disrupt or enhance energy production via the mitochondrial electron transport chain, affecting cell metabolism and ultimately cell survival.

MK486

► Carbidopa

MMN

► Mismatch Negativity

Mobile phase

Definition
The mobile phase is the buffer that is pumped through the chromatographic column. All chemicals used to prepare the buffer should be of at least HPLC grade, and they should be made up using ultrapure, HPLC-grade, water. In addition, the buffer should be thoroughly filtered which is best achieved by vacuum filtration. This has the benefit that it also removes dissolved gas in the mobile phase that otherwise can come out of solution causing minute air bubbles to form. These get lodged in the column, with resultant adverse effects on the separation, or pass through to the detector, where they make irregular baseline noise, and rapid spikes.

Cross-References
► High Pressure Liquid Chromatography

Moclobemide

Synonyms
Aurorix; Manerix

Definition
Moclobemide is an antidepressant that inhibits reversibly and preferentially MAO-A, introduced in 1977, but not approved by the FDA in the USA. It is mainly used in the treatment of ► major depression and ► social anxiety, and it is claimed to have a favorable side-effect profile, but with equal effectiveness to ► tricyclic antidepressants and ► SSRIs within 1 week of treatment. It is rapidly absorbed and has a relatively short ► half-life, but the CNS effects persist for many hours, and it is considered safe.

Cross-References
► Antidepressants
► Monoamine Oxidase Inhibitors

Modafinil

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Synonyms
2-[(diphenylmethyl)sulfinyl]acetamide

Definition
Modafinil is a non-amphetamine ► psychostimulant currently FDA-approved for the treatment of sleepiness in ► Narcolepsy and shift-work sleep disorder.

Pharmacological Properties
Modafinil (brand name Provigil) is a racemate, with the two enantiomers being approximately equipotent in behavioral effects, but different in ► pharmacokinetic profile. The R-enantiomer (armodafinil) reaches higher

plasma concentrations than the racemic form between 6 and 14 h after administration, with a longer duration of wake-promoting activity in healthy adults. Modafinil is readily absorbed after single or multiple oral doses, reaching peak plasma concentrations 2–4 h after administration. The presence of food in the gastrointestinal tract can slow the rate of absorption but does not affect the total extent of absorption. Steady-state plasma concentrations are achieved between 2 and 4 days with repeated dosing. It is highly lipophilic, and approximately 60% bound to plasma proteins, primarily albumin. Major pharmacokinetic parameters are independent of doses in the range of 200–600 mg/day. The major circulating metabolites, modafinil acid and modafinil sulfone, do not exert any significant activity in the brain or the periphery. The ▶ elimination half-life is approximately 12–15 h, and single daily dosing is adequate and common in clinical practice. Elimination occurs primarily in the liver, via amide hydrolysis and, to a lesser extent, by ▶ cytochrome P450-mediated oxidation. Excretion occurs in the urine, with less than 10% of the oral dose excreted as the unchanged drug. Elimination is slowin the elderly or in individuals with hepatic or renal impairment. Some drug-drug interactions are apparent with modafinil. In vitro, modafinil exerts a reversible inhibition of CYP2C19, a smaller but concentration-dependent induction of CYP 1A2, 2B6 and 3A4, and a suppression of 2C9 activity. There are significant interactions of modafinil with ethinylestradiol and ▶ triazolam, though not with ▶ methylphenidate, dextroamphetamine, or warfarin.

Neurochemical Effects of Modafinil

Modafinil Effects on Catecholamine Systems

Modafinil is structurally unrelated to ▶ amphetamine, with a differing profile of pharmacological and behavioral effects. While the in vitro potency of modafinil in binding either the ▶ dopamine transporter (▶ DAT) and ▶ norepinephrine transporter (▶ NET) is low relative to methylphenidate, ▶ bupropion, or benztropine, modafinil shows DAT occupancy comparable to ▶ methylphenidate at clinically relevant doses (Madras et al. 2006).

Modafinil has a complex profile of effects on central dopamine (▶ DA) and norepinephrine (NE) systems, lacking many neurochemical and behavioral effects observed with amphetamine administration. For instance, in contrast to amphetamine, modafinil does not significantly affect DA release or turnover; it shows negligible effects on cerebral cortical blood flow and shows different patterns of metabolic activation compared to amphetamine; it does not produce behavioral stereotypies or rebound hypersomnia; and in healthy humans, modafinil has effects on the resting EEG that are distinct from amphetamine. Nevertheless, a parenteral administration of modafinil does raise extracellular DA levels in the rat ▶ prefrontal cortex (de Saint Hilaire et al. 2001), and in the caudate nucleus of narcoleptic dogs, though only minimally in the rat ▶ hypothalamus (de Saint Hilaire et al. 2001). It causes a modest increase in DA in the accumbens after intraperitoneal doses up to 300 mg/kg. In rat brain slices, modafinil inhibits the activity of ▶ ventral tegmental area DA neurons, an effect that appears to be mediated by D2 receptors. This suggests that modafinil inhibits DA reuptake, leading to DA cell body ▶ autoreceptor activation, to diminish DA cell firing. Modafinil effects on wakefulness are abolished in DAT knockout mice. In a rodent ▶ drug discrimination paradigm, modafinil partially generalizes to a cocaine-like stimulus; in addition, modafinil effects on activity levels in mice are modestly attenuated by D1 receptor antagonism, though not by D2 antagonism. Modafinil reduces blood prolactin levels in humans, without effects on blood growth hormone or thyroid stimulating hormone. Overall, these findings suggest that modafinil effects on arousal and behavioral activity are at least partly mediated by synaptic DA, but in a manner differing from that of amphetamine, and possibly favoring corticostriatal over subcortical limbic circuits.

Modafinil also elevates extracellular NE levels in ▶ prefrontal cortex (along with DA) and hypothalamus. Pretreatment with α-adrenergic receptor antagonists diminishes modafinil-induced increases in arousal and activity in rats and monkeys. However, modafinil does not reduce cataplexy in dogs or humans with narcolepsy, a feature that is similar to other DAT inhibitors, and in contrast to α1B receptor agonists and NET inhibitors. In addition, pretreatment with low doses of the α2 antagonist ▶ yohimbine potentiates modafinil-induced wakefulness and activity, whereas higher doses attenuate the activity increases. This biphasic response to yohimbine suggests that low doses may preferentially block the inhibitory terminal α2 autoreceptor to enhance NE release and thus augment postsynaptic adrenergic receptor activation by modafinil, whereas higher doses also block postsynaptic α2 receptors, attenuating modafinil effects. These findings make it likely that postsynaptic α2 receptors mediate some of the behavioral effects of modafinil. Importantly, modafinil also augments pupillary dilation parameters in a manner consistent with phasic activity of locus coeruleus neurons. This effect may also be mediated through α2 receptor activation; in this case, those receptors (autoreceptors) are located on locus coeruleus cell

bodies. Modest attenuation of modafinil-induced arousal and activity has also been observed after pretreatment with the β-blocker ▶ propranolol, suggesting that postsynaptic β receptors also mediate these modafinil effects.

Taken together, these varied findings suggest that modafinil may potentiate both DA and NE neurotransmission. It appears likely that the elevations in extracellular NE observed after modafinil are responsible for the majority of the adrenergic receptor-mediated effects, which may involve α2, α1, and β receptors. D1 and D2 receptors probably also mediate modafinil effects on cognition and behavior. In addition, however, Wisor and Eriksson (2005) have proposed that the elevated synaptic DA resulting from DAT inhibition may lead to DA activation of adrenergic receptors. There remains the possibility that enhanced DA in the ▶ prefrontal cortex results from competition with increased NE levels for binding to the NET, which plays an important role in terminating DA action in the prefrontal cortex. DA has an affinity for cloned mouse α1B receptors that is on the same order of magnitude as NE and DA can activate adrenergic receptors in various brain regions. These observations suggest a mechanism whereby the modafinil inhibition of DAT inhibition may be related to adrenergic receptor-mediated behavioral effects.

Modafinil Effects on GABA, Glutamate, and Serotonin Systems

Modafinil also has consistent effects on central ▶ glutamate and gamma amino-butyric acid (▶ GABA) neurotransmitter systems. The regional effects on extracellular glutamate occur at ascending doses in this order: thalamus = hypothalamus < striatum = hippocampus. Glutamate levels in the globus pallidus and substantia nigra are unchanged after the highest doses administered. These effects on glutamate may interact with adrenergic mechanisms.

Modafinil also causes a dose-dependent decrease in extracellular GABA. These regional GABA effects occur at ascending doses in this order: cortex < striatum/pallidum = hypothalamus < thalamus = hippocampus = substantia nigra = nucleus accumbens.

The effects on extracellular GABA may be mediated by modafinil effects on other neurotransmitter systems Cortical GABA effects require intact catecholamine neurons. In addition, modafinil elevates extracellular serotonin (5HT) in the frontal cortex, central nucleus of the amygdala, and dorsal raphe nucleus, but minimally in the hypothalamus. Modafinil and the 5HT reuptake inhibitors ▶ fluoxetine, ▶ paroxetine, and ▶ imipramine mutually enhance the effects of each other on elevations in cortical 5HT. Taken together, this literature suggests that modafinil effects on GABA are at least partly mediated by 5HT. Ultimately, modafinil effects on GABA may be mediated by adrenergic effects on 5HT activity.

Modafinil Effects on Orexin and Histamine Systems

The clinical efficacy of modafinil in narcolepsy, a condition characterized by deficient orexin (▶ hypocretin) in the brain, suggests that modafinil may have clinically relevant effects on this neurochemical system. Modafinil does activate orexin cells in the perifornical area of mice and rats. However, modafinil induces wakefulness more potently in orexin knockout mice than in wild-type mice, with similar patterns of Fos-immunoreactivity. In addition, modafinil does not bind to the orexin 1 receptor and retains effects on both extracellular striatal DA and wake-promoting activity in orexin 2 receptor-deficient narcoleptic dogs. Therefore, modafinil effects on arousal do not appear to be mediated through the orexin system, and the precise role of orexin in the cognitive and clinical effects of modafinil remains unknown. Modafinil also elevates extracellular histamine (HA) in the anterior hypothalamus. However, a direct injection of modafinil into the tuberomamillary nucleus (the site of HA cell bodies) does not affect HA release. Given the multiple effects on catecholamines, 5HT and GABA described earlier for modafinil, it appears likely that modafinil effects on HA are mediated by one or more of these other neurotransmitter systems.

Effects of Modafinil on Cognition

Studies in rodents indicate that modafinil can improve ▶ working memory performance in a dose- and delay-dependent manner, and that the processing of contextual cues is also enhanced with modafinil. These effects may be augmented with sustained dosing regimens. In healthy humans (with or without undergoing sleep deprivation), working memory, recognition memory, ▶ sustained attention, and other tasks dependent on cognitive control (and on function of the prefrontal cortex) are enhanced with modafinil. Some evidence suggests that the magnitude of modafinil effects in healthy adults may depend on underlying cognitive abilities. Those with high general intellectual abilities, or high performance in specific cognitive domains, appear to exhibit less improvement after modafinil, suggesting that these individuals already experience optimal levels/patterns of catechalamine activity in the modulation of cognition. Among psychiatric populations, there is now consistent evidence that modafinil (in well-tolerated dosing regimens) improves attention and response inhibition in children and adolescents with attention-deficit/hyperactivity disorder (▶ ADHD). These

improvements in cognition may form the basis for clinical efficacy in ADHD. Among adult psychiatric patients, modafinil improves several cognitive functions dependent on the prefrontal cortex in ► schizophrenia, ► major depression and adult ADHD, with some null findings reported in schizophrenia. However, these studies have significant limitations evident in their design. The range of clinical samples and cognitive functions that are subject to modafinil treatment study is expected to expand in the future.

Clinical Effects of Modafinil

Modafinil has consistently shown efficacy in measures of alertness in narcolepsy and shift-work sleep disorder, in ► randomized, double-blind placebo-controlled studies. In these studies, modafinil has shown efficacy in open-label extension phases extending for as long as 136 weeks, and it has been well tolerated, with no evidence of significant adverse events or abuse. Modafinil has also been evaluated for the treatment of ► fatigue and sedation in a number of other neurological and medical conditions, including multiple sclerosis, idiopathic ► Parkinson's disease, chronic fatigue syndrome, polio, HIV infection, ► dementias, obstructive sleep apnea, post-anesthetic sedation, and fibromyalgia, with generally favorable but somewhat mixed results (Ballon and Feifel 2006).

Among studies of adult psychiatric patients, two studies of patients with ► major depression have found significant improvements in mood symptoms on modafinil compared to placebo, and modafinil has been associated with greater rates of abstinence in cocaine-dependent adults. It also shows clinical efficacy in adults with ADHD. In contrast, adjunct modafinil has shown modest and inconsistent efficacy for symptoms of schizophrenia, though these studies have been plagued by small sample sizes and other methodological limitations.

In childhood/adolescent ADHD, modafinil improves parent, teacher, and clinician ratings of ADHD symptoms in several short-term (4–9 weeks), randomized, double blind, placebo-controlled trials, at mean doses ranging from 195 to 368 mg daily.

Throughout these clinical trials, modafinil has been well tolerated. However, case reports have appeared describing significant adverse events in routine clinical use of modafinil, including the exacerbation of psychosis, acute mania, clozapine toxicity, premature ventricular contractions, and irritability and verbal aggression. Nonetheless, these events have not been observed at a significant rate in modafinil-treated patients compared to placebo-treated patients in clinical trials and no serious (e.g., life-threatening) sequelae have ensued in these reported isolated cases. Modafinil also appears to have a relatively low potential for abuse, which may be a function of its pharmacodynamic profile and/or its physical properties, being insoluble in water and unstable at high temperatures, which minimizes its bioavailability upon smoking or intravenous use. Nonetheless, careful clinical judgment should be exercised in the decision to initiate therapy with modafinil, with particular attention to both its side-effect profile and its potential for drug–drug interactions.

Cross-References

► Attention Deficit and Disruptive Behavior Disorders
► Drug Interactions

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Model Organisms of Hyperkinetic Syndrome

► Attention Deficit Hyperactivity Disorders: Animal Models

Mogadon

► Nitrazepam

Molecular Imaging

► Positron Emission Tomography (PET) Imaging

Molindone

Definition

Molindone, a primarily dopamine D2 blocking dehydroindolone ► antipsychotic with an ► elimination half-life of 6.5 h, is mainly metabolized by 2D6 CYP450 isoenzymes. It is normally regarded as a first-generation antipsychotic.

Cross-References

► First-Generation Antipsychotics

Monoamine Depletion

► Amine Depletors

Monoamine Hypotheses

► Aminergic Hypotheses for Depression
► Aminergic Hypotheses for Schizophrenia

Monoamine Oxidase Inhibitors

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Definition

Monoamine oxidase inhibitors (MAOIs) inhibit the enzyme MAO, of which there are two major isoforms, MAO-A and MAO-B.

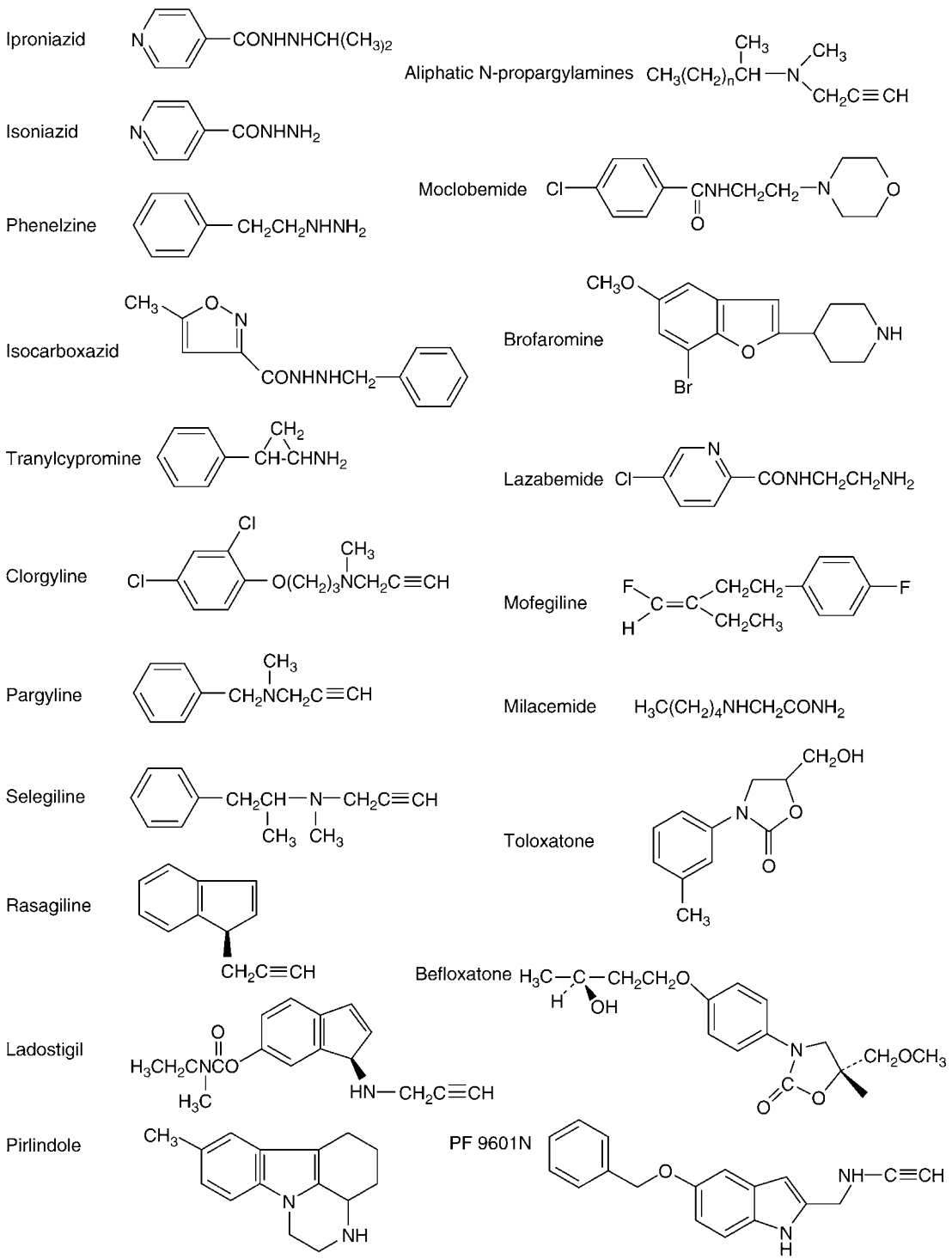
Pharmacological Properties

History

MAOIs were originally developed as ► antidepressants because of their ability to restore brain levels of the biogenic amines ► noradrenaline and 5-hydroxytrytamine (or ► serotonin), both of which are thought to be functionally deficient in depression. Yet, several of these drugs have also proven useful in the treatment of ► panic disorder, ► social anxiety disorder, ► eating disorders, pain syndromes, ► Parkinson's disease, and ► Alzheimer's disease. MAOIs are no longer first-line drugs for most depressive or anxiety disorders. However, they do remain important agents when first- or second-line drugs prove to be ineffective or intolerable, and are especially effective in ► atypical depression and depression associated with anxiety, panic, or phobias (Kennedy 1994; Kennedy et al. 2005). The MAOIs may be classified according to selectivity (for either the MAO-A or MAO-B isoform) and reversibility (reversible or irreversible) (see Kennedy et al. 2005; Stahl and Felker 2008 and Youdim et al. 2006). Noradrenaline and serotonin are preferred substrates for MAO-A, while β-phenylethylamine and benzylamine are selective for MAO-B. Selective inhibitors of MAO-A and MAO-B include clorgyline and l-deprenyl, respectively. Figure 1 and Table 1 show several MAOIs, some of which are currently available clinically, and others that are used only pre-clinically or are at various stages of development.

Side Effects

While the inhibition of MAO-A is required for antidepressant activity, clinically used irreversible inhibitors of MAO prevent the inactivation of dietary sympathomimetic amines, such as tyramine, by MAO-A in the gut wall and by MAO-A and MAO-B in the liver. The resulting increase in systemic tyramine stimulates the release of noradrenaline from sympathetic varicosities in the vascular wall. This also occurs with clorgyline, despite its lack of effect upon hepatic MAO-B. As a consequence of MAO-A inhibition, noradrenaline accumulates and produces a series of symptoms, usually starting with headaches and, if not dealt with appropriately, potentially culminating in a hypertensive crisis. This adverse effect is called the "cheese effect," so-named because it was originally observed in patients taking MAOIs who had ingested foods



Monoamine Oxidase Inhibitors. Fig. 1. Some monoamine oxidase inhibitors and their structures.

Monoamine Oxidase Inhibitors. Table 1. Some monoamine oxidase inhibitors and their actions.

Generic	Reversible/irreversible selectivity
Iproniazid	Irreversible, nonselective
Isoniazid	Irreversible, nonselective
Phenelzine	Irreversible, nonselective
Isocarboxazid	Irreversible, nonselective
Tranylcypromine	Irreversible, nonselective
Clorgyline	Irreversible, MAO-A selective
Pargyline	Irreversible, MAO-B selective
Selegiline	Irreversible, MAO-B selective
Moclobemide	Reversible, MAO-A selective
Brofaromine	Reversible, MAO-A selective
Lazabemide	Very slowly reversible, MAO-B selective
Mofegiline	Irreversible, MAO-B selective
Milacemide	Partially reversible, nonselective
Toloxatone	Reversible, MAO-A selective
Befloxatone	Reversible, MAO-A selective
Pirlindole	Reversible, MAO-A selective
Rasagiline	Irreversible, MAO-B selective
Ladostigil	Irreversible, MAO-B selective
PF 9601N	Irreversible, MAO-B selective
Aliphatic N-propargylamines	Irreversible, MAO-B selective

Table modified from Kennedy et al. 2005

such as aged cheeses that have a high tyramine content. This food–drug interaction can occur with some of the MAOIs used currently in the clinic, including ▶ tranylcypromine, ▶ phenelzine, and ▶ isocarboxazid (all of which act as irreversible inhibitors of both MAO-A and MAO-B). Thus, when patients receive a prescription for such MAOIs, they should be informed by their physician and pharmacist of the foods that should be avoided while on these medications (Stahl and Felker 2008).

Concern about the food–drug interaction mentioned above led to the development of selective MAO-B inhibitors such as l-deprenyl (▶ selegiline) as putative antidepressants. However, this selectivity for MAO-B meant that l-deprenyl did not exhibit antidepressant effects until selectivity was lost at higher doses that also caused irreversible MAO-A inhibition. Nonetheless, l-deprenyl is used in the treatment of Parkinson's disease and has been demonstrated to have ▶ neuroprotective properties in a large number of neurotoxicity tests in vivo and in vitro (Tatton and Chalmers-Redman 1996; Youdim et al. 2006). In fact, the neuroprotective actions of this drug have stimulated considerable research into related drugs as potential neuroprotective agents (▶ rasagiline is an example of productive research in this area). Transdermal selegiline has recently been reported to be effective as an antidepressant (Culpepper and Kovalick 2008; Stahl and Felker 2008); under these conditions, the drug is delivered directly into the systemic circulation, thereby avoiding extensive first-pass metabolism and reaching the brain in sufficiently high concentrations to inhibit both MAO-A and MAO-B.

In a further effort to develop antidepressants that would not precipitate the cheese effect, reversible inhibitors of MAO-A (RIMAs) were developed. ▶ Moclobemide, a competitive RIMA available clinically for several years, retains antidepressant properties, but the risk of a hypertensive crisis is reduced since dietary tyramine can still compete with moclobemide for the active site on MAO-A. RIMAs have a further advantage over irreversible inhibitors in that after cessation of treatment with the latter drugs, a period of approximately 2 weeks is required before MAO fully recovers (following the synthesis of new enzyme). In the case of RIMAs, the recovery of enzyme occurs as inhibitors are cleared from the body and is usually complete in 2–5 days. This is an important consideration when shifting a patient to a drug regimen that would otherwise be contraindicated because it would result in elevated levels of serotonin (e.g., a ▶ selective serotonin reuptake inhibitor [SSRI]).

Although a hypertensive crisis is a feared adverse effect associated with irreversible MAOIs, this is usually the result of a food–drug or drug–drug interaction. Paradoxically, orthostatic hypotension is a more common adverse cardiovascular effect with MAOIs. ▶ Serotonin syndrome may result if an MAOI is given with another drug that also increases the availability of serotonin (see Table 1). ▶ Insomnia can be a problem with tranylcypromine (an MAOI with a structure similar to that of amphetamine), and the irreversible MAOIs can produce weight gain, peripheral edema, and ▶ sexual dysfunction (Kennedy et al. 2005). A discontinuation syndrome (arousal, mood disturbances, and somatic symptoms) may occur with phenelzine or tranylcypromine if they are discontinued abruptly.

Drug–Drug Interactions

In addition to the food–drug interaction mentioned earlier, drug–drug interactions must be taken into consideration when prescribing MAOIs; some of these may be life

Monoamine Oxidase Inhibitors. Table 2. Potential drug–drug interactions involving monoamine oxidase inhibitors.

Interacting drugs	Examples	Possible result
Drugs that stimulate the release of or inhibit the reuptake of noradrenaline at sympathetic neurons; decongestants	Amphetamines, methylphenidate, ephedrine, phenylephrine, phenylpropanolamine, pseudoephedrine, oxymetazoline, some antidepressants, tramadol, sibutramine, phentermine	Hypertension
Drugs metabolised by monoamine oxidase	Phenylephrine (oral), sumatriptan, citalopram	Hypertension, increased serum levels of sumatriptan, citalopram
Drugs that inhibit serotonin reuptake	SSRIs, clomipramine, imipramine, meperidine, dextromethorphan, propoxyphene, venlafaxine, chlorpheniramine, brompheniramine, tramadol	Serotonin syndrome, confusion, agitation, hypomania, sweating, myoclonus, fever, coma, possible fatality
Serotonin agonists	Sumatriptan	Serotonin syndrome
β-Blockers		Increased hypotension, bradycardia
Oral hypoglycemics		Increase hypoglycemic affects

Table modified from Kennedy et al. 2005 and Stahl and Felker 2008

threatening. These potential drug–drug interactions are summarized in Table 2.

Metabolism

Most of the MAOIs are metabolized extensively, and various ► cytochrome P450 (CYP) enzymes are involved in this metabolism (see Kennedy et al. 2005).

Beyond Inhibition of MAO

The MAOIs are multifaceted drugs and have been reported to bind to a wide variety of other enzymes, receptor systems, and uptake pumps that may contribute to their therapeutic and/or adverse effects. Depending on the MAOI involved, interactions with the following have been reported: other amine oxidases; various transaminases, decarboxylases, dehydrogenases, cytochromes P450 (CYPs); biogenic amine receptors and transporters; imidazoline binding sites; and sigma receptors (Holt et al. 2004). Several MAOIs also cause marked increases in brain levels of ► trace amines such as β-phenylethylamine and ► tryptamine, both of which can affect the normal function of classical neurotransmitter amines such as noradrenaline, dopamine, and serotonin. There has been extensive interest in recent years in the possible neuroprotective effects of MAOIs and their potential for the treatment of neurodegenerative disorders. For example, the MAO-B inhibitors l-deprenyl and rasagiline are neuroprotective and are used as anti-Parkinsonian drugs and, to a lesser extent, as therapeutic agents in Alzheimer's disease (Youdim et al. 2006). In many cases, these neuroprotective actions appear to be independent of the inhibition of MAO. l-Deprenyl and rasagiline have been reported to prevent the initiation of apoptotic cascades by up-regulating the anti-apoptotic protein Bcl-2 and down-regulating pro-apoptotic proteins such as Bad and Bax, and to prevent the activation and nuclear localization of glyceraldehyde-3-phosphate dehydrogenase (Youdim et al. 2006). Preliminary reports indicate that l-deprenyl might be useful for the treatment of negative symptoms in ► schizophrenia. Phenelzine has been shown to provide neuroprotection in an animal model (global ischemia) of stroke, and its contribution to neuroprotection might rely on actions as diverse as the inhibition of ► GABA transaminase (GABA-T) and the elevation of brain GABA, the elevation of brain ornithine, and the sequestration of toxic aldehydes such as 3-aminopropanal and acrolein (Baker et al. 2007; Sowa et al. 2004). Although unrelated to MAO, semicarbazide-sensitive amine oxidase (SSAO) is inhibited by some MAOIs (e.g., phenelzine). SSAO has been the subject of extensive research in the areas of

inflammation, neuropsychiatry, and cardiovascular complications of diabetes in recent years, and might play a role in Alzheimer's disease-related pathology (Jiang et al. 2008).

The RIMA moclobemide has been reported to have anti-Parkinsonian activity and neuroprotective effects in a model of cerebral ischemia. Both tranylcypromine and phenelzine have been shown to increase the expression of ► brain-derived neurotrophic factor (BDNF) in rat brain after chronic administration. Clorgyline (an irreversible inhibitor of MAO-A), like l-deprenyl and rasagiline, contains an N-propargyl moiety, and has been reported to be neuroprotective in vitro and in vivo (Baker et al. 2007), albeit at doses lower than are required to inhibit MAO. Increased activity and expression of MAO have been reported in Alzheimer's disease, suggesting that MAOIs should be investigated more thoroughly as adjunctive drugs in this neuropsychiatric disorder. Ladostigil, a drug that combines the properties of rasagiline with anticholinesterase activity, is currently in phase II clinical trials for treatment of Alzheimer's disease (Youdim et al. 2006), while related drugs that also possess iron-chelating properties or inhibitory potency versus ► glutamate release are in preclinical development.

In summary, although MAOIs are not currently used extensively in mood and anxiety disorders because of clinically relevant food–drug and drug–drug interactions, they continue to have an important place in the treatment of psychiatric and neurological disorders and are exciting keys to the development of future drugs with potential neuroprotective activity.

Acknowledgments

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Cross-References

► Antidepressants
► Brain-Derived Neurotrophic Factor
► Depression
► Neuroprotection
► Panic Disorder
► Social Anxiety Disorder
► Trace Amines

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Monoamines

Definition

Monoamines (so-called because they have one organic substituent attached to the nitrogen atom) include ► serotonin, ► norepinephrine, and ► dopamine, all of which are neurotransmitters that are important in the pathophysiology and treatment of psychiatric disorders. Monoamines are subdivided into ► catecholamines and ► indoleamines.

Mood Disorders

Synonyms

Affective disorders

Definition

Depressive, manic, and hypomanic disorders like ► major depression, ► mania, hypomania, ► bipolar disorder, ► dysthymia, or cyclothymia.

Mood Stabilizers

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Synonyms

Long-term treatments for bipolar disorder

Definition

Mood stabilizers are pragmatically defined by their clinical efficacy in ▶ bipolar disorder. Bipolar disorder is a complex condition as it is expressed as episodic periods of contrasting mood disturbance – ▶ mania and ▶ depression – and its long-term or maintenance treatment must prevent new episodes of both. Any medicine that achieves this can be said to be a mood stabilizer.

Pharmacological Properties

History

The first mood stabilizer was ▶ lithium. It was discovered over 60 years ago by guided serendipity. Lithium salts of urea were found by an Australian doctor John Cade to be sedative in animals. He had reasoned that urea itself was an active component, but realized that, in fact, lithium was unexpectedly tranquilizing. Immediate trials in patients with ▶ mania suggested acute efficacy and subsequent experience showed that lithium could markedly modify the course of bipolar disorder (then called manic-depression) in the long term. The effects were anecdotally so dramatic for some extremely disabled patients that a group of psychiatrists and scientists, led most notably by Mogens Schou, quickly became self-proclaimed lithium enthusiasts and by the 1960s, had influenced practice in many parts of the world. The history of lithium's acceptance was interrupted by highly vocal criticism of the methodology of its early adopters. While the critics were right about the methodology, they were wrong about lithium (which they proclaimed on equally little evidence to be a dangerous yet inactive placebo). Subsequent trials have repeatedly shown that lithium is an effective medicine for the prevention of relapse (especially to the manic pole) in bipolar disorder (Geddes et al. 2004). Where the illness starts with and tends to relapse to the manic pole, lithium can produce remarkable mood stability. However, such success is seen in only about 30% of patients with the severe form of the disorder. Therefore, for many patients, other mood stabilizers are required to meet their unmet needs.

▶ Valproate and ▶ carbamazepine are also often described as mood stabilizers, although the evidence is weaker than for lithium. Both also tend to be most active against mania.

There is also good evidence for ▶ antipsychotics in mood stabilization (Mahli et al. 2005): ▶ quetiapine acts against both poles of the illness. It also turns out that other agents can be effective in long-term treatment against, for example, the manic pole of the illness, without having an important impact on depression (e.g., ▶ aripiprazole, ▶ olanzapine, and ▶ risperidone), and vice versa (e.g., ▶ lamotrigine). Some authors have argued for extending the term mood stabilizer to include medicines with all these effects. Even more loosely, there was at one time a tendency to extend the term mood stabilizer to include ▶ anticonvulsants, effectively by extrapolation from the examples of ▶ valproate and ▶ carbamazepine. In the case of ▶ topiramate and ▶ gabapentin, subsequent clinical trials proved to be negative. There seems little advantage to a more liberal definition except for marketing the drugs.

Mechanism of Action

It follows from the definition that there are no pharmacological properties that define mood stabilizers as a class. Moreover, our understanding of the neurobiology of mania and depression remains highly provisional. However, the fact of clinical efficacy has often preceded an understanding of mechanism and has been a major driver to further research. Thus, the individual medicines effective in stabilizing mood have a variety of effects defined for the most part in animal experiments.

Lithium inhibits the phosphoinositide second-messenger system in the brain and peripheral tissues. This may be the basis for its therapeutic (and nontheraputic) effects, although it has not been investigated as fully as might be expected. There are also some effects on the ▶ monoamine function in the brain, which have weak parallels with better-defined psychotropic drugs like ▶ antidepressants and antipsychotics. In recent years, interest has been directed to downstream cellular changes in transcription factors and other molecular pathways that may mediate ▶ neuroprotection. Lithium has some actions in common with valproate in these cellular models.

The net actions of the anticonvulsants are variously pro-GABAergic and antiglutamatergic. The efficacy of lamotrigine in bipolar depression is of particular interest

given its lack of neurotoxicity at effective doses and selective effects on membrane polarization and glutamate release. ► Glutamate is increasingly implicated in the neuronal circuits that are believed to regulate mood, and there is an evolving pharmacology targeted on the glutamate system. Whether this next generation of molecules will be effective is still an open question.

The antipsychotics that can prevent long-term relapse in bipolar disorder have a common action in blocking dopamine receptors. However, most have additional actions on serotonergic function in the brain and; in the specific case of quetiapine, an active metabolite that appears to block noradrenergic reuptake, a property shared with a number of antidepressants. Whether these effects, in addition to dopamine blockade, are important remains an open question.

► Pharmacokinetics

Lithium provides an unusual example for psychopharmacology of a drug whose plasma levels are routinely monitored in clinical practice. It is necessary because the drug has a narrow therapeutic ratio: in other words, the difference between a blood level that is just effective and that which can poison the patient is relatively small. For efficacy, 0.5 mmol/L is regarded as the minimum effective level in plasma taken 18 h after the last dose of lithium. Levels over 1.5 mmol/L are potentially toxic and definitely not recommended. The commonest well-tolerated level is around 0.7 mmol/L, although slightly higher levels (0.8–1.0 mmol/L) are often recommended. Choice of level should always be informed by any symptoms the patient describes. A variety of effects can limit doses to those achieving well below 1.0 mmol/L.

Although not routinely used to guide treatment, levels of valproate and carbamazepine are often available because of their use in epilepsy. A valproate level between 50 and 125 g/mL has been associated with acute response in mania. Importantly, because combined treatments are so often necessary in bipolar patients, carbamazepine promotes enzyme induction and can lower the levels of a range of other agents (including the contraceptive pill); hence, higher doses of comedication may often be necessary. Conversely, valproate approximately doubles the availability of lamotrigine, thus halving the dose required for efficacy.

In the elderly, it is common for the required dosage to be substantially less than those used in younger people. Side effects are an important guide, as ever, to what the dosage should be. The highest *well-tolerated* dose (whatever the actual figure) is usually the best choice in bipolar disorder.

Tolerability and Safety

In general, mood-stabilizing medicines have to be reasonably well tolerated because patients are expected to take them week in and week out for many years – often indefinitely. There is a tendency for doctors to underestimate the adverse impact of medicines on their patients. The most important adverse subjective effects of psychotropic drugs that are used to treat bipolar disorder tend to be tiredness, sedation, and weight gain. In addition, lithium can produce tremor, increased urine volumes, and thyroid dysfunction. Attention to minimizing these problems (by optimizing doses) is essential for good adherence to prescribed medicines.

Weight gain was formerly seen as a largely cosmetic problem. It is now realized to be a much more important because obesity combined with lack of exercise and smoking is associated with the so-called metabolic syndrome. This is a composite term for biochemical, blood pressure, and weight indices associated with older age and higher body mass index. It is the prelude to diabetes, coronary heart disease, and stroke. Several antipsychotics used to treat bipolar disorder, including ► clozapine, ► olanzapine, and ► quetiapine are particularly associated with increased weight gain and the risk of dyslipidaemia, hypercholesterolaemia, and elevated glucose. In an increasingly obese population, this is a growing concern and requires active prevention wherever possible and treatment of risk factors.

In pregnancy, there is a risk of teratogenicity from several of the medicines used as mood stabilizers. Thus, especially in the first 3 months of fetal development, drugs may interfere with the formation of the most complex organs. The neural tube and heart are especially vulnerable. Lowest risks appear to be associated with the antipsychotics. Higher ► teratogenic risks are associated with lithium and especially the anticonvulsants (valproate > carbamazepine > lamotrigine).

Decisions about the use of medication in pregnancy by women with bipolar disorder are always difficult. Sudden discontinuation (Goodwin, 1993) or switching medicines risks destabilizing mood and precipitating relapse of the bipolar disorder. Treatment of an acute episode in a pregnant woman may be both highly stressful and require much higher doses of psychotropic drugs than would be required for prophylaxis.

Treatment issues also arise postpartum. Childbirth greatly increases the risk of relapse in patients with bipolar disorder in the weeks and months after delivery. Bipolar women with a previous history of a severe postpartum episode (puerperal psychosis) and bipolar women with a

family history of puerperal psychosis will have a >50% risk of severe relapse. Medication given to prevent this outcome will often appear in breast milk and have potential consequencies for the neonate.

Conclusion

The term mood stabilizer is in common use, even though it imprecisely describes what such medicines do and certainly does not define a meaningful pharmacological action or even set of actions. The strictest definition, proposed by Bauer and Mitchner (2004) is prophylaxis and the prevention of recurrence *and* evidence of short-term efficacy for both poles of the illness. Lithium may just meet the criterion despite its relative weakness against depression; quetiapine certainly does but clinical experience is less. Therefore, for any agent to be called a mood stabilizer, we probably need to know how it performs in comparison to lithium in the long term. We also need to be able to gauge its relative effects against the manic and depressive poles of the illness.

Medicines that reduce the risk of relapse to mania and/or depression in bipolar patients can contribute to mood stability, whatever we call them. Some contemporary uses of the term are overinclusive. However, mood stability is a goal that patients, their families, and attending doctors share. If a medicine helps, then doctors are more likely to prescribe it and patients are more likely to take it. In other words, the term mood stabilizer is chosen to be comforting and persuading. This does not detract from the scientific challenge to understand the mechanisms underlying mood stabilization and how we improve treatment.

Cross-References

- ▶ Anticonvulsants
- ▶ Antidepressants
- ▶ Bipolar Disorder
- ▶ Classification of Psychoactive Drugs
- ▶ Glutamate
- ▶ Monoamines

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Moperone

Definition

Moperone is a first-generation (typical) antipsychotic drug that belongs to the ▶ butyrophenone type approved in Japan for the treatment of ▶ schizophrenia. It has higher antagonist affinity for D_2- than 5-HT_{2A}-receptors. It also has high binding affinity for sigma receptors. It can induce ▶ extrapyramidal motor side effects, insomnia, and thirst, but it displays generally low toxicity.

Cross-References

- ▶ Butyrophenones
- ▶ Extrapyramidal Motor Side Effects
- ▶ First-Generation Antipsychotics

Morals

- ▶ Ethical Issues in Animal Psychopharmacology
- ▶ Ethical Issues in Human Psychopharmacology

Morphine

Definition

Morphine is a highly potent opiate analgesic drug. It is the principal active ingredient in opium that is derived from the opium poppy, *Papaver somniferum*. It is considered to be the prototypical ▶ μ-opioid agonist. It acts directly on the μ-opioid receptors to relieve pain. Morphine has a high potential for addiction; tolerance and both physical and psychological dependence develop rapidly.

Cross-References

- ▶ Addiction
- ▶ Analgesics
- ▶ Dependence
- ▶ Diamorphine

Morphine-Like Compounds

► Mu-Opioid Agonists

Morphogenesis

► Ontogeny

Morris Water Maze

Synonyms

Morris water navigation task

Definition

The Morris water maze was developed by Richard Morris (Morris 1984) and is used to assess ► spatial learning in rats and mice. The apparatus comprises a pool of varying diameter, typically 1.2–2m (smaller for mice) and depth of approximately 60 cm which is filled with opaque water and contains a hidden platform. The animal is placed in the pool at different starting points and swims to the hidden platform (there are many variations of this to assess, e.g., ► working memory, daily learning, ► delayed match to sample). There are no intramaze cues and the dominant strategy in relocating the hidden platform is thought to be truly spatial. The main measure for the water maze is the latency to find the platform. In order to control for search strategies, other measures can be taken, including time spent in each quadrant during the main trials and probe trials (where the platform is removed), and analyses of the path length. The advantages of the Morris water maze are the rapid acquisition of the task, the ability to assess learning and performance, markers of motivation, and motor ability (e.g., swim speed), and the innate motivation of rats to want to find the platform without being distressed.

Cross-References

► Spatial Learning

References

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Morris Water Navigation Task

► Morris Water Maze

Mosaic

► Chimera

Mosapramine

Synonyms

Y-516

Definition

Mosapramine is a first-generation (typical) antipsychotic drug that belongs to the iminodibenzyl class approved in Japan for the treatment of schizophrenia. It is a potent dopamine antagonist with high affinity for D_2, D_3, and D_4 receptors, but lower affinity for 5-HT_{2A}-receptors. It can induce extrapyramidal motor side effects and drowsiness, but it displays generally low toxicity.

Cross-References

► Extrapyramidal Motor Side Effects
► First-Generation Antipsychotics
► Schizophrenia

Motivational Valence

► Taste Reactivity Test

Motor Activity and Stereotypy

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Synonyms

Exploratory behavior; Locomotor activity; Motor activity; Repetitious behavior; Repetitive behavior; Spontaneous activity; Stereotypy

Definition

Motor activity generally refers to a laboratory animal's horizontal movements within an enclosure that permits the use of a variety of methods for quantifying such

movements. The term is rarely used in the context of laboratory animals exercising in running wheels or on treadmills.

Stereotypy refers to abnormally repetitive behavior that reflects dysfunction of nervous system induced by drugs (especially those that elevate brain ▶ dopamine levels), brain lesions, genetic mutations, or environmental circumstances (e.g., wild animals in captivity). Depending on the context in which the term is used, stereotypy or stereotyped behavior may include specific features of locomotor activity (e.g., moving predominantly in the same direction along the inside perimeter of an enclosure) or may be restricted to repetitive behaviors that primarily occur in the absence of locomotion (e.g., rhythmic head movements, known as focused stereotypy; gnawing on the wire-mesh floor of a cage, known as oral stereotypy).

Impact of Psychoactive Drugs

The locomotor activity assay is one of the most frequently used procedures in the initial exploration of a drug's putative psychoactive effects. Typically, a mouse or rat is administered a fixed dose of a drug and is then placed in an enclosure with a flat floor large enough to enable free movement of several body lengths in any direction in the horizontal plane. A human observer or an instrument is used to quantify the distance an animal moves. Other species-typical rodent behaviors, such as grooming or rearing, may also be recorded depending on the objective of the research, the recording method, and other experimental conditions. Comparisons of a variety of techniques for measuring locomotor activity can be found in Fowler et al. (2001). The success of locomotor activity as a drug assay depends largely on the fact that most types of mice and rats spontaneously engage in "exploratory" behaviors, when placed in environments new to them. As it moves from place to place in the new environment, a mouse or rat uses its sensory organs and information processing endowments to learn the available species-relevant attributes of the environment. Importantly, the study of drug effects on spontaneously expressed behavior is economical because the experimenter does not need to impose any preconditions on the animals (e.g., neither food restriction nor explicit training in a specific task, etc.) in order to assure that easily measurable amounts of species-typical behavior will occur in placebo-treated animals ("controls"). The behavioral output of controls then affords a baseline condition with which the effects of drug treatments can be compared. Depending on type of drug, drug dose, amount of experience in the environment, amount of experience with the drug, duration of the observation period, route of drug administration, lighting conditions, time of day, and many additional variables, the drug treatment may increase, decrease, or have no effect on measures of locomotor activity compared to control performance. When interpreting the results of these kinds of experiments, one should keep in mind the fact that *a priori* suppositions about a drug's "stimulant" or "depressant" activity may not be confirmed in a straightforward manner. For example, the drug, ▶ pentobarbital, which in clinical terms is described as a "sedative-hypnotic," increases locomotor activity in rodents at low doses and decreases or abolishes locomotor activity at higher doses as an anesthestic dose level is neared. The ▶ psychomotor stimulant drug, d-amphetamine sulfate, also increases locomotor activity in rats at doses around 1.0 mg/kg, but at doses around 5.0 mg/kg of ▶ amphetamine produces a focused stereotypy syndrome characterized by the absence of locomotion and the concurrent expression of rapid rhythmic head movements. In research situations where *a priori* information about a drug is lacking, a relatively wide range of doses should be used in locomotor activity assays to detect lower-dose increases and higher-dose decreases in locomotor activity.

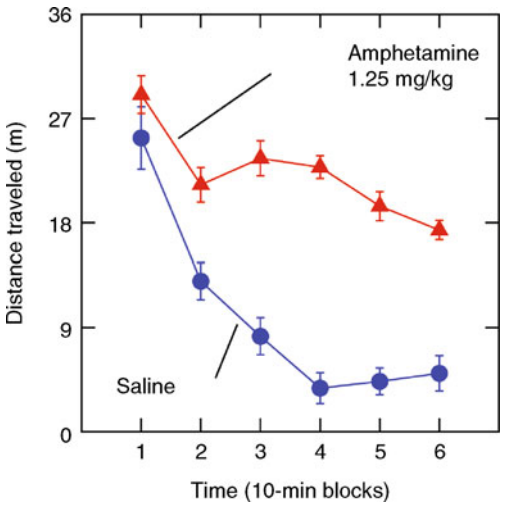
Amphetamine-Induced Locomotor Activity: Illustrative Data

Figure 1 provides data illustrating increased locomotor activity induced by amphetamine. The measure of locomotor activity was the ▶ distance traveled during six 10-min time blocks in a 1-h recording session. Distance traveled was calculated from the rats' center of force x–y coordinates as the rats moved on the 28 cm × 28 cm load plate of a ▶ force-plate actometer (Fowler et al 2001). The saline group exhibited rapid ▶ habituation during the first 40 min, and the distance traveled remained low for the remainder of the hour. Compared with the saline group, the amphetamine-treated rats showed significantly more locomotor activity at all but during the first 10-min interval, the standard errors of the mean (sem) overlapped. The curvature in the amphetamine plot between block 2 and block 6 is likely the result of changes in the brain level of amphetamine. Brain ▶ microdialysis studies have shown that intraperitoneally administered d-amphetamine sulfate reaches a peak level at about 22–26 min after injection and is eliminated with a half-life of about 40–45 min. During the sixth time block (see Fig. 1), the amphetamine group exhibited more distance traveled than the control group in every time block except the first, suggesting that amphetamine continued to induce abnormally high levels of locomotion 1 h after treatment. Given that the time-related diminution of locomotion in the control group is a representative example

of habituation, one can hypothesize that amphetamine, at least in part, produced elevated levels of locomotor activity by interfering with the habituation process. A well designed experiment with ► cocaine, a psychomotor stimulant with many pharmacological effects similar to those of amphetamine, supports this hypothesis (Carey et al. 2003). Thus, the increased locomotor activity induced by a variety of CNS-active drugs is not simply a "motor effect," because the multiple sites of action of such drugs reside in multiple anatomical loci that perform information processing, associative, and motivational functions, as well as motor functions.

Amphetamine-Induced Focused Stereotypy

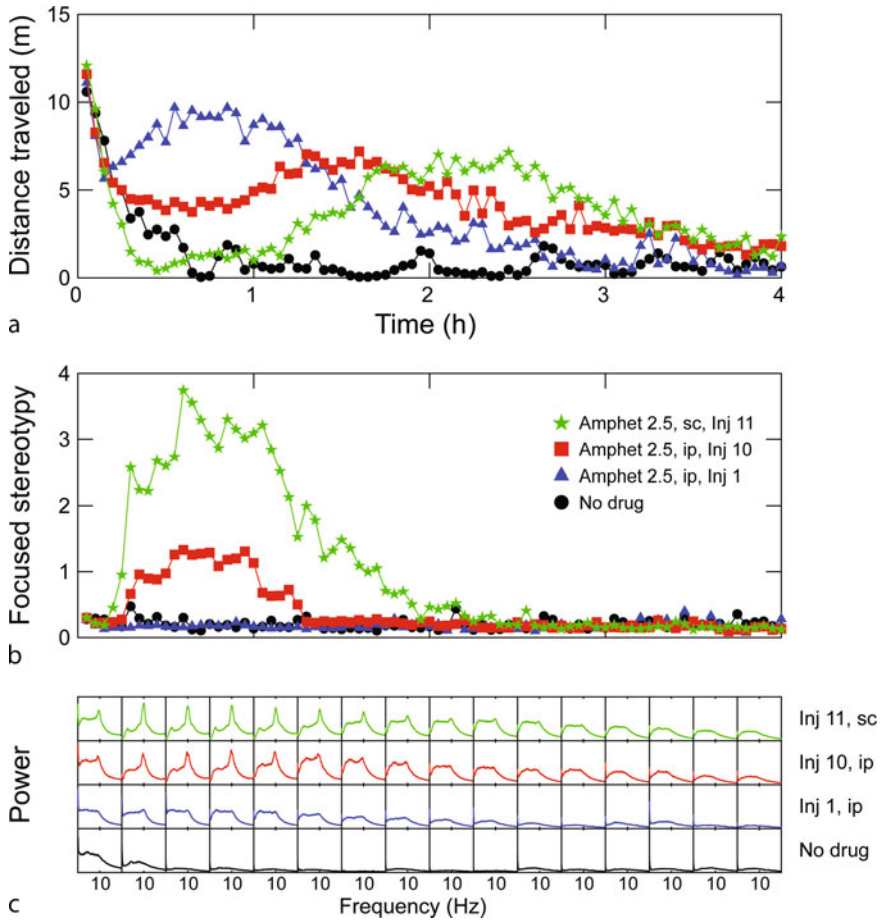
In male Sprague Dawley rats, the first experience with a 2.5 mg/kg, ip, dose of amphetamine will induce an increase in locomotor activity in a large majority of the subjects compared to the untreated controls (see Fig. 2).



Motor Activity and Stereotypy. Fig. 1. Effect of d-amphetamine sulfate on locomotor activity in two separate groups (n=8) of male Sprague Dawley rats. The amphetamine was injected intraperitoneally a few seconds before the rats were individually placed in a dark force-plate actometer for a 1-h recording session. Data are based on the rats' first exposures to the apparatus. The saline group exhibited habituation during the first 40 min, and distance traveled remained low for the remainder of the hour. Compared to the saline group, the amphetamine-treated rats showed hyperactivity throughout the hour. Over the entire hour the saline group mean distance traveled was 59.71 m (s.e.m. 7.23 m), and the amphetamine-treated group traveled 133.51 m (s.e.m. 6.59 m).

However, when given repeatedly, the same dose of amphetamine predominantly evokes, a syndrome characterized by an absence of locomotion accompanied by rapid head movements that have been described as "sniffing" and/or "head bobbing". This syndrome is focused stereotypy or the "stationary phase" of the amphetamine response, and it has been observed in observation arenas as large as 3.0 m × 3.5 m (Schiorring 1971).

The focused stereotypy score in Fig. 2 was calculated by combining a quantitative measure of spatial confinement with the variance of vertical force variation within the boundaries of the space used (see Fowler et al. 2007a for details). This score is low for a sleeping animal (high spatial confinement but low force variance because of a lack of "in-place" movements). The focused stereotypy score is also low when spatial confinement is low (movements are dispersed across the floor), despite the presence of high force variance associated with ambulation. When spatial confinement is pronounced and force variance is also high, a high focused stereotypy score is obtained. In Fig. 2, the switch from first-dose locomotor stimulation to tenth-dose substantial focused stereotypy (Fig. 2, panel b) can be appreciated by comparing the distance traveled data of Injection 1 (panel a, triangles) with the same measure for Injection 10 (panel a, squares), during the second 30 min of the session. Correspondingly, during the same time period, the focused stereotypy scores after Injection 1 were near zero, but averaged higher than 1 after Injection 10. This change in response topography from locomotion to stationarity and focused stereotypy is the result of a ► sensitization process, whereby rats become more sensitive to amphetamine or other psychomotor stimulants as repeated dosing ensues. After injection 10, distance traveled (see Fig. 2, panel a, squares) did not drop to no-drug levels because three rats did not make a complete switch to focused stereotypy and continued to display substantial locomotor activation. However, all but one of the eight rats after the tenth injection showed a *decrease* in distance traveled compared to Injection 1. The aberrant rat actually exhibited evidence of sensitization of locomotor response, as suggested by its 67.9% *increase* in distance traveled between injection 1 and 10. Two important points can be made from these observations: (1) Individual differences in response to drugs are to be expected, especially when genetically heterogenous outbred strains of rats are used, and (2) when amphetamine or similar drugs are under study, at doses near the threshold for expression of focused stereotypy, the observed behavioral effect may be in opposite directions, with a subset of rats showing increased locomotor activity and another subset exhibiting locomotor suppression.



Motor Activity and Stereotypy. Fig. 2. Measures from a force-plate actometer showing how the behavioral effects of d-amphetamine sulfate at 2.5 mg/kg depends on time after treatment, amount of experience with the drug, and the route of administration. After experiencing a 4-h habituation session (black circles, panels a and b), in subsequent sessions eight male Sprague Dawley rats received injections (Inj) of amphetamine eleven times, 3–4 days apart. The first ten injections were given ip, and the 11th injection (green stars) was administered sc in the same volume and dose as the previous ip injections. Panel (**a**) shows distance traveled for successive 3-min periods in the 4-h recording session. In panel (**b**) are plotted, also in 3-min intervals, group mean focused stereotypy scores for the indicated treatment conditions. Panel (**c**) shows the group mean power spectra of the vertical force variations over 15-min periods for the same treatments. The distinctive spectral peaks near 10-hz in the red and green power spectra reflect the rhythm of the head movements of focused stereotypy.

Another important point is that a univariate (i.e., single-dependent-variable method such as distance traveled) approach to behavioral pharmacology with ▶ indirect-acting dopamine agonists can easily lead to erroneous interpretations of a drug's effects. For example, if one did not have a stereotypy score (Figure 2, panel b) and relied only on the distance traveled information (Figure 2, panel a), one may erroneously conclude that, between Injection 1 and Injection 10, ▶ tolerance (decrease in distance traveled) had occurred instead of sensitization.

Effect of Route of Administration on Focused Stereotypy

An 11th injection of 2.5 mg/kg amphetamine was given, but this injection was by the subcutaneous route (sc). Figure 2 (panels a and b, stars) shows that changing the route of administration from ip to sc intensified and lengthened the expression of focused stereotypy. Gentry et al. (2004) also found more pronounced focused stereotypy for 3.0 mg/kg sc ▶ methamphetamine compared to the same dose given ip. The group mean increase in

focused stereotypy after the sc injection resulted from (1) a recruitment of the three previously low-stereotypy rats to full stereotypy and (2) all five rats that were already expressing focused stereotypy had higher scores after sc amphetamine treatment compared to the previous ip treatment with the same dose. ► Pharmacokinetic studies (Gentry et al. 2004) have shown that sc compared with ip amphetamine in male Sprague Dawley rats reaches a lower peak blood concentration, takes longer to reach its peak, and is eliminated more slowly (i.e., longer duration of action). Thus, the pharmacokinetic data indicating a longer duration of action for sc compared to ip administration of amphetamine are consistent with the behavioral data shown in Fig. 2 (in panels a and b, compare behavioral measures for injections 10 and 11). However, neither the reported pharmacokinetic time-to-peak nor peak level achieved is in accord with the behavioral data. In Fig. 2 (panel b), focused stereotypy scores began to rise earlier in the session for the sc injection than for the ip injection (opposite the pharmacokinetic later rise in concentration), and the sc-related focused stereotypy scores reached a substantially higher level than those seen for the ip injection (again, opposite the lower pharmacokinetic peak for sc dosing). While no explanation is yet available for this difference in the stereotypy-evoking efficacy of the ip and sc injection methods, the empirical data show that route of administration can substantially influence the focused-stereotypy-inducing effects of amphetamine.

Rhythmicity of Head Movements During Focused Stereotypy

During the expression of amphetamine-induced focused stereotypy, not only are the head movements observably repetitive they are also strongly rhythmic (Fowler et al. 2001; Fowler et al. 2007a). Application of signal processing techniques, such as ► power spectral analysis, to a rat's variations in vertical force recorded with a force-plate actometer shows that the head movements of focused stereotypy have a tightly regulated rhythm near 10 Hz (Hz=cycles/s). Panel c in Fig. 2 presents group mean power spectra that were calculated for each 15 min interval in the 4-h session. Once the expression of focused stereotypy begins in male Sprague Dawley rats, the near 10-Hz rhythm can be continuously sustained for an hour or more (see Fig. 2, panel c, top row of functions, frames 2, 3, 4, and 5 from left to right). The near 10-Hz rhythm has been recorded in rats separately treated with four different indirect-acting dopamine agonists: amphetamine, ► nomifensine, ► methylphenidate, and cocaine. The precision of rhythm regulation in rats expressing focused stereotypy rivals or exceeds that of consummatory licking (7.0 Hz), hindlimb scratching behind the ear (8.0 Hz), within-bout vibrissal whisking (e.g., 7.0 Hz), or grooming (forepaws/face/head: 7.2 Hz; flank-licking: 3.6 Hz). The existence of these species-typical rhythmic reflexes invite the conjecture that the head-movement rhythm of amphetamine focused stereotypy is also reflexive. Both the atypical ► antipsychotic drug, ► clozapine, and the α-1 noradrenergic antagonist, ► prazosin, have been shown to slow the head-movement rhythm of amphetamine-induced focused stereotypy without abolishing the overall syndrome (Fowler et al. 2007a). The frank ► rhythmicity of amphetamine-induced head movements adds a new measurable dimension to the focused stereotypy response, and experimental analyzes of rhythm production and modulation may provide insights into the neurotransmitter systems and neuroanatomical loci that mediate drug-induced stereotypy.

Locomotor Activity and Stereotypy in ► Drug Self-Administration Experiments

Measurements of locomotor activity and stereotypy in rodents have been used in drug-self-administration research in at least two different ways. One way exemplified by the work of Piazza et al. (1989), used the locomotor activity response to a novel environment (i.e., a 170-cm perimeter, 10-cm wide circular track with photobeams to detect the rats' locomotion) to analyze individual differences in rats' susceptibility to acquiring amphetamine self-administration later in another environment. Piazza et al. (1989) found that rats with a relatively low level of locomotor response to novelty did not acquire the amphetamine self-administration nose-poke response, while those rats exhibiting higher amount of locomotor activity acquired the response. This rodent-based experiment was one of the first to suggest that behavioral response to novelty and susceptibility to drug-abuse-like behaviors are correlated. A second way that locomotor activity and stereotypy have been combined with self-administration research is illustrated by an experiment that used a force-plate actometer as the floor of a self-administration chamber where five lever-presses by rats resulted in an intravenous cocaine infusion in a 24-h "binge" session (Fowler et al. 2007b). The work provided measures of rotational behavior ("circling in the same direction"), distance traveled, power spectra of the vertical force of movements (as in panel c of Fig. 2), and focused stereotypy in order to determine whether or not self-administered cocaine produced the same kind of unconditioned behaviors that are elicited by noncontingently administered bolus doses of cocaine. The results showed that all six

rats displayed behaviors typical of noncontingently administered ▶ bolus doses. The average duration of active cocaine intake was 14.7 h (±1.8 h). During this time, rats rotated in the same direction an average of 1206.5 (±372.7) times, traveled an average of 914.6 m (±65.9 m), and exhibited a power spectral peak near 10 Hz during 32.0% (±8.4%) of the active binge duration. These data show that locomotor activity and focused stereotypy are major behavioral manifestations of self-administered cocaine and raise the possibility that unconditioned behaviors evoked by indirect-acting dopamine agonists contribute to the reinforcing effects of psychomotor stimulant drugs.

Differences in Expression of Stimulant-Induced Behaviors in Rats and Mice

Although it is difficult to offer accurate generalizations that are valid for all strains of rats or mice, mice tend to move more than rats, and mice tend to have shallower locomotor activity habituation functions than rats. Response topographies of stimulant-induced stereotypies of rats and mice have similarities and differences. Generally, amphetamine and other indirect-acting dopamine agonists, in sufficient doses, evoke some degree of spatial confinement in both rats and mice. Also, after very high doses of these drugs, most types of laboratory rats and mice exhibit self-injury (usually biting the dorsal wrist area sufficiently to cause bleeding and exposure of subcutaneous structures). Despite these similarities, the topography of the focused stereotypies in rats and mice can be very different in appearance. For example, while rats exhibit a complete and enduring arrest of locomotion during focused stereotypy, mice tend to retain a substantial locomotor component in their stereotypy response. Typically, mice observed in force-plate actometers do not display the narrow-band head-movement rhythm, characteristic of the rat response to a 5.0 mg/kg dose of amphetamine. Different stereotypy topographies in mice and rats make it difficult if not impossible to devise a rating scale that can be used to quantify stereotypies equally well in both species. Comparing stereotypies in rats and mice is further hindered by the heterogeneity among inbred strains of mice in their responses to amphetamine and other psychomotor stimulants. For example, BALB/cJ mice show a low-dose *decrease* in their locomotor activity response to 1.0 mg/kg amphetamine, and at a higher dose of 10.0 mg/kg, BALB/cJ mice exhibit vertical leaping ("popping") behavior. C57BL/6J, DBA/2J, 129SvJ, and C3H/HeJ mice exhibit neither low-dose suppression of locomotor activity nor higher-dose vertical leaping behavior.

Neurobehavioral Interpretations and Clinical Importance of Stereotypy

Stereotyped behaviors are generally thought to reflect the dysfunction of the central nervous system (Robbins et al. 1990; Teitelbaum et al. 1990). Persons with mental retardation, autism, schizophrenia, Tourette's syndrome, Huntington's disease, or obsessive compulsive disorder (OCD) often exhibit excessively repetitious and apparently purposeless behaviors as do persons who have used excessive amounts of amphetamine over multi-day periods. Substantial clinical and experimental evidence points to ▶ dopamine as the brain neurotransmitter with a major role in the expression of stereotyped behavior in the aforementioned clinical abnormalities. In rodent studies of the behavioral effects of psychomotor stimulants, links have been established between dopaminergically innervated subcortical structures and expression of increased locomotor activation and stereotypy induction. Dopamine agonists are thought to induce locomotor activity by acting on the ▶ nucleus accumbens, while actions of the drugs on the caudate/putamen are believed to be critical for the expression of focused stereotypy. In the clinic, dopamine receptor-blocking drugs (e.g., the antipsychotic drug ▶ haloperidol) can be effective in suppressing the spontaneously occurring stereotypies, such as hand flapping, in persons with autism. In the laboratory, most, but not all, antipsychotic drugs can block the expression of amphetamine-induced focused stereotypy. Although a massive amount of empirical evidence implicates a role for dopamine in the evocation of locomotor activity and the expression of stereotyped behavior, much remains to be discovered about dopamine's interaction with a multiplicity of other neurotransmitters (e.g., glutamate, GABA, acetylcholine, serotonin, neuropeptides) and their receptors in the nucleus accumbens, caudate/putamen, and elsewhere in the brain. Given the large number of drug targets located in these brain regions, the measurement of pharmacologically induced locomotor activity and stereotypy is likely to continue to be important in the conduct of psychopharmacology research for many decades to come.

Acknowledgment

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Cross-References

▶ Aminergic Hypotheses for Schizophrenia
▶ Antipsychotic Drugs
▶ Cocaine
▶ Habituation

- ► Methylphenidate and Related Compounds
- ► Open Field Test
- ► Phenotyping of Behavioral Characteristics
- ► Psychomotor Stimulants
- ► Self-Administration of Drugs
- ► Sensitization to Drugs

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Motor Activity: Repetitious Behavior

- ► Motor Activity and Stereotypy

Motor Inhibition

- ► Behavioral Inhibition

Motor Learning

- ► Verbal and Non-Verbal Learning in Humans

Motor Memory

Definition

A motor memory develops by repetition of movements that the individual is already able to perform. Repetition is supposed to improve motor skills and to enhance some degree of automation. Presumably, long term potentiation is involved in the induction of a motor memory.

Movement Disorder

- ► Tic Disorders with Childhood Onset
- ► Tics

Movement Disorders Induced by Medications

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Synonyms

Antipsychotic-induced movement disorders; drug-induced motor syndromes; EPS; Extrapyramidal side effects

Definition

Discussion of medication-induced movement disorder generally refers to the side effects of ► antipsychotic medication which affect motor behavior. However, other drugs, such as lithium, valproate, antidepressants, and psychostimulants like amphetamine, can cause movement problems, principally tremor. Patients developing antipsychotic drug-induced movement disorders exhibit a range of neurological phenomena: ► dyskinesia, ► dystonia, parkinsonian features including bradykinesia, tremor and rigidity, and restless movements as part of antipsychotic-induced akathisia. While some motor syndromes such as parkinsonism, acute dystonia, and acute akathisia are more common during acute drug treatment, others

such as tardive dyskinesia, tardive dystonia, and chronic akathisia are more common with long-term treatment. The motor phenomena exhibited by those developing these disorders can cause functional impairment and be socially stigmatizing; and parkinsonism, akathisia, and dystonia also have mental manifestations that can be unpleasant and distressing (Owens 1999). Further, the disorders can confound clinical assessment of the psychotic illness. For example, features of parkinsonism such as bradykinesia overlap phenomenologically with symptoms of depression and negative symptoms, while akathisia may be misdiagnosed as anxiety or an exacerbation of psychotic symptoms.

Role of Pharmacotherapy

The four main diagnostic categories of ► extrapyramidal side effects (EPS) associated with antipsychotic medication are ► parkinsonism, ► akathisia, ► dystonia, and ► tardive dyskinesia. The pathophysiology of these movement disorders involves the dopamine D2 receptor-blocking properties of antipsychotic drugs. However, it should be noted that both parkinsonism and dyskinesia are observed in antipsychotic-naive patients with first-episode psychoses, suggesting that such movements reflect a neuro-dysfunction intrinsic to the pathophysiology of schizophrenia (Pappa and Dazzan 2009). While EPS were relatively common with the ► first-generation antipsychotics (FGAs: such as chlorpromazine, fluphenazine, haloperidol, and trifluoperazine), one of the main claims for ► second-generation antipsychotics (SGAs: such as aripiprazole, clozapine, olanzapine, quetiapine, and risperidone) has been a lower risk of developing such disorders, although the individual SGAs vary in their liability for EPS burden. Clinical trials and ► meta-analyses (Leucht et al. 2003) suggest that while SGAs have a lower liability for acute EPS and tardive dyskinesia when compared with haloperidol, even at low dosage, the evidence that this is the case in relation to other FGAs in moderate dosage is less convincing. Further, the common use of high dose or combined SGAs, or combined SGAs and FGAs, in clinical practice may compromise any such advantage. Parkinsonism and akathisia remain major problems despite the widespread use of SGAs. With regard to tardive dyskinesia, the evidence suggests a lower risk with SGAs (Correll and Schenk 2008), but prospective, longitudinal studies of SGAs as monotherapy are required to quantify the risks of tardive dyskinesia with particular drugs.

Parkinsonism

Antipsychotic-induced parkinsonism (sometimes called "pseudoparkinsonism") usually occurs within days of beginning antipsychotic treatment or after a dosage increase. It comprises a triad of bradykinesia, rigidity, and tremor. Bradykinesia is probably the core feature, and manifests itself as difficulty with the initiation of movements and slowness and interruption of the normal flow of movement. When tested by passive movement of the limbs, muscle rigidity may be revealed as being of the lead-pipe (i.e., stiffness that is uniform throughout the range of movement) or cogwheel (i.e., a ratchet-like resistance) type. Other clinical signs include a mask-like expression, lack of spontaneous gesture, and a reduction in the normal arm swing when walking. Subjectively, patients experience slowed thinking ("bradyphrenia"), fatigue, weakness and stiffness, and sometimes apathy, and diminished interest and initiative. There is some evidence that the development of parkinsonism may indicate an increased risk of developing tardive dyskinesia later.

While drug-induced parkinsonism mimics idiopathic ► Parkinson's disease, it is rather more an akinetic rigid syndrome, with the classical resting tremor being relatively uncommon. Nevertheless, the coincidental onset of idiopathic Parkinson's disease should be borne in mind as a differential diagnosis, and if this is suspected because of the nature of the clinical presentation, or because the signs and symptoms prove to be persistent after antipsychotic discontinuation, a neurology referral may be indicated.

Treatment options include reduction of the dose of the causal, or suspected, antipsychotic, or switching to another with evidence for a lower risk of parkinsonism. Prescription of an ► antimuscarinic agent (also called ► anticholinergic or antiparkinsonian) may be useful (Barnes and McPhillips 1996). The anticholinergic agents most commonly used are as follows:

► Benzatropine (benztropine) mesylate –0.5–6 mg/day by mouth in one to two divided doses; can be sedative so if one dose is greater, administered at bedtime. Tablets are not available in the United Kingdom.

► Trihexyphenidyl hydrochloride (benzhexol hydrochloride) –1–2 mg daily, increased gradually; usual maintenance dose 5–15 mg daily in three to four divided doses, to a maximum of 20 mg daily.

► Orphenadrine hydrochloride –150 mg a day by mouth in divided doses initially, titrated slowly upwards if necessary. Usual dose range is 150–300 mg daily in divided doses.

► Procyclidine hydrochloride –2.5–5 mg by mouth up to three times a day initially, titrated slowly upwards if necessary. Usual maximum is 30 mg a day in divided doses.

Biperiden –2 mg by mouth, one to two times a day.

Anticholinergic drug prescription should be regularly reviewed, partly because parkinsonism can wane

spontaneously, and after 3 months or so there may no longer be a need for such treatment, and partly because antimuscarinic drugs are associated with their own unwanted effects such as blurred vision, headaches, dry mouth, increased heart rate, difficulty in urinating and constipation, as well as confusion and disorientation, inability to concentrate, and memory impairment. The elderly are at greater risk of anticholinergic side effects.

Akathisia

► Akathisia is characterized by a subjective feeling of inner restlessness and objectively by increased restless movement (Barnes 1992). These movements are not dyskinetic (involuntary, repetitive movements) but rather resemble normal patterns of restless movement. Most typically, they involve the legs, for example, walking on the spot, pacing around, or shuffling and tramping of the legs when sitting. When required to sit or stand still, patients can experience a mounting sense of tension and a compulsive desire to move in an attempt to gain some respite. The clinical significance of akathisia relates not only to the subjective dysphoria and unease experienced, but also its adverse influence on medication adherence, and its status, like parkinsonism, as a possible risk factor for tardive dyskinesia.

Treatment options include reduction of the dose of the causal antipsychotic, or switching to another with evidence for a lower risk of akathisia. Low-dose ► propranolol (initially 20 mg bd) or other lipophilic beta-blockers, an anticholinergic drug (e.g., procyclidine, see above), or a ► benzodiazepine (e.g., diazepam 2–4 mg tds) may be helpful. The evidence base for such interventions is limited, though strongest for propranolol or other lipophilic beta-blockers (Miller and Fleischhacker 2000). Note that the beta-blockers are contraindicated in those with asthma or peripheral vascular disease. Taylor et al. (2007) also cite evidence for a possible reduction in symptoms with low-dose ► clonazepam, diphenhydramine (an antihistamine), and $5HT_2$ antagonists such as cyproheptadine, ► mirtazapine, ► trazodone, and ► mianserin.

Dystonia

► Dystonia is defined as sustained muscle contractions causing twisting and repetitive movements or abnormal postures, which can be painful. Acute dystonia usually occurs early in drug treatment and is short-lived, although it can be distressing and frightening. It can also occur as an antipsychotic drug-withdrawal phenomenon. Tardive dystonia occurs late in the treatment, tends to be persistent, and in severe cases can be disabling and disfiguring. The neck, and jaw and tongue are the most common sites to be affected by the muscle spasms, but trunk and limbs can also be involved.

With regard to *treatment options for acute dystonia*, the intervention of choice is an anticholinergic drug (Barnes and McPhillips 1996), for example, procyclidine (see above for oral administration if symptoms are mild. Also by intramuscular or intravenous injection as an emergency treatment for acute drug-induced dystonia, 5–10 mg), benzatropine (see above for oral administration if symptoms are mild, but this drug may also be given intramuscularly or even intravenously as an emergency treatment for acute drug-induced dystonia: 1–2 mg repeated if symptoms reappear, to a maximum of 6 mg daily), orphenadrine (see above for oral administration if symptoms are mild), or trihexyphenidyl hydrochloride (see above for oral administration). Patients may be given an oral antimuscarinic drug to take prn ("as required") should there be any signs of recurrence within the next few days. Other drug treatments advocated include antihistamines, such as diphenhydramine and benzodiazepines, such as ► diazepam (Owens 1999).

With regard to *treatment options for tardive dystonia*, clinicians should first consider the differential diagnosis, including ► idiopathic torsion dystonia or secondary dystonia associated with conditions such as ► Huntington's disease or Wilson's disease. Further, there is some overlap with the features of tardive dyskinesia, with which tardive dystonia may coexist. The most common phenomena are sustained, forced, involuntary closing of the eyelids (blepharospasm), twisting of the neck to one side (torticollis) or drawing the head back (retrocollis), and involvement of the laryngeal and pharyngeal muscles affecting speech and swallowing.

The condition can be hard to treat. Withdrawal of antipsychotic medication is not usually a realistic clinical option for people with an established psychotic illness. Switching to an antipsychotic with a lower liability for EPS may be helpful in a proportion of cases over time, and the best evidence is for clozapine. There are also several specific drug treatments that may be beneficial:

Dopamine-depleting agents (► tetrabenazine, ► reserpine) are used in low dose, and have a reasonable evidence base to support their efficacy. They have a range of potentially unpleasant side effects including drowsiness, parkinsonism, depression, and orthostatic hypotension, although tetrabenazine has a lower side-effect burden than reserpine.

There is evidence for benefit with anticholinergic agents, sometimes in high dosage, although the relevant studies have yielded mixed results, and use of these drugs runs the risk of exacerbating any co-existing tardive dyskinesia.

Benzodiazepines (such as clonazepam), which have muscle relaxant properties, are also commonly used.

For focal tardive dystonia which has not responded to standard measures, local injection of botulinum A toxin into the affected muscle by a neurologist with experience of the technique may be effective.

Tardive Dyskinesia

► Tardive dyskinesia is a syndrome of abnormal involuntary movements, repetitive and stereotypic in nature and commonly referred to as choreiform (i.e., rapid, jerky). The condition usually appears late in the course of treatment, and is partly related to advancing age and possibly the psychotic illness for which the antipsychotic medication is prescribed. Tardive dyskinesia most commonly affects the oro-facial muscles; characteristically a combination of movements is observed, including chewing, tongue twisting and protrusion, and lip smacking and puckering. But virtually all parts of the body can be involved including the trunk and limbs, and respiratory muscles. The condition is most pronounced when patients are aroused and tends to ease during states of relaxation. The abnormal involuntary movements of tardive dyskinesia can result in considerable social and physical disability, although patients are usually unaware of them.

Treatment options include reducing the dosage of the antipsychotic or switching to an SGA with evidence for a low liability for tardive dyskinesia, particularly if the patient has been receiving an FGA. Limited data from small studies do not provide convincing evidence of the value of these approaches (Soares-Weiser and Rathbone 2005), but clozapine is probably the antipsychotic most likely to diminish dyskinetic movements in patients with existing tardive dyskinesia. Discontinuing antimuscarinic agents may also be a worthwhile therapeutic option, given the evidence that such drugs can worsen tardive dyskinesia, but the available evidence does not allow for any confident statement on the likely effects of such a strategy.

A range of other potential anti-dyskinetics have been tested (Owens 1999; Taylor et al. 2007), including dopamine depleters (e.g., tetrabenazine, reserpine, oxypertine), cholinomimetic agents (e.g., choline, lecithin, deanol), GABA agonists (e.g., sodium ► valproate, gamma-vinyl GABA), calcium channel blockers (e.g., diltiazem, verapamil), and vitamin E (alpha-tocopherol). But none has the strength of evidence for efficacy or data on adverse effects that would allow for a clinical recommendation as a treatment for tardive dyskinesia (Soares and McGrath 1999).

Cross-References

► Anticholinergic/Antimuscarinic Agents
► Antipsychotic Drugs
► Extrapyramidal side effects
► First Generation Antipsychotics

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m-PD

► Meta-Phenylenediamine

mPFC

► Medial Prefrontal Cortex

MR Image Analysis

Definition

Unlike, for example, X-ray or computer tomography (CT), MR images usually do not provide absolute values of MR contrast parameters, as such measurements are

accompanied with long acquisition times that are not acceptable in clinical applications. For this reason, MR quantification is mostly based on relative measurements in comparison to a defined reference such as baseline data acquired under normal or resting conditions, or data derived from a healthy control group.

In functional MRI, small and relative signal changes caused by the hemodynamic response to changes in neuronal activity are assessed. Sophisticated analysis methods are essential to detect these small changes ranging from approaches that incorporate prior knowledge from the stimulation paradigm applied to solely data-driven or exploratory methods.

Cross-References

► Functional MRI
► Stimulation Paradigm

mRNA Splice Variants

► Alternative Splicing

MSI

► Imaging Mass Spectrometry

Multibarrel Micropipette

Definition

An assembly of glass micropipettes usually fused together and terminating in a common tip; used for the concomitant recording of neuronal activity and the application of transmitters, drugs or other compounds of interest.

Multi-Infarct Dementia

► Vascular Dementia

Multimeric Protein Complex

Definition

A complex formed by several proteins.

Multiple-Unit Spiking Activity

► Multiunit Activity

Multiunit Activity

Synonyms

Multiple-unit spiking activity

Definition

The electrophysiologically recorded multiunit activity (MUA) is thought to represent the average spiking of small neuronal populations close to the vicinity of the placed microelectrode. It is obtained by band-pass filtering the recorded signal in a frequency range of 400 to a few thousand Hz.

Cross-References

► Magnetic Resonance Imaging (Functional)

Mu-Opioid Agonists

Synonyms

Morphine-like compounds; Opioid analgesics

Definition

These are drugs acting selectively on the mu receptors of the endogenous ► opioid system. Examples are ► morphine, ► fentanyl, and sufentanil.

Cross-References

► Endogenous Opioids
► Opioids

Murungu

► Khat

MUS

► Somatoform and Body Dysmorphic Disorders

Muscarine

Definition

A poisonous substance that is found in certain types of mushrooms. The substance mimics the actions of ► acetylcholine at muscarinic acetylcholine receptors.

Muscarinic Agonists

► Muscarinic Cholinergic Receptor Agonists and Antagonists

Muscarinic Antagonists

► Muscarinic Cholinergic Receptor Agonists and Antagonists
► Scopolamine

Muscarinic Cholinergic Receptor Agonists and Antagonists

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Synonyms

Muscarinic agonists; Muscarinic antagonists

Definition

Muscarinic acetylcholine receptors represent one of the two classes of receptors that mediate the actions of acetylcholine in the nervous system and certain body parts. Muscarinic acetylcholine receptors were so named owing to their greater sensitivity to ► muscarine over ► nicotine. Muscarinic agonists activate and antagonists block, muscarinic acetylcholine receptors at an orthosteric or ► allosteric site.

Pharmacological Properties

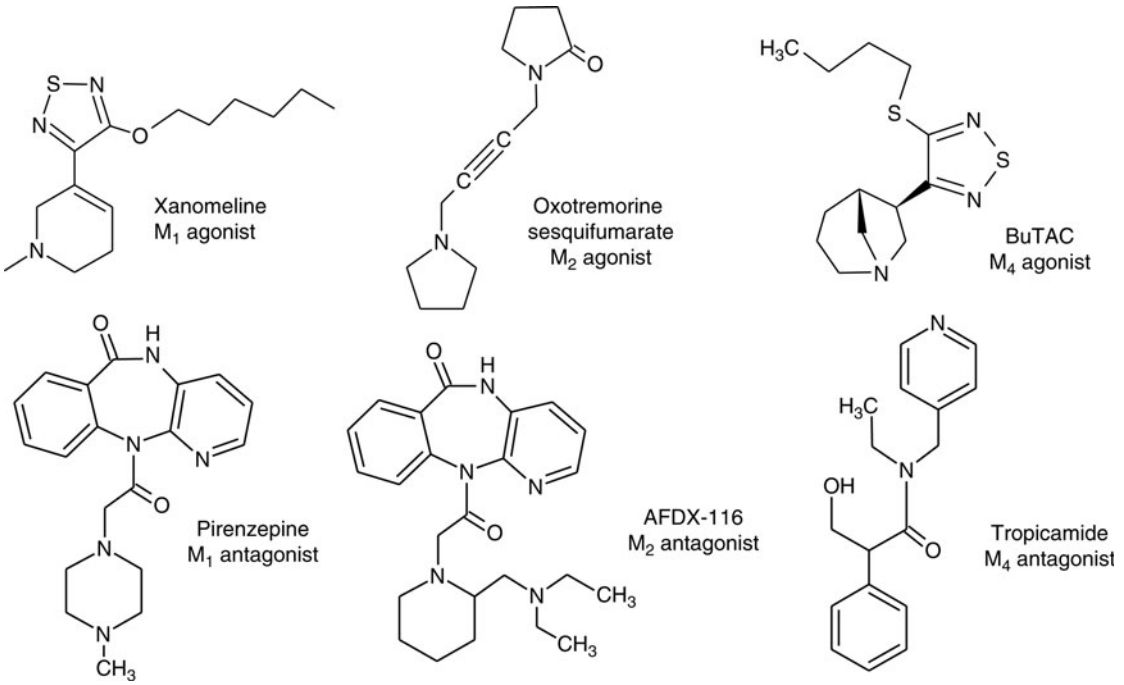
Muscarinic cholinergic receptors are ► G-protein coupled receptors that are ubiquitously expressed in the central nervous system. There are different muscarinic receptor subtypes referred to as M_1–M_5, when a receptor subtype is described based on pharmacology, and m_1–m_5, when based on their molecular properties. The M_1, M_3, and M_5 muscarinic receptor subtypes are coupled with G_q proteins resulting in the mobilization of intracellular calcium. The M_2 and M_4 muscarinic receptor subtypes are linked to G_o proteins with the activation of these receptors producing a decrease of intracellular cyclic AMP. Antibodies specific to the muscarinic acetylcholine receptor proteins indicate that the m_1, m_2, and m_4 receptors are most abundant in the brain (Levey et al. 1991). The m_1 receptor is most concentrated in the neocortex, ► hippocampus, ► striatum, and ► amygdala. These receptors are found to be postsynaptic. The m_2 receptor is most abundant in the basal forebrain, thalamus, neocortex, and striatum. These receptors are located on cholinergic terminals and are also located postsynaptically. The m_4 receptor has its highest density in the striatum and hippocampus. These receptors are found postsynaptically, as well as presynaptically, on cholinergic neurons. The m_3 and m_5 receptors are sparser in the brain, with the m_3 receptor being the most common in the neocortex, thalamus, and hippocampus, while the highest density of m_5 receptors is located in the substantia nigra. It appears that these receptors are present postsynaptically.

The identification of different muscarinic receptor subtypes has led to interest in developing muscarinic agonists and antagonists that target a specific type of muscarinic receptor. The development of selective receptor subtype compounds arises in part to understand the function(s) of muscarinic acetylcholine receptor subtypes. This work has been carried out predominantly in animal models. Interest in the development of drugs that target specific muscarinic receptors has also emerged because various neurodegenerative and psychiatric disorders have shown alterations in specific muscarinic acetylcholine receptor subtypes.

The effects of muscarinic agonists and antagonists that prefer one type of muscarinic acetylcholine receptor to the other subtypes are described in the following text. The focus is on M_1, M_2, and M_4-preferring drugs because most compounds developed preferentially act at these muscarinic receptor subtypes (see Fig. 1).

M_1 Muscarinic Receptor-Preferring Drugs

There has been considerable effort in the development of pharmacological agents that selectively act at the M_1 muscarinic acetylcholine receptor, in particular M_1 muscarinic agonists. This is, in large part, because of studies indicating that M_1 muscarinic acetylcholine receptors are altered in ► Alzheimer's disease and ► schizophrenia (Langmead et al. 2008). Both of these conditions are marked by cognitive deficits and thus there has been an



Muscarinic Cholinergic Receptor Agonists and Antagonists. Fig. 1. Chemical structures of muscarinic M_1, M_2 and M_4 agonists and antagonists.

interest in developing selective M_1 muscarinic agonists to alleviate the cognitive deficits in these conditions. A recent double-blind placebo-control study using xanomeline, a muscarinic M1-preferring agonist, in schizophrenic patients showed significant improvement in overall positive and negative symptom ratings, along with enhanced verbal learning with only mild side effects (Shekhar et al. 2008). Several M_1 muscarinic-preferring agonists have been developed, which have shown learning and memory benefits in animal models, but overall, have not fared as well in clinical trials (Langmead et al. 2008). This is likely due to the lack of high selectivity for the M_1 muscarinic acetylcholine receptor leading to the activation of other muscarinic receptor subtypes and unwanted side effects, e.g., nausea, diarrhea, sweating, and salivation.

Some of the strongest evidence suggesting that M_1 muscarinic receptors support learning and memory comes from experiments examining the effects of M_1 muscarinic-preferring antagonists in animal models. For example, systemic administration of M_1-preferring receptor antagonist, dicyclomine impairs both learning and memory in a variety of behavioral paradigms. Infusions of the M_1-preferring antagonist pirenzepine into specific brain regions of the rodent impair learning or memory (Tzavos et al. 2004). Taken together, several experiments indicate that the blockade of M_1 muscarinic acetylcholine receptors in various brain areas impairs learning and memory indicating that M_1 muscarinic acetylcholine receptors may support several forms of learning and memory.

A main limitation of compounds such as pirenzepine and dicylomine is that they do not exhibit a strong selectivity for M_1 muscarinic receptors compared to the other muscarinic receptor subtypes. Another approach to studying muscarinic receptor activity is through the use of snake toxins that bind to specific muscarinic receptor subtypes. Muscarinic-toxin 7 (MT-7) is one such compound that exhibits greater selectivity for the M_1 muscarinic receptor over other subtypes. Because MT-7 acts as a more selective M_1 muscarinic receptor antagonist compared to that of pirenzepine and dicyclomine, it has been used to study the role of M_1 muscarinic receptors in learning. A recent experiment demonstrated that injections of MT-7 into the rodent dorsomedial striatum does not affect the initial learning of a spatial discrimination, but specifically impairs spatial reversal learning (McCool et al. 2008). Thus, the results from the blockade of M_1 muscarinic receptors indicate that this muscarinic receptor subtype is important for learning, memory, and behavioral flexibility.

Consistent with numerous studies demonstrating that compounds which preferentially block M_1 muscarinic receptors impair learning and memory, treatment with M_1 muscarinic-preferring agonists have shown to facilitate learning and memory. The drug, McN-A-343, is often considered to be a M_1 muscarinic-preferring agonist. Although there is limited muscarinic receptor subtype selectivity for this drug, there is evidence that the drug enhances spatial working memory.

There are several M_1 muscarinic agonists that have been reported to have cognitive benefits in preclinical tests. Furthermore, the activation of M_1 muscarinic acetylcholine receptors may have neuroprotective effects by reducing the amyloid-beta peptide and tau protein associated with plaques and neurofibrillary tangles, respectively. However, M1-preferring agonists have failed or led to significant side effects in clinical trials. Xanolemine, talsaclidine, and WAY 132983 are all examples of compounds that have shown to have pro-cognitive benefits but led to unwanted side effects. The limitations of these drugs that act at the ► orthosteric site of the M_1 muscarinic acetylcholine receptor, likely results because these agents do not display a strong selectivity for the M_1 muscarinic acetylcholine receptor compared to the other muscarinic receptor subtypes.

A new generation of M_1 muscarinic agonists are being developed that act at the allosteric site of the M_1 muscarinic acetylcholine receptor (Langmead et al. 2008). These newer compounds hold further promise for clinical effectiveness because the allosteric binding site for agonists does not seem conserved among the other muscarinic acetylcholine receptor subytpes. Thus, the development of selective allosteric agonists at the M_1 receptor site may be effective in reducing cognitive deficits while minimizing unwanted side effects.

M_2 Muscarinic Receptor-Preferring Drugs

Another pharmacological approach to modify brain cholinergic activity has been through M_2 muscarinic acetylcholine receptors. Some M_2 muscarinic acetylcholine receptors are found to be heteroreceptors in different brain regions. However, many M_2 receptors act as autoreceptors providing negative feedback at cholinergic terminals. The localization of M_2 muscarinic acetylcholine receptors on cholinergic neuron terminals has led to the examination of M_2-preferring antagonists on brain acetylcholine activity and cognitive function. In particular, M_2-preferring antagonists enhance brain acetylcholine efflux as measured by *in vivo* ► microdialysis (Ragozzino et al. 2009). Furthermore, the administration of M_2-preferring antagonists such as SCH 72788, BIBN99, AF-DX 116, or methoctramine given either systemically or centrally improve memory ► consolidation, as well as ► working memory on a variety of tasks (Lazaris et al. 2003). To provide more direct evidence that changes in acetylcholine output are related to learning, a study demonstrated that the infusion of the M_2-preferring agonist, oxotremorine sesquifumarate, into the dorsomedial striatum simultaneously blocked a behaviorally induced increase in striatal acetylcholine output and impaired reversal learning. These effects were reversed by the M_2-preferring antagonist, AF-DX 116. Thus, the blockade of M_2 muscarinic acetylcholine receptors can provide a mechanism for modulating brain acetylcholine release and cognitive functioning (Ragozzino et al. 2009).

The clinical use of M_2 muscarinic acetylcholine receptor antagonists is suggested in diseases involving cholinergic degeneration and cognitive impairment, such as ► Alzheimer's disease (Langmead et al. 2008). A number of compounds have been developed that exhibit significant selectivity for the M_2 muscarinic acetylcholine receptor. One of the serious drawbacks about using a M_2 muscarinic antagonist as a drug therapy is that M_2 muscarinic receptors are located in the heart where they slow heart rate. Thus, treatment with a M_2 muscarinic antagonist can lead to tachycardia.

M_4 Muscarinic Receptor-Preferring Drugs

The M_4 muscarinic acetylcholine receptor is another muscarinic acetylcholine receptor subtype in which there is significant interest in developing selective agents to generate novel treatments for both ► schizophrenia and ► Parkinson's disease. Despite interest in the M_4 muscarinic acetylcholine receptor, there are a relative lack of compounds that are highly selective for this muscarinic receptor subtype. Comparable to developing new targets for the M_1 muscarinic receptor, the development of positive allosteric modulators for the M_4 muscarinic receptor holds promise in generating novel treatments for various disorders and diseases.

Interest in the M_4 muscarinic acetylcholine receptor related to schizophrenia has evolved from findings indicating hyperactivity of the neurotransmitter dopamine in the striatum is observed in schizophrenia (Langmead et al. 2008). Moreover, the activation of M_4 muscarinic acetylcholine receptors may inhibit striatal dopamine efflux. PTAC and BuTAC are two compounds that are M_4-preferring agonists. These drugs have shown to reduce apomorphine-induced ► prepulse inhibition (Jones et al. 2005), a paradigm commonly used to screen the effectiveness of antipsychotic drugs. As with many other muscarinic agonists, these drugs do not display a strong selectivity for the M_4 muscarinic acetylcholine receptor (Langmead et al.

2008). Therefore, there is a real possibility of producing unwanted side effects with such treatments.

Interest in the M_4 muscarinic acetylcholine receptor related to ► Parkinson's disease is also related to dopaminergic–cholinergic interactions in the striatum. Owing to the reduced striatal dopamine activity in Parkinson's disease, treatment with a M_4 muscarinic acetylcholine receptor antagonist may have benefits in enhancing dopaminergic transmission and reducing symptoms in the disease. In support of that idea, tropicamide, a muscarinic acetylcholine receptor antagonist with moderate binding selectivity for the M_4 muscarinic acetylcholine receptor subtype, suppresses tremulous jaw movements in rats, a model of Parkinson's disease, without significant impairment on memory tasks (Betz et al. 2007). Several other compounds that have a high affinity for the M_4 muscarinic acetylcholine receptor and show selectivity over other muscarinic acetylcholine receptor subtypes may prove beneficial in the treatment of Parkinson's disease (Böhme et al. 2002).

Conclusions

Muscarinic acetylcholine receptors are found throughout the central nervous system. There are various neurodegenerative disorders, as well as psychiatric disorders that exhibit abnormalities in muscarinic acetylcholine receptor function. These various diseases and disorders often exhibit altered muscarinic acetylcholine receptor function for specific muscarinic receptor subtypes. Thus, the development of compounds that are selective for the different muscarinic receptor subtypes provides an opportunity for novel treatments that can reduce severe impairments in cognitive or motor functioning.

Cross-References

► Allosteric Site
► Alzheimer's Disease
► Long-Term Potentiation
► Muscarine
► Orthosteric Site
► Parkinson's Disease
► Pre-pulse Inhibition
► Schizophrenia

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M

Muscarinic Receptors

Synonyms

mAChR

Definition

► G-protein-coupled acetylcholine receptors found in the plasma membranes of certain neurons and other cells. They play several roles, including acting as the main end receptor stimulated by acetylcholine released from postganglionic fibers in the parasympathetic nervous system.

Mutant

► Transgenic Organism

Mutant Animal

► Genetically Modified Animals

Myelination

Definition

A process by which axonal trees of major projection neurons (i.e., neurons that project to distant brain regions) are sheathed in myelin, a fatty membrane produced by surrounding neuroglial cells. This myelin sheathing insulates the propagation of action-potentials, the electrical signals that convey information from the cell body to the axonal synaptic terminals, from nonspecific dissipation in the neuropil. Myelin sheathing reduces the energy requirements while increasing the speed of long-range information relays in the brain.

N

NAcc

► Nucleus Accumbens

nAChR

► Nicotinic Receptor

NAD

► Nicotinamide Adenine Dinucleotide

Nafion

Definition

A perfluronated ion exchange resin that allows the passage of cations (such as biogenic amines) and precludes the passage of anions (such as metabolites of biogenic amines and ascorbic acid).

Naloxone

Definition

Naloxone is one of the best-known opioid receptor antagonists that shows high affinity for ► μ-opioid receptors in the CNS and as result of blockade of these receptors often produces rapid onset of withdrawal symptoms in opiate-dependent subjects. Naloxone also blocks with a lower affinity, at κ- and δ-opioid receptors. It is used clinically to counteract the effects of opioid overdose, for example, heroin or morphine overdose, where it is most commonly injected intravenously.

Cross-References

► Naltrexone
► Opioid Antagonist

Naltrexone

Synonyms

ReVia; Vivitrol (injectable)

Definition

Naltrexone is an ► opioid receptor antagonist and is known to bind to all three opioid receptors (mu, delta, kappa) as a function of the dose administered. Approved in oral form (ReVia®) in 1994 for the treatment of alcohol dependence, naltrexone appears most effective in reducing heavy drinking and is believed to act by blocking some of the reinforcing properties of ► alcohol. Problems with compliance led to the development of a long-acting (30 days) injectable form of naltrexone (Vivitrol®), approved in 2006.

Nanospray

► Electrospray Ionization

Narcolepsy

Definition

A chronic disorder of sleep characterized by excessive daytime sleepiness and sudden onset of sleep, without the normal transition through lower levels of arousal, and with an altered circadian pattern. Individuals with narcolepsy often experience cataplexy, which refers to sudden attacks of muscular weakness, often brought on by strong emotional states.

Ian P. Stolerman (ed.), *Encyclopedia of Psychopharmacology,* DOI 10.1007/978-3-540-68706-1,

Narcotic Analgesics

► Opioid Analgesics
► Opioids

Narcotics

► Opioid Analgesics
► Opioids

Narcotics Prison Farm

Synonyms

Federal medical center, Lexington; Lexington narcotics farm

Definition

The U.S. Narcotics Prison Farm was established in 1935 in Lexington, Kentucky, as a prison hospital for drug addicts and was operated by the U.S. Federal Bureau of Prisons and the Public Health Service. Inmates were either committed by courts to serve sentences at the Farm or voluntarily admitted themselves. Patient/prisoners received treatment for their substance abuse problem and were given new employment skills by working on the farm or on related jobs. The Narcotics Prison Farm was home to the Addiction Research Center, a significant research center focused on the study of drug abuse and dependence, particularly opioid dependence, using the inmate population. Research of this type on prisoners is rarely conducted today because of ethical concerns, although prisons remain important locations for the study of treatment programs.

Cross-References

► Abuse Liability Evaluation
► Addiction Research Center
► Opioid Dependence and Treatment
► Sedative, Hypnotic, and Anxiolytic Dependence

Nardil

► Phenelzine

NARI Antidepressants

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Synonyms

Selective noradrenergic reuptake inhibitors

Definition

Selective ► Norepinephrine Reuptake Inhibitors (selective NRIs) are a group of drugs that exert action primarily by the inhibition of norepinephrine reuptake at the norepinephrine transporter protein. The affinity of a drug for such a receptor can be expressed mathematically as the dissociation constant (K_i). To be considered as a selective NRI, the binding affinity of the most occupied receptor, in this case the norepinephrine reuptake pump, must be at least tenfold higher than the binding affinity of the next most occupied receptor. Parenthetically, the lower the K_i value, the higher the affinity of the drug for the receptor. Ki values for the selective NRIs are compared in Table 1.

Pharmacological Properties

Agents that meet the criteria for selective NRIs include ► reboxetine, ► atomoxetine, viloxazine, and several secondary amine ► tricyclic antidepressants (TCAs) (e.g., desipramine). The history, ► pharmacokinetics, and the efficacy of reboxetine, atomoxetine, and viloxazine will be described together, as they are most similar in mechanism of action, having little affinity for receptors other than norepinephrine. Secondary amine TCAs and ► bupropion, a dual ► dopamine and norepinephrine reuptake inhibitor, will be discussed separately within the context of this essay. Safety and tolerability will be described for the selective NRI class as a whole.

Reboxetine, Atomoxetine, and Viloxazine

History

Reboxetine holds the distinction of being the first truly selective norepinephrine reuptake inhibitor and has been used in the treatment of clinical ► depression, ► anxiety disorders, and ► attention deficit disorders. It is licensed for use in several countries but is unavailable in the USA (Fleishaker 2000). Reboxetine has been denied approval

NARI Antidepressants. Table 1. Ki values in nM and reference studies. (Adapted from http://pdsp.med.unc.edu/.)

	5HT-T	5HT1A	Alpha- 1	M1	D2	H1	NET
Reboxetine	107 Millan et al. 2001	>10,000 Millan et al. 2001	>10,000 Millan et al. 2001		>10,000 Millan et al. 2001		15.8 Millan et al. 2001
Atomoxetine	77 Bymaster et al. 2002	>1,000 Bymaster et al. 2002		>1,000 Bymaster et al. 2002	>1,000 Bymaster et al. 2002	>1,000 Bymaster et al. 2002	5 Bymaster et al. 2002
Viloxazine	17,300 Tatsumi et al. 1997						155 Tatsumi et al. 1997
Nortriptyline	279 Owens et al. 1997	294 Cusack et al. 1994	55 Cusack B et al. 1994	40 Stanton, et al. 1993	2,570 Cusack et al. 1994	6.3 Cusack et al. 1994	1.8 Owens et al. 1997
Desipramine	163 Owens et al. 1997	6,400 Cusack et al. 1994	100 Cusack B et al. 1994	110 Stanton et al. 1994	3,500 Cusack B et al. 1993	60 Cusack et al. 1994	0.63 Owens et al. 1997
Protriptyline	19.6 Tatsumi et al. 1997						1.41 Tatsumi et al. 1997
Maprotiline	5,800 Tatsumi et al. 1997					0.79 Kanba S and Richelson E 1984	11.1 Tatsumi et al. 1997
Bupropion	9,100 Tatsumi et al. 1997	>35,000 Cusack et al. 1994	4,200 Cusack et al. 1994	>35,000 Stanton et al. 1993	DT 520 Tatsumi et al. 1997	11,800 Cusack et al. 1994	52,000 Tatsumi et al. 1997

5HT-T serotonin transporter (i.e., uptake pump), $5HT_{1A}$ – serotonin 1A receptor, Alpha 1 – adrenergic alpha 1 receptor, M1 – cholinergic muscarinic receptor, D_2 – dopamine 2 receptor, H_1 – histaminic 1 receptor, NET – norepinephrine reuptake transporter, DT – dopamine reuptake pump.

by the US Food and Drug Administration (FDA) multiple times (Page 2003). Viloxazine has also been unable to gain FDA approval. As first reported in 1976 by Lippman and Pugsley, viloxazine was found to inhibit norepinephrine reuptake in the hearts of rats and mice, but unlike previously discovered agents such as ► imipramine, did not have similar actions in brain tissues. Since that time, more research has been conducted suggesting possible benefits in conditions including ► depression, ► narcolepsy, nocturnal enuresis in children, and alcoholism. Another selective NRI, atomoxetine, is the first nonstimulant drug approved for the management of symptoms secondary to attention deficit hyperactivity disorder (► ADHD). Initially, studies were conducted to evaluate the efficacy of atomoxetine in depression, but these studies were stopped in 1990 as the manufacturer was focusing efforts on a more promising agent for the same indication, ► fluoxetine. Interestingly, the drug was originally named tomoxetine but was changed to atomoxetine after the FDA raised concerns about possible confusion with the previously marketed drug tamoxifen, an agent used in the treatment of breast cancer.

Mechanisms of Action

Antidepressants modulate various neurotransmitter systems involved in mood. Reboxetine selectively inhibits the neuronal reuptake of norepinephrine, which is believed to mediate its antidepressive effects. In contrast to secondary amine TCAs (desipramine) and maprotiline, reboxetine lacks affinity for alpha 1, histaminergic, and muscarinic receptors, and has extremely limited serotonergic properties.

Atomoxetine is closely related in structure to reboxetine. Administration of atomoxetine results in an increase of norepinephrine in the ► prefrontal cortex, an area of the brain associated with attention and memory. An increase of norepinephrine at this site is thought to correlate with improvement in target symptoms of ADHD.

► Pharmacokinetics

Reboxetine is metabolized by cytochrome P450 (CYP) 3A4. Inhibitors of CYP 3A4 could potentially increase reboxetine plasma levels, while potent CYP3 A4 inducers will reduce the plasma concentrations of reboxetine. Reboxetine undergoes hydroxylation, oxidative dealkylation, and oxidation of both the parent compound and its metabolites, with subsequent renal elimination. Patients with hepatic impairment or renal impairment (defined as a creatinine clearance of <50 mL/min) should be started on initial doses of 2 mg twice daily, with maximum daily doses of 6 mg.

The ► metabolism of atomoxetine also warrants discussion, as the ► half-life is largely dependent on CYP 2D6. For extensive metabolizers the reported half-life is approximately 5 h, as compared to poor metabolizers (roughly 7% or Caucasians and 2% of African Americans) where the half-life could be prolonged up to 20 h (Caballero and Nahata 2003). Dose adjustment may be warranted when using atomoxetine in combination with CYP 2D6 inhibitors. As reboxetine, atomoxetine, and viloxazine have only weak serotonergic activity, these agents can be safely used in combination with ► selective serotonin reuptake inhibitors (SSRIs) with virtually no overlap in mechanism of action, although metabolic drug interactions may occur.

Efficacy

Reboxetine has not been granted approval in the USA due to a lack of compelling evidence of efficacy. A meta-analysis of four short-term (4–8 week), double-blind, multicenter trials was published in 2002. The ► Hamilton Depression Rating Scale was used as the primary assessment tool. In these studies, improvements were observed in psychomotor retardation, cognitive disturbance, anxiety, and insomnia. Interestingly, depressive symptoms were not discussed, leaving the reader to question the efficacy of reboxetine in the treatment of mood symptoms. Reboxetine in total daily doses of 8–10 mg may be effective in the management of depressive symptoms (Ferguson et al. 2002).

Atomoxetine should be considered as a treatment option in ADHD patients who do not tolerate stimulants, especially if insomnia and impact on growth are areas of concern. When the administration of atomoxetine is started, it can take 2–4 weeks before a therapeutic effect is appreciated, a timeframe that is comparable to other selective NRIs. This latency period could be viewed as a disadvantage of atomoxetine, as the effects of stimulants, such as ► methylphenidate, occur within 1–3 h of achieving an effective dose. Atomoxetine does not have ► abuse potential and is not labeled in the USA as a controlled substance. These features make it a particularly appealing choice over stimulants in the treatment of patients who have a history of ► substance abuse disorders.

Few advantages of viloxazine over other selective NRIs have been reported, although viloxazine may be a less cardiotoxic alternative to imipramine.

Tricyclic Antidepressants (TCAs)

History

Several TCAs are considered to be selective NRIs, including ► nortriptyline, ► lofepramine with its active metabolite desipramine, protriptyline, and the tetracyclic agent maprotiline (Preskorn 2009). TCAs were developed from ► phenothiazines to be used as possible sedatives, antihistamines, analgesics, and antiparkinsonian drugs in the 1950s (Brunton et al. 2006). Imipramine, the first TCA developed, was tested in 500 patients with various psychiatric disorders. Of the patients who were tried on ► imipramine, only depressed patients with psychomotor retardation treated daily for 1–6 weeks showed improvement in symptoms (Domino 1999).

Mechanism of Action

Unlike reboxetine, atomoxetine, and viloxazine, TCAs bind to a variety of receptors in addition to the norepinephrine reuptake pump, including serotonin reuptake pumps, muscarinic acetylcholine receptors, histamine 1 receptors, norepinephrine alpha 1 receptors, and fast Na channels (Table 2). Activity at these receptor sites is more prominent with ► tertiary than secondary amine TCAs, and is responsible for efficacy as well as side effects.

Pharmacokinetics

► Pharmacokinetics of TCAs that are considered to be selective NRIs are similar. They are well absorbed from the gastrointestinal tract independently of food. First-pass metabolism accounts for 40–50% of the total metabolism that occurs in the intestine and the liver.

The main pharmacokinetic drug–drug interactions take place on plasma proteins involved in the distribution of the medication, and during hepatic metabolism involving enzymes CYP 450. TCAs have a high affinity for plasma proteins and share this trait with other medications such as ► phenytoin, ► valproic acid, aspirin, and warfarin. If used concomitantly with these agents, displacement from the plasma proteins can occur, thus increasing the unbound form to toxic levels, although this mechanism is more theoretical than actual. CYP 450 enzymes involved in the metabolism of TCAs include 2D6, 2C19, 1 A2, and

NARI Antidepressants. Table 2. TCA receptor binding profile. (Adapted from Preskorn 2009.)

Receptor	Effect associated with blockade	
Histamine 1 (H1)	Sedation Antipruritic effect	Increase of appetite and weight
Muscarinic receptor	Dry mouth Sinus tachycardia Constipation	Urinary retention Memory impairment
Serotonin 5HT2 uptake pump	Antidepressant Nausea	Loose stools Insomnia Anorgasmia
Serotonin HT2C	Antianxiety Decrease of motor restlessness	Appetite decrease
Serotonin HT3	Decreases nausea	Decreases vomiting
Fast Na + channels	Delayed repolarization leading to arrhythmia, seizures, delirium	

3A3-4, with the 2D6 enzyme pathway identified as the rate-limiting step in the elimination of TCAs. Inducers and inhibitors of the enzymes aforementioned can increase or decrease the metabolism of TCAs, causing either inadequate levels with poor therapeutic response or increased levels leading to toxicity (Preskorn et al. 2004).

Efficacy

There are multiple double-blind placebo-controlled studies showing the effectiveness of TCAs in treating acute depression. The therapeutic response usually starts with the improvement of somatic symptoms. The main indication for protriptyline (dose 15–60 mg/day), nortriptyline (75–150 mg/day), desipramine (75–200 mg/day), and maprotiline (75–225 mg/day) is the treatment of depression in adults, but nortriptyline is also used as a treatment for neuropathic pain, nocturnal enuresis, and as a second-line treatment in attention deficit hyperactivity disorder in children, adolescents, and adults. Currently, lofepramine is not approved for use in the USA, but is used for the treatment of depression and anxiety in Europe.

TCA serum levels can be used as a clinical guide to achieving adequate therapeutic response. TCAs have a narrow therapeutic index and therapeutic drug monitoring (TDM) is needed to assure safe use of TCAs (Janicak et al. 2001). The optimal therapeutic plasma concentrations of desipramine and nortriptyline are 50–150 ng/ml.

Bupropion

History

► Bupropion has a long and complex history. First discovered in 1969 by Mehta, bupropion was granted approval as an antidepressant by the FDA in 1985 under the trade name Wellbutrin. Prior to marketing, subjects involved in clinical trials were reported to experience increased risk of seizures. At the time of approval, doses up to 900 mg daily were used. Subsequently, marketing was halted and further research revealed that the risk of seizures was dose dependent. Bupropion was released in 1989 with a lower maximum daily dose and more strict contraindications for use. Since that time, bupropion has become widely prescribed for depression and has also been granted indications for smoking cessation and, as an extended-release form, for seasonal affective disorder.

Mechanisms of Action

Bupropion is not a true selective NRI as it exhibits more potent reuptake of dopamine than norepinephrine. Bupropion has only weak serotonergic activity (Table 1).

Pharmacokinetics

Currently, bupropion is available in three dosage forms: an immediate-release tablet intended to be taken thrice daily, a sustained-release tablet to be taken twice daily, and an extended-release form to be taken once daily. In April of 2008, the FDA approved a fourth form of bupropion. Previous forms have all shared the same hydrochloride salt form, but the newest version differs in that it is bupropion hydrobromide. It is not commercially available now, but will be marketed in the USA as Aplenzin™ as a once-daily dosage form. Caution should be used when bupropion is used concomitantly with drugs dependent on CYP 2D6 for clearance, as doses $\geq$300 mg of bupropion can cause appreciable inhibition of drugs metabolized by this CYP enzyme.

Efficacy

Bupropion has proven to be effective for the treatment of depressive symptoms as monotherapy. It is also used off-label as an adjunct antidepressant, particularly in patients who have only partially responded to SSRIs. Additionally, bupropion has been evaluated in the management of symptoms associated with ADHD, but to date does not have an indication for this disorder.

Selective NRI – Safety and Tolerability

The side-effect profiles of reboxetine, atomoxetine, and viloxazine can be attributed to the unwanted effects of norepinephrine, as activity at other receptors is limited. The concept of selectivity can thus be a bit deceiving. While an agent such as reboxetine is selective for the neurotransmitter ► norepinephrine, its activity is nonselective in terms of distribution, contributing to effects not only in the brain but in the body as well (Table 3). In the limbic system, the stimulation of noradrenergic receptors has been correlated with agitation. Acute stimulation of norepinephrine receptors in the brainstem and spinal cord can contribute to elevations in blood pressure, although the extent of these elevations does not appear to reach clinical relevance in most cases. Such elevations have been reported with atomoxetine use. In most cases, the side effects that are present with selective NRIs lessen over time. The most frequent side effects of reboxetine include dry mouth, constipation, urinary retention, blurred vision, headache, drowsiness, dizziness, excessive sweating, and insomnia. When looking at these side effects, one might associate dry mouth, constipation, urinary retention, and blurred vision with anticholinergic activity, but as was already mentioned, reboxetine does not directly block muscarinic cholinergic receptors. Instead, anticholinergic-like effects are the result of norepinephrine receptor stimulation in the sympathetic nervous system, which in turn causes a reduction of parasympathetic cholinergic tone, frequently referred to as sympathomimetic effects. This is observed clinically in the fact that reboxetine, atomoxetine, and viloxazine are generally better tolerated than tertiary amine TCAs, which elicit full effects at these receptor sites. In addition to anticholinergic effects, TCAs are linked to lethal cardiac arrhythmias, seizures, and neurotoxicity associated with elevated serum TCA levels. Toxic levels are generally accepted as >500 ng/ml for desipramine and nortriptyline.

Selective NRIs should be used cautiously in several patient populations. The potential of antidepressants to lower the seizure threshold is a class effect, and as such, all drugs in this class should be used with caution in patients with seizure disorders. Bupropion is contraindicated in patients who have epilepsy or concomitant medical conditions that may lower the seizure threshold, including the active discontinuation of ► alcohol or ► benzodiazepines

NARI Antidepressants. Table 3. Noradrenergic pathways. (Adapted from Stahl 2004)

Beginning of the pathway	Projecting to	Control of
Locus Coeruleus	Frontal cortex Alpha-2 receptor	Attention Concentration Cognition Libido increase
Locus Coeruleus	Frontal cortex Beta-1 receptor	Mood
Locus Coeruleus	Limbic cortex	Energy Fatigue Emotions Psychomotor agitation and retardation
Locus Coeruleus	Cerebellum	Tremors
Locus Coeruleus	Brainstem	Blood pressure
Locus Coeruleus	Spine Alpha-2	Pain modulation
Spinal sympathetic neurons	Heart Beta-1 receptor	Heart rate
Spinal sympathetic neurons	Urinary Bladder Alpha-1	Bladder emptying

and eating disorders. Daily doses greater than 450 mg of bupropion are associated with increased incidence of seizure.

As a class, selective NRIs depend on hepatic function for proper metabolism. Caution should be used, and dosage adjustments may be warranted, in hepatic insufficiency. In 2004, the FDA mandated that a warning be added to the atomoxetine drug label following two reports in which patients with no documented liver insufficiencies presented with elevated bilirubin levels and hepatic enzymes.

Selective NRIs are contraindicated with ▶ monoamine oxidase inhibitors (MAOIs). Concurrent use can result in increased catecholamine concentrations, which present, clinically, as hypertensive crisis, confusion, and seizures. Reboxetine has the ability to block the neuronal uptake of tyramine and, as a result, would theoretically be protective against hypertensive crisis secondary to the dietary ingestion of tyramine. As the threshold and duration of these effects are unknown, the combination of reboxetine and MAOIs should be avoided.

The effects of selective NRIs have not been extensively studied in pregnancy or breast-feeding, and should be used only when it is determined that the benefits outweigh the potential risks. Currently, maprotiline is the only selective NRI that is classified as pregnancy category B. Bupropion was previously classified as ▶ pregnancy category B but this labeling was changed by the FDA to category C. All other selective NRIs are category C, with the exception of nortriptyline, which is classified as category D due to its increased risk of teratogenicity, and therefore should be avoided in pregnancy.

The FDA mandated the addition of a ▶ black box warning disclosing the risk of suicide in children and adolescents in October 2004 and later extended the warning to include young adults. Close monitoring for suicidal ideation or changes in behaviors is warranted in patients who are started on therapy, particularly during the first few months of therapy or following dosage changes. Along with the warning, manufacturers in the USA must provide Patient Medication Guides that are to be given to the patient with all prescriptions for antidepressants.

Conclusion

In summary, selective NRIs can be divided into two main categories: those that have primary activity only on norepinephrine receptors such as reboxetine, atomoxetine, and viloxazine, and those that have significant activity at other receptor sites in addition to norepinephrine, including secondary amine TCAs, maprotiline, and bupropion. With respect to the first group, the effects of norepinephrine activity alone result in increased alertness and concentration. For this reason, atomoxetine is beneficial in treating symptoms associated with attention deficit disorders. Agents with solitary norepinephrine activity, such as reboxetine and viloxazine, have not been overwhelmingly advantageous in the treatment of depressive symptoms. When looking at the second group, it appears that activity at other receptor sites including serotonin and dopamine, may be beneficial in the treatment of depressive symptoms. This interpretation is supported by the fact that the TCAs and bupropion result in more robust clinical response when used to treat depressive illness.

Cross-References

▶ Anticholinergic Side Effects
▶ Antidepressants
▶ Anxiety
▶ Attention Deficit Hyperactivity Disorder
▶ Major Depressive Disorder (MDD)

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N-Back Test

Definition

In this test, subjects are presented with a series of stimuli (e.g., spatial locations, visual objects, letters, etc.) and required to decide whether the current stimulus is the same as the stimulus seen *n* trials back. In variants of this test, subjects have to respond to the current trial with the stimulus presented *n* (e.g., two) trials back.

Necrosis

Definition

A term used to define the mechanism by which cells die due to the degradative action of enzymes. Necrosis follows an initial causative factor such as ischemia, a neurotoxin, or injury.

Cross-References

► Apoptosis

Negative Antagonists

► Inverse Agonists

Negative Reinforcement Theory

Definition

Like positive reinforcement, negative reinforcement increases the likelihood that a behavior associated with it will be continued. However, a negative reinforcer is an unpleasant stimulus that is removed after a behavioral response. Negative reinforcers can range from uncomfortable physical sensations to actions causing severe physical distress. Taking drug to relieve the withdrawal distress is, arguably, an example of negative reinforcement. If a person's withdrawal syndrome (stimulus) goes away after taking drug (behavior), then it is likely that the person will seek for drug as soon as the first withdrawal discomfort will appear in the future.

Negative Reinforcer

Definition

An aversive event whose removal follows an operant response.

Negative Symptoms Syndrome

Synonyms

Deficit symptoms syndrome

Definition

A syndrome that involves the lacking of a number of mental features or capacities that would be expected to be present in a healthy individual. These features and capacities include: the ability to sustain an adequate level of attention during tasks, activities, or social encounters; a full range of genuine, appropriately responsive, and appropriately sustained affect; an adequate quantity of spontaneous speech that contains objective content and that is delivered without disruptive delays in either initiating or sustaining the speech; an appropriate level of attention and caring concerning grooming and personal hygiene; an appropriate level of motivation and persistence concerning work, school, or other productive activities; an appropriate level of energy for initiating and sustaining activities, and capacity for self-starting and self-direction; an appropriate level of interest and investment in, and pleasure derived from, enjoyable or recreational activities; and an age-appropriate interest in, and

capacity for, friendship, cooperation, and interpersonal closeness or intimacy.

Cross-References
► Depressive Disorder of Schizophrenia

Nemonapride

Definition
Nemonapride is a first-generation (typical) antipsychotic drug that belongs to the benzamide class approved in Japan for the treatment of schizophrenia. It is a potent dopamine antagonist with high affinity for D_2, D_3, and D_4 receptors. In addition, it is a potent 5-HT_{1A} receptor agonist and has relatively high affinity for sigma receptors, with little affinity for 5-HT_{2A} receptors. It can induce extrapyramidal motor side effects and has a propensity to elevate prolactin secretion, but it displays generally low toxicity.

Cross-References
► Extrapyramidal Motor Side Effects
► First-Generation Antipsychotics
► Schizophrenia

Neologisms

Definition
Creation of new words not corresponding to linguistic conventions.

Neonatal Abstinence Syndrome

Definition
Expression of drug withdrawal behavior in neonates of drug-addicted mothers, a syndrome best characterized in neonates exposed prenatally to opiates such as heroin or methadone.

Neostriatum

► Striatum

Nerve Growth Factor

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Definition
Nerve growth factor (NGF) is a protein primarily responsible for the differentiation and survival of sympathetic and ► spinal cord primary sensory neurons in the peripheral nervous system and for the differentiation and survival of cholinergic neurons of the basal forebrain during the development of the nervous system and responsible for the maintenance of their neuronal phenotype after maturity. NGF has other broader effects over endocrine and inflammatory mechanisms.

Pharmacological Properties

Preamble
NGF was the first molecule identified as having well-defined trophic actions over cells of the nervous system. Following the discovery of NGF, a plethora of other proteins with differential trophic effects over PNS or CNS neurons has also been identified. The discovery of NGF introduced the concept that neuronal survival, differentiation, and growth are controlled by ► trophic factors and initiated a major research field in the neurosciences and neuropharmacology.

History
The discovery and identification of NGF is one of the most fascinating chapters in the history of neuroscience. The immediate roots of this discovery can be found in the pioneering investigations of Rita Levi-Montalcini and Viktor Hamburger who demonstrated that the grafting of sarcoma tumors in chick embryos elicited a remarkable hypertrophic growth of spinal cord primary sensory and sympathetic ganglia with an ingrowth of the corresponding nerves into the sarcoma (Levi-Montalcini 1987). The possibility that a "diffusible factor" was responsible for such a remarkable neurotrophic response was consecutively investigated *in vitro* by Rita Levi-Montalcini who, while in Rio de Janeiro, demonstrated that the culture media of sarcoma tissue induced a remarkable "halo" of radially outgrowing neurites emerging from the ganglia. These powerful microscopic images have remained iconic, given these dramatic effects and their significance. Stanley Cohen and, later, Rita Levi–Montalcini, serendipitously identified similar trophic

effects with material extracted from snake venom glands and from rodent submaxillary glands. These highly purified preparations allowed them to establish the proteinaceous nature of NGF, and to generate antibodies for immunoneutralization and biological characterization. Later, these preparations allowed Angeletti and Brashaw to establish NGF's amino acid sequence. Because of these pioneering findings, the Nobel Prize in Medicine was granted in 1986 to both Rita Levi-Montalcini and Stanley Cohen. A family of NGF-like molecules (the neurotrophins) and their receptors was consequently identified after these seminal contributions.

Neurobiology and Mechanisms of Action

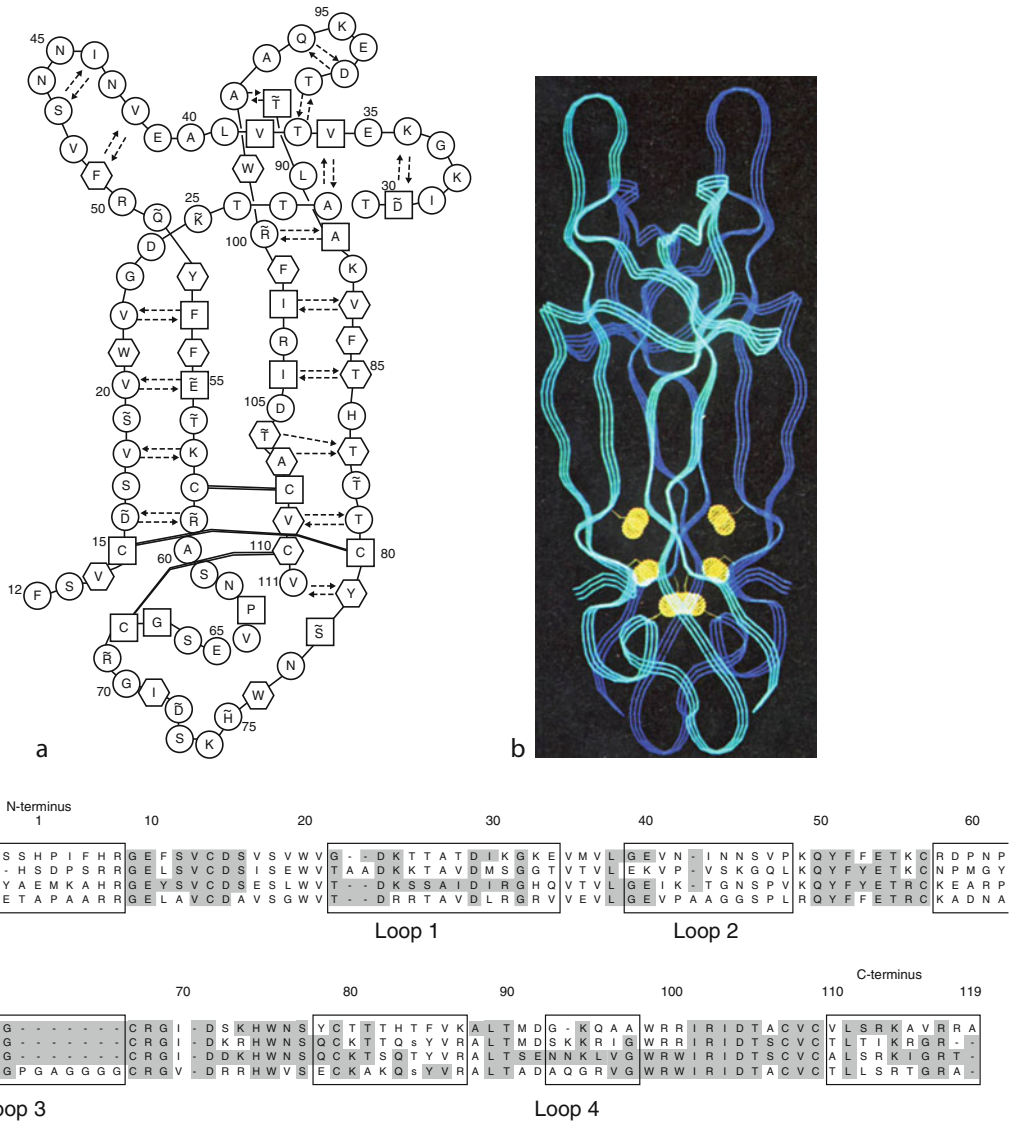
It is currently known that NGF is a member of the so-called neurotrophin family of trophic factors which is composed of NGF, brain derived neurotrophic factor (BDNF), and the neurotrophins, NT3 and NT4/5. These proteins have a high degree of homology with NGF and their tertiary structure reveals antiparallel strands and four hairpin loops. Three disulfide bridges known as a "cysteine knot" maintain the 3D configuration. The neurotrophins can be differentiated from each other principally by the amino acid sequence of their hairpin loops, which apparently grants them their biological specificity (Skaper 2008). The neurotrophins have subunit molecular masses in the range of 12–14 kDa and are found as noncovalently linked homodimers of approximately 26 kDa. The 3D molecular structure of NGF and its relative homology with other members of the neurotrophin family is represented in Fig. 1.

Three main high-affinity receptor tyrosine kinases have been identified and referred to as TrkA, TrkB, and TrkC, responding preferentially to NGF, BDNF, and NT3 respectively, and NT4 to NT4. While NGF acts fairly narrowly on TrkA, some overlap regarding receptor responses can be expected of the rest of the neurotrophins (Chao 2003; Kaplan and Miller 2000; Skaper 2008), as illustrated in Fig 2.

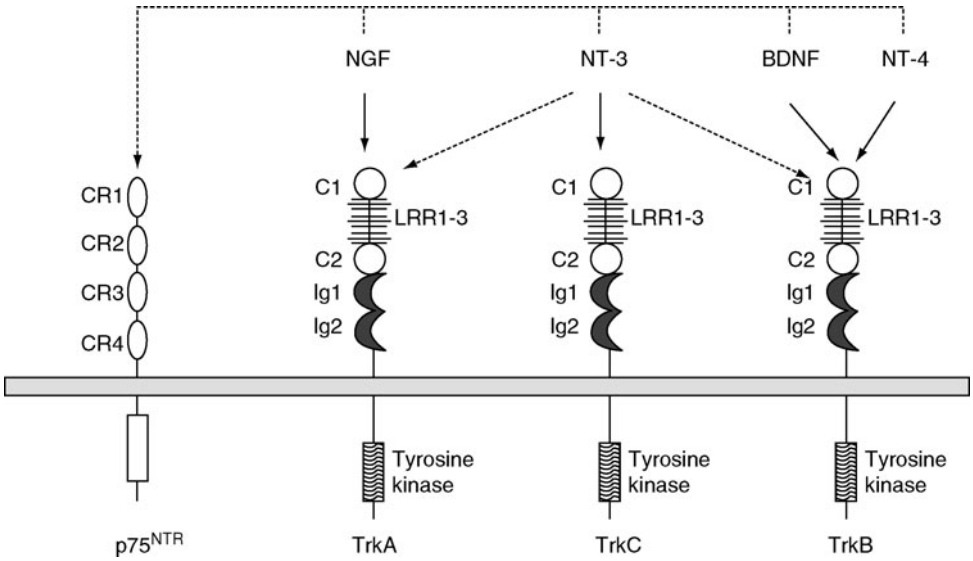
These receptors are mainly responsible for the diverse and specific neurotrophic responses elicited by the neurotrophins over defined groups of CNS and PNS neurons. An ubiquitous and less discriminating "co-receptor," p75 neurotrophin receptor (NTR), appears to act cooperatively with Trk receptors in eliciting neurotrophic actions. However, in certain conditions, in the absence of Trk receptors, $p75^{NTR}$ are thought to mediate cell death via apoptotic mechanisms, acting cooperatively with the sortilin receptor (Nykjaer et al. 2004), a receptor for neurotensin, which is also present in NGF-rich CNS regions. Both TrkA and $p75^{NTR}$ receptors are nowadays considered to be high-affinity receptors for NGF. NGF is generated by a variety of tissues and cell types. In the mature CNS, it is mainly produced by neurons located in target regions for NGF-dependent neurons (target derived trophic support) where their axonal branches and presynaptic boutons terminate. NGF is synthesized as a larger precursor molecule, preproNGF, whose signal peptide is cleaved in the endoplasmic reticulum to produce proNGF. ProNGF is a secreted molecule and is the most abundant molecular species of NGF in the adult CNS. It is the preferred ligand of the $p75^{NTR}$/sortilin complex. It can also bind TrkA, but with weaker affinity than mature NGF (Fahnestock et al. 2004). The mature form of NGF (mNGF), on the other hand, is most likely generated extracellularly and binds more tightly to TrkA. The biological activities of proNGF and NGF are determined by the relative levels of TrkA and $p75^{NTR}$ (Masoudi et al. 2009). The best-characterized biological actions of mNGF are its neurotrophic effects. These are achieved by mNGF binding to monomeric or homodimeric TrkA receptors and also to hetero-TrkA-$p75^{NTR}$ complexes; dimeric complexes result in higher ligand-receptor affinity (Fig. 3).

Synthesis, Release, and Metabolism of NGF

As indicated earlier, mature and biologically active NGF is the immediate product of a larger precursor protein, proNGF. Western blot analysis reveal that the predominant form of NGF in the adult CNS is proNGF (Fahnestock et al. 2001). It has been proposed that proNGF can be cleaved intracellularly by the action of furin converting proNGF into NGF. However, the degree to which the "conversion" of proNGF into mNGF takes place intra or extracellularly is debatable. Studies with transfected cell lines have shown that a furin-resistant form of proNGF can be released into the extracellular space and induce cell death via the activation of $p75^{NTR}$ (Lee et al. 2001), possibly when TrkA levels are low. Cell biology studies indicate that the secretion of NGF is activity-dependent. *Ex-vivo* studies with superfused cerebral cortex tissue of adult rats have revealed that proNGF is the molecular form released in an activity-dependent manner, following depolarization or neurotransmitter stimulation (Bruno and Cuello 2006). These studies also indicate that in the adult and fully differentiated nervous system, the conversion of proNGF occurs in the extracellular space by the coordinated action of plasminogen and tissue plasminogen activator (tPA) producing plasmin which converts proNGF into mNGF (Bruno and Cuello 2006). Mature NGF and corresponding activated TrkA receptor are internalized in endosomal vesicles, which are transported retrogradely by axonal processes from nerve terminals to perinuclear regions of neurons, where the



Nerve Growth Factor. Fig. 1. (**a**) Schematic representation of the β-NGF monomer subunit highlighting structurally important residues. Bold, absolutely conserved residues for all NGF and NGF-related sequences. Squares, buried residues in the β-NGF subunit with a relative side-chain. The hexagons represent residues involved in the dimer interface as identified using computer imaging techniques. The side-chain of the residue participates in a hydrogen bond with either a side-chain or a main chain atom. The main chain hydrogen bonds involved in the β-sheet structure are displayed as arrows, pointing in the direction of the donor acceptor. The cysteine knot is shown as three solid lines linking six cysteine residues near the bottom of the molecule (From McDonald et al. (1991) Nature; with author's and publisher's permission). (**b**) Ribbon representation of the β-NGF dimer. The cyan and dark blue ribbons each represent a subunit. The Sγ atom for each half-cystine residue is also shown drawn as a sphere. (From McDonald et al. (1991) Nature; with author's and publisher's permission). (**c**) Structure-based sequence alignment of the neurotrophins. Numbering refers to the sequence of mature human NGF. Positions are numbered from the first residue in each neurotrophin. Note that, because of differences in the lengths of the N-termini of the different neurotrophins, homologous positions in different molecules do not have equivalent numbering. Conserved residues are shaded and low sequence homology (boxes) and sequence of hairpin loops are represented. Dashes indicate gaps introduced for the sake of alignment. (From Skaper 2008. CNS Neurol Disord Drug Targets; with author's and publisher's permission.)



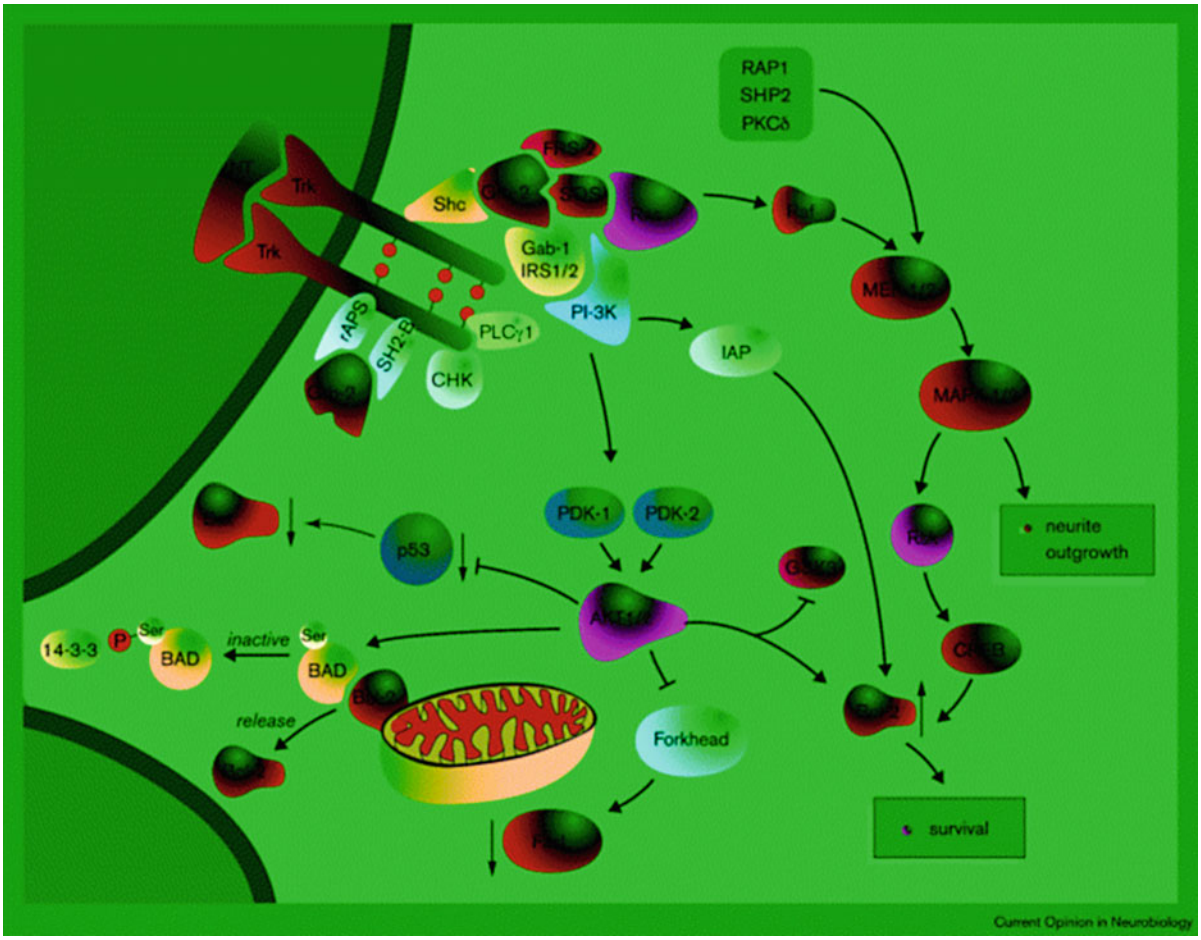
Nerve Growth Factor. Fig. 2. Neurotrophins and their receptors. The neurotrophins display specific interactions with the three Trk receptors: NGF binds TrkA, BDNF and NT-4 bind TrkB, and NT-3 binds TrkC. In some cellular contexts, NT-3 can also activate TrkA and TrkB albeit with less efficiency. All neurotrophins bind to and activate $p75^{NTR}$. CR1-CR4, cysteine-rich motifs; C1/C2, cysteine-rich clusters; LRR1-3, leucine-rich repeats; Ig1/Ig2, immunoglobulin-like domains. (From Skaper 2008. Drug Targets. CNS Neurol Disord; with author's and publisher's permission.)

vesicles continue signaling via the Erk-CREB pathway (Grimes et al. 1996). These studies also indicate that the metalloproteinase MMP9 rapidly degrades and inactivates any remaining mNGF, which is not bound to the cognate receptor (TrkA) and rapidly internalized.

The above metabolic pathway involving plasmin for the maturation of NGF and MMP9 for its degradation has been pharmacologically validated *in vivo,* showing that the inhibition of tPA results in the brain accumulation of proNGF and, conversely, the inhibition of MMP9 in the accumulation of mNGF (Bruno and Cuello 2006). Fig. 4 illustrates the activity-dependent release of proNGF and its consequent conversion to mature NGF, binding to its cognate receptors and its eventual degradation in the extracellular space as well as the protease cascade and endogenous inhibitors.

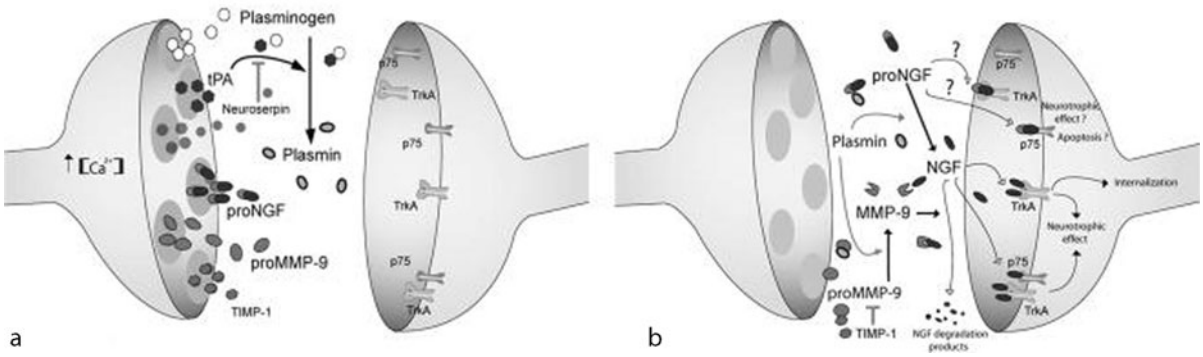
The best-defined and most dramatic actions of the endogenously generated NGF are illustrated during embryonic stages and the early postnatal period. In brief, in *in vitro* conditions, the deprivation of NGF support leads to cell death of NGF-dependent embryonic neurons, typically small-size spinal cord primary sensory and ▶ sympathetic neurons. The early studies on the deprivation of NGF trophic support were performed by immunoneutralization with anti-NGF polyclonal antibodies and more recent studies were done with NGF knock-out (KO) or NGF-deficient animal models. Mice lacking NGF or TrkA (KO models) do not survive beyond weeks after birth. The phenotype of NGF(−/−) or TrkA(−/−) mice is one of dramatic loss of NGF-dependent spinal cord sensory neurons and sympathetic neurons, but with a lesser effect on NGF-dependent forebrain neurons. However, mice carrying a single NGF allele have shown marked atrophy of forebrain cholinergic neurons of the nucleus basalis and medial septum. The most accepted view is that during development, the presence of NGF in defined target areas will attract axonal growth to the sites of termination (synapses in the CNS) and secure the eventual survival of NGF-dependent neurons (Sofroniew et al. 2001).

Many of the concepts derived from investigations on embryonic tissue have been applied to the adult nervous system. Thus, the concept of "target derived" NGF support of CNS neurons in the adult brain was readily accepted. It was shown early on that axotomy of the septal-hippocampal cholinergic pathway in the adult brain resulted in the loss of the corresponding NGF sensitive cholinergic neurons. Their recovery by the application of NGF was interpreted as an indication of a similar NGF-dependency for neuronal survival in the adult and fully differentiated CNS. However, the substantial excitotoxic destruction of the target tissue (hippocampus),



Nerve Growth Factor. Fig. 3. Trk signaling pathways regulating survival and neurite growth in neuronal cells. Neurotrophin (NT) binding to Trk stimulates receptor transphosphorylation, resulting in the recruitment of a series of signaling proteins to docking sites on the receptor. These proteins include Shc, which activates Ras through Grb-2 and SOS, FRS-2, rAPS, SH2-B and CHK, which participate in activating MAPK, and PLC-γ1 and CHK bind to phosphorylated Tyr 785. MAPK activity is also regulated through Raf, Rap 1, SHP-2, and PKCδ . The MEK and MAPK pathway is thought to regulate neurite growth and survival. Trk activates PI-3K through the RAS and the Gab-1/IRS-1/IRS-2 family of adapter proteins. PI-3K activity stimulates the activities of PDK2, which in turn activate Akt. The targets of PI-3K/Akt anti-apoptotic activity, including BAD, Forkhead, GSK-3, Bcl-2 IAP, and the p53 pathway involved in cell death. (From Kaplan and Miller 2000. Curr Opin Neurobiol; with author's and publisher's permission.)

while sparing their axonal input, resulted in atrophy, but not cell death, of the NGF-dependent cholinergic neurons of the medial septum, unequivocally demonstrating that NGF in the adult is key for the maintenance of neuronal phenotype, but not survival (Sofroniew et al. 2001). A similar NGF-dependency for the phenotypic characteristics of cholinergic neurons of the nucleus basalis has also been amply documented (Cuello 1994). Further confirmation of the essential role of NGF in the maintenance of the CNS cholinergic phenotype in the mature brain is provided by the evidence that blocking "endogenous" NGF function through the application of either antibodies mapping out the ligand (NGF) or NGF mimetic peptides with antagonist actions over the receptor (TrkA) in the cerebral cortex of adult rats results in the loss of preexisting cortical cholinergic synapses (Debeir et al. 1999). Such an observation indicates that the "steady-state" number of CNS cholinergic synapses is dependent on a continuous supply of endogenous NGF, in line with the classical Hebbian concept that brain activity unleashes a



Nerve Growth Factor. Fig. 4. Schematic representations of events leading to proNGF conversion into mNGF and its degradation. Neuronally stored proNGF, plasminogen, tPA, neuroserpin, proMMP-9, and TIMP-1 would be released into the extracellular space upon neuronal stimulation. Released tPA would induce the conversion of plasminogen to plasmin, where its activity is tightly regulated by secreted neuroserpin. The generated plasmin would convert proNGF into mature NGF and activate proMMP-9 into active MMP-9. Mature NGF would interact with its cognate receptors (TrkA and $p75^{NTR}$) or suffer degradation by activated MMP-9. (From Bruno and Cuello 2006. PNAS; with author's and publisher's permission.)

growth-dependent synaptic efficacy. While the evidence for a target-derived action of NGF is strong, it is not clear whether endogenous NGF can also act in a paracrine fashion. However, it has been shown both in rodents and primates that exogenously applied NGF can also act in a paracrine fashion (Tuszynski et al. 2005), a concept (see below) which might have therapeutic applications.

NGF Pharmacology

Both NGF purified from submaxillary glands and genetically engineered recombinant forms of NGF have been successfully applied in a large variety of *in vitro* and *in vivo* experimental models. Both forms have been shown to be equally effective. In most *in vitro* models, NGF displays trophic effects at concentrations as low as 10^{-13} M. In the adult CNS, the recovery of target-deprived or lesioned NGF-dependent neurons can be achieved with the application of doses as low as 1 μg/kg/daily typically administered in the cerebrovascular space for period of a week or longer. The drawback of the application of the NGF protein resides in its broad actions over a large variety of target cells and tissues in the CNS and periphery, its rapid proteolytic degradation and the difficulty with which it crosses the ▶ blood-brain barrier (BBB) for potential CNS reparative applications.

A number of strategies have been explored to develop smaller molecular weight compounds with NGF agonist or antagonistic actions. The initial efforts have involved the testing of NGF diverse fragments, then synthesis of cyclic-peptides mimicking NGF loops and lately, the use of dimeric peptide-mimetic molecules. The majority of these molecules displayed some TrkA antagonistic actions in either *in vitro* or *in vivo* conditions (Longo et al. 2007; Skaper 2008). A recently developed dimeric NGF mimetope named D3 has been shown to display similar efficacy to NGF in recovering the CNS cholinergic phenotype and correcting memory impairments of aged and cognitively impaired rats (Bruno et al. 2004). Whether analogous low molecular weight compounds capable of crossing the BBB will find therapeutic applications remains to be established.

NGF in Health and Disease

The multifaceted aspects of NGF have been repeatedly signaled by Rita Levi-Montalcini, Luigi Aloe and collaborators and they would indicate the possible involvement of NGF in a multitude of functions beyond the classical neurotrophic effects. Two areas of potential therapeutic applications have been given the most attention. These are the potential reparative effects of NGF in ▶ Alzheimer's disease (AD) and the control of the NGF proinflammatory/pronociceptive effects in the periphery.

It is well established that the experimental, exogenous application of NGF in the cerebrovascular space can rescue the cholinergic phenotype and memory functions in the axotomy model of the septo-hippocampal pathway and in the model of retrograde degeneration of nucleus basalis neurons following large stroke-type lesions of the cerebral cortex (Cuello 1994). Furthermore, CNS cholinergic axonal sprouting and synaptogenesis have resulted from the application of NGF in rodent and primate animal models (Cuello 1994). Likewise, it has been

shown that NGF is capable of reversing the well-known age-related CNS cholinergic atrophy. Since ► acetylcholine is known to play a key role in higher CNS functions such as attention, learning and memory, and since this transmitter system is the most vulnerable to AD neuropathology, it was naturally considered early-on as a possible trophic factor for reparative therapy for this neurodegenerative disease. The first therapeutic attempts in AD were made by the intracerebral application of highly purified murine NGF. Despite anecdotal cognitive improvements, these trials were interrupted as the patients developed an unacceptable weight loss and pain. More recently, application of NGF has been restricted to the forebrain in order to overcome these undesirable effects. This has been done in the knowledge that NGF, besides acting as a "target-derived" neurotrophin, also displays paracrine trophic effects. Thus, autologous fibroblasts genetically modified to express human NGF have been grafted in the area of the nucleus basalis in a limited number of AD sufferers (Tuszynski et al. 2005). The drawback of this approach is the invasive nature of the procedure. The development of small molecular weight TrkA agonists capable of crossing the BBB and eliciting neuroregeneration without the activation of pain receptors or provoking loss of body weight would be a desirable objective.

AD pathology occurs concurrently with a marked atrophy of NGF-dependent ► basal forebrain cholinergic neurons. However, in AD there are no signs of a diminished synthesis of NGF, but on the contrary, an elevation of the NGF precursor, proNGF, has been consistently reported (Fahnestock et al. 2001). This creates the paradoxical availability of an abundance of NGF precursor along with cholinergic atrophy. This can now be explained by the finding of an altered metabolism of NGF in AD such that the conversion of proNGF to mNGF is impaired and the degradation of mNGF exacerbated. Such circumstances could offer a conceptual framework for a less invasive pharmacological strategy to correct the NGF dysmetabolism observed in AD.

As noted by Levi-Montalcini and Aloe and observed by others, NGF is capable of recruiting/activating mast cells and inducing an inflammatory response in animal models and in arthritic tissue in the human (Watson et al. 2008). Furthermore, there is good evidence that NGF is elevated in a variety of severe pain conditions in humans. These include arthritis, chronic cystitis, and pancreatitis. The application of NGF or the overexpression of NGF in transgenic animal models results in hyperalgesia and even allodynia. The production and release of NGF is stimulated by a variety of cytokines and inflammatory reagents present in damaged or inflamed tissues. In turn, NGF acts in a pro-inflammatory fashion by recruiting mast cells and facilitating mast cell degranulation. The pronociceptive effects of NGF are thought to be elicited mainly by the stimulation of TrkA receptors present in small diameter spinal cord primary sensory afferents of type Aδ and C. These fibers contain and release either substance P or calcitonin gene related peptide (CGRP), or both. NGF stimulates the production and release of these pronociceptive peptides orthodromically in the spinal cord (first CNS pain signal) and antidromically in the periphery, facilitating further plasma extravasation and mast cell degranulation(Watson et al. 2008). NGF modulates a number of ligand- and voltage-gated ion channels participating in nociception. In particular, NGF enhances the synthesis, membrane expression, and density of the ligand-gated transient receptor potential cation channel of the vanilloid subfamily, member 1 (TRPV1). This receptor responds to capsaicin and a number of noxious stimuli and agents released by injured tissue such as bradikinin. It also sensitizes spinal cord primary sensory fibers to nociceptive stimuli. In consequence, NGF has "feed forward" properties in enhancing and prolonging both inflammation and pain. A number of pain-controlling strategies aimed at blocking NGF actions in the periphery have been explored. Thus, chimeric molecules with dimeric TrkA domains fused to the constant region (Fc) of human IgG domains have been shown to be effective in controlling pain and inflammation in the carrageenan-inflamed rat hind limb model, when injected locally. However, the large molecular size and immunological reactions are potential drawbacks for the clinical application of this molecule. More recently, a recombinant and refolded protein with the amino acid sequence of the d5 domain of TrkA has been shown to be equally effective in a variety of preclinical models. The clinical application of such an approach has not, as yet, been explored. Antibodies against NGF are known to control nociceptive effects. The development of a monoclonal antibody capable of reducing pain and inflammation in a number of preclinical models including bone fractures has encouraged the humanization of these antibodies for further, ongoing, clinical trials with some apparent success (Watson et al. 2008). Small molecular weight molecules acting as NGF antagonists on TrkA receptors may also find an application on this front (Skaper 2008).

Cross-References

► Brain-Derived Neurotrophic Factor
► Mild Cognitive Impairment
► Neuroprotection

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Nerve Impulse

► Action Potentials

Nerve Spikes

► Action Potentials

NET

► Norepinephrine Transporter

Network Oscillations

► Electroencephalography

Neural Plasticity

► Molecular Mechanisms of Learning & Memory

Neuroactive Steroids

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Definition

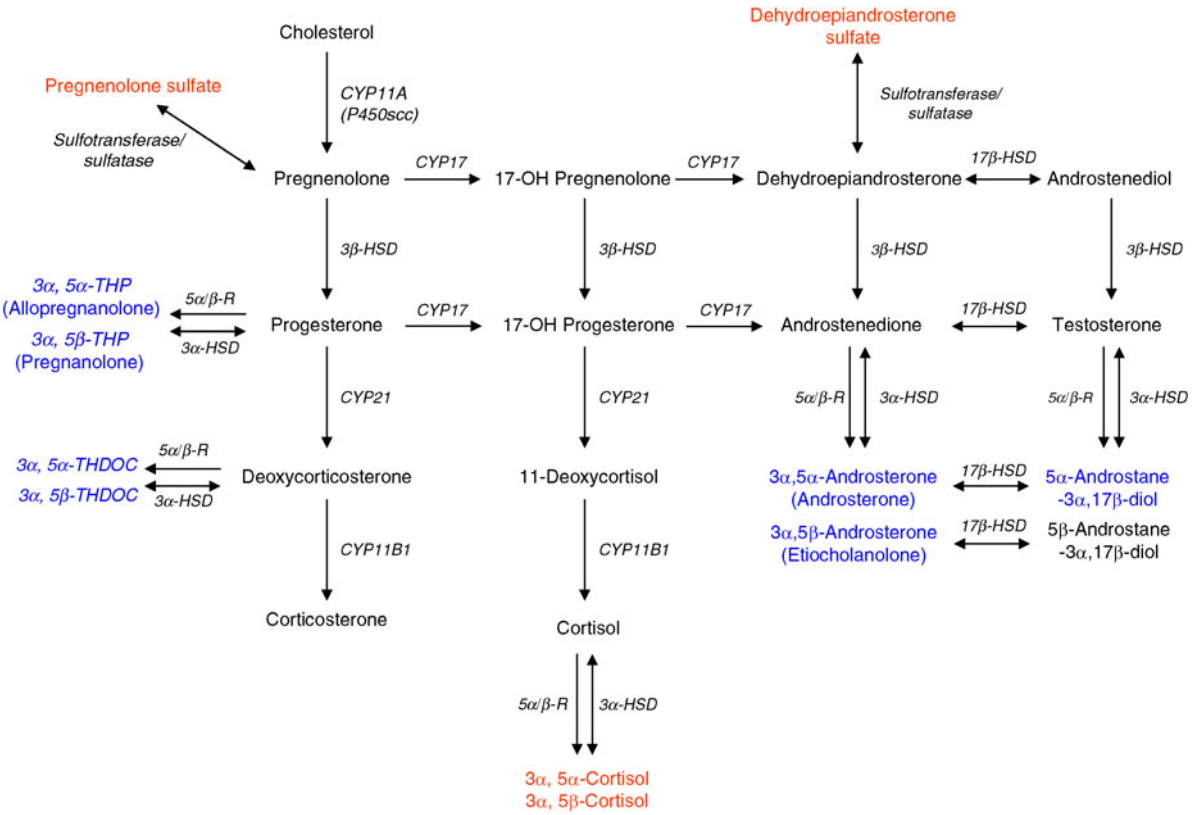
This essay delineates the pharmacological, physiological, pathological and therapeutical relevance of ► neuroactive steroids. These steroids are endogenous or synthetic compounds that can cross the ► blood–brain barrier and rapidly alter neuronal excitability via membrane receptors. We focus on neuroactive steroids that have specific binding sites on γ-aminobutyric acid type-A (► $GABA_A$) receptors which directly influence both synaptic and

extrasynaptic transmission and indirectly alter many physiological processes including ► hypothalamic–pituitary–adrenal (HPA) axis function, inflammation, and myelin formation. Neuroactive steroid levels are modulated by stress, ovarian cycle, pregnancy, as well as numerous pharmacological agents. We summarize the sites of neuroactive steroid actions, the systemic and molecular consequences of these actions, and the potential therapeutic relevance of their effects for neuropsychiatric disease.

Pharmacological Properties

Neuroactive steroids are a class of endogenous neuromodulators that influence brain processes in fundamental ways that affect mood, behavior and all organ systems controlled by brain function. Pioneering work from Baulieu and collaborators in the early 1980s demonstrated the persistence of substantial amounts of pregnenolone, progesterone, dehydroepiandrosterone (DHEA) and their sulfate metabolites in the brain of adrenalectomized/gonadectomized animals. This suggests that the brain was capable of local synthesis of these steroids that were thus termed ► Neurosteroids. Subsequent studies have shown that neurons and glial cells in the brain have the ability to locally synthesize neurosteroids *de novo* from cholesterol (Baulieu 1998). The biosynthetic pathway for neuroactive steroids is shown in Fig. 1. Neuroactive steroids with inhibitory activity on neurons are shown in blue while steroids with excitatory activity on neurons are show in red.

The classical action of steroid hormones is to regulate transcriptional activity and protein biosynthesis over minutes to hours via interaction with nuclear steroid receptors. However, neuroactive steroids have the ability to rapidly (milliseconds to seconds) alter the neuronal excitability by binding to membrane receptors such as ion channels or receptors in the plasma membrane (see Paul



Neuroactive Steroids. Fig. 1. Biosynthetic pathway for neuroactive steroids. While neuroactive steroids with inhibitory activity on neurons are shown in blue, neuroactive steroids with excitatory activity on neurons are show in red. *3α,5α-THP* (3α,5α)-3-hydroxypregnan-20-one; *3α,5β-THP* (3α,5β)-3-hydroxypregnan-20-one; *3α,5α-THDOC* (3α,5α)-3,21-dihydroxypregnan-20-one; *3α,5β-THDOC* (3α,5β)-3,21-dihydroxypregnan-20-one; *3β-HSD* 3β-hydroxysteroid dehydrogenase; *5α/β-R* 5α/5β-reductase; *3α-HSD* 3α-hydroxysteroid dehydrogenase; *17β-HSD* 17β-hydroxysteroid dehydrogenase.

and Purdy 1992, for review). Neuroactive steroids may include any steroid that acts on membrane receptors in brain to alter physiological properties of neurons. These steroids include glucocorticoids, ► estrogens, progesterone, DHEA, as well as the 3α,5α-reduced metabolites of progesterone and deoxycorticosterone that are the primary focus of this essay.

GABAergic Neuroactive Steroids

The 3α,5α- and 3α,5β-reduced metabolites of progesterone, deoxycorticosterone, DHEA and testosterone enhance ► GABAergic transmission and produce inhibitory neurobehavioral effects (see Morrow 2007, for review). The most studied are the progesterone metabolite (3α,5α)-3-hydroxypregnan-20-one (3α,5α-THP or allopregnanolone) and the deoxycorticosterone metabolite (3α,5α)-3,21-dihydroxypregnan-20-one (3α,5α-THDOC or allotetrahydrodeoxycorticosterone). The demonstration of the GABAergic activity of these endogenous compounds (Majewska et al. 1986) initiated decades of further studies, including recognition of their nanomolar potency at ► $GABA_A$ receptor. In contrast, the excitatory neuroactive steroids include the sulfated derivatives of pregnenolone and DHEA, as well as the 3α,5α- and 3α,5β-reduced metabolites of cortisol. While these latter steroids are weak inhibitors of the $GABA_A$ receptors, both pregnenolone sulfate and DHEA sulfate also act as weak ► N-methyl-d-aspartate (NMDA) receptor agonists (micromolar potency).

Pharmacological Activity

Systemic administration of GABAergic neuroactive steroids exerts a variety of pharmacological activities. In the 1940s, Hans Selye reported the sedative, anesthetic and anticonvulsant actions of progesterone. However, in the mid 1980s it was discovered that these properties are due to its GABAergic metabolites (see Rupprecht 2003, for review). Likewise, 3α,5α-THP, 3α,5α-THDOC and their precursor progesterone have potent, dose-dependent, sleep-inducing properties in rats while the 5β-isomer, 3α,5β-THP (pregnanolone) has soporific and anesthetic properties in humans. Moreover, progesterone has been found to ameliorate the symptoms of catamenial epilepsy, a seizure disorder associated with the cyclical variations of steroid hormones during the menstrual cycle. Presently, clinical trials are under way in humans to investigate the antiepileptic activity of the synthetic, neuroactive steroid ganaxolone.

Progesterone and its metabolites, 3α,5α-THP and 3α,5α-THDOC, have ► anxiolytic, antidepressant-like and analgesic properties in animal and human studies. 3α,5α-THP (both after intracerebroventricular and systemic administration) has anxiolytic properties in several different animal models of anxiety-like behavior, such as light–dark transition test, ► open-field test, mirrored chamber test and the ► elevated plus-maze. Similar anxiolytic effects have been found for 3α,5α-THDOC and 3α,5β-THP. In addition to the GABAergic neuroactive steroids, lower doses of pregnenolone sulfate are also anxiolytic, while higher doses are ► anxiogenic, likely due to a combination of mechanisms including metabolism to progesterone and its metabolites. Likewise, DHEA and DHEA sulfate also have anxiolytic activity in mice. Progesterone and 3α,5α-THP have antidepressant-like properties in the Porsolt swimming test and the tail suspension test in rats. Systemic administration of 3α,5α-THP, 3α,5α-THDOC and progesterone also induces analgesic effects in rats, as measured by decreased-pain sensitivity to the tail-flick test. Furthermore, progestins and androgens, respectively, activate and inhibit feminine ► sexual behavior of rodents via their GABAergic metabolites 3α,5α-THP and the 5α-reduced testosterone metabolite (3α,5α,17β)-androstane-3,17-diol.

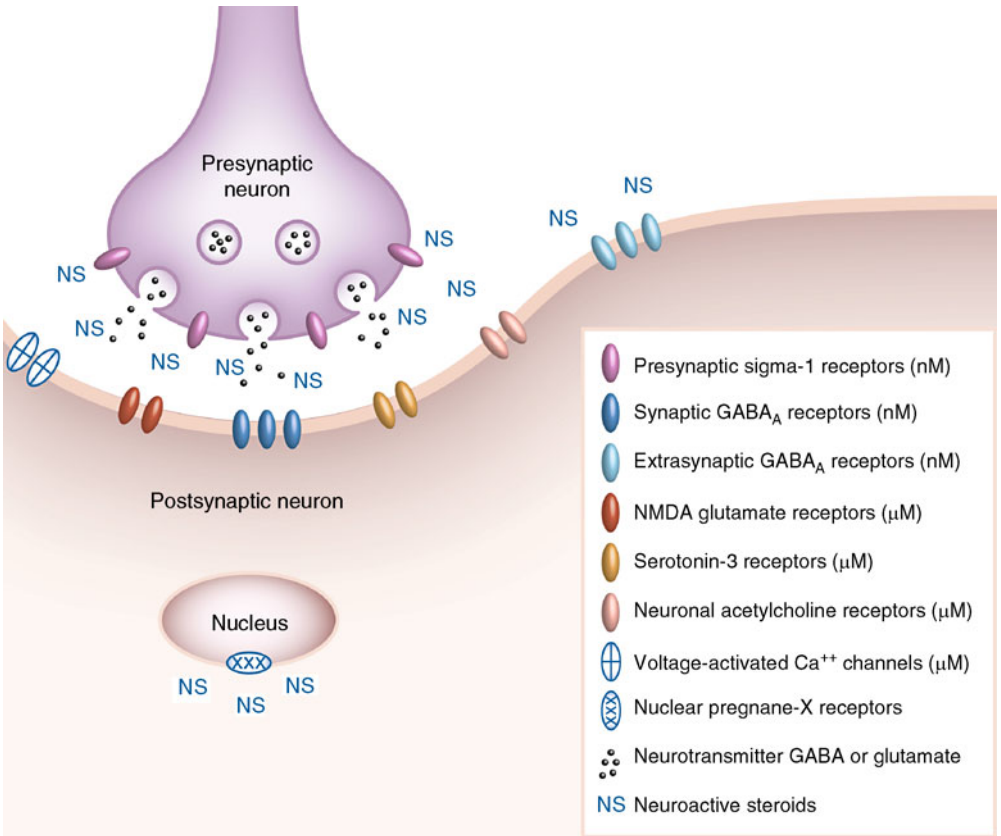
Neuroactive steroids, like various ► drugs of abuse, can have rewarding properties too (see Biggio and Purdy 2001, for review). 3α,5α-THP and (3α,5α,17β)-androstane-3,17-diol appear to have reinforcing properties via $GABA_A$ receptor activation. In addition, 3α,5α-THP and other GABA agonist neuroactive steroids modulate ethanol intake in animal models of ethanol self-administration, increasing consumption when administered at low doses or when modulating low levels of ethanol intake and reducing consumption when administered at high doses or for modulation of high levels of ethanol intake. Furthermore, ethanol-dependent rats show enhanced $GABA_A$ receptor sensitivity to 3α,5α-THP and 3α,5α-THDOC. Further, ethanol-dependent rats are sensitized to the anticonvulsant actions of neuroactive steroids, suggesting that the above class of compounds may be therapeutic during ethanol withdrawal. Indeed, neuroactive steroid therapy may have advantages over benzodiazepine therapy since ► benzodiazepines exhibit ► cross tolerance with ethanol.

In the past decade, studies have shown that 3α,5α-THP has neuroprotective and neurotrophic effects (see Schumacher et al. and Mellon in Morrow 2007). 3α,5α-THP reduces brain swelling and inflammatory cytokines after traumatic brain injury, suggesting a role for neuroactive steroids in the inflammation process. In addition, progesterone and its GABAergic metabolites have neuroprotective effects after traumatic brain injury, spinal cord injury, or cerebral ischemia, and promote remyelination

after peripheral nerve damage. While estradiol has also been shown to promote neurogenesis, DHEA sulfate and 3α,5β-THP hemisuccinate are neuroprotective in experimental models of ischemia and stroke, respectively. Furthermore, 3α,5α-THP, DHEA and DHEA sulfate also have antiapoptotic effects.

Mechanisms and Sites of Action

The sites of action of both excitatory and inhibitory neuroactive steroids are depicted in Fig. 2. The inhibitory actions of the GABAergic neuroactive steroids are mediated by synaptic and extrasynaptic $GABA_A$ receptors. These steroids interact with $GABA_A$ receptors via specific binding sites on α subunits that allosterically modulate binding to GABA and benzodiazepine recognition sites (Hosie et al. 2006). $GABA_A$ receptor function is enhanced by potentiation of GABA-mediated Cl^- conductance as well as direct stimulation of Cl^- conductance in both ►voltage clamp studies and [$^{36}Cl^-$] flux studies. $GABA_A$ receptors appear to have multiple neurosteroid recognition sites that likely reflect distinct recognition sites on $GABA_A$ receptor subtypes. Neuroactive steroids modulate both synaptic and extrasynaptic $GABA_A$ receptors with lower potency at synaptic receptors that contain γ2 subunits and higher potency at extrasynaptic receptors that contain δ subunits (see Belelli and Lambert 2005, for review). These steroids also have modulatory actions at serotonin type-3 receptors neuronal ►nicotinic



Neuroactive Steroids. Fig. 2. Sites of action of inhibitory and excitatory neuroactive steroids. The inhibitory actions of GABAergic neuroactive steroids are mediated by synaptic and extrasynaptic γ-aminobutyric acid type-A ($GABA_A$) receptors. The excitatory actions of sulfated steroids such as pregnenolone or dehydroepiandrosterone (DHEA) sulfate are partially mediated by direct, but low potency, activation of NMDA receptors and inhibition of $GABA_A$ receptors. Pregnenolone sulfate also potently inhibits GABA or glutamate release at nerve terminals. These effects are mediated by presynaptic sigma-1 receptors. Neuroactive steroids have modulatory actions at serotonin type-3 receptors, neuronal nicotinic acetylcholine receptors and voltage-activated calcium channels, albeit with micromolar potency at these sites. Another site of action includes the nuclear pregnane-X receptor that regulates P450 enzymes and steroid hormone levels across many tissues.

acetylcholine receptors and voltage-activated calcium channels, albeit with micromolar potency at these sites (see Rupprecht 2003, for review).

Studies of the structural requirements for neuroactive steroid activity at $GABA_A$ receptors include 3α reduction and 5α/5β reduction of the A ring as well as hydroxylation of C21. The 5β-reduced metabolites of progesterone and deoxycorticosterone, 3α,5β-THP and 3α,5β-THDOC, are equipotent modulators of GABAergic transmission. Humans synthesize these 5β-reduced neuroactive steroids and the concentrations of 3α,5β-THP are physiologically relevant and are comparable with those of 3α,5α-THP in human plasma and cerebrospinal fluid. In addition, 3α,5α- and 3α,5β-reduced cortisol have antagonist properties at both GABA and neurosteroid recognition sites of $GABA_A$ receptors, and these compounds are the most abundant metabolites of cortisol in human urine.

The excitatory actions of sulfated steroids such as pregnenolone or DHEA sulfate are partially mediated by direct, but low potency, interactions with ► NMDA receptors (Fig. 2). Pregnenolone sulfate also potently inhibits GABA or ► glutamate release at different neuronal sites, effects that are blocked by sigma-1 receptor antagonists and therefore thought to be mediated by these receptors. Another site of action includes the nuclear pregnane-X receptor that regulates P450 enzymes and steroid hormone levels across many tissues, but there are no effects of the excitatory or inhibitory neuroactive steroids on nuclear progesterone or ► glucocorticoid receptors.

Physiological Significance

Stress and HPA Axis Activation

► Stress increases plasma and brain levels of GABAergic neuroactive steroids in rodents (Purdy et al. 1991). In rat brain, the increase in 3α,5α-THP reaches pharmacologically significant concentrations in brain between 50–100 nM that is sufficient to enhance $GABA_A$ receptor activity and produce behavioral effects. Similarly, stress or ► corticotropin-releasing factor (CRF) infusion elevates 3α,5α-THP levels in human plasma. The increase in neuroactive steroid levels elicited by stressful stimuli appears to be mediated by activation of the HPA axis, since it is no longer apparent in adrenalectomized animals. Although adrenalectomized animals exhibit no circulating concentrations of 3α,5α-THP and 3α,5α-THDOC, brain levels are still detectable, suggesting that brain synthesis may play an important role in neuroactive steroid actions. In addition, anxiogenic drugs that inhibit GABAergic transmission, activate the HPA axis and produce stress which in turn increases brain and plasma levels of 3α,5α-THP.

The activation of HPA axis in response to acute stress increases the release of CRF from the ► hypothalamus that stimulates the release of adrenocorticotropic hormone (ACTH) from the pituitary, which, in turn, stimulates the adrenal cortex to release glucocorticoids and the GABAergic neuroactive steroids. Glucocorticoids provide negative feedback upon the hypothalamus and pituitary. Likewise, GABAergic neuroactive steroids inhibit CRF production and release, ACTH release, and subsequent corticosterone levels following stress in rodents. The ability of these steroids to reduce HPA axis activation may play an important role in returning the animal to homeostasis following stressful events. The restoration of hypothalamic and pituitary homeostasis may be critical for the maintenance of normal responses to subsequent stress challenges.

Ovarian Cycling

Neuroactive steroid concentrations vary throughout the ovarian cycle in both rodents and humans. 3α,5α-THP levels are increased in rodent brain and plasma during estrus. Likewise, increased circulating levels of 3α,5α-THP have been reported during the luteal phase of the menstrual cycle in women, and treatment with oral contraceptives prevents this increase. Neuroactive steroid concentrations are also dramatically elevated during pregnancy in both rats and women. Rat studies have shown that levels of progesterone and 3α,5α-THP decrease immediately before parturition and return to control levels 2 days after parturition. These abrupt changes in steroid concentrations may contribute to postpartum depressive symptoms. Levels of 3α,5α-THP remain low throughout development and increase immediately before puberty in both humans and rodents. Moreover, 3α,5α-THP levels decline during menopause in women (see Smith et al. in Morrow 2007).

Modulation by Pharmacological Agents

Numerous psychoactive drugs induce an increase in the brain and plasma concentrations of GABAergic neuroactive steroids and their precursors in rats (see Biggio and Purdy 2001 for review). For instance, systemic administration of ethanol increases the brain and plasma concentrations of 3α,5α-THP and contributes to ethanol actions in rats (VanDoren et al. 2000). Likewise, acute administration of psychotropic drugs like ► caffeine or ► nicotine induces a dose- and time-dependent increase in the brain and plasma concentrations of 3α,5α-THP and its precursors pregnenolone and progesterone in rats. All these effects are mediated by activation of the HPA axis, since ethanol, caffeine and nicotine do not alter neuroactive steroids in adrenalectomized rats.

In contrast, chronic ethanol consumption or chronic administration of nicotine to rats does not increase neuroactive steroids. However, ethanol dependence induces adaptations in HPA axis function, with blunted neuroactive steroid responses to stress or to ethanol challenge in both animals and humans. Furthermore, while cigarette smoking in humans does not alter the HPA axis response to pharmacological challenges, serum 3α,5α-THP levels are positively correlated with the nicotine metabolite cotinine, suggesting they may be higher in heavy smokers.

Several other drugs of abuse including ► cocaine, ► morphine, Δ9-tetrahydrocannabinol and γ-hydroxybutyric acid also activate the HPA axis. While acute administration of morphine, Δ9-tetrahydrocannabinol and γ-hydroxybutyric acid increased cerebral cortical levels of 3α,5α-THP, cocaine had no effect at doses that normally increase corticosterone levels. Cocaine may inhibit neuroactive steroid synthesis since other precursor steroids are elevated. For the most part, these drug-induced elevations of 3α,5α-THP levels are dependent on HPA axis activation. Further studies are needed to determine if the effects of acute administration are reversed by chronic exposure or whether humans exhibit elevations under conditions of drug abuse.

Neuroactive steroid concentrations are increased by several drugs that are used to treat ► mood disorders, and it is hypothesized that this increase may contribute to their therapeutic efficacy (see Girdler et al. in Morrow 2007 for review). Acute injection of ► fluoxetine, ► reboxetine, ► venlafaxine or ► imipramine increases the cerebrocortical and plasma concentrations of progesterone and its metabolites 3α,5α-THP and 3α,5α-THDOC in rats. Fluoxetine, ► paroxetine and ► sertraline may increase 3α,5α-THP levels by a direct action on the 3α-hydroxysteroid dehydrogenase enzyme that promotes the formation of neuroactive metabolites. Moreover, chronic treatment with fluoxetine increases cerebrospinal fluid concentrations of 3α,5α-THP of depressed patients. Treatment with other antidepressants, like ► amitriptyline, ► clomipramine, viloxazine, ► nortriptyline, ► mirtazapine and ► lithium, also induced an increase in circulating 3α,5α-THP levels that was associated with improved symptomatology in depressed patients. Other drugs that are used to treat mood disorders, including lithium and ► carbamazepine also increase brain levels of 3α,5α-THP in rats.

The atypical antipsychotic drugs, ► clozapine and ► olanzapine increase the brain and plasma concentrations of pregnenolone, progesterone and their metabolites, 3α,5α-THP and 3α,5α-THDOC, as well as the serum levels of corticosterone (see Payne et al. 2008 for review). The increase in neuroactive steroids is prevented by adrenalectomy, suggesting the involvement of HPA axis activation. In contrast, the typical antipsychotics, ► risperidone and ► haloperidol, induce a modest increase in serum progesterone and corticosterone levels, but do not alter brain 3α,5α-THP. Pregnenolone is elevated in the postmortem brain of patients with ► schizophrenia, though it is unknown if this is secondary to the disease or antipsychotic treatment. Nonetheless, elevations of pregnenolone and the GABAergic neuroactive steroids may contribute to the therapeutic efficacy of clozapine and olanzapine in patients with schizophrenia.

Regulation of $GABA_A$ Receptors

Changes in neuroactive steroid levels that occur *in vivo* under physiological conditions such as puberty, ovarian cycle, pregnancy or lactation are associated with changes in ► $GABA_A$ receptor function and expression (see Smith et al. in Morrow 2007). Likewise, the chronic administration of progesterone, 3α,5α-THP or oral contraceptives to rats also results in changes in $GABA_A$ receptor subunit function and expression. The onset of puberty is associated with abrupt increases in 3α,5α-THP levels and a marked increase in α4 and δ subunit expression in the mouse. Furthermore, administration of 3α,5α-THP, which is normally anxiolytic, increases anxiety in pubertal female mice, perhaps via decreased outward currents at the highly expressed α4βδ $GABA_A$ receptors. The diestrus phase of the mouse ovarian cycle is accompanied by elevated levels of progesterone and 3α,5α-THP, as well as increased expression of the δ subunit and decreased expression of the γ2 subunit of the $GABA_A$ receptor, with consequent increase in tonic inhibition and decreased seizure susceptibility and anxiety.

The regulation of $GABA_A$ receptor subunit expression during pregnancy in rodents is complicated by differential changes across different brain regions. However, the increase in neuroactive steroid levels observed during pregnancy appears to be consistently associated with a decrease in γ2 subunit expression in several regions. This decrease is reversed during lactation when neuroactive steroid levels normalize. More recently, it has been found that the expression of δ subunit is also decreased during pregnancy in mice and this decreased expression is associated with decreased activity of the receptor. Moreover, δ subunit knockout mice exhibit anxiety- and depression-like maternal behavior during the postpartum period, suggesting that δ subunit plasticity may be relevant to the development of postpartum depression (see Smith et al. in Morrow 2007).

Pharmacological treatment with steroids also has the ability to alter $GABA_A$ receptor subunit expression. Thus, administration of oral contraceptives to female rats is associated with increased expression of γ2 subunit mRNA and peptide, decreased levels of pregnenolone, progesterone and 3α,5α-THP, and increased anxiety-like behavior. Likewise, progesterone or 3α,5α-THP administration to female rats increased expression of α4 and δ subunits and decreased expression of the α1 subunit in the ► hippocampus, but the effects are no longer observed after 4–5 days, suggesting a compensatory mechanism to counteract the effects of continued steroid exposure on $GABA_A$ receptors. Furthermore, steroid withdrawal from long-term exposure of both progesterone and 3α,5α-THP results in marked increases in α4 and δ subunit expression in the hippocampus with subsequent changes in receptor function, sensitivity to ► benzodiazepines, and increased anxiety and seizure susceptibility (see Smith et al. in Morrow 2007).

Pathological Significance

Neuroactive steroid concentrations are altered in various pathological conditions including ► depression, premenstrual ► dysphoric disorder, alcoholism and schizophrenia (Morrow 2007; Payne et al. 2008). However, the pathological significance of these alterations remains a matter of speculation. Because neuroactive steroids contribute to regulation of the HPA axis response to stress and are modulated by drugs that are used as medications for neuropsychiatric disease, neuroactive steroids may play a homeostatic role that both reflects and influences the allostatic state of the person and contributes to the wide range of symptomatology associated with all of these disease states.

Patients with major depression have elevated cortisol levels, hypersecretion of CRF and suppression of feedback mechanisms marked by blunted dexamethasone suppression of cortisol levels. Some neuroactive steroid concentrations are decreased in patients with major depression as well as in ► animal models of depression, and administration of antidepressant-specific serotonergic reuptake inhibitors increases these neuroactive steroids in patients and in rodent brain and plasma (see Rupprecht 2003, for review). This increase might be mediated by a direct effect of specific serotonergic reuptake inhibitors on the biosynthetic enzyme 3α-hydroxysteroid dehydrogenase that produces GABAergic neuroactive steroids or by increased serotonin neurotransmission that stimulates the release of CRF to activate the HPA axis. The acute anxiolytic and antidepressant-like effects of neuroactive steroids, demonstrated in rodent models, may be important for prevention and recovery from major depression. Hence, neuroactive steroids may contribute to the therapeutic efficacy of antidepressant medications by contributing to GABAergic inhibition, modulation of the HPA axis, as well as the unknown mechanisms that underlie their acute antidepressant-like activity.

Neuroactive steroid levels are also altered in premenstrual dysphoric disorder, although the literature is controversial with reports of increases, decreases, and no change in 3α,5α-THP plasma levels (see Girdler in Morrow 2007). Differences in analytical methods, diagnostic criteria or presence of other comorbid psychiatric disorders might account for these discrepancies. Premenstrual dysphoric disorder results in dysregulation of the HPA axis and sympathetic nervous system responses to stress. Furthermore, these patients have a blunted 3α,5α-THP response to stress. Women with a history of depression, regardless of premenstrual dysphoric disorder symptoms, also had a blunted 3α,5α-THP response to stress. All this experimental evidence emphasizes the important link between HPA axis function and neuroactive steroid levels in the maintenance of homeostasis and healthy brain function.

Like depression, alterations in HPA axis responsiveness are found in alcoholism during drinking and abstinence (see Morrow in Morrow 2007). ACTH and cortisol secretion increased during ethanol intoxication and acute alcohol withdrawal, but attenuated responsiveness of the HPA axis is found in both drinking and abstinent alcohol-dependent patients. Alcohol-dependent patients have low cortisol and 11-deoxycortisol basal levels, and have a reduced cortisol response to exogenous ACTH challenge. Moreover, they have attenuated ACTH and cortisol responses after pituitary stimulation by ovine or human CRF. Altered cortisol and ACTH responses to ovine CRF and naloxone have also been found in sons of alcoholics. The levels of the GABAergic neuroactive steroids have not been studied under these conditions, but are likely to be impacted since both human and animal studies show that neuroactive steroid responses to stress or HPA axis activation are blunted when ACTH or glucocorticoid responses are blunted. Basal levels of the GABAergic neuroactive steroid 3α,5α-THP are reduced during ethanol withdrawal in humans, when circulating cortisol levels are elevated. Furthermore, abstinent alcoholic patients show a blunted pregnenolone sulfate response to adrenal stimulation and a delayed deoxycorticosterone response to ovine CRF challenge, supporting the idea that blunting of the HPA axis also impacts the GABAergic neuroactive steroid responses to stress in alcoholics.

The levels of neuroactive steroid precursors pregnenolone and DHEA as well as 3α,5α-THP have been studied in postmortem brain of patients with schizophrenia (see Payne et al. 2008, for review). Pregnenolone and 3α,5α-THP were present in human postmortem brain tissue at considerably higher concentrations than typically observed in serum or plasma. Pregnenolone and DHEA levels were higher in both posterior cingulate and parietal cortex of subjects with schizophrenia versus control subjects. 3α,5α-THP levels tended to be decreased in parietal cortex in subjects with schizophrenia when compared with control subjects. Furthermore, pregnenolone, DHEA and 3α,5α-THP levels determined in human postmortem brain in these investigations are known to be physiologically relevant and therefore may have a functional impact on pathophysiology and not merely represent an epiphenomena. In addition, neuroactive steroid induction represents a potential mechanism contributing to the efficacy of clozapine and olanzapine, which in turn increase plasma pregnenolone and 3α,5α-THP levels in rodents. Clinical evidence suggests antipsychotic properties for neuroactive steroids. Progesterone administration ameliorates symptoms of postpartum psychosis in women. Furthermore, adjunct treatment with pregnenolone or 17β-estradiol improves schizophrenia symptomatology in both men and women. Most recently, two independent studies show that pregnenolone improves cognition and negative symptoms in patients with schizophrenia. These findings suggest that neuroactive steroids are candidate modulators of schizophrenia pathophysiology and/or therapeutics.

Progesterone and its GABAergic metabolites promote the viability of neurons in the brain and spinal cord. Neuroprotective effects have been documented in animal models of traumatic brain injury, experimentally induced ischemia, spinal cord lesions and Nieman–Pick type-C disease (see Schumacher et al. and Mellon in Morrow 2007). It is unknown if GABAergic neuroactive steroid levels are deficient or contribute to the etiology of these diseases, but their ability to promote recovery suggests a role in pathophysiology. Indeed, progesterone had remarkable efficacy in a clinical study of traumatic brain injury where it dramatically reduced mortality and increased recovery of function. This is a new area of avid investigation that will likely lead to a better understanding of the role of neuroactive steroids in health and disease.

Therapeutic Potential of Neuroactive Steroids

The preceding sections have alluded to the therapeutic potential of GABAergic neuroactive steroids and their precursors for behavioral disorders that involve anxiety, dysregulation of the HPA axis, ▶ cognitive impairment and brain inflammation. Many neuropsychiatric disorders exhibit these attributes as components of different syndromes that may contribute to severity of disease or recovery under standard treatment protocols. Therefore, neuroactive steroids might be considered as primary or adjunctive therapy that supports normal brain function and cognition, normalization of HPA axis function and the reduction of inflammatory processes that contribute to neuronal dysfunction and cellular death. Since brain inflammation is implicated in depressive disorders, alcoholism, brain lesions, traumatic brain injury and possibly cognitive disorders such as schizophrenia and ▶ Alzheimer's disease, the use of neuroactive steroids or precursors may ameliorate this component of the pathology and thereby support recovery or disease management.

Few neuroactive steroid compounds are under development for neurological or psychiatric disease, despite the data reviewed here. No GABAergic neuroactive steroids are presently approved for clinical use in any disease, therefore compounds are not readily available for clinical testing. The precursor pregnenolone is commercially available as a nutritional supplement and therefore, little impetus exists for clinical trials sponsored by the pharmaceutical industry. The GABAergic neuroactive steroids could also have abuse or dependence potential, and this factor increases the risk of untoward effects – a deterrent to investment in the development of new compounds. Despite these limitations, clinical trials are underway for traumatic brain injury, schizophrenia, alcoholism and anxiety and depressive disorders. Indeed, stimulation of steroidogenesis by direct activation of the 18-kDa cholesterol translocator protein has recently been shown to have therapeutic potential for anxiety disorders, without the side effects concomitant with the use of benzodiazepine anxiolytics (Rupprecht et al. 2009). In addition, ongoing basic research may uncover the role of GABAergic transmission, sigma receptors or pregnane-X receptors in the therapeutic efficacy of neuroactive steroids in animal models. Further studies are needed to evaluate the therapeutic potential of neuroactive steroids.

Cross-References

▶ Alcohol Abuse and Dependence
▶ Anticonvulsant
▶ Antidepressants
▶ Antipsychotic Drugs
▶ Premenstrual Dysphoric Mood Disorder

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Neurobehavioral Teratogens

► Perinatal Exposure to Drugs
► Teratogens

Neurobiological

Definition

Neurobiology is the study of the nervous system and the organization of parts (neurons, glia, and nerve fibers) into circuits that process information and mediate behavior.

Neurocognitive Dysfunction

► Cognitive Impairment

Neurodegeneration

Definition

The progressive neuronal loss caused by cell death.

Cross-References

► Apoptosis
► Neuroprotectants: Novel Approaches for Dementias

Neurodegeneration and Its Prevention

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Definition

"Neurodegeneration" is a common expression and most frequently it is not defined in manuscripts dealing with what authors think it is or could be. An important question is how we define aging, and it is often difficult to differentiate between age-related processes and neurodegenerative ones. This includes neuronal systems that are vulnerable to aging but also to degenerative pathology, and this may happen in certain brain regions while others are spared. Degeneration (in one system only or in several ones?) thus may start with only a functional disturbance triggered by dose-related genetic aberrations or by environmental circumstance.

This article focuses on a classical neurodegenerative disorder for which aging is a major risk factor but with significant differences between the pathology of Alzheimer's disease and the physiological aging process. Thus, we regard this article as a "teaching example." But in addition, Alzheimer's disease presents many pathological features and mechanism which are unspecific, that is, they are common in many neurodegenerative disorders, such as Parkinson's disease, etc. For example, we present many pathological processes which are a general basis of

"neurodegeneration," such as loss of adenosine triphosphate (ATP), disturbances of the respiratory chain activity, disturbances of the energy metabolisms, apoptosis, and ► reactive oxygen species (► ROS).

Impact of Psychoactive Drugs

Among all dementia (see DeDeyn and Pemberton; this volume) ► Alzheimer's disease (AD) is the most frequent dementia disorder in old age. In origin, AD can be divided into two different forms. (1) A very small proportion of 1% or less of all Alzheimer cases is caused by missense mutations in presenilin 1 and 2 on chromosomes 14 and 1, respectively, or in the amyloid precursor protein (APP) gene on chromosome 21, leading to autosomal dominant familial AD with an early onset (Rocchi et al. 2003). These currently known three types of mutations are involved in both the overexpression and abnormal cleavage of APP, and increased formation of its derivative amyloid peptide(s) (e.g., $A\beta_{1-40;\ 1-42;\ 1-43}$) being the inevitable starting point for the disease process of familial AD in the form of the cause–effect principle (► β-amyloid cascade hypothesis) (2). In contrast, millions of people worldwide suffer from sporadic AD, and no such mutations were found as yet for this dementia form. However, two susceptibility genes may contribute to the development of sporadic AD: (1) a ► single nucleotide polymorphism in the gene coding for 11β-hydroxysteroid dehydrogenase I that may amplify the glucocorticoid action in the brain; (2) allelic abnormalities of the apolipoprotein E (APOE) 4 gene on chromosome 19 involved in the lipid transport in the brain and in the metabolism of the plasma membrane constituent cholesterol.

Morphologically, AD is characterized by cell loss in susceptible brain regions, extracellular deposition of β-amyloid containing neuritic ► plaques and ► neurofibrillary tangles mainly composed of hyperphosphorylated tau protein.

Beside the above risk factors, aging has been found to be the main risk factors for AD.

A multitude of inherent variations in fundamental metabolic processes are set into motion at the cellular, molecular, and genetic levels which result from functional imbalances of regulative systems such as

- Energy production (reduced) and energy turnover (increased)
- Insulin action (reduced) and cortisol action (increased)
- ► Acetylcholine action (reduced)
- ► Noradrenaline action (increased) indicative of an increased sympathetic tone, in brain areas due to environmental stress, which in addition causes hypercortisolemia via chronic disturbance of the hypothalamic–pituitary–adrenal axis
- Formation of ROS (increased) and capacity of their degradation (reduced)
- Loss of membrane lipids and shift of unsaturated fatty acids in membranes in favor of saturated fatty acids
- Dysregulation of intracellular pH
- Shift of gene expression profile from anabolic site (reduced) to catabolic site (increased)

to name the functionally most important ones. These variations/shifts may indicate an uncoupling of synchronization of biological systems that may correspond to increased entropy, that is, increased mess-up of a biological system. Smaller additional internal or external events, even one that is ineffective in itself, may change biological and/or biophysical properties of the aging brain. Such events may shift a system in a stepwise manner to increased entropy/decreased criticality ending in a catastrophic reaction (disease) (Hoyer and Froelich 2007; Hoyer and Plaschke 2004).

Physiologically, the mature mammalian brain uses the nutrient glucose exclusively to ensure its structure and function. From the ► glycolytic glucose metabolite fructose-6-phosphate (F-6-P), UDP-*N*-acetylglucosamine (UDP-GlcNAc) is formed and used for protein *O*-glycosylation, for example, for ► tau protein (Hart 1997). The metabolite acetyl-CoA serves as the source of the generation of (1) the neurotransmitter acetylcholine for learning and memory processes and (2) the membrane constituent cholesterol in the 3-hydroxy-3 methyl-glutaryl-CoA cycle. Finally, the energy-rich compound ATP is formed which is essential to most cellular and molecular activities. A hierarchy of ATP-utilizing processes has been proposed in the following order: protein synthesis > RNA/DNA synthesis > Na^+ cycling > Ca^{2+} cycling > proton leak. The position in this hierarchy may be determined by the sensitivity of each process to changes in energy charge.

Highly ATP-dependent processes are (Hoyer and Froelich 2007)

- Sorting, folding, transport, and degradation of proteins
- Maintenance of pH 6 in the endoplasmic reticulum/Golgi apparatus
- Heat shock protein-guided transport across the latter compartments
- Axonal transport of proteins
- Regulation of the conformational state of insulin degrading enzyme
- Maintenance of intracellular/extracellular ion homeostasis

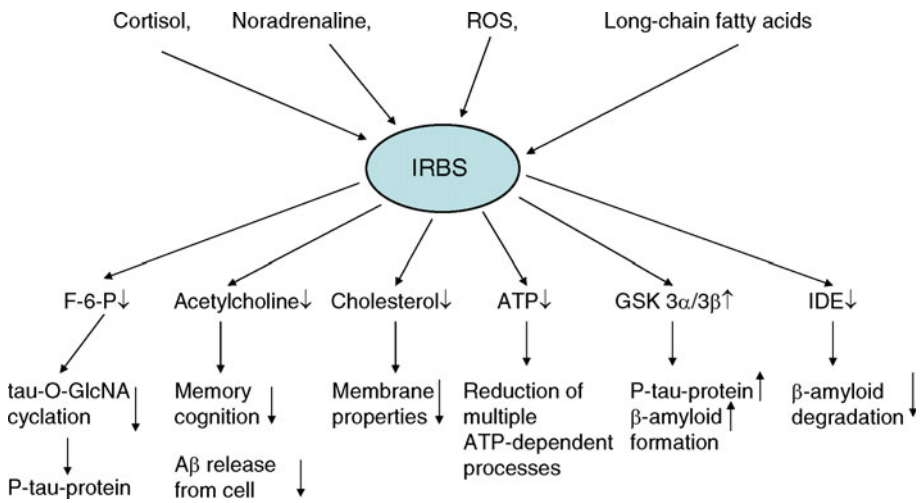
- Maintenance of biophysical membrane properties
- Maintenance of a membrane potential in neurons
- Regulation of synaptic membrane composition
- Maintenance of synaptic transmission
- Control of the metabolism of both APP and tau protein

β-amyloid deposits as a hallmark of AD tell us they are important. However, in contrast to familial AD, it has to be proven yet that the mismetabolism of APP and the increased formation of the derivative β amyloid contribute to the generation of sporadic AD. Recent evidence has been provided that an ► insulin resistant brain state (► IRBS) may play a pivotal role in the generation of the latter dementia form (Grünblatt et al. 2007; Riederer and Hoyer 2006; Salkovic-Petrisic et al. 2006). Several age-related candidates may contribute to the causation of an IRBS:

- Increased concentration of cortisol that may cause neuronal insulin receptor desensitization by inhibition of its tyrosine residues phosphorylation
- Increased activity and metabolism of noradrenaline and increased concentration of cAMP that lead to the decrease of the receptor's tyrosine kinase activity
- Increased concentration of ROS (the uncharged species hydrogen peroxide) that may persistently inhibit the activity of phosphotyrosine phosphatase, thus inhibiting its dephosphorylation and rendering the insulin receptor ineffective
- Increased concentration of long-chain fatty acids that may reduce insulin's receptor binding

An IRBS may induce diverse abnormalities in cellular and molecular brain metabolism (Hoyer 2004) (Fig. 1), among which is the reduction of glucose metabolism including the compound F-6-P, acetyl-CoA, and ATP. F-6-P decrease favors tau hyperphosphorylation; the fall of acetyl-CoA diminishes the formation of both acetylcholine and cholesterol. The reduction of the former decreases the cellular release of APP via its muscarinic receptors; likewise, learning, memory, and cognitive capacities decline. The reduction of cholesterol in the cell membrane changes its properties and may, thus, damage receptor function. The deficit in ATP has a cascade-like effect on diverse ATP-dependent cellular and molecular processes (see above) which may damage cell functions and may jeopardize the survival of the cell. The compromised insulin signaling downstream of the insulin receptor may activate glycogen synthase kinase-3α/β which may result in hyperphosphorylated tau protein and increased production of β-amyloid (Hoyer 2004). The reduced insulin signal may downregulate IDE resulting in a reduced capacity to degrade β-amyloid and, thus, favoring its cellular accumulation.

In contrast to the hereditary form of AD, sporadic AD may be considered to be a complex and self-propagating metabolic brain disease showing predominating abnormalities in oxidative/energy metabolism including decreases in the formation of both acetylcholine and cholesterol finally ending in the formation of neuritic plaques and neurofibrillary tangles. Therefore, a "rational" therapy may be based upon different strategies.



Neurodegeneration and Its Prevention. Fig. 1. Candidates which may induce an insulin resistant brain state (IRBS) and a survey of diverse effects thereafter.

According to all available information about the pathology of sporadic AD, it is evident that multiple drug regimes are necessary in order to come closer to a "disease modifying" treatment strategy. Therefore, multifunctional drugs are necessary to be developed. While the development of anti-Alzheimer (dementia) drugs involves all currently known pathological principles driven by globally acting industry as well as smaller companies and start-up companies, the concept of developing multifunctional drugs is still the one followed by relatively few (Riederer and Gerlach 2009). Worldwide enormous capacity focuses developments into (1) new substances to inhibit acetylcholine esterase or to block glutamatergic *N*-methyl-D-aspartate (NMDA) receptor subunits. Currently, several drug companies develop novel compounds as ▶ acetylcholine esterase inhibitors and also various types of glutamatergic receptor antagonists (Riederer and Gerlach 2009). Other strategies are related to nicotinergic and muscarinergic receptor subtype modulation (see Ragozzine; this volume). These are not expected to be ▶ disease-modifying strategies. The therapeutic potency, side effects, and adverse reaction profile of receptor subtype specific nicotinic and muscarinic drugs still have to be evaluated. (2) There is profound knowledge about the β-amyloid pathology. Based on this, many companies try to develop (1) protein aggregation inhibitors, (2) β- and γ-secretase inhibitors, or (3) vaccination strategies against Aβ-induced plaques (see Le Sage and Pentel; this volume). For the latter, caution is suggested if the data from Holmes et al. (2008) are taken into consideration. These postmortem human brain studies performed on AD patients who have deceased after vaccination with AN 1792 give evidence that reduction of plaque load is not correlated with any cognitive improvement. However, it has been suggested that vaccination at progressed stages of AD comes too late. Therefore, early vaccination strategies are envisaged.

Much less efforts are taken into the reduction of tau-protein related pathology. The reason might be that the focus has been on amyloid because of the proven genetic link between AD and amyloid in the admittedly small number of familiar AD cases.

Current pharmacotherapeutic strategies of sporadic AD consist of supplementation of central acetylcholine deficit by acetylcholine esterase inhibitors (see Newhouse; this volume) and by an ▶ NMDA receptor antagonist. In addition to this standard therapy, other options for interfering with pathological mechanisms are antioxidants to defeat the action of ROS (vitamins-A, -E and -C or Ginkgo biloba). All these therapeutic interventions together are suitable to improve the ▶ quality of life of AD patients for about 1–2 years, but they are unable to reduce or even halt the progression of this devastating disorder.

Antioxidative drug developments are of more general interest as oxidative stress is proven in all neurodegenerative disorders. The same holds true for anti-inflammatory drug developments.

One aspect that, at least in our minds (see above), deserves more attention is influencing the "glucose metabolism." Drug-related interactions are given by (1) α- and β- (PPAR) γ-agonists, (2) glycogen synthase kinase (GSK)-3-α and -β-inhibitors, as well as (3) inhibitors of advanced-glycation-end (AGE) product biosynthesis or inhibitors of AGE-receptors. It is to hope that part of such research will come from antidiabetic research and respective drug developments. Influencing the "IRBS" is right now the most plausible mode of action to causally treat sporadic AD (Grünblatt et al. 2007; Riederer and Hoyer 2006; Salkovic-Petrisic et al. 2006).

There is still a debate about cholesterol, hypercholesterolemia (as measured in plasma/serum), and the use of antihypercholesterolemia directed drugs, statins. As we have pointed out earlier (Hoyer and Riederer 2007) it is necessary to distinguish between the peripheral and central cholesterol-related pathology. There is no question that the treatment of peripheral hypercholesterolemia is useful to reduce and avoid, for example, cardiovascular disturbances. Chronic increase of plasma/serum cholesterol may also disturb the functioning of brain capillaries and thus may provoke β-amyloid pathology within the capillaries epithelium. If so, "peripheral" antihypercholesterolemia treatment by peripherally acting statins may be useful. Experimental proof for this working hypothesis, is, however, still lacking.

As peripheral cholesterol does not pass the ▶ blood-brain barrier, knowledge about soluble and membrane-bound cholesterol in brain regions involved in the pathology of sporadic AD is speculative. While there is evidence for (1) reduced cholesterol in membranes undergoing degeneration and (2) disturbed membrane fluidity based on an imbalance of the cholesterol/fatty acid ratio, there is no data available to judge the role of soluble neuronal/extraneuronal cholesterol. In case of such lack of knowledge, it is not justified to use centrally acting statins, as they may lead to worsening of AD if used in a chronic treatment design. In line with this are all the negative outcomes of prospective clinical studies using statins for sporadic AD (Hoyer and Riederer 2007).

However, all pharmacotherapeutic actions are too late to be effective as "disease-modifying" or even neuroprotective or neurorestorative strategy (see Rhodes and Green; this volume). Therefore, development of biomarkers in

order to detect early phases of pathological development, for example, in the population of "► mild cognitive impaired patients" or even earlier on the basis of "health-control check-ups" is as important as drug development. In fact, there is current effort by both basic/clinical research and industrial interest to get this dual concept into a reality (Riederer and Gerlach 2009).

Conclusion: While early phases of familiar AD show a deficit in glucose consumption but unchanged O_2 consumption, thus giving no evidence for an energy deficit, in later phases of familiar AD a loss of energy may be assumed. In contrast, sporadic AD is based on multiple pathological mechanisms, the more causally related disturbances in the metabolism of glucose and energy being still underestimated by molecular biological and genetic approaches. As such development of multifunctional drugs deserves apparent urgency.

Cross-References

► Acetylcholinesterase Inhibitors as Cognitive Enhancers
► Cognitive Enhancers: Role of the Glutamate System
► Dementias and Other Amnestic Disorders
► Muscarinic Agonists and Antagonists
► Neuroprotectants: Novel Approaches for Dementias
► Neuroprotection

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Neurodevelopmental Hypothesis

Definition

The neurodevelopmental hypothesis suggests that ► schizophrenia results from abnormalities in neuronal connectivity, which arise during fetal life but are not expressed until the onset of illness.

Neuroendocrine Markers for Drug Action

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Definition

The ► hypothalamic-pituitary-adrenal (HPA) axis is a neuroendocrine system that coordinates adaptation of body and brain function to environmental demands: i.e., day- and sleep-related events and ► stressors (Chrousos and Gold 1992). The hormones of the HPA axis operate in a feedforward cascade from hypothalamic ► corticotropin releasing hormone (CRF) and vasopressin via pituitary ► adrenocorticotropin hormone (ACTH) to adrenocortical secretion of glucocorticoids in the circulation. Glucocorticoids in turn feedback on brain and pituitary to shut down the activated HPA axis. In this chapter the mechanism underlying HPA axis functioning is first described, and subsequently the different tests being used to evaluate HPA axis reactivity. Then, specific psychiatric disorders characterized by dysregulation of the HPA axis are discussed and genetic and early life susceptibility factors are referred to. The chapter concludes with an analysis of HPA axis responses that may serve as predictors for the efficacy of psychoactive drugs in humans.

Impact of Psychoactive Drugs

HPA Axis Regulation

Corticotrophin releasing hormone on factor (CRF) and its co-secretagogue vasopressin (AVP) organize the behavioral, sympathetic, and neuroendocrine response to daily- and sleep-related events and stressors (de Kloet et al. 2005). The neuroendocrine response proceeds via the hormones of the HPA axis, e.g., hypothalamic CRF and AVP, pituitary ACTH, and adrenal glucocorticoids. CRF, AVP, and POMC peptides also have elaborate ► neuropeptide networks in the limbic-midbrain which modulate the processing of circadian and stressful information (Herman et al. 2003). Additionally, many neurotransmitter systems influence dynamically at several levels the activity of the HPA axis. These include among others ► GABA, ► glutamate, monoamines, neuropeptides, and gas-based messengers. More recently, the ► endocannabinoid system has been proposed to exert an inhibitory action on HPA axis activation.

Under basal conditions the hormones of the HPA axis are released in hourly pulses (Lightman et al. 2008). The magnitude of these pulses changes during day and night with the largest amplitude at the start of the activity period. Awakening triggers an additional distinct HPA response. The pulsatile HPA axis pattern shows gender differences. The frequency of the pulses alters during chronic stressful or inflammatory conditions. The ultradian rhythm becomes disordered during Cushing and Addison's disease and during the aging process. The pulse generator resides in the hypothalamus, but its nature is unknown and pulses are amplified on the adrenal level. Frequency encoding is a common mechanism in information processing by hormonal systems and evidence is accumulating that resilience in target tissues depends on pulsatile exposure to glucocorticoids.

Superimposed on the ultradian rhythm is the response to stressors. In fact, it has been shown in rats that the magnitude of the HPA axis response depends on the phase of the rhythm: corticosterone responses were larger when a stressor is experienced at the ascending rather at the descending phase. The onset, duration, and magnitude of the HPA axis response is affected by the previous experience, and, in particular, early life events are potent stimuli capable to program the reactivity of the axis to stressors in later life. The most profound psychological stressors are characterized by loss of control, no information, and no prediction of upcoming events combined with a sense of fear and uncertainty. This condition results in a profound and long-lasting activation of the HPA axis.

Receptors

The actions of the various HPA axis hormones are mediated by receptors. CRF has a high affinity to the CRF-1 receptors and a lower affinity to the CRF-2 receptors, which have actually their own privileged ligands urocortin II and III. CRF-1 receptors are on pituitary corticotrophs and have a discrete localization in limbic-midbrain circuitry: such as e.g., in the amygdala, where CRF promotes emotional arousal. Activation of the CRF-2 receptor ligands produces complimentary responses. There is evidence that CRF-1 and CRF-2 receptors mediate different phases of the ► stress-response from activation to later adaptations. CRF-1 antagonists have been developed which suppress fearful and emotional responses in animals and humans (Ising et al. 2007). These antagonists potentially represent a new generation of ► anxiolytic and/or ► antidepressant agents that have an action mechanism within the stress system.

AVP binds to AVP-1 receptors regulating the pressor response, to AVP-2 receptors mediating its antidiuretic action in the kidney, and to AVP-3 receptors in pituitary corticotrophs inducing ACTH release. These AVP receptors are also localized in discrete brain regions. The oxytocin receptor which is localized in central ► amygdala, ventromedial nucleus, ventral subiculum, and olfactory tubercle also displays high affinity to AVP. Peptides such as AVP and OT have long been known to act potently in ► fear conditioning paradigms and have an important modulatory function in psychosocial aspects of behavior.

The glucocorticoids cortisol (man) and corticosterone (man and rodent) readily penetrate the brain and bind to two types of nuclear receptors: high affinity mineralocorticoid receptors (MR) and lower affinity glucocorticoid receptors (GR), which are colocalized in high density in the limbic system. These nuclear receptors also have lower affinity membrane variants that can mediate rapid actions of glucocorticoids in brain. The action of glucocorticoids mediated by the two types of receptors operates in complimentary fashion. The low and high affinity MR are involved in appraisal processes and involved in the onset of the stress response, while the termination of the stress response is facilitated via the GR types (negative feedback) and the way the stressful experience is handled and stored in the memory for future use.

An organism is healthy and resilient when the HPA axis is readily activated as long as it is also turned off efficiently. If coping with stress fails HPA axis regulation is compromised, CRF is usually hyperactive, and stress-induced glucocorticoid secretion can be inadequate or excessive and prolonged. Psychoactive drugs that interact with the stress neurocircuitry in the limbic-midbrain have

the potential to modulate HPA axis regulation, either by direct interaction with the "core" of the HPA axis or indirectly by modulation of afferent pathways. Recovery of HPA axis responsiveness and pulsatility by, e.g., antidepressants precedes recovery from depression.

Testing of HPA Axis Reactivity

Cortisol, the human's principal glucocorticoid, binds in plasma to serum albumin and with higher affinity to corticosteroid binding globulin or transcortin. Hence, total cortisol can be measured as index for adrenocortical output; free cortisol is considered to be the biologically active fraction. Currently, the free cortisol concentration is often determined in saliva, which can be obtained by a much less stressful procedure than blood via venipuncture. In 24 h urine cortisol and 17-ketosteroids (17-OHCS) are measured and are an index for daily production.

Basal values of cortisol are often reported, but these levels must be judged with care. In single measurements, hourly pulses of the hormone may produce variable data unless temporal patterns are measured. Moreover, the amplitude of the cortisol pulse displays a strong circadian rhythm producing high levels of the hormone during awakening and low levels from usually 11.00 p.m. to 5.00 a.m. Finally, 30 min after awakening a sharp rise in cortisol is observed on top of the circadian rhythm. This rise is called the cortisol awakening response (CAR).

Chemical challenges of the HPA axis date back to the 1970s, when administration of 1 mg dexamethasone was used to test the negative feedback capacity of the HPA axis; this is the so-called dexamethasone suppression test (DST). Glucocorticoid receptors (GR) in the pituitary corticotrophs are probably the primary target of dexamethasone, which at these low dosages is hampered to penetrate the brain by multi drug resistance P-glycoprotein located in the ►blood brain barrier. Lower doses of dexamethasone of 0.5 mg and even 0.25 mg can detect more subtle differences in negative feedback function.

An extension of the DST, the combined dexamethasone–CRF challenge was developed as a pharmacological test of reactivity of the HPA axis, further amplifying differences in dexamethasone sensitivity. The principle of the test is that the individuals receive dexamethasone at 23.00 p.m. and then the next afternoon the pituitary–adrenal response to a CRF injection is measured. The CRF in this test enhances escape from dexamethasone suppression. Several other pharmacological challenges of the HPA axis have been developed and applied. To test the integrity of the pituitary gland, ovine CRF or AVP was administrated to depressed patients. Furthermore, ACTH challenges are being performed often using high (250 μg) or low (1 μg) dose Synacthen (synthetic ACTH), to test synthesis and secretion of corticosteroids by the adrenal cortex.

Physical challenges of the HPA axis may involve, for example, strenuous exercise for 20 min on a tread-mill under controlled conditions of O_2 usage and CO_2 production. This condition results in a profound activation of the HPA axis. Such conditions in which energy metabolism is challenged usually are accompanied by a profound increase in adrenal sensitivity to ACTH.

Psychological challenges characterized by lack of control and lack of social support trigger the largest ACTH and cortisol response. The ►Trier Social Stress Test (TSST) is a well-established psychosocial stress test (Dickerson and Kemeny 2004). This test involves a public speaking and mental arithmetic task which needs to be performed in front of an audience and camera, and results in a large increase in ACTH, cortisol and sympathetic activity.

Hypo- and Hypercortisolistic States

Health and resilience are characterized by a reactive HPA axis that is readily turned on and off. Several disease states have been associated with changes in basal and activated HPA axis responses. Thus, *hyper*cortisolemic states usually enhance the risk for infection because of suppression of the immune system. Examples are Cushing syndrome, melancholic depression, ►panic disorder, ►anorexia nervosa, sleep deprivation, ►addiction, and malnutrition. Alternatively, *hypo*cortisolism enhances the risk for inflammatory disorders because the cortisol action is insufficient to restrain the initial stress reactions. Examples are Addison's disease, atypical depression, chronic fatigue syndrome, fibromyalgia, ►post traumatic stress disorder (PTSD), and autoimmune diseases.

Common functional genetic variants that are associated with changes in HPA axis reactivity have been described (DeRijk 2009). Most evidence for specific genetic components is provided by ►single nucleotide polymorphisms (SNPs) in the MR- and GR-genes found to modulate both negative feedback and stress-induced activity of the HPA axis. Importantly, these SNPs in the MR- and GR-genes also associate with aspects of ►depression, indicating their importance as vulnerability factors. Alternatively, a trait defect might be acquired as a result of unfavorable environmental circumstances, particularly during early life (Champagne et al. 2009). These so-called "programming" effects cause changes in the expression of MR and GR with consequences for HPA axis reactivity, neuronal activity, and behavior. In addition, also gender and aging have been found to modulate HPA axis reactivity.

Depression

In depressed patients, basal plasma ACTH and cortisol have been found to be elevated (Holsboer 2000). Also urinary free cortisol, saliva free cortisol, or cerebrospinal fluid (CSF) cortisol levels are increased. Escape from dexamethasone suppression was observed in a subgroup of depressed patients suggesting resistance to corticosteroid action. Hypercortisolism in depression is further supported by the enlarged adrenal glands of the patients. This indicates enhanced adrenal sensitivity to ACTH stimulation. The combined dexamethasone suppression–CRF stimulation test (Dex-CRF test) appears to be the most sensitive tool to detect depression related changes in HPA axis reactivity. Moreover, several studies reported that normalization of the HPA axis precedes or parallels the clinical response to antidepressant treatment (Binder et al. 2009).

Post Traumatic Stress Disorder

Core features of HPA axis changes in PTSD include low basal cortisol secretion and enhanced negative feedback control of the HPA axis (Yehuda 2002). The enhanced negative feedback was found using low-dose dexamethasone (0.25 mg) or metyrapone tests. Blunted ACTH responses to CRF stimulation are explained by downregulated CRFR1, possibly as a result of sustained, increased endogenous CRF levels. However, findings have not been consistent. Differences could involve disease stages, gender, genetic background, or type of trauma among others. Using the combined Dex–CRF test did not reveal HPA-axis abnormalities in PTSD patients when compared to trauma controls (also exposed to trauma but without PTSD). However, PTSD patients with a comorbid MDD showed an attenuated ACTH response compared to PTSD patients without comorbid MDD. This indicates the presence of PTSD subgroups with different HPA-axis regulation.

Psychoactive Drugs that Modulate HPA Axis Reactivity

First, almost all drugs that change central neuronal processes initially modulate basal and stress-induced HPA axis activity, because they acutely change homeostasis (Table 1). Here, drugs that affect parts of the regulatory mechanisms of the HPA axis and that are used in clinical practice are described.

Benzodiazepines. ▶ Benzodiazepines are a major first line of treatment in anxiety disorders. However, little is known of their effect on HPA axis reactivity in man. Administrations of 1 mg ▶ Alprazolam strongly inhibits psycho(social) stress-induced increases in ACTH and cortisol in males. Other ▶ GABA agonists such as Pivagabine (PVG), a hydrophobic 4-aminobutyric acid derivative (7 days treatment, 900 mg, twice a day), could inhibit ACTH and cortisol responses following a psychosocal stressor. Basal levels of cortisol are decreased following administration of Codeine (an opiate), ▶ diazepam, or ▶ oxazepam (benzodiazepines). Prolonged use of benzodiazepines results in profound suppression of the basal and stress-related HPA activity, and discontinuation of these drugs results in rebound activation. ▶ Flumazenil, which has been proposed to exert GABA R antagonistic properties, did show however a decrease in plasma ACTH and cortisol, following administration. ▶ Valproate used to treat bipolar disorders and epilepsy, has several modes of action including inhibition of GABA breakdown. Administration leads to enhanced HPA axis responsiveness. Taken together, drugs that stimulate GABAergic transmission decrease the activity of the HPA axis. ▶ Carbamazepine, acting on voltage dependent sodium channels, is used for mood stabilization in bipolar disorder and in epilepsy. This drug enhances both basal as well as ACTH and cortisol concentrations as outcomes of the Dex–CRF test following prolonged treatment. Also ▶ lithium did enhance Dex–CRF responses but also to increased morning cortisol levels in the DST (1.5 mg).

Cholinergic agents. These agents are mainly used to control blood pressure (hypertension Glaucoma), Myasthenia Gravis and are used during anesthesia. Furthermore, they are suggested to improve clinical signs of ▶ Alzheimer's disease. ▶ Physostigmine, an acetylcholine esterase inhibitor used in Myasthenia Gravis, did not change basal ACTH and cortisol secretion per se, excluding direct effects on basal HPA secretion under these conditions. However, eating-induced ACTH and cortisol responses were further increased. Also acute administration of physostigmine increased plasma cortisol lasting for several hours. Neostigmine (a parasympathomimetic, acetylcholine esterase inhibitor) given epidurally significantly reduced the plasma levels of cortisol in the early surgical period. Ectothiopate (parasympathomimetic, irreversible acetylcholine esterase inhibitor), used as eyedrops in glaucoma, has not been tested on HPA axis parameters. ▶ Scopolamine used to treat motion sickness or together with atropine in anesthesia, is a muscarinic antagonist but did not have an effect on the HPA axis. Pirenzepine, a muscarine 1 receptor antagonist used in peptic ulcers, enhanced the circadian differences of basal cortisol levels. ▶ Rivastigmine, ▶ tacrine, ▶ donepezil, and ▶ galantamine (all cholinesterase inhibitors) used in Alzheimer's diseases, have not been tested on HPA axis parameters and no clear data are available. ▶ Nicotine was

Neuroendocrine Markers for Drug Action. Table 1. Drug effects on HPA axis activity

Drugs				HPA axis			
System involved	Indication	Drugs	Action	Acute effects		Prolonged effects	
Biogenic monoamimes				Basal cortisol	Reactivity	Basal cortisol	Reactivity
NE 5-HT DA		Amphetamine	Reuptake inhibition	No effects			
	Antidepressant drugs	TCA	Reuptake inhibition	Increase		Decrease	Normalization
	Antidepressant drugs	TCA/SSRI	Reuptake inhibition	Increase		Decrease	Normalization
	Antidepressant drugs	Mirtazepine	NSSA, antagonist of 5-HT_2 and H_1	Decrease			
	Antidepressant drugs	Moclobemine	MAO-inhibitor	Decrease			
	Antidepressant drugs	Nefazodone	Antagonist 5-HT_{1a} and alpha1	Small increase			
	ADHD	Methylphenidate	Reuptake inhibition, agonist 5-$HT_{1A\ and\ 2B}$	Increase		Decrease	
NE	Hypertension, migraine	Clonidine	Alpha2 agonist	Decrease			
	Nasal congestion	Methoxamine	Alpha1 agonist	Increase			
	Hypertension	Prozasin	Alpha1 antagonist		Decrease		
	Hypertension	Doxazosin	Alpha2 antagonist	Decrease			
	Hypertension	Propranolol	Beta2 antagonist		Increase		
	Hypertension	Nebivolol	Beta1 antagonist	No effect	No effect		
	Heart failure	Carvedilol	Alpha1/beta antagonist	Increase			
	Depression	Yohimbine	Alpha2 antagonist	Increase	Increase		
	Hypertension	Reserpine	Vesicle depletion	Decrease			
5-HT	Anxiety	Buspirone	5-HT_{1A} agonist	Increase	Increase		
	Anxiety	Gepirone	5-$HT_{1A\ and\ 2A}$ agonist	Increase	Increase		
DA	Schizophrenia	Haloperidole	Antagonist	No effect			
	Schizophrenia	Olanzapine	5-HT_{2C} antagonist	Decrease	Decrease		
	Schizophrenia	Quetiapine	DA NE 5-HT antagonism	Decrease			
	Schizophrenia	Clozapine	DA NE 5-HT Ach H antagonism	Decrease	Decrease		
	Schizophrenia	Respiridone	DA 5-HT antagonism	Small decrease			
	Schizophrenia	Sulpiride	D_2 antagonism		Decrease		
	Parkinson	Levidopa		Decrease	Decrease	Decrease	Decrease
	Parkinson	Pramipexole	D_2 agonist	Unclear			
Acetylcholine		Nicotine	nAch agonist	Increase	Increase	Small effects	Attenuation
	Motion sickness, anesthesia	Scopolamine	mAch Agonist				
	Peptic ulcers	Pirenzepine	mAch Agonist				
	Myasthenia Gravis	Physostigmine	Cholinesterase inhibitor	Enhanced			
	Surgery	Neostigmine	Cholinesterase inhibitor	Decreased			

Neuroendocrine Markers for Drug Action. Table 1. (continued)

Drugs				HPA axis			
System involved	Indication	Drugs	Action	Acute effects		Prolonged effects	
Amino acids							
GABA	Anxiety suppression	Alprazolam	Agonist		Decrease		
	Anxiety suppression	Pivagabine (PVG)	Agonist		Decrease		
	Anxiety suppression	Diazepam	Agonist			Decrease	
	Anxiety suppression	Oxazepam	Agonist			Decrease	
	Anesthesia	Propofol	Agonist	No effect			
	Surgery trauma	Etomidate	Agonist	Decrease			
	Anesthesia	Thiopental	Agonist barbiturate	Decrease			
	Overdosis Bezo's	Flumazenil	Antagonist	Decrease			
Glutamate	Anesthesia	Ketamine	NMDA antagonist	Increase			
	Amyotrophic lateral sclerosis	Riluzole	Blocks release, antagonist	No effect	No effect		
Neurotransmitter release	Anesthesia	Halothane	Reduced transmitter release and action	Increase			
	Anesthesia	Isoflurane	Reduced transmitter release and action	Increase			
	Anesthesia	Sevoflurane	Reduced transmitter release and action	Increase			
	Anesthesia	Droperidol+Opioid	Dopamine antagonist	Increase			
	Inflammation	Aspirin	Inhibition of PG synthesis	No effect			
Neuropeptides							
CRH		NBI-34041	CRHR1 antagonist		Decrease		
Corticosteroids	Inflammation	Dexamethasone	GR agonist	Decrease	Decrease	Decrease	Decrease
	Depression, pregnancy	Mifepristone	GR antagonist	Large increase		Large increase	
	Salt wasting	Fludrocortisone	MR agonist	Decrease	Decrease		
	Hypertension	Spironolactone	MR antagonist	Increase	Increase		
Cannabinoids	Marijuana	Tetrahydrocannabinol (THC)		Increase			
Opioids	Pain	Codeine		Decrease			
	Pain	Cocaine	Reuptake inhibition	Increase			
	Anesthesia, pain	Remifentaxil	Agonist	No effect			
	Addiction	Naloxone	Mu antagonist	Increase			
	Addiction	Methadone	Antagonist	Increase			
Ion channels	Bipolar Epilepsia	Valproate	Inhibition GABA breakdown		Enhanced		
			Inhibition sodium channels				
	Bipolar Epilepsia	Carbamazepine	Inhibition sodium channels	Enhanced	Enhanced		
	Bipolar	Lithium		Enhanced	Enhanced		

found to be a strong activator of the hypothalamus pituitary adrenal (HPA) axis. In habitual smokers, a few cigarettes activate the HPA axis, but only small changes of basal HPA axis activity are observed, with an attenuated responsiveness of the HPA axis to psychological stress but not to injection of CRF. Etomidate, used in trauma settings to intubate patients, is short acting and activates GABA R and possibly also mACh receptors. It lowers plasma cortisol levels because of inhibition of the 11 β hydroxylase blocking the conversion of deoxycortisol to cortisol.

Biogenic monoamines and antidepressants. Monoamines clearly activate the HPA axis. Modulators of ▶ monoamines are used for the regulation of blood pressure and in psychiatric disorders. Oral administration of 5-HTP, the direct precursor of ▶ serotonin (5-HT) induces fast dose-dependent increases in circulating ACTH and cortisol. Also administration of the 5-HT releasing agent ▶ D-fenfluramine or the piperazine-based 5-HT receptor agonist mCPP increases acutely ACTH and cortisol responses. ▶ Buspirone, a 5-HT_{1A} agonist used to treat anxiety disorder, induces ACTH and cortisol responses following acute challenges. Gepirone, a partial 5-HT_{1A} agonist having ▶ anxiolytic properties, also resulted in large increases in plasma cortisol.

Noradrenaline (NE) or serotonin (5-HT) reuptake-inhibiting antidepressants such as ▶ reboxetine or ▶ citalopram acutely stimulate cortisol and ACTH release in healthy volunteers. ▶ Mirtazapine, a noradrenergic and specific serotonergic antidepressant (NaSSA), acutely inhibits the ACTH and cortisol release, probably due to its antagonism at central 5-HT_2 and/or H_1 receptors. The classic TCAs, such as desipramine, ▶ imipramine, and ▶ clomipramine, also induce an acute increase in ACTH and cortisol levels. Following longer treatment with most reuptake inhibitors, including SSRI's and noradrenergic specific reuptake inhibitors, a gradual normalization of the hyperactive HPA axis is found in depressed patients (Binder et al. 2009). These chronic effects probably depend, at least in part, on the increased expression of MR and GR, leading to a normalization of HPA axis reactivity. Nefazodone, a 5-HT_{2A} and alpha1 adrenergic antagonist also inhibiting NE and 5-HT reuptake, increased slightly cortisol levels following administration in healthy subjects. ▶ Moclobemide, a selective MAO-A inhibitor mostly used in refractory depression, slightly decreases cortisol levels upon acute administration.

▶ Methylphenidate is a norepinephrine and dopamine reuptake inhibitor with affinity for the serotonergic 5-HT_{1A} and 5-HT_{2B} is used in ADHD as a psychostimulant. Acute administration induces increases in cortisol while prolonged treatment with methylphenidate did not seem to affect basal cortisol or cortisol levels during exercise. ▶ Amphetamine increases levels of norepinephrine, serotonin, and dopamine in the brain by actions on the transporter and synaptic vesicles. However, acute amphetamine administration up to 20 mg did not activate the HPA axis. Cocaine is a dopamine, norepinephrine, and a serotonin reuptake inhibitor and acute administration induces an increase in plasma ACTH and cortisol.

Clonidine is an alpha2-adrenergic agonist used in hypertension and migraine, and its acute administration resulted in a strong decrease of the activity of the HPA axis, with low ACTH and cortisol levels. Methoxamine, an alpha1 agonist used for nasal congestion, enters the CNS following peripheral administration. ACTH and cortisol increased early during methoxamine infusion and ACTH returned to baseline promptly after the infusion ceased.

▶ Prazosin, an alpha1 antagonist used as an antihypertensive, lowers challenge induced activation of the HPA axis. ▶ Yohimbine is an alpha2-adrenergic antagonist acting on presynaptic terminals that inhibit (nor)adrenaline release. Acute administration of yohimbine results in increases in CSF noradrenaline levels leading to increases in plasma ACTH and cortisol. Following a serotonergic challenge, coadministration of yohimbine further increases cortisol values. Doxazosin, an alpha2 antagonist for treatment of severe hypertension, resulted in a short-lasting decrease of plasma cortisol. For ▶ propranolol, a beta receptor antagonist, mixed results have been reported ranging from no effects (psychosocial stress) to increased cortisol responses (exercise). Prolonged administration of Carvedilol, having alpha1 and beta receptor antagonistic properties, leads to a noticeable increase in serum cortisol levels. Nebivolol, a beta1 selective blocker with vasodilator properties, did not seem to affect basal cortisol or during exercise.

▶ Reserpine, which depletes stores of NE by inhibiting vesicular uptake, decreased basal excretion of urinary 17-OHCS significantly in Cushing patients and caused normalized suppression of plasma cortisol by 1 mg dexamethasone.

Glutamate. ▶ Ketamine is a clinical available NMDA receptor antagonist also used as an anesthetic, because of its effects on opioid receptors at higher dosages. Furthermore, ketamine is found to reduce the symptoms of opiate withdrawal, suggesting its potential role in the treatment of addiction. Acute administration of ketamine (e.g., 0.5 mg/kg) induces increases in plasma cortisol. The antiglutamatergic drug riluzole did not have any effects upon HPA system activity under baseline and cognitive-stress-induced conditions in elderly subjects.

Dopaminergic Drugs

Drugs activating the dopamine system are typically used to treat ▶ Parkinson's disease while antagonists of the dopamine system are used to treat psychotic symptoms, which often occur in ▶ schizophrenia and ▶ depression.

▶ Haloperidol, a dopamine antagonist used in schizophrenia, did not lower basal cortisol levels in control subjects. Among the atypical antipsychotic medication, olanzapine, an antagonist of several 5-HT receptors, the histamine H_1 receptor and the dopamine (D2) receptor, lowers basal cortisol levels at night in healthy male controls following a standard 8 days treatment. Similar effects on cortisol have been observed in patients with schizophrenia. Treatment of patients with ▶ olanzapine resulted in a blunted ACTH and cortisol responses following a mCPP challenge. Also ▶ quetiapine, showing dopaminergic, adrenergic and serotonergic receptor antagonism, lowers nocturnal cortisol output in healthy subjects. ▶ Clozapine, used for treatment resistant schizophrenia shows antagonist properties for different subtypes of dopaminergic, adrenergic, cholinergic, and histaminergic receptors. Basal cortisol levels decrease slightly during clozapine treatment. Clozapine might also inhibit mCPP-induced cortisol responses. ▶ Risperidone, acting at dopamine (D_2) and serotonergic ($5\text{-}HT_{2A}$) receptors, induced a modest decrease of cortisol levels following treatment. ▶ Sulpiride, a selective antagonist at postsynaptic D_2-receptors, suppresses increases in plasma cortisol levels induced by repetitive blood sampling at 180–240 min, compared with the response to placebo.

▶ Levodopa, first line treatment for Parkinson's disease, decreases plasma cortisol after acute administration. Also during physical exercise which increases cortisol, Levodopa resulted in a decrease of plasma cortisol in patients with Parkinson's disease. However, in children, administration of levodopa in combination with propranolol increased plasma cortisol. ▶ Pramipexole, a D_2 receptor agonist used in Parkinson's disease does not have a clear effect on cortisol levels. In conclusion, antagonists of dopaminergic transmission seem to inhibit HPA axis reactivity.

Anesthetic and Sedative Agents

This class of drugs generally inhibits excitatory channels (e.g., glutamate) and facilitates inhibitory channels (e.g., GABA). Ether induces a profound activation of the HPA axis with high levels of ACTH and cortisol. Halothane also induces an increase in plasma ACTH following administration without surgery in healthy volunteers. General anesthesia maintained with an isoflurane-nitrous oxide-oxygen mixture or sevoflurane is followed by a sharp increase in plasma cortisol. The combination of droperidol, a dopamine D_2 antagonist, with an opioid analgesic induced plasma cortisol elevations. In contrast, a mixture of propofol (acting at $GABA_A$ and maybe glycine and endocannabinoids) and remifentanyl (mu opiate receptor agonist) did not activate the HPA axis, and even blocked HPA axis responses during surgery. However, still under anesthesia with propofol, synthetic ACTH was still capable of inducing a profound cortisol plasma level elevation. Thiopental, a barbiturate acting on GABA receptors, also decreased plasma levels of cortisol during anesthesia and surgery. Other analgesic drugs such as aspirin did not affect basal or stress-induced HPA axis responses.

Opioids. ▶ Endogenous opioids, such as POMC-derived ▶ endorphins and the ▶ enkephalins, exert inhibitory influences on HPA axis activity; see remifentanyl (mu opiate receptor agonist) above. ▶ Naloxone, a mu opiate receptor antagonist, increases HPA axis activity by blocking the inhibitory tone of opiates on hypothalamic CRF secretion. However, the acute administration of ▶ methadone, an opioid agonist results in a profound short-lasting activation of the HPA axis.

Cannabinoids. Smoking of marijuana or acute administration of tetrahydrocannabinol (THC) induces release of ACTH and cortisol. However, ▶ endocannabinoids limit activation of the HPA axis. This difference in action probably results from context-dependent effects of endocannabinoids or a dose-dependency.

CRF antagonists. CRF is central in the activation of the HPA axis and increased expression is thought to play a role in several stress-related disorders. CRFR1 antagonists (e.g., NBI-34041) are currently explored as new antidepressants. CRFR1 antagonist decreased psychosocial stress-induced ACTH and cortisol responses, but not following CRF injection. This indicates that their effects are primarily in the brain to modulate behavioral appraisal rather than ACTH release from the pituitary and thus act not directly at the HPA axis.

Corticosteroids. Dexamethasone has been used to test negative feedback of the HPA axis. To test for Cushing's disease, dosages of 4 mg are used which in all healthy subjects results in suppression of morning ACTH and cortisol levels. Lower dosages such as 1.5, 1, 0.5, or 0.25 mg test for negative feedback at the level of the pituitary gland for more subtle changes, as observed in patients suffering from depression or PTSD. Also hydrocortisone (cortisol) has been used to test HPA axis negative feedback.

Mifepristone (RU 486) is a compound with progesterone as well as cortisol blocking activities. Within a day of treatment (e.g., 200 mg/day) increases in plasma ACTH and cortisol are observed, as a results of loss of the

feedback action of endogenous glucocorticoids. The compensatory increase in ACTH also resulted in increases in deoxycortisol, progesterone, and ► androgens. During prolonged treatment a resetting of the HPA axis at higher levels occurred showing an increase in the amplitude of circadian rhythmicity and an enhanced responsiveness to CRF administration, whereas sensitivity to dexamethasone decreased.

Fludrocortisone, a MR agonist, exerted a significant inhibition of ACTH and cortisol after acute administration (0.5 mg p.o.). Spironolactone, a MR antagonist, induces acute increases in plasma ACTH and cortisol, which supports a function of the MR in inhibiting the HPA axis under basal conditions.

Conclusions

Stress-induced HPA axis activation is blocked by corticosteroids as well as GABA and opioid agonists. HPA axis activity also is induced by glutaminergic, noradrenergic, and serotonergic agonists. The ► pharmacokinetic characteristics of the drugs need to be taken into account with respect to their penetration through the ► blood brain barrier and their site of action in the complex neural circuitry underlying HPA axis activation.

Prolonged use of drugs may result in adaptation of the HPA axis leading to *hypo* or *hyper*cortisolemic states. Alternatively, antidepressants such as SSRI's and TCA's and, to some extent, benzodiazepines, may normalize an overactive HPA axis. Hence, drugs may affect a wide range of peripheral and central functions through their action on the HPA axis.

These actions exerted by the drugs may be either directly targeted to the core of the HPA axis – the adrenal, pituitary, or PVN, or the drugs may act indirectly on circuits involved in processing of stressful information underlying emotional, motivational, and/or cognitive processes. Irrespective of the site and mode of action of the drugs it is often difficult to disentangle primary or secondary psychotropic effects proceeding through the HPA axis.

Cross-References

► Addictive Disorder: Animal Models
► Aminergic Hypotheses for Depression
► Analgesics
► Anticonvulsants
► Antidepressants
► Anti-Parkinson drugs
► Antipsychotic drugs
► Anxiety: Animal Models
► Arginine Vasopressin
► Benzodiazepines
► Beta-Adrenoceptor Antagonists
► Cannabinoids and Endocannabinoids
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► Corticosteroid Receptors
► Corticotrophin Releasing Factor
► Depression: Animal Models
► Glucocorticoid Hormones
► Opioids
► SSRIs and Related Compounds
► Stress: Influence on Drug Action
► Traumatic Stress (Anxiety) Disorder
► Trier Social Stress Test

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Neuroethics

Definition

Neuroethics is the study of the ethical, legal, and social questions that arise when scientific findings about the

brain are carried into medical practice, legal interpretations, and health and social policy. Neuroethics is a subfield within the broader domain of bioethics, which encompasses the ethical and moral implications of all biological and medical advances. Neuroethics was established to address the rapid developments within cognitive neuroscience and neuropsychiatry and addresses findings relating specifically to the sciences of the mind encompassing the central nervous system and the underlying brain mechanisms of human behavior.

In response to the advances in cognitive neuroscience and neuropsychiatry and their increasing potential for broader application in the "real world," and in part to the use of pharmacological cognitive enhancers in healthy individuals, the Neuroethics Society (www.neuroethicssociety.org) was established.

Cross-References

► Cognitive Enhancers: Neuroscience and Society
► Ethical Issues in Human Psychopharmacology

Neurofibrillary Tangles

Definition

Intraneuronal pathological fibers consisting of neurofilament and neurotubules based on hyperphosphorylation of cytoplasmic tau protein.

Neurogenesis

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Synonyms

Adult neurogenesis; Postnatal neurogenesis

Definition

Neurogenesis refers to the production of new neurons in the brain; it is a complex process that begins with the division of a precursor cell and ends with the formation of a fully differentiated, functioning neuron.

Impact of Psychoactive Drugs

Neurogenesis

Postnatal cell proliferation in the brain of mammals has been occasionally reported during the first half of the twentieth century; however, this phenomenon only gained momentum in the 1960s (Altman 1962). By then, it was not clearly established if these newly born cells could develop into functional neurons and the potential importance of the original observations was not fully appreciated. In the 1990s, however, a clear-cut demonstration of neurogenesis in the adult brains of various species (from rodents to humans) was provided (Manganas et al. 2007); it was later shown that after maturation and differentiation, newly generated neurons are functionally integrated into preexisting neuronal circuits (most notably in the hippocampus). In the subventricular zone, neurogenesis gives rise to neurons that migrate through the rostral migratory stream and which are integrated as interneurons in the olfactory bulb.

How Is Neurogenesis Measured?

Early studies used [^{3}H]-thymidine, which incorporates into replicating DNA during the S-phase of the cell cycle, to label dividing cells by autoradiography. An important technical improvement was the introduction of the synthetic thymidine analog BrdU (5-bromo-3-deoxyuridine) that substitutes for thymidine in the newly synthesized DNA of proliferating cells. BrdU incorporated into DNA can then be easily visualized with immunocytochemical techniques using specific antibodies against BrdU. This technique allows quantitative analysis of proliferation, migration, differentiation, and survival of newborn cells by varying the time interval between the pulse administration of BrdU and the sacrifice of animals. Other specific antigenic or histochemical markers are usually combined with BrdU immunocytochemistry to reveal cell phenotypes, differentiation state, and survival. While BrdU labeling is the most commonly used method for studying adult neurogenesis, other markers, such as proliferating nuclear antigen (PCNA) and Ki-67, may substitute or complement analysis by BrdU labeling.

Neurogenesis, Depression and Antidepressant Treatments

Several thousand new cells are added to the adult rodent hippocampus each month, although the rate of constitutive neurogenesis declines with age. At the same time, however, there is a parallel loss of cells in this brain region through the process of apoptosis; therefore, neuronal turnover is likely to be of greater relevance than either neurogenesis or ► apoptosis alone.

While early studies in songbirds suggested a functional role for adult neurogenesis in seasonal song learning, the functional importance of this process in mammals remains unclear (Shors et al. 2002). However, it is a highly regulated process through the actions of hormones, growth factors, neurotransmitters, and environmental factors. In particular, glucocorticoids (e.g., cortisol) exert a strong negative influence on neurogenesis, an effect that may explain the marked reduction in hippocampal granule cell proliferation after exposure to ► stress; on the other hand, ► antidepressants stimulate hippocampal neurogenesis and can reverse the effects of stress. Since many depressed subjects display glucocorticoid hypersecretion (as a result of HPA axis dysregulation), a link between high levels of circulating adrenal steroids with reduced neurogenesis and depression is plausible. This view has been supported by observations of hippocampal atrophy in depressed patients (Sheline et al. 2003).

In contrast to adrenal steroids and stress, ► antidepressant drugs (including tricyclics and selective serotonin reuptake inhibitors ► SSRIs), as well as ► electroconvulsive therapy, lead to increased neurogenesis in the ► hippocampus in association with decreased depression-like behavior in animal models (Malberg et al. 2000). Altered monoaminergic transmission provides the best mechanistic explanation for these changes; two neurotransmitters of particular relevance are ► noradrenaline (NA) and ► serotonin (5-HT), the latter being a major regulator of adult neural cell proliferation. In adult rats, d,l-► fenfluramine, which releases 5-HT throughout the central nervous system, has a significant stimulatory effect on hippocampal dentate granule cell division, whereas reductions of 5-HT by lesioning 5-HT neurons with 5,7-dihydroxytryptamine (5,7-DHT) or the inhibition of 5-HT synthesis with parachlorophenylalanine (PCPA) result in long-term disruption of the proliferative capacity of the hippocampus. The neurogenic actions of 5-HT are mediated primarily by 5-HT_{1A} receptors but also by 5-HT_{2A} and 5-HT_{2C} receptors. Additionally, the recently introduced antidepressant, ► agomelatine, which is a mixed MT1/MT2 melatonin receptor agonist and 5-$HT_{2B/2C}$ receptor antagonist, also increases hippocampal neurogenesis and can reverse the anti-neuroproliferative effects of prenatal stress. Likewise, stress-induced reductions in neurogenesis can be reversed with ► corticotropin releasing factor type I receptor (CRF-R1) and ► arginine-vasopressin V1b receptor (AVP-1bR) antagonists, consistent with their ability to suppress adrenocortical secretion. However, the antidepressant clinical efficacy of these drugs remains to be established. Finally, the neurokinin type 1 receptor (NK1R) antagonists, which have been shown to increase neurogenesis in animal models, have failed to reveal significant antidepressant efficacy in clinical studies. Besides the antidepressants mentioned above, the atypical antidepressant tianeptine and the mood stabilizer ► lithium have also been found to increase proliferation and survival of new neurons in the dentate gyrus.

Together, the observations described, especially those derived from validated animal models of depression (► Depression: animal models) form the backbone of the notion that the therapeutic actions of antidepressants in patients depend on the generation of new hippocampal neurons. Irradiation of the hippocampus of naive ("non-depressed") mice abolishes the ability of antidepressants to relieve signs of anxiety behavior (Santarelli et al. 2003); anxiety is one behavioral element commonly seen in depressed patients but does not fully reflect the depressed state. However, other experiments in which hippocampal neurogenesis was blocked by chemical means clearly indicate that a wide range of antidepressants can improve depressive-like behavior in an appropriate model of the disease (rats exposed to a chronic mild stress paradigm) even in the absence of ongoing neurogenesis (Bessa et al. 2009). Accordingly, while the role of adult neurogenesis in the etiology of depression remains unclear, some researchers have focused on the potential importance of neurogenesis for other dimensions of recovery from depression, such as cognitive improvement (Perera et al. 2008).

If not Neurogenesis, then what?

Although the exact mechanisms by which stress and glucocorticoids on one hand, and antidepressants and serotonin on the other, affect neurogenesis have not been completely elucidated, there is evidence that implicates changes in the expression of cAMP response element binding (CREB) protein and, in turn, of ► brain-derived neurotrophic factor (BDNF). BDNF plays key roles in the survival and guidance of neurons during development, and is required for the survival and normal functioning of neurons in the adult brain. Stress triggers a decrease in brain levels of BDNF, thus potentially compromising neuroplasticity and neuronal development and survival. Since all current antidepressant treatments (drugs and electroconvulsive therapy) upregulate CREB and BDNF expression, it can be inferred that the cAMP-CREB cascade and BDNF are common targets of both stress (through elevated glucocorticoid secretion) and antidepressant treatments, with the opposing stimuli acting to influence neuroplasticity.

To gain an insight into how stress and antidepressants act, it is important to note that their effects are not

restricted to the regulation of adult neurogenesis. Exposure to chronic stress induces significant atrophy, debranching and synaptic reorganization of neurons in all divisions of the hippocampus, changes that negatively correlate with hippocampus-dependent cognitive functions such as learning and memory. Further, the changes in dendritic and ▶ synaptic plasticity correlate with decreased expression of neural cell adhesion molecule (NCAM) and synaptic related proteins such as synapsin 1 and are reversible with a variety of antidepressant drugs. Importantly, some of the stress-induced alterations in hippocampal plasticity propagate to other brain regions; for example, chronic stress interferes with dendritic and synaptic structure of pyramidal neurons in the prefrontal cortex in association with the onset of deficits in working memory and behavioral flexibility. In parallel, other brain regions show signs of hyperactivity, consistent with the consensual view that the cluster of depressive symptoms results from a "push-and pull" interplay between different brain regions. For example, anhedonia, a core symptom of depression that is characterized by decreased interest in pleasurable activities or the inability to experience pleasure, has been associated with a dysfunction of the brain reward pathway. ▶ Dopamine (DA) released from cell bodies in the ▶ ventral tegmental area (VTA) at terminals in the ▶ nucleus accumbens (NAc) plays a central role in this pathway and dysfunctional or suboptimal DA transmission has been implicated in the pathophysiology of depression. Altered dopaminergic neurotransmission in the VTA-NAc pathway modulates depressive-like behavior in animals and antidepressants influence dopaminergic activity in the VTA and its targets, including the NAc.

Neurogenesis, Schizophrenia and Antipsychotics

Psychopharmacological interest in neurogenesis extends beyond depression and the actions of antidepressant drugs to other psychiatric disorders, as recently evidenced by studies suggesting a role of disturbed neurogenesis in the pathogenesis of ▶ schizophrenia (Reif et al. 2006) and its modulation by ▶ antipsychotic drugs. Patients with schizophrenia show reduced volumes of the frontal lobes as well as of the medial temporal lobes, in particular of the hippocampus, with the dentate gyrus displaying a reduced number of cells with the potential to proliferate. Further, preclinical studies indicate that chronic antipsychotic treatment can stimulate neurogenesis in both the subgranular zone of the hippocampal dentate gyrus as well as in the subventricular zone. Neurogenesis in the subventricular zone is stimulated by the first-generation antipsychotic drug (▶ first-generation antipsychotics) ▶ haloperidol, a strong D_2 receptor antagonist. In contrast, the ▶ second-generation antipsychotics such as ▶ olanzapine, ▶ risperidone, ▶ clozapine, and ▶ quetiapine induce neurogenesis mainly in the hippocampus (Newton and Duman 2007), thus resembling the actions of antidepressants. Interestingly, the second-generation drugs are poorer D_2 receptor antagonists, as compared to haloperidol, but have affinity for 5-HTergic receptors. Since treatment with atypical antipsychotics improves neurocognitive function, it seems likely that hippocampal neurogenesis may play a role in the amelioration of the cognitive symptoms in schizophrenia.

Conclusions

Neurogenesis occurs during immediate postnatal life, right through adulthood, although at an ever-diminishing rate. However, the relevance of neurogenesis in the actions of psychoactive drugs and the etiopathophysiology of psychiatric illnesses remains uncertain. Evidence that neurogenesis occurs in parallel with the apoptotic loss of neurons suggests that neuronal turnover and accompanying changes in neuroplasticity may be more important than neurogenesis *per se*. Although hippocampal neurogenesis appears not to be essential for manifestation of the mood-improving actions of antidepressant drugs, the phenomenon might serve to rectify behaviors in associated behavioral domains such as anxiety and cognition.

Cross-References

▶ Animal Models of Depression
▶ Antidepressants
▶ Antipsychotic Drugs
▶ Apoptosis
▶ Arginine – Vasopressin
▶ Brain-Derived Neurotrophic Factor
▶ Corticotropin Releasing Factor
▶ First-Generation Antipsychotics
▶ Lithium
▶ Schizophrenia
▶ Second-Generation Antipsychotics
▶ SSRIs and Related Compounds
▶ Synaptic Plasticity

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Neuroimaging

Synonyms

Brain imaging; Brain mapping

Definition

Neuroimaging is a family of techniques used for obtaining images of the structure or the function of the human brain. Neuroimaging studies investigate structural and functional brain maturation in health or in diseases of the brain, such as schizophrenia, bipolar disorder, depression, ADHD, drug dependence, and autism. These studies often aim to find genetic and environmental markers of variance in brain structure and function over time. Through additions to diagnostic radiology, neuroimaging has broadened to become a distinct field in neuroscience. The neuroimaging techniques that are currently used in research include single-photon emission computerized tomography (SPECT), positron emission tomography (PET), distinct forms of magnetic resonance imaging (MRI) including structural and functional MRI, MR spectroscopy (MRS), and diffusion tensor imaging (DTI).

Cross-References

- ▶ Magnetic Resonance Imaging (Functional)
- ▶ Magnetic Resonance Imaging (Structural)
- ▶ Positron Emission Tomography (PET) Imaging
- ▶ SPECT Imaging

Neuroinformatics

Definition

Biophysical rules and mechanisms by which neuronal networks gather, represent, store, integrate, transform, and implement information for behavioral output. Understanding information representation and computational processing as a biophysical product of neural tissue is an emerging field of neuroscience that relies on a non-traditional integration of biological, mathematical, engineering, and computer science fields. Aims of this area of research are to define the information-processing and learning and memory capabilities and limits of biological neural networks and to characterize how physical mechanisms that integrate gene–environment interactions result in changes in neural information processing.

Neurokinin 1

▶ Substance P

Neurokinin 2

▶ Neurokinin A

Neurokinin 3

▶ Neurokinin B

Neurokinin-α

▶ Neurokinin A

Neurokinin A

Synonyms

Neurokinin 2; Neurokinin-α; Neuromedin L; NK2; NKA; Substance K

Definition

NKA is a neuropeptide from the tachykinin family similar in structure to SP and generated by alternative splicing

from the same preprotachykinin gene as SP. NKA is mostly expressed in smooth muscles and in discrete areas of the central nervous system implied in mood disorders. NKA binds and activates the NK2 receptor.

Neurokinin B

Synonyms
Neurokinin 3; Neuromedin K; NK3; NKB

Definition
NKB is a 10 amino acids neuropeptide from the tachykinin family generated by alternative splicing from the same preprotachykinin gene as substance P. It is present in smooth muscles and widely expressed in the central nervous system. NKB binds and activates the NK3 receptor.

Neuroleptic

Synonyms
Antipsychotic drug; Major tranquillizer

Definition
A term currently used to refer to antipsychotic drugs prescribed for schizophrenia and bipolar disorder. However it was also defined, notably in Janssen Pharmaceutica, as a centrally-active drug that specifically blocked dopamine receptors in a set of in vitro and in vivo laboratory preparations, a definition that formed the core of many searches for novel antipsychotic drugs.

Cross-References
► Antipsychotic Drugs
► First Generation Antipsychotics
► Second and Third Generation Antipsychotics

Neuroleptic Malignant Syndrome

Synonyms
NMS

Definition
A severe, potentially lethal adverse effect of antipsychotic treatment of unclear pathophysiology. Features include muscle rigidity, fever, altered consciousness, and autonomic symptoms such as dysregulations of blood pressure and respiration. Most patients also show elevations of creatine phosphokinase levels. NMS represents a psychiatric emergency. Treatment, next to intensive care measures, includes dopaminergic drugs such as ► bromocriptine as well as dantrolene.

Cross-References
► Antipsychotic Drugs

Neuromedin K

► Neurokinin B
► Tachykinins

Neuromedin L

► Neurokinin A
► Tachykinins

Neuronal Plasticity

► Synaptic Plasticity

Neuropeptide Y

Definition
► Orexigenic peptide produced primarily by cells in the hypothalamic arcuate nucleus. This peptide potently increases appetite and decreases energy expenditure via its actions in the hypothalamus. In the hippocampus and cortex, neuropeptide Y is associated with antiepileptic effects.

Neuropeptides

Definition
Neuropeptides are substances with a peptide structure that are synthetized in nervous tissue and used there as messenger molecules. Some neuropeptides fulfill all criteria for a neurotransmitter and may have additional roles as neuromodulators or growth factors.

Neuropeptidomics

Synonyms

Peptidomics of the brain

Definition

Neuropeptidomics is the technological approach for detailed analyses of endogenous peptides from the brain.

Cross-References

- ▶ Electrospray Ionization (ESI)
- ▶ Imaging Mass Spectrometry (IMS)
- ▶ Mass Spectrometry (MS)
- ▶ Matrix-Assisted Laser Desorption Ionization (MALDI)
- ▶ Post-Translational Modification

Neuroplasticity

Definition

A general term referring to changes in information content and processing within neural networks, instantiated by a large variety of biophysical changes of constituent neurons embracing molecular to cellular to higher scales of observation. Changes in neuronal gene-expression correspond to phenotypic changes, including, but not limited to, alterations in neuronal excitability, neurotransmitter release and receptor densities, location and number of axodendritic synaptic contacts, and branching morphology of axons and dendrites. Net up or down changes in neuron-to-neuron synaptic strength are characterized electrophysiologically by ▶ long-term potentiation (LTP) and ▶ long-term depression (LTD). These changes underlie an inherent structural and functional flexibility (i.e., plasticity) of neurons and neurocircuits brought on by a combination, and interaction, of developmentally timed patterns of gene expression and environmental stimuli. Incorporating all the physical processes and learning and memory capabilities of brain systems, neuroplasticity seeks to achieve the most adaptive mapping of behavioral programming on present and future conditions of the external world.

Neuroprotectant

- ▶ Neuroprotective Agent

Neuroprotectants: Novel Approaches for Dementias

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Definition

Neuroprotection can be defined as a pharmacological activity that promotes the survival and function of neurons. Drugs that offer neuroprotection may be used to slow or prevent loss of brain function in a neurodegenerative disease.

Pharmacological Properties

▶ Dementia can be defined as a loss of memory function accompanied by impairments in other cognitive domains, including language, decision making, object recognition, spatial navigation, and other functions (American Psychiatric Association 2000). In order for a patient to be classified as demented, their impairments in memory and other cognitive abilities must be sufficient to affect routine aspects of daily life. Many types of dementia are caused by progressive, age-related neurochemical and neurodegenerative changes in areas of the brain required to support memory and other cognitive functions. As a result, efforts in drug discovery and development have focused on the identification of neuroprotective drugs as a means to reduce or prevent neurodegeneration and thereby slow or reverse ▶ cognitive impairment and dementia. Although many diseases of the central nervous system are accompanied by dementia, by far the most prevalent and devastating cause of dementia worldwide is ▶ Alzheimer's disease (AD). Because the incidence and prevalence of AD are increasing rapidly as the world's population ages, strategies for preventing or reversing the neurodegenerative changes of AD have become areas of intense focus for academic and industry research and will be the focus of this brief review.

The pathophysiology of AD has been the subject of intensive study for the past several decades. Tremendous progress in our understanding of disease mechanisms has been stimulated by the integration of genetics, histopathology, biochemistry, and animal models. As a comprehensive review of the scientific literature on AD pathophysiology is well beyond the scope of this encyclopedia, this review will focus on neuroprotective strategies centered on the role of ▶ amyloid-β (Aβ), a 38–43 amino acid peptide fragment derived from the amyloid

precursor protein (APP), and its contributions to the cognitive impairment and neurodegeneration of AD. Aβ is the core molecular component of the neuritic ► plaque, one of the hallmark neuropathological features of AD. The production and accumulation of Aβ is thought to contribute directly to defects in neuronal communication, amyloid plaque deposition, ► neurodegeneration, and cognitive impairment in AD.

The Aβ peptide is generated as a result of a two-step enzymatic cleavage of transmembrane APP. The first enzymatic cleavage, which generates the amino-terminus of Aβ and liberates a 99-amino acid C-terminal APP fragment (C-99), is termed β-site APP cleavage enzyme (β-secretase, BACE). The second enzymatic cleavage, which cuts within the C-99 fragment and generates the carboxyl-termini of Aβ, is mediated by a multi-subunit, integral membrane aspartyl protease termed γ-secretase (GS). In AD patients and normal healthy adults, there are two predominant forms of the Aβ peptide; Aβ40 and Aβ42. Aβ42 is less soluble than Aβ40, and rapidly and spontaneously assembles into soluble dimmers, fibrils, and insoluble higher molecular weight aggregates, which likely deposit in brain tissue as amyloid plaques. Mutations in APP that enhance cleavage by BACE are associated with increased Aβ production and early onset, familial AD. Mutations of GS or APP that enhance the production of Aβ, and specifically increase the production of Aβ42, are also associated with early onset, familial AD. Recently, dimers and higher molecular weight multimers of Aβ42, produced in vitro or isolated from AD brain tissue, have been shown to directly impair synaptic function and cause neuronal death in vitro (Shankar et al. 2008). These dimers and multimers isolated from human AD brain have also been shown to impair memory processes when infused directly into the brains of experimental animals. Together, there is now a wealth of preclinical data to indicate that the cascade of events, triggered by the formation of Aβ42, evokes detrimental changes in brain physiology leading to clinical symptoms of dementia as well as progressive neuropathology and neurodegeneration in AD.

The precise mechanisms whereby dimers and multimers (hereafter termed oligomers) of Aβ cause neurotoxicity are not well understood. Proposed mechanisms include the activation of specific cell surface receptors, including the direct or allosteric modulation of ion channels. These channels, when stimulated, are through to allow the entry of sodium and calcium ions into the neuron, thereby activating proteases, kinases, and other signaling molecules. The signaling events evoked by the binding of Aβ oligomers to the neuronal surface may lead to the removal of neurotransmitter receptors from synapses, thereby impairing neuronal communication, or may trigger processes that lead to neuronal injury or death (Kamenetz et al. 2003).

The primary goals of neuroprotective strategies in AD are to prevent the formation of Aβ peptides or increase their rate of removal from the brain. To this end, several companies are pursuing strategies to inhibit or modulate BACE or GS. Of these two strategies, GS inhibitors (GSIs) have progressed furthest into clinical development, with potent and selective GSIs (LY-450139, BMS-788163) currently in later stages of clinical development (see Harrison et al. 2004). GSIs potently and dramatically inhibit GS activity and thereby reduce the production of Aβ peptides by blocking the cleavage of the C-99 fragment of APP. GSIs have been shown to improve cognitive function in transgenic mice that over express mutant human APP. However, these compounds typically suffer from dose-limiting toxicities that may stem from inhibiting the cleavage of GS substrates other than APP, such as Notch. Notch is a cell surface receptor that, upon cleavage by GS, releases an intracellular C-terminal fragment that regulates a gene expression program critical for cell fate decisions in the gastrointestinal tract and in the immune system. A crucial component of GSI development is finding dose levels or a dose regimen that provides sufficient GS inhibition to reduce Aβ formation and AD pathology without causing intolerable digestive or immunological toxicity. Currently there is little evidence to indicate that GSIs reduce Aβ-mediated toxicity in vitro or in transgenic models of AD in vivo. Nevertheless, the hypothesis that GSIs, by their ability to halt Aβ production, will or prevent progressive neurodegeneration and preserve cognitive function in AD patients. This hypothesis is currently being evaluated in large, multinational clinical trials.

BACE inhibitors have also been the focus of intense drug discovery activity (see Ghosh et al. 2008). On the basis of data from BACE1 knock-out mice, a deletion of the BACE1 gene nearly completely suppresses Aβ production in vivo. Over the last several years, many pharmaceutical companies and academic laboratories have been pursuing BACE inhibitors as potential disease modifying therapies for AD. Although many potent and selective BACE inhibitors have been identified, these compounds typically suffer from poor oral absorption or are substrates for transport molecules that efficiently clear drugs out of the central nervous system, resulting in insufficient concentrations of drug in the brain to effectively inhibit BACE. The far, CTS-21166 has progressed into early phases of clinical development and has shown pharmacological activity by reducing plasma and CSF Aβ levels. Additional clinical testing is required to evaluate

the ability of this or other BACE inhibitors to ameliorate the cognitive decline and neurodegeneration in AD.

Another strategy to provide neuroprotection from toxicity mediated by Aβ is to neutralize or clear Aβ peptides once they are formed or deposited in amyloid plaques. This approach stems from the observation that transgenic animals expressing mutant human APP, which develop plaque-like Aβ deposits with increasing age, show a reduced accumulation of Aβ and a reduced plaque density following immunization with aggregates of Aβ or when they are treated systemically with antibodies that recognize Aβ peptides. This observation stimulated active and passive immunotherapy approaches targeting Aβ removal in AD patients. A clinical trial of active vaccination with aggregated Aβ42 (AN1792) was conducted by Elan and Wyeth (see Vellas et al. 2008). Although the trial was halted due to development of aseptic meningoencephalitis in some trial participants, long-term follow-up of trial subjects revealed several important findings. First, patients who developed strong antibody titers to Aβ42 aggregates, and specifically antibodies that recognized aggregated Aβ in plaques, showed a reduced rate of cognitive decline as compared to patients who did not develop such antibodies (Hock et al. 2003). Moreover, vaccine responders in the AN1792 study, followed up to 4 years, showed significantly reduced cognitive decline. Second, when their brains were examined after death, patients in the AN1792 study who developed sustained anti-Aβ titers showed unexpectedly low densities of Aβ plaques (Vellas et al. 2009). Together, these findings suggest that antibodies to Aβ can affect amyloid pathology in the AD brain and reduce the severity of the clinical course in AD. Whether this strategy reduced the overall rate of neurodegeneration, as evidenced by the preservation of brain gray matter volume, remains to be determined.

Although the AN1792 trial was halted, strong interest remains in exploring passive immunotherapy using monoclonal antibodies that target specific amino acid sequences within the Aβ peptide (see Nitsch and Hock 2005). In experimental animals, passive immunotherapy with anti-Aβ antibodies dramatically reduces amyloid pathology, improves behavioral performance, and seems to prevent neurodegeneration. Several humanized anti-Aβ antibodies, including Elan/Wyeth's bapineuzumab, and Eli Lilly and Company's solanezumab, are now in Phase III clinical trials as disease modifying therapies for AD. The outcome of these large, multinational trials will provide incredibly valuable information about the role of Aβ in neurodegenerative processes and cognitive impairment in AD.

Another approach to AD targeting Aβ involves the modulation of GS activity with the goal of selectively reducing the formation of Aβ42. Compounds that selectively reduce Aβ42 are called GS modulators (GSMs), because they reduce the generation of Aβ42 without affecting the total amount of Aβ that is produced. In contrast to GSIs, which reduce the production of all Aβ isoforms (and inhibit cleavage of all GS substrates), GSMs typically reduce the production of Aβ42, have no effect on Aβ40, and increase production of nonpathogenic Aβ38 roughly in proportion to the decrease in Aβ42. Although it is presumed that GSMs work by binding to an allosteric site on the GS enzyme complex, the binding site for GSMs and their mechanism of action have not been clearly elucidated. One potential advantage of GSMs over GSIs is that GSMs may avoid the toxicities associated with GS inhibition. GSMs alter the ratios of cleavage products that result from GS activity but do not inhibit GS activity completely. In the case of Notch, for example, although the site of Notch cleavage may be altered by a GSM, Notch C-terminal fragment is still generated and its ability to signal is not affected.

The first prototype GSM to enter large-scale clinical development was R-flurbiprofen (Flurizan). Although this molecule has very weak GSM activity in vitro ($IC_{50} > 150\,\mu M$) and penetrates the brain poorly, it was shown to reduce Aβ42 production in experimental animals and was advanced into clinical development (see Wilcock et al. 2008). Although a large Phase III clinical trial of R-flurbiprofen failed to demonstrate efficacy, considerable interest remains in developing more potent GSMs that achieve brain tissue concentrations sufficient for the effective and selective reduction of Aβ42. Several companies and academic laboratories are currently working to achieve this goal.

Other approaches to neuroprotection in dementia that are currently under active investigation in clinical trials are the disruption of Aβ fibrils (e.g., PBT2 – a chelator of divalent metal ions that seems to disrupt Aβ production and fibril formation), the inhibition of excitotoxicity by blocking excitatory amino acid receptors (e.g., ► memantine, Dimebon), preventing neuronal apoptosis by preserving mitochondrial function (e.g., Dimebon). There is generally a limited amount of published preclinical data from animal models to substantiate the activity of these novel agents as neuroprotective therapies in AD.

Future Directions

Exciting avenues for future research on neuroprotectants for dementia and AD center on the identification of a cell surface receptor or receptors for Aβ oligomers and an elucidation of the signaling events that link Aβ binding to neuronal membranes with altered activity and

morphology of synapses (Kamenetz et al. 2003; Shankar et al. 2008). A better understanding of these pathways may allow for the generation of therapies that specifically target the impaired synaptic function and early structural defects of AD. It seems likely that the modulation of these fundamental processes in synaptic transmission and memory may also provide novel therapeutic approaches to preserving cognitive function across many types of dementias.

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Results and commentary about the latest research and clinical trial findings in Alzheimer's disease can be found at the following internet site: http://www.alzforum.org

Neuroprotection

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Definition

The term neuroprotection is used to refer to either an endogenous mechanism within the central nervous system that protects neurons from cell death or, more commonly, the action of a drug to prevent cell death following the action of a neurotoxic drug or the consequences of brain injury.

Current Concepts and State of Knowledge

Mechanisms Involved in Cell Death

Neurons can die by one of two distinct mechanisms. One is programmed cell death or ▶ apoptosis, the other is ▶ necrosis. Both types of cell death have been reported to occur following a variety of insults to the brain (Chalmers-Redman et al. 1997). Insults to the integrity of the brain can be chemical, for example, ▶ neurotoxins, or traumatic, for example, ▶ stroke. Both chemical and traumatic insults result in neurodegeneration (▶ neurodegeneration and its prevention).

Neuroprotection Following Stroke and Traumatic Brain Injury

Stroke

Tissue damage following a stroke can be mitigated either by restoring blood flow with a thrombolytic ("clot busting") drug or by interfering with the biochemical changes which occur following the ischemic insult and thereby minimizing the damage. At present only the thrombolytic drug recombinant tissue plasminogen activator or rt-PA is in clinical use for the acute treatment of stroke (Green 2008).

Any compound that protects the brain from cell death following an acute ischemic stroke is known as a ▶ neuroprotective agent or neuroprotectant and its mechanism of action is generally based on trying to interfere with the biochemical changes which occur in the brain following an acute ischemic insult (Green and Cross 1997). The biochemical chain of events following ischemia is often referred to as the ischemic cascade. The initial change that occurs during ischemia is a pathological release of glutamate, an excitatory amino acid (▶ excitatory amino acids and their antagonists). This release produces further changes including depolarization of the cells, the production of ▶ free radicals, excitotoxicity, and cell death. It should also be noted that reperfusion, while mitigating neurodegeneration also results in the production of free radicals and is thus subject to studies examining whether additional treatment with a neuroprotective agent might be advantageous (Green and Shuaib 2006).

Neuroprotection can be determined in various ways in ► animal models of acute stroke. Primarily, neuroprotection is measured by histological evidence that the size of the damaged tissue (infarct area) is smaller. This can be achieved by staining tissue or counting intact cell populations. Such studies should be followed up by measuring the degree of motor impairment in living animals. Clinically, the use of scales which quantify the degree of motor impairment is the generally accepted outcome measure.

Since the initial event following the onset of cerebral ischemia is ► glutamate release, considerable efforts have been made to provide neuroprotection by producing drugs that are antagonists at the glutamate receptor. Antagonists of both the glutamate ► NMDA receptor and the ► AMPA receptor have been examined in animal models of acute stroke. Some of these have also been investigated in clinical trials with stroke patients. Glutamate antagonist compounds include the NMDA receptor antagonists, dizocilpine, aptiganel, and selfotel. Clinical studies have also been conducted with the NMDA glycine-site antagonist gavestinel, the NMDA polyamine-site antagonist eliprodil and the NMDA channel blocker magnesium. AMPA receptor antagonists such as NBQX have also been examined but less actively pursued, primarily because of safety concerns. All these compounds were effective in providing neuroprotection in animal models of stroke. However, all failed in clinical trials, either because the trial had to be terminated early because of safety issues or because the compound failed to demonstrate efficacy (Green 2008).

Another approach to providing neuroprotection in stroke has been to administer compounds which increased the function of GABA, an inhibitory amino acid neurotransmitter (► Inhibitory amino acids and their antagonists). Such approaches have included administration of the ► benzodiazepine diazepam or clomethiazole, a drug that increases GABA function at its receptor. Again, despite clear evidence for efficacy in animal models of acute stroke, both drugs failed to provide neuroprotection in patients as indicated by a decrease in stroke-induced disability.

Since a major consequence of both ischemia and reperfusion is excessive free radical production, attempts have been made to provide neuroprotection in stroke as well as other degenerative conditions such as Parkinson's disease (► Anti-Parkinson drugs) and Alzheimer's disease (► Dementias and other amnesic disorders) by the use of compounds that scavenge or trap free radicals. In stroke research, such compounds included ebselen, a selenium compound with glutathione peroxidase-like activity, the lazaroid compound tirilazad and edaravone, a hydroxyl radical scavenger. Only edaravone is claimed to be of clinical benefit but, at present, its use is restricted to Japan. One compound that showed considerable preclinical promise was the nitrone-derived compound NXY-059. However, despite the efficacy of this compound in a variety of animal models of stroke, it failed to demonstrate efficacy in late phase clinical trials. This failure, in particular, has resulted in considerable discussion in the scientific press as to the reasons for the failure of compounds to show translation from experimental to clinical efficacy, but an unequivocal answer has yet to be provided (O'Collins et al. 2006).

The failure of compounds acting on the ischemic cascade to provide neuroprotection in stroke patients has led to an increase in approaches that interfere with the role of ► cytokines in cerebral ischemia. Both tumor necrosis factor alpha (TNFα) and interleukin 1beta (IL-1β) are known to be involved in the inflammatory response to brain injury, and TNFα and IL-1β antibodies are neuroprotective in experimental stroke studies in animals. A recombinant IL -1 receptor antagonist is being examined clinically. Due to the possible problems in producing and administering protein-based compounds, research is also being undertaken to produce non-peptide compounds (Green 2008).

Traumatic Brain Injury

Traumatic brain injury (or TBI) is the term used to describe injury to the brain caused by mechanically induced damage such as that resulting from impact to the skull induced by a car accident or by a firearm. The pathological changes seen include those which occur following stroke, but also additional changes such as bleeding (hemorrhage) and mechanical damage to cerebral tissue due to impact. Several of the compounds developed to treat acute ischemic stroke are also being examined in TBI. Compounds such as aptiginal, the excitatory amino acid antagonist and IL-1β antibodies have shown to provide modest benefit in animal models of TBI but no compound has yet proved to have efficacy in human TBI.

Neuroprotection and Neurotoxic Amphetamines

3,4-Methylenedioxymethamphetamine (► MDMA or "ecstasy") is an ► amphetamine and a commonly used recreational drug, often ingested at warm and crowded dance clubs and raves. There is substantial evidence that the compound produces long-lasting neurotoxic changes in the brains of experimental animals. In the rat, MDMA, given either as a single high dose or several lower doses over a relatively short period of time, induces a long-term loss of 5-hydroxytryptamine (5-HT or ► serotonin) nerve

terminals in several regions of the brain. This effect is reflected in a substantial decrease in the activity of tryptophan hydroxylase, the first (and rate-limiting) enzyme responsible for the synthesis of 5-HT, and in the concentration of 5-HT and its metabolite, 5-hydroxyindole acetic acid (5-HIAA). There is also a reduction in the number of 5-HT transporters and a decrease in the immunoreactivity of 5-HT axons in several brain areas (Green et al. 2003).

In contrast to its effects in rats, MDMA is generally accepted to behave as a selective dopamine neurotoxin in mice, inducing a long-term decrease in the concentration of ► dopamine and its metabolites, a reduction in the number of dopamine transporters, and a decrease in the immunoreactivity of tyrosine hydroxylase in striatum and substantia nigra (Colado et al. 2004; Granado et al. 2008). Neurotoxicity in mice is evident following repeated and higher doses of MDMA than those administered to rats.

Another substituted amphetamine, ► methamphetamine (METH), is also known to induce neurotoxic loss of dopamine axon terminals in the striatum and cell body in the substantia nigra of mice. The fact that direct administration of MDMA and METH into the brain does not produce toxicity suggests that the parent compounds are not responsible for the toxicity and that toxicity probably results from the effects of metabolic products (Esteban et al. 2001).

The mechanisms producing this neurodegeneration are not totally understood at present, but evidence indicates that several factors play an essential role: acute hyperthermia, monoamine transporters, an oxidative stress process, strong microglia activation, and the release of pro-inflammatory cytokines such IL-1β and TNFα (Orio et al. 2004). Some of these potential mechanisms are also almost certainly involved in ischemia-induced neurodegeneration.

There have been a variety of compounds which, when given concurrently with MDMA or METH, have been shown to provide protection. However, recent studies have indicated that a significant number of such compounds, including several with clear efficacy as neuroprotective agents in animal models of acute ischemic stroke, only prevent amphetamine-induced damage because they either prevent the acute hyperthermia which follows amphetamine administration (for example, ► antipsychotics such as ► haloperidol) or because they induce hypothermia. Compounds in this latter class include ► barbiturates such as ► pentobarbitone, and NMDA antagonists such as dizocilpine and CGS 19755. Hyperthermia is one of the major features of acute MDMA toxicity in both rodents and humans and its presence is shown to markedly enhance the neurotoxic damage induced by MDMA administration (Green et al. 2003).

In contrast, there are some other compounds that are able to protect against MDMA-induced damage through some specific neurochemical mechanism and not merely by decreasing body temperature. The 5-HT uptake inhibitors (► SSRIs and related compounds) ► fluoxetine and ► fluvoxamine, coadministered with MDMA, completely prevent the long-term loss of 5-HT concentration without altering the hyperthermia following MDMA. Both compounds inhibit the 5-HT transporter and could be blocking the entry of a toxic metabolite of MDMA into the 5-HT nerve terminal. Monoamine transporters also appear to be involved in MDMA-induced neurotoxicity in mice since GBR 12909, a selective dopamine uptake inhibitor, also provided protection against long-term dopamine depletion induced by MDMA and METH without altering body temperature.

The role of free radicals in the damage induced by MDMA and METH has been demonstrated by several different approaches. α-Phenyl-N-tert-butyl nitrone (PBN) is a hydroxyl radical trapping agent that partially prevents the neuronal damage induced by MDMA on 5-HT nerve terminals as a result of its free radical scavenging activity. PBN, at a dose that did not modify hyperthermia, was shown to prevent MDMA-induced hydroxyl radical formation. Other free radical scavenging drugs (sodium ascorbate, L-cysteine) are also found to protect against MDMA-induced damage. Supporting the existence of an oxidative stress process is the fact that the antioxidant alpha-lipoic acid prevented the long-term loss of 5-HT in the striatum but did not alter the hyperthermia induced by MDMA. In addition to hydroxyl radicals, nitrogen reactive species are also shown to be involved in MDMA-induced neurotoxicity. In mice, there is also evidence for a key role of ► oxygen and nitrogen reactive species in the MDMA-induced neurotoxicity on dopamine neurons. Pre-treatment with nitric oxide synthase (NOS) inhibitors S-methylthiocitrulline (S-MTC), AR-R17477AR, or 3-bromo-7-nitroindazole provides significant neuroprotection against the long-lasting MDMA-induced dopamine depletion suggesting that MDMA leads to radicals that combine with nitric oxide to produce peroxynitrites. Peroxynitrites are also formed following neurotoxic doses of METH and NOS inhibitors attenuate the dopamine damage induced by METH (Colado et al. 2001; Sanchez et al. 2003).

Microglial activation is also emerging as an important element of the MDMA and METH neurotoxic cascade. Microglia are considered as the resident immune cells of the brain and are activated in response to brain injury

leading to the secretion of a variety of cytotoxic factors such as cytokines, prostaglandins, and reactive oxygen/nitrogen species, many of which have been involved in amphetamine-induced neurotoxicity. On the other hand, microglia may also initiate tissue repair and regeneration through secretion of growth and neurotrophic factors, thereby exerting a beneficial neuroprotective role. MDMA and METH cause a prompt and transient increase in microglial activation that seems not to be related to increased rectal temperature. There have been several attempts to implicate microgliosis in amphetamine-induced neurotoxicity but results have not always been successful. Thus, while dizocilpine and dextromethorphan prevent microgliosis following METH and provide neuroprotection against the loss of dopamine nerve terminals, some ► cannabinoid CB2 receptor agonists do not prevent MDMA-neurotoxicity. These data suggest that microglial activation occurs in response to amphetamine-induced neuronal damage but does not cause it. MDMA and METH also induces an increase in the brain levels of proinflammatory cytokines such as IL-1β and TNFα, respectively. Nevertheless, further studies are required in order to establish the specific role of these cytokines in amphetamine neurotoxicity, and, therefore, develop appropriate approaches for providing neuroprotection.

Hypothermia and Neuroprotection

There is a substantial body of evidence that hypothermia produces neuroprotection, not only in animal models of stroke, but also when neurodegeneration is produced by administration of neurotoxins such as methamphetamine and MDMA. This has meant that all experimental studies on neuroprotection must both monitor body temperature (and ideally also brain temperature) and must also ensure that body temperature is also adjusted where necessary to attenuate any body temperature changes. Only when this is done, can the experimenter be confident that the drug under investigation is producing neuroprotection by interfering with pathological processes involved in neurodegeneration rather than merely lowering body temperature. This is particularly important in rodent studies, as many administered compounds have been reported to lower body temperature though non-specific mechanisms.

Lowering body (or brain) temperature deliberately by the use of specific drugs or by cooling techniques such as exposing the head or body to low temperature using ice baths or cooling helmets is being investigated clinically. It is the only approved neuroprotective approach in persons who have suffered global cerebral ischemia due to cardiac arrest. Both the severity of the hypothermia and the speed of temperature decrease have to be controlled closely for benefit to occur.

The generally accepted explanation for the efficacy of hypothermia as a neuroprotectant is that free radical formation induced by either the ischemic insult or by the administration of the neurotoxin is markedly attenuated during hypothermia.

Cross-References

► Anti-Parkinson Drugs
► Antipsychotics
► Apoptosis
► Barbiturates
► Benzodiazepines
► Cannabinoids and Endocannabinoids
► Dementias and Other Amnesic Disorders
► Excitatory Amino Acids and Their Antagonists
► Inhibitory Amino Acids and Their Antagonists
► Methylenedioxymethamphetamine (MDMA)
► Neurodegeneration and its Prevention
► Neurotoxins
► SSRIs and Related Compounds

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Neuroprotective Agent

Synonyms

Neuroprotectant; Neuroprotective drug

Definition

A drug or novel pharmacological agent that when administered after a cerebral trauma or neurotoxic compound attenuates the neuronal cell damage induced by the trauma or neurotoxin and thereby lessens the subsequent functional problems induced by the cerebral trauma.

Neuroprotective Drug

► Neuroprotective Agent

Neuropsychiatric Disorders

Synonyms

Mental disorders; Psychiatric disorder

Definition

Neuropsychiatric disorders are any illness with a psychological origin manifested either in symptoms of emotional distress or in abnormal behavior. Neuropsychiatric disorders (psychiatric disorders) have been classified according to criteria defined in the Diagnostic and Statistical Manual of Mental Disorders (APA – American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders – DSM-IV-TR, 2000) into major (clinical) depression, bipolar disorder, schizophrenia, anxiety disorders and attention-deficit hyperactivity, and subsequent subcategories. Due to the absence of sharp boundaries to and high occurrence as comorbidities in neurological disorders (i.e., stroke, Alzheimer's disease) an integrative view of psychiatric- and neurological disorders is currently discussed.

Neuropsychopharmacology

► Psychopharmacology

Neuroreceptor Mapping

► Positron Emission Tomography (PET) Imaging

Neurotensin

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Definition

Neurotensin (NT) is a tridecapeptide that functions both as a hormone and a neurotransmitter. It regulates intestinal motility, feeding behavior, ► nociception, thermoregulation, and anterior pituitary hormone secretion. In the central nervous system (CNS), NT modulates classical monoamine neurotransmitter systems, most notably dopamine (DA). Because of its modulation of DA circuits, NT has been implicated in the pathophysiology of ► schizophrenia and ► drug abuse, and may represent a potential therapeutic target for treatment of these disorders.

Pharmacological Properties

Introduction

NT was first isolated from bovine hypothalamus by Carraway and Leeman in 1973. The NT gene is highly conserved between species and consists of a 10.2 kb segment containing four exons and three introns. The gene encodes an 170 amino acid precursor protein containing both tridecapeptide NT and a closely related hexapeptide, neuromedin N (NN). Post-translational processing yields both peptides. The amino acid sequence of NT is N-Glu-Leu-Tyr-Glu-Asn-Lys-Pro-Arg-Arg-Pro-Tyr-Ile-Leu-C. NT is stored in presynaptic vesicles and its release is Ca^{2+}-dependent. The half-life of NT in brain tissue is approximately 15 min with the primary mode of signal termination being cleavage of the peptide by a variety of peptidases. In addition, based on sequence homology, other structurally related

endogenous peptides that bind to NT receptors such as, NN, xenin, xenopsin, LANT-6, contulakin-G, and kinetensin, have been identified demonstrating the existence of a family of NT-related peptides (Boules et al. 2007; Kinkead and Nemeroff 2006).

NT is distributed throughout the central and peripheral nervous system with about 10% found in brain. In the CNS, high concentrations of NT are found in ▶ hypothalamus, ▶ amygdala, substantia nigra, ▶ ventral tegmental area (VTA), and olfactory tubercle (Binder et al. 2001b for anatomy review). There are intermediate concentrations in a variety of other areas, including the basal ganglia, brainstem, and dorsal horn of the spinal cord. Lower concentrations of NT are found in the thalamus and cortex. NT-positive cell bodies are located in the arcuate nucleus, extended amygdala, striatopallidum, basal forebrain, and numerous brainstem regions that give rise to cholinergic, DAergic, serotonergic, noradrenergic, orexinergic, and histaminergic ascending neuromodulatory projections. NT cell bodies also exist in the periaqueductal gray (PAG).

Mechanisms of Action

There are four known NT receptors (Kinkead and Nemeroff 2006 for review). The NT_1 and NT_2 receptors are ▶ G protein-coupled with the classic seven transmembrane-spanning regions. NT_2 is a receptor with low affinity for NT that also binds the histamine H_1 receptor antagonist levocabastine. The NT_1 receptor is a levocabastine-insensitive receptor with high affinity for NT. Two other identified receptors, NT_3 (sortilin) and NT_4 (SorLA/LR11) are members of the family of Vps10p domain receptors with high affinity for NT. In contrast to NT_1 and NT_2, the NT_3 and NT_4 receptors are type I amino acid receptors with a single transmembrane-spanning region. The majority of NT_3 and NT_4 receptors are found intracellularly and have been theorized to play a role in intracellular sorting processes. NT_3 has also been posited to play a role in cell death, and NT_4 may play a role in terminating NT function.

One of the most studied effects of NT is its modulation of DA neurotransmission. NT differentially modulates DAergic activity in the mesocortical, mesolimbic, and nigrostriatal pathways (Binder et al. 2001b). In general, the effect of NT is to decrease DA D_2 receptor-mediated effects with an overall effect on cell firing depending on the brain region. For example, within the midbrain where NT_1 receptors are found on DA cell bodies, NT functions to increase DAergic cell activity by attenuating D_2 receptor-mediated ▶ autoinhibition. The behavioral effects of increased NT neurotransmission in the midbrain resemble those of peripherally administered DAergic agonists. In contrast, in the ▶ nucleus accumbens (NAcc), receptor colocalization takes place primarily on postsynaptic GABAergic neurons. Allosteric receptor/receptor interactions between the activated NT receptor and DA D_2-type receptors lead to decreased D_2 receptor agonist binding affinity and to reduced DA agonist effects behaviorally.

Several small molecule NT receptor antagonists have been identified; SR 48692 and SR 142948A are the best characterized (Kinkead and Nemeroff 2006). Both these antagonists cross the ▶ blood–brain barrier and possess nanomolar ▶ affinity for the NT_1 receptor. Although SR 48692 has a lower affinity for NT_2 than NT_1 receptors, neither SR 48692 nor SR 142948A discriminate well between the NT_1 and NT_2 receptors, and there is some evidence that SR 48692 binds to the NT_3 receptor as well. SR 142948A and SR 48692 do not block all NT-mediated effects, indicating that there are pharmacological subtypes of NT receptors with which the available antagonists have low affinity. Whether these two NT receptor antagonists interact with the NT_4 receptor is yet to be determined.

NT is easily degraded by peptidases and must be injected directly into the brain in order to exert CNS effects. Thus, over the years, many groups targeting brain NT receptors for drug development have sought a compound that could be delivered peripherally (Boules et al. 2007). The last six amino acids on the NT C-terminus carry the full biological activity of NT, and several NT analogs that can be delivered systemically have been developed, including PD149163, NT66L, NT67L, NT69L, and NT77L. To date, all identified NT receptor agonists are modified peptide analogs of NT(8–13).

Effects in Disease States

NT has been implicated in the pathophysiology of ▶ schizophrenia, and it has been suggested that NT may function as an endogenous antipsychotic agent or neuroleptic (Nemeroff 1980). Decreased concentrations of NT are found in the cerebrospinal fluid (CSF) of a subset of schizophrenic patients, and NT levels normalize following effective treatment with ▶ antipsychotic drugs (Cáceda et al. 2006). Based on these findings as well as decades' worth of biochemical and behavioral preclinical data, it has been proposed that NT receptor agonists may represent a novel treatment for schizophrenia.

In addition to the possibility that NT receptor agonists may represent a novel class of antipsychotic drugs, evidence suggests that modulation of NT neurotransmission may be involved in the mechanism of action of the

existing antipsychotic drugs (Binder et al. 2001c). To date, all clinically effective antipsychotic drugs, none of which bind to NT receptors, have been shown to increase NT neurotransmission (mRNA expression, NT peptide concentrations, or NT release) in the NAcc. In addition, the viral vector overexpression of NT_1 receptors in the NAcc has many of the same behavioral effects as antipsychotic drugs (Cáceda et al. 2006). This has led to the hypothesis that increased NT release in the NAcc may mediate some of the therapeutic effects of antipsychotic drugs.

In fact, endogenous NT neurotransmission appears to be involved in the behavioral effects of some, but not all, antipsychotic drugs (Binder et al. 2001a; Kinkead and Nemeroff 2006; Cáceda et al. 2006). Pretreatment with an NT receptor antagonist blocks the behavioral effects of the typical antipsychotic drug haloperidol in two animal models of sensorimotor gating, ▶ prepulse inhibition (PPI) of the acoustic startle response, and ▶ latent inhibition. Likewise, mice lacking the NT gene exhibit deficits in PPI (similar to those seen in schizophrenia) that are restored by the antipsychotic drug ▶ clozapine, but not ▶ haloperidol, ▶ quetiapine, or ▶ olanzapine. These results suggest that increased endogenous NT is critically involved in the mechanism of action of a subset of antipsychotic drugs. In combination with the clinical data indicating that there is a subset of schizophrenic patients with deficits in NT neurotransmission, these findings raise the possibility of preselecting an effective antipsychotic drug for this subgroup of patients, thereby dramatically improving patient outcomes and reducing the risk of inadequate treatment.

NT has also been suggested to play a role in drug abuse. Drug abuse is characterized by a loss of control leading to compulsive drug use, despite obvious detrimental consequences. It has been theorized to be, in part, due to dysregulation of the mesocorticolimbic DA system, which mediates reward processing and learning. Because of its close association with the mesocorticolimbic DA system, NT is implicated in mechanisms underlying reward and addiction (Cáceda et al. 2006; Dobner 2005); and in particular, the development of ▶ sensitization to drugs. Although NT, as demonstrated by studies utilizing direct CNS injection of NT, does have rewarding properties in the VTA and does modulate the behavioral effects of ▶ psychomotor stimulants in the NAcc, this is not necessarily an indication of the role of endogenous NT in spontaneous locomotion or psychomotor stimulant-induced behavioral effects. In fact, though NT/NN mRNA expression and NT peptide concentrations are increased in the NAcc, striatum, and prefrontal cortex following acute ▶ cocaine or amphetamine administration, this acute release of endogenous NT does not appear to mediate the acute locomotor effects of these drugs. Indeed, peripherally administered NT receptor antagonists have no effect on the acute locomotor effects of psychomotor stimulants. In contrast, supra-activation of NT systems following intra-NAcc injection of NT, peripheral administration of NT receptor agonists, and NT_1 receptor overexpression in the NAcc significantly reduce amphetamine-induced hyperlocomotion. Therefore, while endogenous NT does not appear to modulate spontaneous locomotor activity or the acute locomotor effects of psychomotor stimulants, increased NTergic neurotransmission counteracts the acute locomotor effects of these drugs.

Much evidence implicates the endogenous NT system in psychomotor stimulant-induced behavioral sensitization. In humans, the repeated use of psychomotor stimulants can result in long-lasting alterations in the response to subsequent drug use, including the emergence of drug craving. In rats, this phenomenon, termed behavioral sensitization, is considered a useful animal model for drug craving. Repeated intra-VTA or ICV injection of NT leads to behavioral and chemical sensitization. Perhaps, most intriguing is the finding that pretreatment with an NT receptor antagonist (while not affecting acute stimulant-induced hyperlocomotion) prevents the development of locomotor sensitization. From these data, it can be inferred that NT neurotransmission is critically involved in the initiation of behavioral sensitization to psychomotor stimulants. There is some evidence that the role of NT in sensitization can be generalized to other drug classes including ▶ alcohol, ▶ nicotine, and NMDA receptor antagonists (Cáceda et al. 2006). Based on these findings, it is possible that genetic vulnerability within the NT system may contribute to drug addiction and provide a rationale for the development of compounds modifying NT neurotransmission in the treatment of drug addiction.

In addition, NT may also be involved in the pathophysiology of obesity. Within the CNS, the hypothalamus plays a key role in regulation of satiety and feeding behavior. As noted above, NT is found in high concentrations in the hypothalamus. In conjunction with other peptides (including ▶ leptin, galanin, ▶ neuropeptide Y, and others), NT modulates appetite and feeding behavior and is an important regulator of the central feeding circuit (Sahu et al. 2001). Activation of the NT system decreases feeding in rats, an effect which is downstream of ▶ leptin activation. Central injections of leptin increase hypothalamic NT mRNA expression as well as reduce food intake and decrease body weight in rats. In addition, NT receptor antagonists block leptin-associated ▶ appetite

suppression. Thus, the NT system may be a potential novel target for the development of anti-obesity drugs.

NT also plays an important role in modulating nociception (Dobner 2006). NT fibers and cell bodies are found in multiple brain regions involved in pain transmission and modulation, including the PAG, the rostroventral medulla (RVM), and the dorsal horn of the spinal cord. NT dose-dependently modulates nociception. When low doses of NT are injected into the RVM, the result is an enhanced nociceptive response and hyperalgesia. When higher doses of NT are injected into the RVM, the result is an antinociceptive response which is not mediated by endogenous ▶ opioids. Thus, NT modulates nociception via differences in intensity of signaling. Mice lacking the NT gene also exhibit deficits in ▶ antinociception. In addition, NT also plays a role in ▶ stress-induced antinociception, or decreased pain transmission in response to stressful stimuli, as blocking NT transmission in rats and mice causes hyperalgesia in response to stress (Dobner 2006). Because of NT's role in nociception, medications targeting NT transmission may be potential ▶ analgesics.

Cross-References

▶ Alcohol
▶ Analgesics
▶ Antipsychotic Drugs
▶ Appetite Suppressants
▶ Blood–Brain Barrier
▶ Cocaine
▶ Future of Antipsychotic Medication
▶ Latent Inhibition
▶ Leptin
▶ Nicotine
▶ Opioids
▶ Prepulse Inhibition
▶ Psychomotor Stimulants
▶ Schizophrenia
▶ Schizophrenia: Animal Models
▶ Sensitization to Drugs

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Method to estimate serotonin and norepinephrine transporter occupancy after drug treatment using patient or animal serum (provisional filing April, 2001).

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Neurotic Depression

▶ Dysthymic Disorder

Neurotoxicity

Definition

The tendency of substances (called ▶ neurotoxins), conditions, or states to alter the normal activity of the nervous system. This can eventually disrupt or even kill neurons; key cells that transfer and process signals in the

brain and parts of the nervous system. Neurotoxicity can result from exposure from drug therapies and certain drug (ab)use.

The "neurotoxicity theory" of schizophrenia states that an (untreated) psychosis is neurotoxic to the brain and that cortical thinning is an inherent feature of the neurobiological disease process in schizophrenia. Although the pathophysiology of this disorder is still unknown, we do know that antipsychotics (dopamine receptor blockers) reduce symptoms of schizophrenia but that party drugs like cocaine and amphetamine increase dopamine in the brain and may induce psychosis.

Neurotoxicity and Schizophrenia

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Definition

Neurotoxicity is the tendency of substances (also called neurotoxins), conditions, or states to alter the normal activity of the nervous system. This can eventually disrupt or even kill neurons; key cells that transfer and process signals in the brain and parts of the nervous system. Neurotoxicity can result from exposure to drug therapies and certain drug (ab-)use.

The "neurotoxicity theory" of ▶ schizophrenia states that an (untreated) psychosis is neurotoxic to the brain and that brain changes are an inherent feature of the neurobiological disease process in schizophrenia. Although the pathophysiology of this disorder is still unknown, we do know that antipsychotics; (dopamine receptor blockers), reduce symptoms of schizophrenia, but that party drugs like cocaine and amphetamine increase dopamine in the brain and may induce psychosis.

The term *neurotoxic* is used to describe a substance, condition, or state that damages the nervous system and/or brain, usually by killing neurons. The term is generally used to describe a condition or substance that has been shown to result in observable physical damage.

Current Concepts and State of Knowledge

Introduction

Although Kraepelin (1919) suggested that ▶ schizophrenia, dementia praecox, was a chronic, deteriorating psychotic disorder, evidence was lacking to prove this; in postmortem studies, no or little abnormalities in brains of patients with schizophrenia were found. In the 1960s and 1970s, schizophrenia was not thought to be a brain disease at all. Clinical investigators considered failing-family interactions instead as a cause. Especially, failing mother–child interaction was thought to cause or worsen schizophrenia.

This all changed when new in vivo ▶ neuroimaging techniques, such as Computer Tomography (CT) in 1976 revealed that patients with schizophrenia had enlarged ventricles when compared with a group of age-matched controls (Johnstone et al. 1976). In the early 1900s, the first evidence of brain ventricular enlargement was already provided by a pneumoencephalography (PEG) study in a small sample of schizophrenia patients (Jacobi and Winkler 1927).

Because of the lack of progression of cerebral ventricular enlargement of the earlier studies, the ▶ neurodevelopmental hypothesis began to emerge by which schizophrenia is suggested to result from abnormalities in neuronal connectivity, which arise during fetal life but are not expressed until the onset of illness. Despite the evidences in favor of the neurodevelopmental hypothesis, such as delayed milestones, there are some substantial symptoms of schizophrenia that cannot be explained with the neurodevelopmental hypothesis. The apparent progression of clinical aspects of the syndrome in some patients, including deterioration, dilapidation, and treatment resistance may suggest that schizophrenia is a progressive illness. Furthermore, recent longitudinal magnetic resonance imaging (MRI) studies in patients with schizophrenia have shown that through the course of the illness the brain volume reduces progressively. It remains unclear what the underlying neuropathological mechanisms are causing these progressive brain volume changes in schizophrenia, but it is thought that ▶ psychosis could be neurotoxic.

This essay will briefly describe the scientific evidence in favor of schizophrenia being a progressive brain disease. It will then discuss the neurotoxicity hypothesis of schizophrenia and the concept of neuroprotection.

Neuroimaging Studies

In 1976, a new in vivo neuroimaging technique, CT was first used in schizophrenia research by Johnstone et al. (1976). In this study, patients with schizophrenia showed enlarged ventricle volumes when compared with age-related healthy control subjects. In the last two decades, numerous studies were conducted using MRI techniques. In 2000, a cross-sectional meta-analysis (Wright et al. 2000) convincingly showed that brain volume changes are present in schizophrenia. Lateral ventricle volume was found to be increased (16%) while cerebral volume

was reduced (2%). The latter was primarily attributed to a decrease in gray matter volume (2%). Nevertheless, a small but significant reduction was found in white matter volume (1%). Furthermore, the improved quality of the MRI scans made it also possible to manually delineate brain areas of interest. Regional pathology indicates larger reductions in temporal and frontal lobe and more specifically in medial temporal structures (► hippocampus and ► amygdala). The finding of reduction in frontal and (medial) temporal areas of the brain in patients with schizophrenia has been corroborated by using a voxel-based morphometry approach.

It has long been argued that the brain volume changes found in schizophrenia are (partly) caused by the antipsychotic medication. Indeed, in the early stages of schizophrenia progressive decreases in gray matter (Cahn et al. 2002) and frontal lobe volume (Gur et al. 1998; Madsen et al. 1999) have been found associated with the amount of antipsychotic medication taken. Those patients who were prescribed the highest doses of ► antipsychotic medication also had the greatest progressive decreases in brain volumes. Nevertheless, this brain volume decrease might not be a direct effect of the medication as those who are prescribed the highest doses of antipsychotic medication are generally the most severely ill patients. Increases and decreases in brain volumes depend on the type of antipsychotic medication. Basal ganglia volumes decrease on typical antipsychotic medication and increase (or normalize) on atypical medication or ► clozapine (Hakos et al. 1994; Scheepers et al. 2001). Recent longitudinal MRI studies have shown that ► olanzapine and ► clozapine actually attenuates brain tissue loss in schizophrenia, whereas typical antipsychotic medication do not (DeLisi 2008; Lieberman et al. 2005; van Haren et al. 2008).

In the last decade, many studies have focused their attention on investigating the effects of first psychotic episode on the brain. Studying the early phase of the illness is useful since the confounding effects of chronicity and long-term medication can be excluded. MRI studies in antipsychotic naïve patients appear to show a relative paucity of ► brain abnormalities which stands in marked contrast with findings in more chronic schizophrenia patients. Several explanations can be contemplated to elucidate the discrepancy in brain abnormalities between those patients who are chronically ill and those who are in the early phase of the illness. Medication might increase brain abnormalities and could contribute to these brain volume changes. Finding few brain abnormalities in antipsychotic naïve patients with schizophrenia could also be the result of a selection bias favoring the inclusion of patients who have a less severe form of schizophrenia; and last but not least, progression of the illness may lead to an increase of brain abnormalities.

Indeed, there is a growing body of evidence that brain abnormalities become greater in schizophrenia over the course of the illness. Various reviews of (longitudinal) MRI studies in patients with (first-episode) schizophrenia conclude that there is accelerated loss of gray matter particularly in the frontotemporal cortical areas, as well as sulcal and ventricular expansion over time. In schizophrenia, a 3% gray-matter decrease is found with a 0.5% decrease per year, which is consistent with the result of postmortem studies in schizophrenia (Hulshoff Pol and Kahn, 2008). Although changes in brain volume over time are reported in both first-episode patients and chronic patients with schizophrenia, the magnitude in first-episode patients (e.g., −1.2% in 1 year for whole brain volume) suggest that these brain volume reductions are particularly prominent during the first years of illness (Cahn et al. 2002).

Nevertheless (progressive), brain-volume reductions are only relevant if they are associated to the clinical characteristics and outcome in schizophrenia. The most consistent finding of longitudinal MRI studies in first-episode and chronic schizophrenia is the relationship between reduced brain volume (gray matter decrements and ventricular increments) and poor outcome. Psychotic symptoms have also been examined in relation to brain-volume loss over time. A recent MRI study investigated the relationship between psychosis and brain-volume change in first-episode patients with schizophrenia over the first 5 years of illness. Associations between gray-matter volume loss, lateral and third ventricle volume increase, and longer duration of psychosis were found. Total duration of psychotic symptoms was further associated with greater decreases in total brain and cerebellar volume (Cahn et al. 2009). Other MRI studies, which examined smaller brain structures found reduced volumes of the medial temporal lobe, superior temporal gyrus, and hippocampal volumes in patients with psychotic symptoms. Furthermore, a long duration of untreated psychosis (DUP) is associated with poor clinical and social outcome. Various research groups have now found that patients with a longer DUP have more decreased gray matter volume than patients with a shorter DUP (Lappin et al. 2006). These findings suggest that brain-volume loss over time could be attributable to the "toxic" effects of the psychotic state.

Nevertheless, besides the (untreated) psychosis, there are other factors that could be neurotoxic in schizophrenia, such as cannabis use and stress. About 28–50% of patients with schizophrenia use cannabis. Clinically, patients who

use cannabis have more positive (but not negative) symptoms, an earlier disease onset and an increased number of psychotic episodes when compared with patients who do not use cannabis. Rais et al. (2008) found significantly more decrease in brain volume in patients using cannabis when compared with nonusing patients over a 5-year period.

Until now, there is only indirect evidence that life events might affect brain volumes in schizophrenia, as lower gray- and white-matter volumes in schizophrenia are associated with a dysregulated dopaminergic/noradrenergic-mediated stress response.

Neurotoxicity

The ▶ neurotoxicity theory of schizophrenia states that an (untreated) psychosis is neurotoxic to the brain and that brain changes are an inherent feature of the neurobiological disease process in schizophrenia. As mentioned previously, MRI studies show volume reductions over time, particularly of gray matter. Nevertheless, the brains of schizophrenia patients do not reveal characteristic histopathology like other neurodegenerative diseases do. Moreover, postmortem studies have not found evidence of neuronal injury or degeneration. A neurodegenerative process in the brain normally accompanies loss of neuronal cells and microglial cells (a type of glial cells that are the resident macrophages of the brain).

In schizophrenia, a lack of microglial cells has been found. Some researchers have postulated that neuronal cell death occurs in schizophrenia, but that this cell death is programmed (▶ apoptosis) instead of ▶ necrosis, where microglial cells "eat" the injured cells and leave scar tissue at the place where the necrotic cell used to be. Various intracellular and extracellular events, like increased ▶ glutamate stimulation, can induce a programmed apoptotic cascade which results in cell destruction. This apoptotic cascade could then produce synapse loss and synaptic remodeling, and would compromise cell function and alter brain morphology (Lieberman 1999).

Postmortem studies in schizophrenia have also reported reduced dendritic spines; a measure of the amount of synaptic contacts between neurons. Furthermore, they found smaller dendritic arbors on the pyramidal cells of the cortex, damage to myelinated fiber tracts, and increased neuronal density because of reduced neuropil; the synaptic syncytium between neurons where synaptic connections are formed between branches of axons and dendrites (Davis et al. 2003). This decreased interneuronal neuropil could cause functional and anatomic hypoconnectivity in a schizophrenic brain and would explain the decreased cortical volumes as seen on MRI (Davis et al. 2003).

Thus, a higher concentration of neurotransmitters in the brain can lead to excitotoxication and could induce cell death which in turn could result in brain-volume reduction. Although the pathophysiology of schizophrenia is still unknown, we do know that ▶ antipsychotics, dopamine receptor blockers, reduce symptoms of schizophrenia, and that party drugs like ▶ cocaine and ▶ amphetamine increase dopamine in the brain and may induce psychosis. So, it is thought that in schizophrenia there is an increase in dopamine in the mesolimbic system. This is the so-called ▶ dopamine hypothesis of schizophrenia. Nevertheless, this hypothesis only explains the positive symptoms and does not explain the negative and cognitive problems seen in schizophrenia (▶ aminergic hypotheses of schizophrenia). ▶ Phencyclidine (PCP), an *N*-methyl D-aspartate (NMDA)-receptor (a glutamate receptor) antagonist, which disinhibits excitatory glutamatergic pathways causing neuronal damage, induces symptoms more similar to those seen in schizophrenia. The ▶ glutamate hypothesis of schizophrenia postulates that there is a hypofunction of the ▶ NMDA receptor in the schizophrenic brain. The reduced activity of the NMDA-receptor affects the glutamate concentration, but influences other neurotransmitter systems, such as dopamine and GABA in the brain.

The NMDA receptor is an ionotropic excitatory receptor with glutamate as its ligand. Binding of glutamate causes an influx of Na^+ and $Ca2^+$ and thereby, postsynaptic membrane depolarization. When there is a reduced amount of NMDA receptors, the excess of glutamate stays in the synaptic cleft and increases stimulation of other ionotropic receptors like those for α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (▶ AMPA) and kainite receptors. This overstimulation, also called excitotoxication, leads to dysregulation of the $Ca2^+$ homeostasis and causes oxidative stress and thereby, apoptosis (Deutsch et al. 2001).

Antagonism, or reduced activity, of the NMDA receptor and thus a hypofunctioning of glutamate signaling may also result in changed dopamine concentration. Prefrontal D_1 receptors are hypostimulated, which may lead to negative and cognitive symptoms of schizophrenia. A later developed episodic hyperactivity of the mesolimbic dopamine system may lead to positive symptoms of schizophrenia (Jarskog et al. 2007).

The NMDA receptors are also present at the GABAergic inhibitory interneurons within the cortex. Glutamate activation normally leads to the release of GABA to inhibit glutamatergic neurons and the release of glutamate. With reduced NMDA-receptor activity, a decreased amount of GABA will inhibit glutamate activity and thereby

cause a heightened activity of glutamatergic neurons. GABAergic inhibition is of great importance in critical circuits of normal brain function and could be the cause of the cognitive symptoms in patients (Reynolds et al. 2004).

Neuroprotection

► Neuroprotection refers to treatment that helps to maintain the functional integrity of the brain in response to neurobiological stress, such as apoptosis and less synaptic activity due to neurotoxicity. Neuroprotection is already a rapidly advancing concept in the treatment of neurological disorders. Moreover, it is also seen as a therapeutic treatment for psychiatric disorders to improve loss of function or prevent neurodegeneration from occurring. The most common treatment for schizophrenia is ► antipsychotic medication. Almost all patients with schizophrenia receive antipsychotic medication during their illness; therefore, it is not clear whether the progressive brain changes occurring in the brains of the patients are due to the illness itself (untreated psychosis) or perhaps due to the use of antipsychotic medication. In other words: Are antipsychotics neurotoxic or neuroprotective to the brain (Hulshoff Pol and Kahn 2008)?

Increases and decreases in brain volumes appear to depend on the type of antipsychotic medication. Basal-ganglia volumes decrease on typical antipsychotic medication and increase (or normalize) on atypical medication or clozapine. Recent longitudinal MRI studies have shown that olanzapine and clozapine actually attenuates brain-tissue loss in schizophrenia, whereas typical antipsychotic medication does not. It has been suggested that antipsychotic drugs, specifically the atypicals, have an effect on synaptic remodeling and neurogenesis, and thereby ameliorate the pathophysiology of schizophrenia (Lieberman et al. 2008). The progressive brain loss seen in patients who are treated with ► haloperidol and other typical antipsychotics could be due to the fact that typical antipsychotics are not neuroprotective, and thus, the progressive brain loss continues to increase despite the treatment.

Furthermore, it has been suggested that physical exercise, psychoeducation, and cognitive therapy in schizophrenia are neuroprotective, but very limited research has been done so far. Future studies need to be conducted to examine the neuroprotective effects of medication and (psychosocial) treatments in schizophrenia.

Cross-References

► Aminergic Hypotheses for Schizophrenia
► Antipsychotic Drugs
► Antipsychotic Medication: Future Prospects
► Apoptosis
► Cannabis Abuse and Dependence
► Classification of Psychoactive Drugs
► First-Generation Antipsychotics
► Magnetic Resonance Imaging (Structural)
► Movement Disorders Induced by Medications
► Neurodegeneration and Its Prevention
► Neurogenesis
► Neurotoxins
► Schizophrenia
► Second- and Third-Generation Antipsychotics

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Neurotoxins

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Synonyms

Catecholamine toxins; Excitotoxins; Immunotoxins; Metabolic toxins; Plant toxins

Definition

Neurotoxins are poisons that disable or kill neurons.

Current Concepts and State of Knowledge

Some neurotoxins have been discovered as synthetic chemicals, whether intended for neuronal targeting (e.g., ▶ 6-hydroxydopamine, MPTP) or as side effects of other applications (e.g., paraquat and other pesticides). Others are signaling molecules of normal cells but delivered in excess (e.g., nitric oxide, ▶ glutamate). Nevertheless, the most powerful neurotoxins come from the natural world, having evolved for use by animals and plants both for predation and for defense, such as snake, insect, and spider venoms or plant toxins. Neurotoxicology is a wide field in its own right, seeking to understand the pharmacology and mechanisms of neuronal action of toxins in order to promote safety, whether in the testing of manufactured products or protection of the environment, in humans and animals alike. Neurotoxins have also, however, emerged over the last four decades as a powerful tool in experimental neuroscience and this is the focus of the present chapter. In particular, I briefly consider the development of a range of molecules that allow selective targeting, disruption, and death of specific populations of neuronal cells in the CNS. These tools can then be used to make lesions for experimental analysis of the normal function of the targeted neurons; to generate effective and efficient animal models of human diseases; to study mechanisms of neurodegeneration; and to develop novel therapeutics.

The utility of particular toxins relates to multiple factors, including *specificity* for the particular target population alone; *validity* to reproduce the specific neuropathology, and ideally the pathogenic process, involved in the target disease; *reliability* to yield consistent toxicity from one application to the next; and *practicality* for safe, simple, efficient, and cost effective handling and use within the laboratory environment.

Monoamine Neurotoxins

6-Hydroxydopamine (6-OHDA)

6-OHDA is structurally related to dopamine (DA) and is selectively incorporated via active uptake channels into catecholamine (DA and noradrenaline, NA) neurons, where it is metabolized to produce toxic products that cause cell death. When injected systemically, 6-OHDA will induce ▶ sympathectomy, but will not cross the ▶ blood–brain barrier; so, direct administration into the brain is required to induce lesions in the central neurons. The precise stereotaxic placement of the injection will determine which population of central catecholamine neurons are targeted. Thus, injection into the nigrostriatal pathway is effective in producing an effective lesion of central DA neurons of the ventral mesencephalon (substantia nigra and ▶ ventral tegmental area) resulting in widespread DA denervation of the neostriatum, ventral striatum, and associated cortical and limbic projections, and provides a widely used animal model of ▶ Parkinson's disease (PD). In adult animals, bilateral 6-OHDA lesions, whether made by intraventricular or nigrostriatal injection, are associated with a profound akinetic syndrome and failure to engage in any voluntary behaviors results in ▶ catalepsy, aphagia, and adipsia, making these animals

extremely difficult to maintain in good health and suitable for experimental analysis. By contrast, unilateral lesions produce a marked motor asymmetry involving neglect of contralateral space, postural and response bias to the ipsilateral side, and marked head-to-tail turning response ("rotation") when activated by an arousing stimulus or stimulant drug. Rotation in unilateral lesioned animals has been very widely used as a simple, reliable, quantitative functional test of experimental therapeutics – including neuroprotective agents, trophic factors, cell therapies, and novel pharmaceutics – targeted at DA system function, in particular with respect to PD, and also covering applications in schizophrenia, ADHD, and addiction.

Centrally administered 6-OHDA will affect all catecholamine neurons and their projections within the vicinity of the spread of the injection. To some extent, the lesions can be made selective to an individual population of neurons by the judicious placement of the injection, but for example, nigrostriatal placement will inevitably also affect collateral NA projections in the medial forebrain bundle. If selective targeting of DA neurons is required, NA neurons can be protected by pretreatment i.p. with the selective uptake inhibitor desipramine. Conversely, selective NA depletion can be achieved by use of a selective NA toxin, such as DSP-4 (see below), or by 6-OHDA injection caudal to the ventral mesencephalon where the ascending DA neurons are located. Moreover, the forebrain projections of brainstem NA cell groups to hypothalamic, limbic, and cortical targets separate in dorsal and ventral bundles that can again be selectively disrupted by differential placement. Such manipulations were important in the pioneering studies that first distinguished the specific substrates for reward and motivational systems in the brain.

Dihydroxytryptamines (DHTs)

5,6-DHT and 5,7-DHT are structurally related to ▶ serotonin (5-hydroxytryptamine, 5-HT) and cause death of these neurons by a similar process of active uptake and intraneuronal cytotoxicity. Thus, injection into the cerebral ventricles or into the ascending fiber pathways in the medial forebrain bundle can produce relatively extensive depletion of forebrain serotonin. This has proved useful in studies of the role of 5-HT systems in the ▶ hippocampus, and in particular in the interdependence and interaction of serotoninergic and cholinergic afferents in regulating hippocampal function, both physiologically (such as in maintenance of the theta rhythm) and in studies of the central substrates of learning and memory. However, the DHTs do not have the same degree of potency and selectivity as 6-OHDA. Both 5,6-DHT and 5,7-DHT cross-react with catecholamine neurons, and greater attention needs to be paid to selective blockade of uptake into both DA and NA neurons, and to selective placement into the target terminal areas such as the hippocampus.

DSP-4

An alternative catecholamine neurotoxin is DSP-4 (N-2-chloroethyl-N-ethyl-2-bromobenzylamine) which, following peripheral administration, appears to have a relatively selective toxicity against NA neurons and nerve terminals, in particular the cortical and hippocampal projections of the locus coeruleus. In spite of the ease of administration and the relative selectivity for NA neurons within the brain, the toxin has been reported to also produce collateral damage in DA and 5-HT systems and lasting changes within the periphery as well as center, which may be overcome by direct central injection into circumscribed brain regions. Moreover, the precise mechanisms of DSP-4 toxicity remain ambiguous. This neurotoxin may nevertheless prove useful in combination with other toxins, such as 5,7-DHT, in comparing the interaction of NA and complementary 5-HT projections in the forebrain on the profiles of anatomical compensation, behavioral and electrophysiological changes within the target nuclei, in particular in the hippocampus or neocortex.

Other Models of Parkinson's Disease (PD)

1-Methyl-4-Phenyl-Tetrahydropiridine (MPTP)

MPTP was discovered as a by-product of a failed illegal synthesis of meperidine analogs, when it caused a profound parkinsonian syndrome in drug addicts who self-administered the substance. The peripheral administration of the drug in monkeys and mice induces major mesencephalic DA cell loss and a similarly marked PD-like motor syndrome. As in the idiopathic disease, MPTP-induced PD is responsive to L-DOPA.

MPTP is not itself the toxic agent. Rather it is metabolized by monoamine oxidase (MAO-B) to the active form, MPP+, which is taken up into cells via active DA uptake channels, and acts on mitochondria to cause cell death via mechanisms believed to involve reduced oxidative phosphorylation, lipid peroxidation, and disturbance of calcium homeostasis. MAO inhibitors such as deprenyl inhibit toxicity. Interestingly, the drug has little effect in rats which is believed to be due to the fact that the dominant isoform of MAO in this species, MAO-A, does not provide an equivalent substrate for MPTP conversion to MPP+, whereas if MPP+ itself if injected into the rat brain, it is as toxic in rats as it is in mice and monkeys.

MPTP continues to be widely used to model PD in mice and monkeys. Animals exhibit an acute parkinsonian

syndrome that recovers rapidly after a single injection, and they need to be treated chronically to achieve stable bilateral cell loss, associated with profound parkinsonian debility, including ► akinesia, aphagia, and adipsia. As a consequence, unilateral lesions that retain the animals in better health are more suitable for long term studies of reparative and neuroprotective therapeutics, and can be achieved in monkeys by unilateral infusion of the toxin into the ascending carotid artery, thereby restricting drug distribution to just the ipsilateral hemisphere.

Industrial and Agricultural Chemicals

A variety of other toxins – including paraquat, rotenone, other industrial pyridines and agricultural fertilizers – have been identified that appear to induce preferential toxicity against DA neurons after peripheral administration. This may relate to these neurons being particularly sensitive to oxidative stress and associated sensitivity of nigral neurons to iron toxicity. Indeed DA agonists such as ► methamphetamine and DA itself can be toxic to DA neurons both in vitro and in vivo when administered in high concentration. Although heavily investigated in terms of seeking to understand mechanisms of pathogenesis in PD, none of these toxins have been found to be sufficiently reliable, consistent, and specific to provide a practical alternative to 6-OHDA and MPTP.

A variety of other pharmaceutical agents are associated with extensive disruption of dopamine metabolism, such as ► reserpine and α-methyl-para-tyrosine. These drugs offer reversible tools to study acute dopamine depletion and were widely used in particular in early studies of experimental Parkinsonism. Repeated high doses of ► amphetamines (in particular methamphetamine) can also induce partial cell loss in substantia nigra.

► Ubiquitin–Proteasome System (UPS) Inhibitors

The UPS is the major system of the cell for tagging and digesting damaged, misfolded, and aberrant proteins. PD has been associated with impairment in proteolytic activity of the 20/26S proteasomes in the substantia nigra, leading to the investigation of UPS blockade as a model of PD. Thus, the injections of UPS inhibitors such as lactastatin, epoxomicin, or synthetic inhibitor peptides into the substantia nigra have been reported to produce not just selective DA depletion, but also protein aggregation in nigral neurons and formation of ► Lewy body-like protein inclusions in the cells, characteristic of the major neuropathological hallmark of the human disease. Although this remains a plausible and attractive model of PD, there continues considerable debate about the reproducibility of the model, which seems to depend on quite precise lesion parameters to reproduce the specific pathology.

Excitotoxins

Excitatory Amino Acids (EAAs)

The excitotoxins are a class of neurotoxins with the common feature of being glutamate receptor (GluR) agonists. The first discovered EAAs with neurotoxic potential in the brain were monosodium glutamate (active after peripheral administration) and kainic acid (requiring central injection). Their common action as GluR agonists led to the "excitotoxicity hypothesis," *viz.* that at a sufficient dose such EAAs induce a prolonged depolarization of glutamate receptive neurons, resulting in their cell death through some process of overactivation or overstimulation. Subsequent studies have identified a cascade of changes following GluR depolarization producing a "cycle of toxicity," which includes sodium influx, osmotic imbalance and cell lysis, calcium influx, activation of the mitochondrial energy chain and oxidative stress, inflammatory response, induction of specific cell death gene expression pathways, and other metabolic changes that combine to cause neuronal death via both necrotic and apoptotic mechanisms.

Kainic Acid (KA)

EAAs such as kainic acid offered a distinct advantage over older lesion methods such (as aspiration, electrolytic and radiofrequency lesions) in permitting localized induction of cell loss while sparing axons of passage. This allowed for the first time making selective lesions in areas traversed by *en passant* fiber bundles, such as in the hypothalamus and neostriatum in rodents, and permitted important studies for the first time of the relative role of discrete hypothalamic nuclei vs. ascending brainstem regulatory systems in the central control of essential motivational and reward related processes; and early studies of behavioral anatomical and neurochemical changes in the striatum to produce the first usable animal models of ► Huntington's disease (HD).

Nevertheless, the excitatory potential of kainic acid was also associated with a marked potential for inducing sustained neuronal firing originating from the lesion focus, but inducing epileptogenic activity throughout the brain, overt seizures, and cell loss in susceptible neuronal populations in remote areas of the brain, in particular in the ► hippocampus and piriform lobe.

Receptor Subclass Selectivity

The profile of EAA-induced hyperactivity and cell toxicity depends on the match between the profile of glutamate

receptor distribution on the different populations of neurons in the target area and the GluR selectivity of the agonist. EAAs with excitotoxic properties have been identified binding to all major classes of GluR, notably the kainate, ► AMPA, and ► NMDA selective subclasses of ionotropic receptors, and ► metabotropic receptors sensitive to quisqualate. Some EAAs are relatively selective for a single receptor subclass, such as kainate, AMPA, and NMDA themselves, whereas others have mixed receptor targets, such as ibotenic acid.

With different cell populations in a nucleus or brain area expressing different receptors, judicious selection of toxin can provide different profiles of cell death. Thus, a comparison of alternative toxins following injection into the nucleus basalis magnocellularis (NBM) identified quisqualic acid and AMPA as the toxins of choice for the (relatively) selectively targeting of the cholinergic neurons of the basal forebrain-cortical projection system in comparison to the damage in non-cholinergic neurons produced by ibotenic acid, NMDA, and kainate.

Targeting NMDA receptors using NMDA itself has emerged as the neurotoxin of choice in ► hippocampus and cortex, and NMDA has provided a potent toxin for demonstrating the effects of hippocampal lesions on a range of learning phenomena. Moreover, the NMDA receptor antagonist AP-5 has been particularly influential in mapping parallel effects of hippocampal NA denervation disrupting behavioral and electrophysiological function, supporting the hypothesis that hippocampal LTP both in vivo and in slice preparations provides a valid cellular substrate of the neural processes underlying learning and memory within hippocampal circuits.

More recently, quinolinic acid has emerged as the EAA of choice within the striatum. After intrastriatal injection, quinolinic acid is relatively selective for the median spiny (► DARPP-32 positive) projection neurons of the striatum with relative sparing of the large ACh and medium NADPH-diaphorase-positive and other aspiny interneurons. It has proved of additional interest as an animal model of HD because this molecule is found in the normal brain as an endogenous product in one of the two main pathways of tryptophan metabolism, and the lesion has been widely used to explore the development of novel cellular, neurotrophic, and neuroprotective therapeutics for the human disease.

Nevertheless, receptor distribution is not the sole determinant of selectivity. Alternative excitotoxins also differ in (1) epileptogenic potential, as a consequence of which kainic acid is seldom used today for in vivo lesion studies; (2) lipophilicity, as a consequence of which ibotenic acid shows much greater diffusion through myelinated fiber tracts causing e.g., more damage in deep layers of the cortex after striatal injection than does, say, quinolinic acid; and (3) inflammatory activity that can cause the demyelination of passing axons and reduce the fiber sparing benefits originally claimed for the EAAs. Thus, the selection of an appropriate excitotoxin may be suggested by theoretical considerations, but will require systematic empirical validation before use within any new model application.

Metabolic Toxins

3-Nitropropionic Acid (3-NP)

3-NP is a plant and fungal toxin associated with a toxic dystonic syndrome in man, and has its action as an inhibitor of succinate dehydrogenase, a component of ► mitochondrial complex II energy metabolism. In the 1990s, 3NP was optimistically adopted as a particularly efficient metabolic toxin since it appeared to provide selective striatal lesions even after peripheral administration. For reasons that remain poorly understood i.p. injections produce selective destruction of the medium spiny projection neurons of the neostriatum, with relative sparing of the striatal interneurons. This seemed to reproduce the profile of cell loss in HD and was adopted in several labs as a simple and efficient method to reproduce the human pathology. However, the toxin has a number of practical difficulties for experimental application. Standardized dosing can produce very great variability of toxicity with some animals exhibiting very extensive nonspecific lesions and large necrotic holes in the striatum, whereas other identically treated animals have no detectable pathology at all. In order to achieve consistent and relatively selective striatal lesions, it is necessary to administer very many small injections over a regular and extended time period, typically daily over weeks or even months, combined with daily testing with a functional readout that will allow setting a criterion for the cessation of dosing each animal at a comparable stage. The only effective protocols for achieving reliable and reproducible lesions that can be used to then test experimental therapeutics involve a major investment in time and resources that largely offsets the original promise of efficiency offered by the peripheral route of administration.

Other Mitochondrial Toxins

Although 3-NP may be relatively unreliable in its toxicity and specificity, a variety of other toxins similarly affect the mitochondrial energy chain, including malonic acid (MA, malonate), which inhibits the same mitochondrial complex II enzymes as 3-NP, and aminooxyacetic acid (AOAA). Unlike 3-NP, these toxins do not cross the

► blood–brain barrier and so require central injection. Thus, when injected into the striatum, both MA and AOAA induce effective striatal lesions. These toxins have been described as inducing secondary or "indirect" excitotoxicity to neurons in the area of injection, since the profile of lesion toxicity is similar to that induced by GluR agonists, they potentiate the effects of low doses of the latter EAAs, and their toxicity is partially blocked by the NMDA antagonist MK-801. These metabolic toxins have again been of particular interest as another model of HD since they are associated with a similar cellular impairment in metabolic function as seen in the human disease, and have been argued to model a final common pathway in cell death. Moreover, toxicity is age dependent and selective for medium spiny neurons with relative sparing of striatal interneurons. However, in contrast to the human disease, malonate appears to have a toxic effect also on DA afferents to the striatum, and can be more variable in its effects than the consistent results obtained with the classic EAA excitotoxins.

Immunotoxins

Cholinergic Neurotoxins

The selective targeting of cholinergic neurons for a long time relied on the selective placement of excitotoxins into the circumscribed cell body nuclei in the medial septum and the NBM. This achieved effective lesions of the target neurons and extensive cholinergic deafferentation of the targets of cholinergic projections in the cortex and hippocampus, respectively, but could never be demonstrated to be specific; co-localized non-cholinergic neurons and parallel projections were typically equally affected (e.g., damage to the parvalbumin-positive ► GABA neurons of the medial septum projecting in parallel to the hippocampus). A claim was made for cholinergic selectivity for the ethylcholine mustard axiridinium ion, AF-64A, but this has not been well supported. In the hands of most people, AF-64A produces cavitation at the site of injection and extensive nonspecific lesions. Greater specificity has subsequently been demonstrated for the immunotoxin, 192-IgG ► saporin.

Immunotoxins

Following a similar logic to the familiar neuroanatomical use of antibodies to label specific target molecules on cells in a range of sensitive immunohistochemistry techniques, immunotoxins involve conjugating an immunoglobulin antibody (or immunoglobulin fragment) to target cell surface receptors or channels with a cytotoxin that will then induce death of the target cell. The trick is to select targets such as neurotrophic factor receptors, which will internalize the ligand, thereby allowing the toxin to be transported into the cell for intracellular concentration, often with active transport back to the cell body where its primary toxic action takes effect. A range of antibody fragments and cytotoxins have now been developed for a range of application, the first of which to receive major attention was 192-IgG saporin.

192-IgG Saporin

192-IgG saporin was the first used and most extensively explored of the burgeoning range of immunotoxins. The 192-IgG immunoglobulin recognizes the p^{75} low affinity NGF receptor which is widely expressed on cholinergic neurons in the forebrain. After central injection, 192-IgG saporin binds to the NGF receptor, achieving selective internalization preferentially in cholinergic neurons, retrograde transport of the cytotoxin saporin to the cell body and consequent death of the cell. Although the preparation and stability of the toxin and precise parameters of injection are important, 192-IgG saporin has proved the most successful technique for selective lesion of septal and basal forebrain neurons sparing co-localized cells, and has been widely used to confirm that many of the electrophysiological and behavioral changes in learning and memory function associated with excitotoxic lesions of the medial septum and NBM are indeed attributable to the selective depletion of the cholinergic innervations of the hippocampus and cortex respectively.

Other Immunotoxins

More recently, other immunotoxins have been developed using a similar conjugate strategy to develop tools for simple and effective lesion of NA neurons by targeting the synthetic enzyme dopamine-ß-hydroxylase; DA neurons by targeting the ► DA transporter; striatal neurons by targeting the substance P receptor; and selective lesions of basal forebrain neurons receiving glutamatergic projections by conjugating saporin to the NMDA receptor. Indeed, the selectivity provided by immunotoxins allows a variety of previously intractable experimental issues to be addressed, such as the relative contributions of striosome and matrix compartments of the striatum by targeting the striosome projection neurons with a saporin-antibody complex recognizing the ► μ-opiate receptor.

Conclusions

The last three decades has provided a wide range of novel neurotoxins that allow selective disruption and death of targeted populations of neurons within the brain. Targets may be selected by anatomical location, morphological

cell type, specific neurotransmitter (via selective uptake channel), pharmacological and immunological targeting of identified receptors, or disruption of subcellular metabolic cell processes. These then provide powerful tools for making selective manipulations as the independent variable in physiological, pharmacological, and behavioral analyzes of normal and abnormal brain function in health and disease. Nevertheless, while most available toxins are effective in reproducing particular profiles of cell loss and features of cellular and subcellular pathology of the corresponding human disease, they frequently do not reproduce the neuropathogenic process accurately, and the lesions are typically acute rather than slowly progressive as is characteristic of most human neurodegenerative diseases. Consequently, neurotoxin-based lesions can provide effective models to study functional organization in the nervous system and have value for evaluating symptomatic and reparative approaches to treatment. However, such lesions are less suitable for the experimental analysis of neuroprotective processes and for the development of therapeutic strategies to alter or reverse the progressive course of disease. For such applications, alternative genetic models are increasingly considered preferable.

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Cross-References

- ► Amine Depletion Techniques
- ► Anti-Parkinson Drugs
- ► Apoptosis
- ► Blood–Brain Barrier
- ► Dementias: Animal Models
- ► Excitatory Amino Acids and their Antagonists
- ► Long-Term Potentiation and Memory

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Neurotransmitter

Definition

Neurotransmitters are chemical substances that relay, amplify, and modulate signals between one neuron and another, or between a neuron and another cell. Typically, neurotransmitters are packaged into vesicles that cluster beneath the membrane on the presynaptic side of a synapse, and are released into the synaptic cleft, where they bind to receptors in the membrane on the postsynaptic cell. Release of neurotransmitters usually follows arrival of an action potential at the synapse, but may follow graded electrical potentials. Low level "baseline" release may also occur without electrical stimulation.

Neurotransmitter Transporters

Definition

Proteins that function to take up neurotransmitters from the extracellular milieu into cells such as neurons and glia. These transporters are targets for many psychotherapeutic drugs (e.g., ► Fluoxetine, Prozac©) and sites of action of abused (e.g., ► cocaine) drugs.

Neurotrophic Factors

Definition

A neurotrophic factor is a neuropeptide that regulates the growth, differentiation, and survival of certain neurons in the peripheral and central nervous systems.

Cross-References

- ► Brain-Derived Neurotrophic Factor

Neurovascular Unit

Definition
In addition to the capillary endothelial cells, the site of anatomical blood–brain barrier, neurons, and nonneuronal cells such as pericytes, astrocytes, microglia together constitute a functional unit, often referred to as a neurovascular unit.

Cross-References
► Blood–Brain Barrier

Neutral Antagonists

Definition
A ligand that binds to a receptor, does not increase or decrease cellular activity, but can block the actions of both agonists and inverse agonists.

Newer Anticonvulsants

► Second-Generation Anticonvulsants

Nicotinamide Adenine Dinucleotide

Synonyms
NAD

Definition
Coenzyme utilized during alcohol breakdown; rate-limiting factor of ADH-related metabolic tolerance.

Nicotine

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Synonyms
(−)-1-Methyl-2-(3-pyridyl)pyrrolidine

Definition
Nicotine is by far the most extensively studied chemical in tobacco smoke. This chapter summarizes its pharmacokinetics, mechanisms of action, and behavioral effects in humans and animals. Particular attention is paid to the role of nicotine in tobacco addiction, as currently understood from the perspective of animal and human studies. Finally, the possibility that tobacco addiction is facilitated by additional chemical components of tobacco smoke or by nonchemical reinforcers interacting with nicotine is discussed.

Pharmacological Properties

Pharmacokinetics
Nicotine is a tertiary amine and weak base, such that it is more than 50% ionized at physiological pH. In its nonionized form, nicotine tends to pass rapidly through membranes. For example, when nicotine reaches the brain via the carotid arteries, it is swiftly taken up and then released slowly into the bloodstream. Animal studies have shown that the brain can maintain a three-fold higher nicotine concentration than plasma, although how much of the drug is free to act on brain receptors is unclear. Nicotine is metabolized by a number of hepatic CYP450 enzymes, and its plasma ►elimination half-life in humans is around 2 h (1 h in rats), with notable interindividual differences resulting from genetic variation. Peripherally formed nicotine metabolites appear to have only minor pharmacological effects. However, in animals and potentially in humans, nicotine is also metabolized within the brain. One metabolite formed locally within the rat brain, nornicotine, is a weak nicotinic agonist (► Nicotinic Agonists and Antagonists) but may accumulate with repeated nicotine dosing.

It was long believed that cigarette smoking extracts nicotine rapidly from the lungs, such that each puff would promptly deliver a highly concentrated bolus to the brain. However, empirical evidence now suggests that arterial levels of nicotine rise quite gradually, peaking only after 20–25 s. This finding potentially has major implications for our understanding of nicotine reinforcement (see below).

Mechanisms of Action
Nicotine exerts almost all of its known actions via nicotinic acetylcholine receptors (nAChRs). Each nicotinic receptor comprises five protein subunits, arranged around a water-filled channel. The receptor is normally closed, but opens upon the binding of the agonist. Channel opening allows the passage of ions, notably Na^+ and/or Ca^{++}. These

positively charged species rapidly enter the cell, causing depolarization. This depolarization in turn stimulates the opening of voltage-gated ion channels, with a consequent cascade of intracellular signaling events. Hence, at the cellular level, the stimulation of nAChRs can trigger contraction (skeletal muscle), action potential generation, and modulation of transmitter or hormone release.

Nicotinic receptors are widely expressed by neurons in brain, spinal cord, autonomic ganglia, and by primary sensory neurons. Indeed, there is scarcely a nucleus in the brain that does not express nicotinic receptors. Although most CNS nAChRs are located in or on neurons, some appear associated with glial cells. Nicotinic AChRs also occur on other nonneuronal cells, for example in skeletal muscle, lung, skin, immune cells, and vascular endothelium.

Neuronally expressed nicotinic receptors are highly heterogeneous (Gotti et al. 2006; see also Nicotinic Agonists and Antagonists). This diversity partly reflects the diversity of protein subunits which can combine to form a receptor. Each type of nAChR subunit is encoded by a different gene, and neuronal nAChRs are formed from combinations of α2–α7 and β2–β4 subunits. Theoretically, then, a vast number of nAChR subtypes might exist, but the real number appears far smaller, with perhaps one dozen accounting for most pharmacological actions of nicotine (Gotti et al. 2006). Subtypes of nAChR are named according to their constituent subunits, with the stoichiometry indicated if known (e.g., α4β2 or $\alpha4_2\beta2_3$). By convention, an asterisk indicates the possible presence of additional subunits (e.g., α4β2*). Most nAChR subtypes comprise combinations of both α and β subunits, but α7 subunits can additionally form homo-oligomeric receptors (i.e., $\alpha7_5$). Individual neurons are capable of expressing more than one nAChR subtype, each of which may contain several different types of subunit.

Nicotinic AChR subtypes differ in several important respects. First, each subtype possesses a unique anatomical pattern of expression. Second, nAChR subtypes differ in their channel properties. For example, α7-containing receptors are unusually permeable to Ca^{++} relative to Na^{+}ions, and this property has important implications for transmitter release and other intracellular functions mediated by Ca^{++}. Third, nAChR subtypes differ in their sensitivity to nicotinic agonists and antagonists, and in their propensity to desensitize and resensitize. Fourth, some receptor subtypes proliferate in response to chronic agonist administration, although the functional consequences of such upregulation are not well understood.

Nicotinic receptors transition through three main functional states: resting, activated, and desensitized. In the absence of agonist, the receptor-associated channel is predominantly closed. The binding of agonist leads to channel opening, an extremely rapid transition typically occurring within milliseconds. The activated receptor may subsequently enter a desensitized state in which the channel is again closed. With time, the desensitized receptor assumes the resting, activatable state. Certain nAChR subtypes desensitize rapidly (e.g., α7 in less than 1 s), whereas others desensitize slowly if at all. Although desensitization was once thought to require high agonist concentrations, it is now known that even very low (nanomolar) concentrations of nicotine can desensitize some nAChR subtypes, without significant receptor activation. This is potentially significant, since in habitual smokers, plasma nicotine levels remain in this range even after a night of abstinence. With prolonged agonist exposure, nicotinic receptors can enter a more persistent desensitized state, termed inactivation (Gentry and Lukas 2002). Here, functional recovery may require several days or more.

It is not at all clear to what extent cigarette smoking stimulates versus desensitizes neuronal nAChRs. The answer will surely depend on the nAChR subtype, previous nicotine exposure, and the temporal pattern and amount of nicotine intake. Most animal models related to tobacco smoking employ relatively brief nicotine exposures, which are unlikely to mimic the complexity of tobacco smoking.

Behavioral Effects of Nicotine in Humans and Animals

Nicotine exerts a plethora of acute behavioral effects, which is unsurprising given that nAChRs are very widely expressed in the brain and elsewhere. Certain behavioral effects depend not only on the dose administered, but also on recent or remote drug history; some effects undergo transient or persistent ▶ tolerance, whereas others show ▶ sensitization or else remain largely stable across repeated tests.

Comparison of behavioral effects in humans versus animals is hindered by several factors. First, behavioral procedures are usually quite different. Second, most human studies are conducted with tobacco smokers; these individuals often have many years of drug experience. Third, very few animal studies have attempted to mimic the complex ▶ pharmacokinetics associated with tobacco smoking. Instead, nicotine is typically administered as an acute subcutaneous or intraperitoneal "depot" injection, in doses providing plasma levels higher than those found in most habitual smokers (Matta et al. 2007). The use of relatively high doses in animals leads to numerous behavioral effects, not all relevant to tobacco

smoking. Behavioral responses to nicotine that are most related to reinforcement are described in a later section.

In drug-naïve rats, nicotine can produce marked behavioral disruption, associated with prostration and ▶ ataxia. However, upon repeated dosing, persistent tolerance develops, such that a generalized stimulant effect emerges in tests of locomotor stimulation and ▶ operant responding. This transition is often viewed in terms of behavioral sensitization (▶ Sensitization to drugs), although it is at least partly due to tolerance to the initial depressant effect. The behavioral activating effect of nicotine appears quite general, since operant responding is also increased during time-out periods when reinforcers are unavailable and also in tasks where low rates of responding are preferentially reinforced.

Nicotine's status as a mild ▶ psychostimulant drug is supported by several other findings. For example, like ▶ amphetamine and similar drugs, nicotine improves sustained attention and produces an amphetamine-like discriminative stimulus (▶ Drug Discrimination) (i.e., drug cue) in nicotine-experienced rats (Smith and Stolerman 2009). Pharmacological and lesion studies that have been conducted in animals further suggest that like psychostimulants, nicotine can increase locomotor activity and serve as a ▶ reinforcer via a mechanism dependent on mesolimbic dopaminergic transmission (see below).

Many other behavioral effects of systemic nicotine administration have been reported in rodents or human subjects, or both. These include antinociception (▶ Analgesics), improved cognition (▶ Cognitive enhancers), reduced or increased anxiety (▶ Anxiety: animal models), attenuated ▶ aggression, reduced food intake (▶ Appetite suppressants), and ▶ conditioned taste aversion.

Antinociceptive effects of nicotine have been observed in several animal pain models (▶ Antinociception Test Methods). Neuronal and receptor mechanisms have been partially elucidated. Pain-suppressing effects of tobacco smoking have also been demonstrated in human subjects; limited evidence suggests that nicotine is at least partly responsible.

Sustained ▶ attention is improved by nicotine in both animals and humans (Levin et al. 2006) (▶ Rodent Tests of Cognition). Improvements have been documented using several procedures in rats, including the ▶ five-choice serial reaction time task. In the latter procedure, major differences between rat strains were observed. Interestingly, attentional enhancement by nicotine was not fully mimicked by amphetamine, suggesting divergent mechanisms. Attentional processing is also increased in human subjects receiving nicotine via skin patches. Enhancement has been found not only in abstinent smokers, but also in nonsmokers. Patients suffering from ▶ schizophrenia or ▶ attentional deficit hyperactivity disorder have also shown improvements in attention.

Learning and/or memory is improved by nicotine in a wide variety of vertebrate species and procedures (Levin et al. 2006). In rodents, nicotine tends to enhance these cognitive aspects more strongly than attention, whereas the reverse has been found in humans. It is unclear whether this divergence represents a species difference or reflects the particular behavioral tests used in rodents versus humans. In rats, nicotine-associated improvements in working memory have been extensively studied using the eight-arm ▶ radial maze (▶ Short-term and Working Memory in Animals). Here, several nicotinic agonists have proven effective, and nicotine is also effective when given chronically. Mechanisms of memory improvement have been partially elucidated in terms of nAChR subtypes, transmitter systems, and brain structures (Levin et al. 2006).

Although in most animal and human studies, subjects are exposed to nicotine during acquisition and test sessions, a few reports employing post-trial administration suggest that nicotine can also improve memory consolidation (Levin et al. 2006) (▶ Reference Memory and Consolidation). Nicotine has had beneficial effects in rodents with impaired learning or memory due to brain lesions. However, nicotine does not appear to improve memory in Alzheimer's disease (▶ Dementias and Other Amnesic Disorders) or schizophrenic patients, despite improvements in attentional processing.

Tests of anxiety in rodents have provided clear evidence of both ▶ anxiolytic and ▶ anxiogenic effects, with dose and baseline anxiety acting as modulating variables (▶ Anxiety: animal models). Genetic deletion of different nAChR subunits suggests that multiple nAChR subtypes modulate anxiety levels in complex ways. Rodents undergoing nicotine withdrawal show signs of anxiety, and in smokers, tobacco withdrawal-related anxiety is alleviated by nicotine replacement. Although smokers commonly expect that smoking or nicotine will reduce stress-induced negative affect, published evidence is equivocal.

Aggressive behavior, elicited in various ways, is reduced by acute systemic administration of nicotine in several species, including rats and human subjects (▶ Aggression). In some studies, the effect is demonstrably not due to motor impairment. Irritability and aggressiveness commonly occur during smoking cessation, and are alleviated by nicotine replacement therapy especially in subjects with high trait hostility. Mechanisms underlying these effects of nicotine remain unexplored.

Tobacco smoking reduces the body weight setpoint, and weight gain is a common consequence of cessation. Many smokers, especially young women, regard body weight gain as a deterrent to quitting. However, smokers tend to eat as much as nonsmokers, and an acute administration of nicotine appears not to reduce hunger or caloric intake in hungry smokers, suggesting that metabolic factors may be critical instead. Nicotine deprivation does not appear to contribute much to post-cessation weight gain, since the latter is only mildly inhibited by nicotine replacement therapy. In rodents, nicotine not only exerts complex effects on peripheral energy metabolism but also suppresses appetite. The ► anorexigenic effect of nicotine likely arises from peripheral and central actions, especially within the lateral hypothalamus.

► Conditioned taste aversion is readily produced by nicotine in some strains of mice and in adult, but not in periadolescent, rats. The effect is due to a central action of nicotine, and it appears dependent on dopaminergic transmission in the ► nucleus accumbens.

Nicotine provides a recognizable and reliable ► discriminative stimulus (cue), in humans, monkeys, and rodents (Drug Discrimination). Typically, nicotine has been administered by nasal spray (humans) or by systemic injection (animals). In rats, the nicotine cue has been identified as central in origin, likely involving multiple nicotinic receptor subtypes, transmitter pathways, and brain regions (Smith and Stolerman 2009). The multiplex nature of the nicotine cue, together with the potential for redundancy across different neural pathways, has hindered mechanistic dissection. As mentioned, the nicotine cue has psychomotor stimulants-like properties in rodents, with contributions from ascending dopaminergic projections as well as α4β2 nAChRs. However, the nicotine cue is not critically dependent upon mesolimbic dopamine transmission in rats, unlike the drug's reinforcing and locomotor stimulant effects (Smith and Stolerman 2009). Candidate trigger sites have been identified in medial ► prefrontal cortex and ► hippocampus.

Subjective Effects of Nicotine in Human Subjects

Nicotine acutely elicits multiple and complex subjective effects, including changes in mood, alertness, and anxiety (Kalman and Smith 2005). These effects depend on a host of factors, such as personality, smoking status, degree of abstinence, situational context (e.g., stress), passive versus self-adminstration, other drug use, and dose. Nicotine has been administered intravenously or via nasal spray in most studies. Stronger subjective responses have been seen in nonsmokers than in smokers. Generally, low to moderate doses tend to improve mood in smokers, especially during abstinence. However, dysphoria is commonly encountered as well, particularly at higher doses. Nicotine increases subjective arousal in smokers but reduces it in subjects who have never smoked; it can also make both types of individual feel less relaxed. A number of studies have suggested that nicotine can exert euphoric, "head-rush" effects resembling ► cocaine. However, such findings have little relevance to tobacco smoking, since they were obtained in known substance abusers given rapid (10-s) intravenous infusions of nicotine in doses equivalent to one or two cigarettes (i.e., 0.01–0.04 mg/kg). Puff-size doses of nicotine (e.g., 0.1 mg/infusion IV), in contrast, have only mild subjective effects.

Nicotine as a Contributor to Tobacco Addiction

In many individuals, cigarette smoking represents an addiction: it is a compulsive behavior, unaided quitting is rare, and relapse is common. Nicotine has been accorded a leading role in tobacco addiction, mostly notably in the 1988 US Surgeon General's Report. This document concluded that "nicotine is the drug in tobacco that causes addiction" (► Nicotine Dependence and its Treatment). The main arguments that have been forwarded in support of this conclusion are as follows. Nicotine is consumed in ways that avoid the many pyrolysis products found in tobacco smoke (e.g., snuff, chewing tobacco). The tobacco ► withdrawal syndrome can largely be attributed to nicotine withdrawal, since most symptoms are countered by nicotine replacement therapy, and a nicotine withdrawal syndrome can be produced reliably in animals. Nicotine replacement therapy doubles the chance of quitting. In the absence of tobacco, nicotine can serve as a positive reinforcer in human and animal self-administration studies. Nicotine shares important characteristics with other drugs of abuse such as amphetamine (e.g., cue properties, sensitization, release of mesolimbic dopamine, facilitation of brain stimulation reward). However, as discussed below, several of these statements are subject to important qualifications, and consequently a more nuanced view of nicotine's role in tobacco addiction is beginning to emerge.

Animal Models Related to Nicotine Reward

"Reward" is a multifaceted concept, and the rewarding effects of nicotine are commonly operationalized as intravenous self-administration, conditioned place preference, or facilitation of ► intracranial-self-stimulation. Most animal studies have been performed using rats.

Intravenous self-administration (► Self-administration of Drugs). It is well-established that intravenous infusions of nicotine can serve as a primary reinforcer in several mammalian species including humans (Le Foll

and Goldberg 2008). However, the great majority of studies have employed rates of drug delivery and doses outside the range experienced by smokers. In particular, nicotine has been virtually always given as a rapid (e.g., 1-s) bolus, whereas after a cigarette puff, the drug is released only slowly into the circulation, with arterial levels peaking after some 20–25 s. In addition, most animal and human studies have used doses of 15–30 μg/kg per infusion, whereas smokers receive only 1–2 μg/kg per puff (Matta et al. 2007). In contrast, recent evidence suggests that doses as low as 3 μg/kg can support self-administration behavior in monkeys and rats; indeed, rats worked for this dose even when it was delivered in a slow infusion. To date, studies of brain mechanisms related to nicotine self-administration have relied on the conventional fast infusion-high dose procedure. This work has established a critical role for ▶ mesolimbic dopamine transmission. However, it should be recalled that in human subjects, high doses of nicotine have also been reported to produce psychostimulant-like subjective effects, whereas smoking-relevant doses have not.

Conditioned place preference (▶ Conditioned place preference and aversion) has been observed after acute nicotine administration in rats and mice (Le Foll and Goldberg 2008). Many positive reports have relied on the use of "biased" procedures, which are methodologically questionable, and conditioned place aversion has also been reported. Nicotine place preference, where observed, is neither as reliable nor as large as with drugs such as ▶ morphine and psychostimulants. Recent evidence suggests that the rewarding and aversive effects of nicotine in this procedure can be dissociated by brain lesions and pharmacological manipulations.

▶ Intracranial self-stimulation is facilitated by acute nicotine administration in rodents. In particular, nicotine reduces reinforcing thresholds of electrical brain stimulation. This action, which is shared by psychostimulants and opiates, is thought to reflect the sensitization of a neural substrate of reward. A persistent lowering of self-stimulation thresholds has also been observed more than 1 month after a period of intravenous nicotine self-administration. Whether this reflects a general increase in sensitivity to reinforcers remains to be established.

Nicotine Withdrawal in Humans and Animals

Many of the signs and symptoms of tobacco withdrawal (▶ Withdrawal syndromes) can be alleviated by nicotine replacement therapy, giving rise to the notion that tobacco withdrawal is principally due to *nicotine* abstinence. However, several caveats are in order (Hughes 2007). For example, even in placebo-controlled trials, nicotine patch and nicotine gum can produce detectable cues, suggesting that some nicotine-treated subjects may expect to obtain withdrawal relief. It has also been argued that some tobacco withdrawal symptoms are nonspecific to nicotine but would also be seen upon loss of other reinforcers. Another puzzling feature of tobacco withdrawal is that it is not readily precipitated by the administration of the centrally active nicotinic antagonist ▶ mecamylamine. Just as it is unclear to what extent tobacco withdrawal reflects nicotine abstinence, opinions differ as to the importance of positive versus negative reinforcement in the maintenance of cigarette smoking (Hughes 2007).

Rodents readily express signs of nicotine withdrawal following a period of chronic exposure (Malin and Goyarzu 2009). Withdrawal signs can be induced spontaneously after a period of intravenous nicotine self-administration. In most studies, however, nicotine is delivered via subcutaneous osmotic minipumps, providing constant 24 h exposure. The standard minipump infusion dose used in adult rats (3 mg/kg/day) would be expected to provide nicotine plasma levels of 50 ng/mL or higher, beyond the range of most smokers.

Both spontaneous and nAChR antagonist-precipitated types of withdrawal are manifested by "somatic" and "affective" signs. Somatic signs include behaviors (e.g., ptosis, writhing, and grasping) and pharmacological features reminiscent of opiate withdrawal, although there is little evidence of opioid involvement in tobacco withdrawal signs in humans. "Affective" signs are manifested by elevations in brain simulation reward thresholds and conditioned place aversion. Somatic signs derive at least partly from the inhibition of central nAChRs, hence they are also termed "somatically expressed signs" (Malin and Goyarzu 2009). Affective signs, in contrast, exclusively reflect central nAChR function. Somatic and affective signs are also distinguishable in terms of nAChR subtype mediation.

Nicotine in Relation to Nicotinic Cholinergic Transmission

Nicotinic AChRs represent an important target for the neurotransmitter acetylcholine (ACh). Although nAChRs and ACh are both widely expressed in the brain, evidence for nicotinic cholinergic transmission in the brain has only emerged in the past two decades. For several reasons, it is not known how many nAChRs actually participate in cholinergic transmission. First, many published attempts to localize nAChRs using immunocytochemistry are now considered unreliable because of doubts about antibody specificity. Second, some evidence suggests that ACh may be capable of acting not only as a synaptic transmitter, but also via volume (extrasynaptic) transmission. Third, α7-containing nAChRs may also be activated by endogenous

levels of *choline*. To date, there has been little attempt to integrate knowledge about nicotinic cholinergic transmission with the known behavioral effects of nicotine.

Nicotine or Nicotine-plus?

Nicotine is only mildly rewarding in standard animal models (intravenous self-administration and conditioned place preference), although it does reliably increase the reinforcing strength of electrical brain stimulation. How, then, might it be critical to tobacco addiction? Several explanations have been proposed. First, standard behavioral procedures may not capture the full reinforcing potential of this drug. For example, animal studies tend to be of short duration, lasting at most a few weeks. This limitation may be important because it is known that in the case of cocaine, rats become much more motivated to seek the drug after they have had several months of drug exposure. Equally, if cigarette smokers use nicotine as a cognitive tool or for emotional support, these aspects would not be modeled in standard self-administration and place preference animal tests. A second possibility is that nicotine simply serves as a stronger reinforcer in humans, or perhaps primates in general, than in rodents. Thirdly, extensive evidence from rodent studies suggests that nicotine's ability to support self-administration behavior is critically dependent on its capacity to make drug-associated reinforcers more powerful (Caggiula et al. 2009). Translated into the human arena, nicotine would enhance the intrinsic or conditioned reinforcing effects of stimuli that are associated with smoking.

An additional explanation for why nicotine may be particularly reinforcing in cigarette smokers relates to the enzyme monoamine oxidase (MAO). It is known that smokers possess reduced levels of MAO-A and MAO-B isoforms, both in the CNS and periphery. This reduction is at least partly due to the presence of identified MAO-inhibiting chemicals in tobacco smoke. Monoamine neurotransmitters, and dopamine in particular, are metabolized by MAO, giving rise to the suggestion that MAO inhibition enhances neurochemical actions of nicotine that reinforce tobacco smoking. Research to date suggests that several MAO-inhibiting drugs (►Monoamine Oxidase Inhibitors) do indeed make rats more motivated to self-administer intravenous nicotine. However, in all studies published to date, the degree of MAO inhibition far exceeded that reported to occur in smokers.

Cross-References

► Aggression
► Analgesics
► Antinociception Test Methods
► Anxiety: Animal Models
► Appetite Suppressants
► Attention
► Cognitive Enhancers
► Conditioned Place Preference and Aversion
► Conditioned Taste Aversions
► Dementias and Other Amnesic Disorders
► Drug Discrimination
► Monoamine Oxidase Inhibitors
► Nicotinic Agonists and Antagonists
► Nicotine Dependence and its Treatment
► Reference Memory and Consolidation
► Rodent Tests of Cognition
► Schizophrenia
► Self-administration of Drugs
► Sensitization to Drugs
► Short-Term and Working Memory in Animals
► Withdrawal Syndromes

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Nicotine Dependence and Its Treatment

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Synonyms

Tobacco addiction and smoking cessation

Definition

Dependence is part of a diagnostic system (► DSM-IV) designed to classify the nature and extent of problems that people have in controlling their use of chemical substances. The concept of ► dependence can apply to any drug that people use on a regular basis, including tobacco, alcohol, marijuana, opiates, and stimulants. Since ► nicotine is thought to be the main chemical that makes tobacco use addictive, nicotine and tobacco dependence are often used synonymously. Features of dependence include excessive time spent acquiring, using, and recovering from the use of drugs; using larger amounts of them and for longer periods of time than intended; having difficulty in stopping them(repeated unsuccessful quit attempts); developing tolerance to drug effects; having withdrawal symptoms when the use of the drug is stopped; interference in social, recreational, or work activities; and continued use despite knowledge of adverse consequences. Not all these criteria apply to cigarette smoking, but many of the key criteria (e.g., continued use despite knowledge of adverse consequences; withdrawal symptoms, and difficulty quitting with repeated attempts) do apply.

Role of Pharmacotherapy

It is not difficult for people to start smoking, since tobacco cigarettes worldwide are a legal, readily available, and often heavily promoted product. Smoking prevalence may still be rising in many countries, but in the USA, rates have steadily declined over the past 50 years with growing recognition of the health risks associated with smoking, as well as increasingly stringent environmental restrictions and rising cost of cigarettes. Today, the smoking rate in the US general population stands at 21%. With much lower than historical rates of smoking, this is still a remarkably high prevalence rate for something that is known to be a very serious behavioral risk factor for premature morbidity and mortality.

Interestingly, at least among US smokers, about 70% at any given time claim that they want to quit smoking. Furthermore, many of these smokers, perhaps 25–30%, do attempt to quit each year. The problem is that the quit attempt for many is short-lived with a return to smoking being the ultimate outcome. This return to smoking following a quit attempt is called relapse. Scientists have been trying to understand when, why, and how people relapse during a quit attempt to get clues to help smokers succeed in quitting permanently.

Relapse Circumstances

Smokers have been asked to report on the circumstances of their return to smoking both in retrospective and real-time surveys, and the factors surrounding relapse have been well documented (Shiffman et al. 1996). Withdrawal symptoms are a clinical reality when smokers try to quit and are a factor contributing to relapse. These symptoms include irritability, anxiety, restlessness, and cravings for cigarettes, and they last for about 2–3 weeks after quitting. Interestingly, withdrawal symptom intensity has not been clearly linked to smoking cessation outcomes, but craving levels do appear to be important. Specifically, higher ► craving levels at any given point of time are associated with poorer outcomes at later points of time, whether the timeframe examined is early or later in the quit attempt. Intensity of post-quit craving may reflect the smoker's level of dependence on cigarettes. Alleviation of withdrawal symptoms can make people feel less irritable and more comfortable after quitting; at the same time, a reduction in craving may be especially important for improving quit success.

A second important factor associated with relapse is negative affect. While relapse can occur in positive mood states, people frequently report going back to smoking when they feel negative emotions including anger, frustration, stress, and even boredom. Emotions may serve as a strong cue for smoking, particularly if people have previously used smoking to enhance positive emotions and/or to feel better in the presence of negative mood states. Thus, any intervention that can help people avoid or improve postquit negative mood states may be beneficial.

Drinking alcohol increases the likelihood of a relapse. Not only is ► alcohol a cue for smoking, it may directly enhance the pleasant effects of smoking and promote continued smoking through behavioral disinhibition. Due to this interaction between alcohol and cigarettes, smokers are often advised to avoid alcohol during their quit attempt. Finally, self-confidence in being able to stay away from cigarettes is often associated with better outcomes in a quit attempt. Self-confidence may be influenced by many factors, but encouragement and support

from people in the social network of a smoker who is trying to quit may be helpful for boosting self-confidence.

All relapses must by definition begin with the first inhalation of tobacco smoke following the start of a quit attempt. This initial re-exposure, whether it happens within the first 24 h after the quit attempt or after several weeks or months, is called a slip or lapse. Theoretically, the smoker who slips by taking several puffs or even smoking a whole cigarette could just stop and return to abstinence. However, research shows that slips indicate a poor prognosis and are associated with long-term failure in the quit attempt. People who have an initial slip or lapse within the first 2 weeks after they quit would have only a 10% chance of succeeding in their quit attempt (vs. a 90% chance of failing), whereas those who do not smoke at all in the first 2 weeks have a much better chance (about 50%) of long-term success (Kenford et al. 1994). Thus, it would be beneficial if treatments could prevent or reduce the negative impact of smoking slips during a quit attempt.

Successful treatments must simultaneously address all the factors that contribute to relapse, which include withdrawal symptoms and cravings, response to environmental and internal emotional cues, and the negative impact of smoking slips. There are currently two things that smokers can do to improve their chances of quitting. One is to use an approved medication and the other is to use behavioral counseling support for smoking cessation. Many smokers quit on their own with no help from medicines or therapy. It is estimated that the success rate for unaided quit attempts is about 5% on a given try. In contrast, when modern treatments for smoking cessation are tested, long-term (e.g., 6–12 months) success rates may be as high as 30% (Fiore et al. 2008).

Medications: Nicotine Replacement Products

There are several places to find reviews of medications for smoking cessation (Fiore et al. 2008; Foulds et al. 2006; Le Foll and George 2007; Nides 2008). The first medications approved for smoking cessation were the nicotine replacement products (NRT). These products come in five different forms: patch, gum, lozenge, inhaler, and nasal spray. All the products deliver pure nicotine to the body to provide a short-term substitute for cigarettes when the smoker is trying to quit, and these can lower the intensity of withdrawal symptoms and cravings. Further, all the NRT improve smoking cessation outcomes, approximately doubling the chances of a successful quit when compared with placebo medication. The NRT products differ primarily in the route and speed at which nicotine is absorbed, as well as in their convenience and ease of use (see Table 1). Nicotine delivered in medications is much safer than nicotine delivered by smoking tobacco. This is because all the toxins and carcinogens delivered in smoked tobacco are eliminated, while nicotine itself is not cancer-causing. Nicotine does stimulate heart rate and blood pressure, but it can be used safely even by people with heart disease, because it is safer than smoking cigarettes (Benowitz and Gourlay 1997).

Nicotine can be absorbed from any surface of the body; this includes any part of the skin, mouth, and nasal membranes as well as the surface of the lung, as in smoking. (Nicotine is not well absorbed by the stomach owing to the acid content of that organ.) The various NRT formulations have taken advantage of this absorption versatility to deliver nicotine by different routes.

Nicotine patches are perhaps the most widely used method of nicotine delivery. They are very convenient to use, being applied and changed only once daily, and may be used for 16 or 24 h per day. Patches are the only formulation that delivers steady levels of nicotine throughout the day, and this is their advantage. Patches are meant to be used for 8–12 weeks after quitting to suppress withdrawal symptoms and cravings. Most patches deliver about 21 mg/day of nicotine. The dose content of patches can be tapered during the later weeks of use (e.g., to 14 then 7 mg/day), to gradually wean away from nicotine, or the patches can be stopped abruptly with no ill effects. Side effects are few and include skin irritation and disturbed sleep. Nicotine patches can be obtained either by prescription or over the counter (OTC).

With all the remaining nicotine replacement products, the number and timing of doses is controlled by the smoker. This is both the advantage and down-side of these products. The advantage is that the products can be used "as needed" when difficult situations arise, in which the individual may be tempted to smoke. The disadvantage is that people sometimes fail to use the medications in adequate amounts to gain the full benefits of nicotine replacement. Gum, for example, should be used at about nine pieces per day for full effect but many people use less. Gum and lozenge are very similar in that they both deliver nicotine through the mouth membranes; lozenge may be easier and more socially acceptable to use since it does not require chewing. Both are available OTC. Both gum and lozenge comes in 2 mg and 4 mg doses. The higher dose is recommended for heavier smokers (e.g., more than 1 pack per day).

The nicotine inhaler also delivers nicotine across mouth mucous membranes. This product requires a hand-to-mouth behavior that some smokers find comforting since it mimics smoking behavior. The disadvantage of the inhaler is that intensive puffing is

Nicotine Dependence and Its Treatment. Table 1. Pros and cons of smoking cessation therapies.

Treatment	Pros	Cons
Medications		
Nicotine patch	Easy to use (applied once daily); available OTC; provides steady nicotine levels	No smoker control
Nicotine gum	Smoker controls dose and timing; available OTC	Acceptability/effort of use; difficult to use with dentures
Nicotine lozenge	Smoker controls dose and timing; available OTC	Side-effects include nausea, hiccups, heartburn
Nicotine inhaler	Mimics hand-to-mouth behavior of smoking; smoker controls dose and timing	Needs prescription; intensive puffing required to get adequate dose
Nicotine nasal spray	Rapid onset effect; smoker controls dose and timing	Needs prescription; side effects include burning nose, runny eyes, sneezing
Bupropion (Zyban)	Twice per day pill	Needs prescription; Side effects include insomnia and dry mouth; Contraindicated with seizures, head trauma, eating disorders
Varenicline (Chantix)	Twice per day pill; few medical contraindications to use	Needs prescription; side effects include nausea and sleep disturbance; possible suicidal thoughts
Behavioral Support		
Group	Tips for successful quitting; social support from leader and group members	Effort required to find and use groups; location and scheduling barriers
Individual	Intense, tailored help	Hard to find
Telephone (quit lines)	Easy to use; provides guidance and social support	Therapy may be less intense and less structured than in-person methods
Internet	Easy to use; provides good information and suggestions	Less social support than in-person help; quality may vary across sites
Self-help booklets	Easy to use; provides good information and suggestions	Not shown to be efficacious in boosting quit rates

required to obtain adequate doses of nicotine, and there may be initial side effects including throat burning, watery eyes and nose, and coughing. The inhaler is only available by prescription. For all NRT taken by mouth, acidic drinks such as coffee and juice should be avoided for 15 min before product use, since these can reduce nicotine absorption.

Nicotine nasal spray delivers nicotine through nasal mucous membranes. This product delivers a relatively high dose with rapid absorption that most closely mimics nicotine delivery from cigarettes. Side effects include burning, runny nose and eyes, and sneezing but these effects subside with continued use. The spray is only available by prescription and is recommended for heavier smokers.

It is important to note that the use of NRT product combinations has recently been shown to further improve the chances of success beyond those obtained with the use of a single medication. In particular, combined use of patch plus a short-acting smoker-controlled medication such as gum or nasal spray can produce better cessation outcomes than either medication alone (Fiore et al. 2008). This may be because the advantages of steady nicotine replacement levels and smoker-controlled dosing are combined.

Medications: Non-Nicotine Products

In addition to all the NRT, there are also two non-nicotine medications that have been approved by the FDA for smoking cessation based on evidence of efficacy. ► Bupropion (Zyban) is an anti-depressant medication whose benefits for smoking cessation were discovered by chance during its use as an ► anti-depressant. Subsequent research has shown that bupropion doubles quit rates when compared with a ► placebo control and appears to

reduce both withdrawal symptoms and craving. Interestingly, the medication is equally effective for smokers with and without a history of depression, so it can be used by any smoker. Bupropion comes in 150 mg pills and is taken twice daily starting 1–2 weeks prior to the quit date; it needs to be obtained by prescription. There are some limitations on who can take it, related to medical conditions. For example, people with a history of head trauma, seizures, or eating disorders should not take this medicine (Fiore et al. 2008). Side effects are primarily insomnia and dry mouth. Even though this medication works in people with and without a history of depression, smokers who are concerned about negative affect may want to try this medication.

Varenicline (Chantix) is the most recent medication approved for smoking cessation. This drug, ► a partial agonist, was specifically developed as a smoking cessation aid. It attaches to the receptor responsible for nicotine effects in the brain, acting like a substitute to reduce withdrawal symptoms and cravings. However, there is also some evidence that ► varenicline can reduce the reinforcing effects (e.g., satisfaction) of nicotine when smokers have a post-quit slip or lapse, thus potentially addressing this important relapse risk factor (West et al. 2008). The research on which FDA approval of this drug is based showed that varenicline efficacy is better than that of both placebo and of bupropion, and that the medication can triple the chances of a successful quit attempt when compared with placebo (Gonzales et al. 2006; Jorenby et al. 2006). Varenicline must be obtained by prescription; the only medical contraindication is severe kidney impairment. Side effects are mainly nausea and disturbed sleep, but concerns have also been raised about increased suicidal thoughts in people taking this medication.

Table 1 summarizes the available smoking cessation medications and highlights their pros and cons. Smokers generally choose a smoking cessation product based on convenience and availability, the advice of their doctor, and their own personal experience with the use of these products. Because smokers generally require several attempts before they can quit for good, there is an opportunity to try different medications and see which ones work best for each individual.

The medications listed earlier are broadly recommended for use by all types of smokers, but there are two specific groups for whom the medications may not be recommended (Fiore et al. 2008). Research with adolescent smokers (under 18 years of age) has shown that counseling therapy is beneficial but has not shown that medications (NRT or bupropion) improve the chances of successful quitting. Therefore, medications are not currently recommended for adolescent smokers. Pregnant women are the second group where recommendations must be qualified. In this case, there has been only limited research conducted with medications because of safety concerns. Nicotine most likely does have adverse effects on the fetus, which is why it is important for pregnant women to stop smoking. However, they should try to stop with behavior therapy alone, if possible. If this does not work, pregnant smokers should consult with their doctor about the use of smoking cessation medications.

Behavior Therapies

Smokers trying to quit will benefit from using a behavior therapy program in addition to medications. Behavior therapy is frequently available through hospitals or community agencies and should consist of individual or group counseling sessions offered both before and after the target quit day. In these programs, smokers are taught how to prepare for a quit attempt and what to expect when they quit. Relapse prevention skills are also stressed with interactive discussion of how to handle difficult situations, in which the newly abstinent smoker may be tempted to light up a cigarette. Research has shown that behavior therapy can improve the chances of successful quitting through problem solving and social support, and that in general, the more therapy people get, the better their outcome is likely to be. Specifically, 4–8 or more in-person therapy sessions have been shown in research to be optimal for improving outcomes (Fiore et al. 2008).

More recently, there is evidence that therapy delivered over the telephone via quit lines is efficacious (Fiore et al. 2008). This is an encouraging finding, since some people find it difficult or inconvenient to go to an in-person therapy program and some may be reluctant to engage in face-to-face therapy. Ideally, quitlines should offer a structured series of calls following the initial contact, with calls initiated by the therapist who provides guidance and support during the quit attempt comparable with what would be found in an individual or group therapy program. There are also internet programs now available that can help smokers quit. The quality of these programs may vary. An ideal program would include personalized help with specific issues and problems, monitoring and feedback on personal progress, and a chance to interact with others who are trying to quit.

In summary, there are several ways that smokers can improve their chances of success in smoking cessation but the most important principle is that a combination of medication and behavior therapy has been shown in research to be the optimal approach for best outcomes. There are seven FDA approved medications available either by prescription or OTC, and behavior therapy is

more available than ever with the advent of telephone and internet-based counseling. Smokers attempting to quit are advised to take full advantage of these resources.

Cross-References

► Nicotine
► Nicotinic Agonists and Antagonists
► Withdrawal Syndromes

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Nicotine/Tobacco Addiction

► Nicotine Dependence and Its Treatment

Nicotinic Acetylcholine Receptor Subtypes

Definition

Receptors formed by different combinations of subunits.

Nicotinic Agonists and Antagonists

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Synonyms

Nicotinics

Definition

The wide range of pharmacologic effects of ► nicotine and other nicotinic natural products, such as epibatidine, anabasine, lobeline, and cytisine, together with increasing knowledge of the role and function of nicotinic acetylcholine receptors (nAChRs; ► nicotinic receptor), has led to great interest in the potential of ► antagonists, ► agonists, and ► partial agonists of nAChRs, as treatments for central nervous system (CNS) disorders. Focused efforts to design selective nAChR ligands as new therapeutic agents have been going on for more than two decades, but to date, few synthetic nAChR ligands have been approved for clinical use – nAChR antagonists such as mecamylamine for hypertension in 1950 and the nAChR partial agonist varenicline for smoking cessation in 2006. Evidence is accumulating for the involvement of nAChRs in several CNS disorders in addition to nicotine dependence, including alcoholism, ► depression, ► schizophrenia, pain, ► attention-deficit/hyperactivity disorder (ADHD), and neurodegenerative diseases. Advances have been made in the design and development of selective compounds targeting these disorders.

Current Concepts and State of Knowledge

Pharmacologic Properties of Neuronal Nicotinic Acetylcholine Receptors

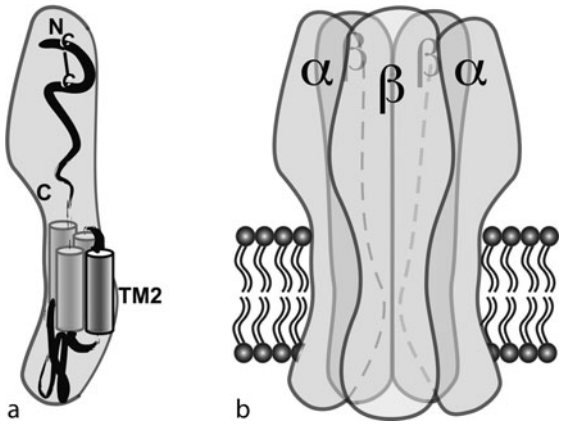
When the French doctor Jean Nicot brought tobacco plant powder to cure the headache of his queen in the sixteenth century, it would have been impossible to predict that Nicot would leave his name in the history of pharmacology. The natural alkaloid in the tobacco plant was termed nicotine; however, it is only centuries later, with the discovery of receptors that are specifically activated by nicotine, nicotinic acetylcholine receptors (nAChRs), that we are beginning to

understand nicotine's effects on the CNS and peripheral nervous system.

nAChRs belong to a superfamiliy of ligand-gated ion channels characterized by a conserved sequence in the N-terminal domain flanked by linked cysteines that also includes 5-HT_3, GABA and glycine receptors. These highly conserved, integral membrane proteins are pentameric structures, composed of α and β subunits. To date, nine α (2–7, 9–10) and three β (2, 3, and 4) subunits have been identified in the CNS. nAChRs may consist of five identical subunits (homomeric) or two or more different subunits (heteromeric). The α7 subunit forms homomeric receptors, a major component of the nAChRs in the CNS. Heteromeric receptors formed by the α4 and β2 subtypes are the principal receptor types in the mammalian brain. Some subunit combinations are more widely expressed in the CNS than others, while some are restricted to well-defined neuronal pathways. For example, the α6-containing receptor, which predominantly results from coassembly with α4 and β2 subunits, is preferentially expressed in the mesolimbic system (Albuquerque et al. 2009; Dani and Bertrand 2007). Since receptors can contain multiple α and β subunit types and the subunit composition varies in different species, insight into receptor composition and localization, especially in the human brain, is critically important. However, our knowledge remains limited due to a lack of sufficiently specific antibodies/ligands to detect the receptors.

To understand the relevance of receptor composition for signal transduction during receptor activation, key properties of the ligand-binding site should be examined. nAChR subunits are arranged in a doughnut-like manner, forming an ionic pore in their center. They have an extracellular ligand-binding site, N- and C-termini, and four membrane-spanning domains. Figure 1 is a schematic representation of the receptor. Three loops in the N-terminal of the α subunit form the major component of the ligand-binding site and appose three loops of the adjacent subunit that form the complementary binding site. In this specific arrangement, both subunits interact with the ligand and, therefore, determine the binding properties.

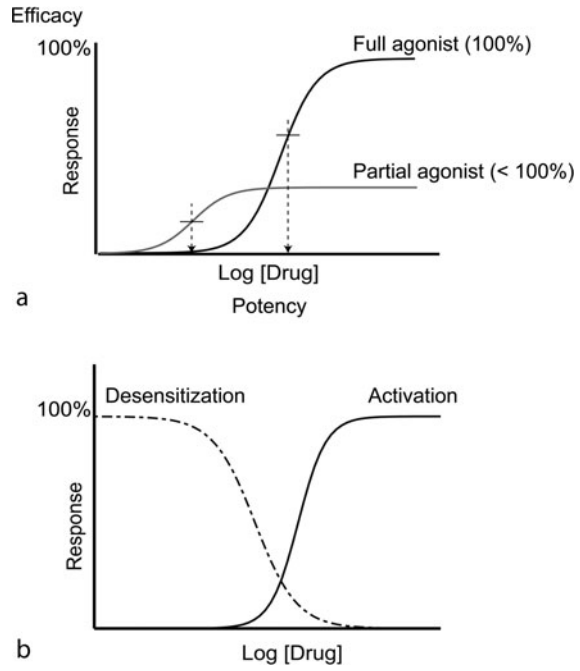
The simplest representation of nAChR ligand binding is a bimolecular reaction, in which the ligand binds and is released with a single association and dissociation constant. Accordingly, ligand affinity is characterized by a binding constant, that is, the equilibrium between the ON and OFF rates. However, such data provide little or no information on the conformational states that are stabilized by ligand binding, so that agonists, which stabilize the open active state, are indistinguishable from antagonists, which



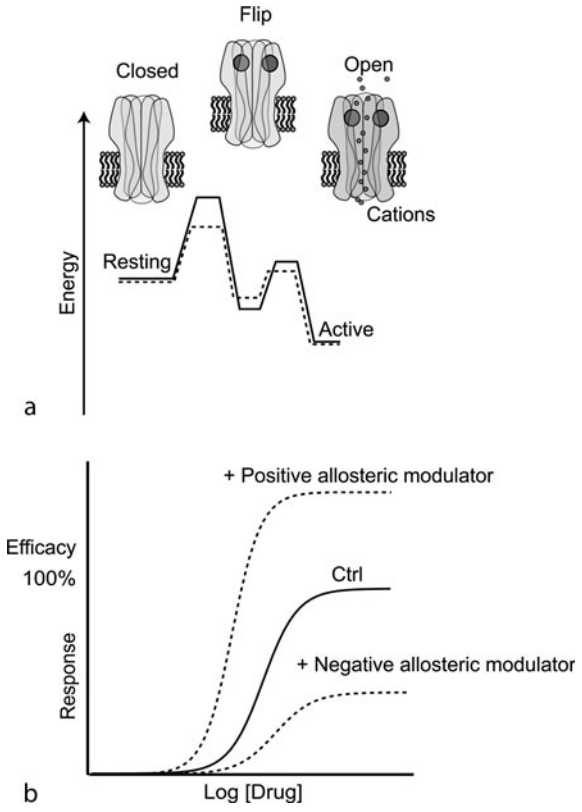
Nicotinic Agonists and Antagonists. Fig. 1. Schematic representation of the nAChR and the ACh binding site. (**a**) Representation of a single subunit formed of α-helices (cylinders), spanning the membrane four times with the N- and C-termini facing the extracellular domain. Note the position of the second transmembrane domain (TM2) that is facing the ionic pore. (**b**) Schematic drawing of the nAChR inserted into the cell membrane lipid bilayer represented to scale. The ligand-binding site lies at the interface between two adjacent subunits.

stabilize a closed conformation. Additionally, radioligand binding affinities provide no insight into the functional efficacy needed to classify ligands according to their pharmacologic effects. Typically, ligands are subdivided according to their physiologic effects – full agonists are as efficacious as ▶ acetylcholine (ACh) in activating the receptor; partial agonists are less efficacious than ACh; and antagonists inhibit ACh receptor activation. Importantly, functional efficacy (the amount of receptor activation at maximal concentration) is not correlated with potency (the concentration of ligand required to cause half activation of the receptor; Fig. 2a). It should be noted that the continuous presence of a partial agonist in the vicinity of the receptor will alter its response to a full agonist (Hogg and Bertrand 2007). Such a condition is typically encountered when a compound is given systemically and interacts with the endogenous release of the neurotransmitter.

A further complexity, common to all ligand-gated channels, is that sustained presence of an agonist progressively stabilizes the receptor in a desensitized and nonconducting state. Thus, exposure to an agonist is expected to cause transient activation, followed by sustained inhibition due to desensitization, which typically occurs at concentrations one or two orders of magnitude lesser than those required for activation. This indicates



Nicotinic Agonists and Antagonists. Fig. 2. Concentration activation profiles for nAChR activation and desensitization. (**a**) Typical concentration activation curves for a full agonist (100% efficacy) and a partial agonist (<100% efficacy) with different EC_{50} values (dotted arrows). Note that the potency of the compound (EC_{50}) does not correlate with its efficacy (relative activation vs. ACh). (**b**) Concentration relationships for activation and desensitization are represented on the same graph. Note that desensitization occurs at lower concentrations when compared with that of activation, indicating that sustained exposure to an agonist will mainly cause receptor desensitization.



Nicotinic Agonists and Antagonists. Fig. 3. Activation and modulation of the nAChRs. (**a**) Schematic representation of the energy barriers between the closed (resting) and the active (open) state. The intermediate state, also referred to as the "flip state," has been recently shown to play an important role for partial agonists. (**b**) Effects of positive (+) or negative (−) allosteric modulators on the concentration activation profiles. Note that positive allosteric modulators cause an enhancement of the evoked response, the agonist potency, and increase in the apparent cooperativity (slope of the curve).

that ligands display a higher affinity for receptors in the desensitized state than in the active state, which is easily seen when plotting activation and desensitization profiles in one graph (Fig. 2b). Since radioligand binding data are acquired during prolonged incubation (>0.5 h) with the ligand to reach equilibrium, agonist binding affinities correlate best with receptor desensitization potencies.

Transition from the resting (closed) to the active (open) state reflects changes in the three-dimensional structure of the receptor. The probability of conversion from the resting to the active state in the absence of a ligand is very low, as shown by the low frequency and brief duration of channel opening. Though the simplest model involves only one transition between the resting and active states, evidence points toward the existence of an intermediate state, thought to be closed and termed as the "flip state" (Fig. 3) (Lape et al. 2008; Mukhtasimova et al. 2009).

The complex receptor structure allows high-affinity binding at sites other than the ligand-binding (► orthosteric) site. Molecules that bind at these so-called ► allosteric sites can either increase (positive ► allosteric modulators) or decrease (negative allosteric modulators) the evoked current and thereby affect nAChR function (Changeux and Edelstein 2005).

nAChR Antagonists and Partial Agonists as Pharmacotherapies

Given the diversity of physiologic roles of specific nAChR subtypes and their relationship with disease states, the

possibility of subtly modulating the function of these receptors with agonists, partial agonists, antagonists, and allosteric modulators has fueled interest in developing selective ligands as potential pharmacotherapeutic agents for a number of CNS disorders (Table 1).

nAChR subtypes are widely distributed throughout the human body and it is beyond the scope of this chapter to give a complete overview of all known nAChRs and locations. However, Fig. 4 shows a schematic representation of the major nAChRs subtypes that are most relevant as CNS targets for therapeutic intervention, as well as peripheral nAChR subtypes that could mediate adverse events.

Addiction

Nicotine Dependence Nicotine dependence (► Nicotine Dependence and Its Treatment) is a chronic, relapsing condition that makes smoking cessation extremely difficult because of pronounced withdrawal symptoms (► Nicotine). The current thinking is that the addictive effects are mediated following the interaction of inhaled nicotine with high-affinity nAChRs, such as α4β2 or α4α6β2 receptors, which results in rapid, pulsatile increases in the mesolimbic ► dopamine release (Benowitz 2009). Pharmacotherapy for nicotine dependence is highly cost effective and improves long-term abstinence, although quit rates for the first two approved treatments, nicotine replacement therapy (NRT) and ► bupropion, are modest, with odds ratios $\leq$2. NRT provides a constant delivery of nicotine to the brain, where it interacts with nAChRs to reduce craving and withdrawal symptoms when quitting. Bupropion (Fig. 5), a dopamine–norepinephrine reuptake inhibitor initially approved as an ► antidepressant, has moderate ► efficacy in nicotine dependence, and it was recently shown that bupropion and especially a hydroxy metabolite (Fig. 5) have weak nAChR antagonist properties.

To improve efficacy, pharmacotherapy should not only provide nicotine-like reinforcement to relieve craving during abstinence, but also attenuate the rewarding effects of nicotine when smoking, by blocking access to the receptor. In 1992, Rose and Levin proposed that this could be achieved via concurrent agonist–antagonist administration by combining the agonist nicotine (as NRT) with a nonselective nAChR antagonist, ► mecamylamine (Fig. 5). This suggested that the use of a partial agonist with specificity for the nicotine high-affinity nAChRs could exert such a dual effect. A partial agonist will exert a mild nicotine effect to relieve craving during abstinence, and prevent nicotine binding when smoking, thereby attenuating nicotine's reinforcing effects (Rollema et al. 2007). This dual action, predicted to improve quit rates, was borne out by the efficacy of a potent and highly selective α4β2 nAChR partial agonist, varenicline (Fig. 5). Since most (partial) agonists are more potent in desensitizing than activating the nAChRs (see section "Pharmacologic properties of neuronal nicotinic acetylcholine receptors"), an antagonist effect will significantly contribute to the clinical activity of a partial agonist. However, at least some degree of receptor activation is required for efficacy, since the nAChR antagonist mecamylamine lacks efficacy in nicotine dependence.

Two natural alkaloids with α4β2 nAChR antagonist and partial agonist properties, lobeline and cytisine (Fig. 5), have been examined as smoking cessation aids. There is no clinical evidence that lobeline has an effect on smoking behavior, whereas the partial agonist cytisine, used as a smoking cessation aid in Eastern Europe, was found to have moderate efficacy. Additionally, abstinence rates achieved by a synthetic α4β2 nAChR partial agonist, dianicline (SSR591813; Fig. 5), were insufficient and its development was halted. The lower efficacy of cytisine and dianicline compared with that of varenicline is likely due to the poor brain penetration of cytisine and the weak binding affinity and functional potency of dianicline at α4β2 nAChRs. Further progress in this area may arise from refining the selectivity of nAChR ligands for subtypes that have recently been shown to play an important role in modulating mesolimbic dopamine release, such as α4α6β2-containing nAChRs.

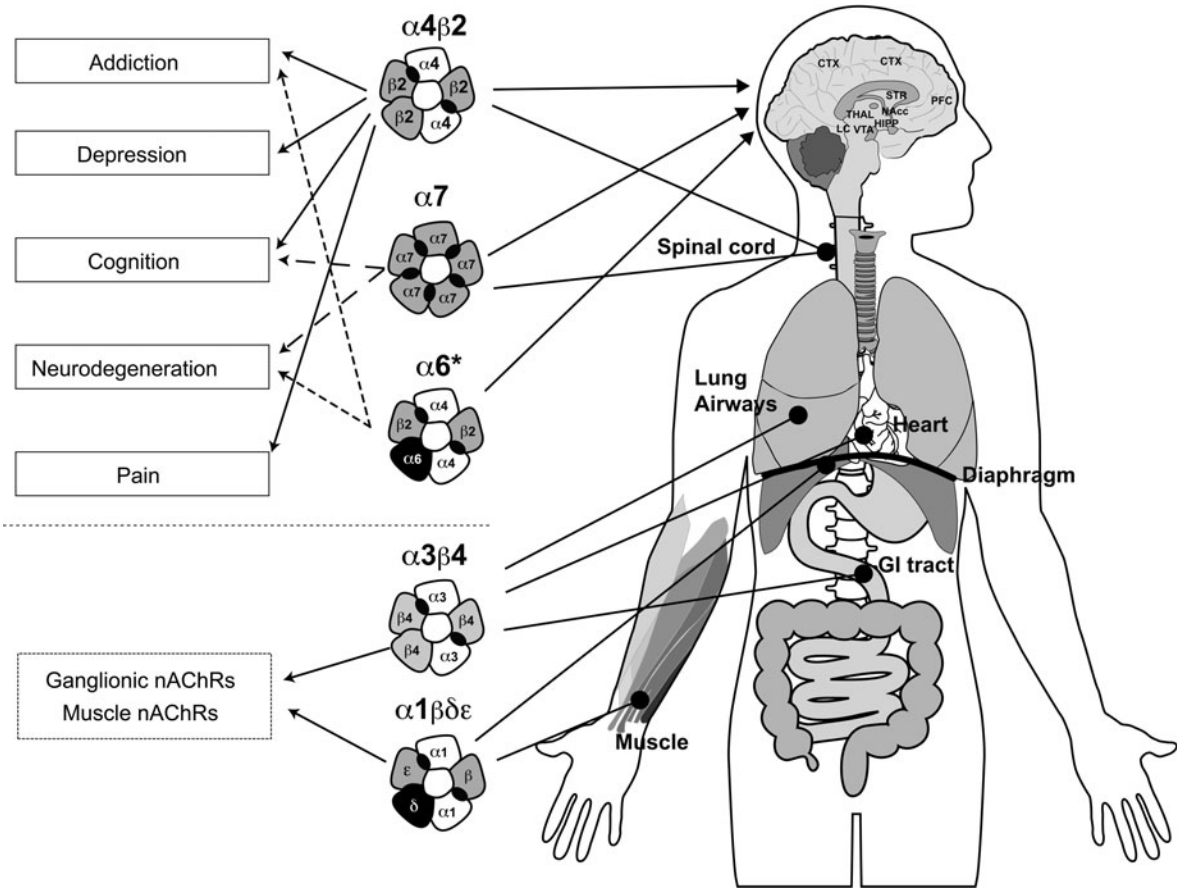
Alcohol Dependence There is a great need for new alcohol dependence treatments with improved efficacies and side-effect profiles over those currently available (► disulfiram, ► acamprosate, and ► naltrexone). Common mechanisms may be involved in alcohol and nicotine dependence, since ethanol also activates the brain's reward system through nAChRs, most likely α4β2, α3β2, and/or α7 subtypes, but nAChRs have not received much attention as potential therapeutic targets for alcohol dependence. However, the demonstrated efficacy and safety of varenicline for smoking cessation and preliminary data indicating that mecamylamine reduces the stimulant and euphoric effects of ► alcohol, combined with the high comorbidity of nicotine and alcohol dependence, prompted studies on varenicline's potential as a treatment method for alcohol dependence. In preclinical studies carried out in a rodent model of alcohol dependence, varenicline selectively reduces alcohol seeking and consumption, without a rebound increase in intake when treatment ends.

Clinical data support these findings, with varenicline treatment decreasing alcohol self-administration in

Nicotinic Agonists and Antagonists. Table 1. Overview of nAChR ligands in preclinical or clinical development or used as pharmacological tools that are discussed in this chapter.

Compound	Application	Testing stage
Nonselective agonists		
Epibatidine	Pharmacological tool	Preclinical
Nonselective antagonists		
Mecamylamine	Hypertension	Approved
Bupropion	Addiction (nicotine dependence)	Approved
(+) Mecamylamine (TC-5214)	Depression	Phase 2
α4β2 selective (partial) agonists		
Nicotine (NRT)	Addiction (nicotine dependence)	Approved
Varenicline	Addiction (nicotine dependence)	Approved
Cytisine	Addiction (nicotine dependence)	Used in E. Europe
Lobeline	Addiction (nicotine dependence)	Phase 2
Dianicline	Addiction (nicotine dependence)	Halted in Phase 3
Altinicline (SIB 1508Y)	Neuroprotection (Parkinson's disease)	Phase 2
Ispronicline (TC-1734, AZD 2389)	Cognition (AD)	Phase 2
Tebanicline (ABT 594)	Pain	Halted in Phase 2
Pozanicline (ABT-089)	Cognition (ADHD)	Phase 2
ABT 894	Pain, ADHD	Phase 2
ABT 418	Cognition (AD, ADHD)	Preclinical
TC-2696	Pain	Halted in Phase 2
TC-6499	Pain	Halted in Phase 1
RJR-2303	Cognition (ADHD), Depression (AD)	Preclinical
α4β2 selective antagonists		
Dihydro-β-erythroidine (DHβE)	Pharmacological tool	Preclinical
α7 selective (partial) agonists		
R3487 (MEM 3454)	Cognition (schizophrenia, AD)	Phase 2/3
DMXB-A (GTS-21)	Cognition (schizophrenia, AD)	Phase 2
SSR-180711	Cognition (schizophrenia, AD)	Phase 1
ABT-107	Cognition (AD)	Phase 1
EVP-6124	Cognition (AD)	Phase 1
AZD-0328	Cognition (AD)	Phase 1
PHA-568487	Cognition (schizophrenia)	Halted in Phase 1
PHA-543613	Cognition (schizophrenia)	Halted in Phase 1
PNU-282987	Pharmacological tool	
TC-5619	Cognition (AD)	Preclinical
JN403	Cognition (AD)	Preclinical
Nornicotine	Pain	Preclinical
α7 allosteric modulators		
PNU-120596	Cognition (schizophrenia)	Preclinical
NS-1738	Cognition (schizophrenia)	Preclinical
A867744	Cognition (schizophrenia)	Preclinical
α7 selective antagonist		
Methyllycaconitine (MLA)	Pharmacological tool	Preclinical

NRT nicotine replacement therapy; *ADHD* attention-deficit/hyperactivity disorder; *AD* Alzheimer's disease

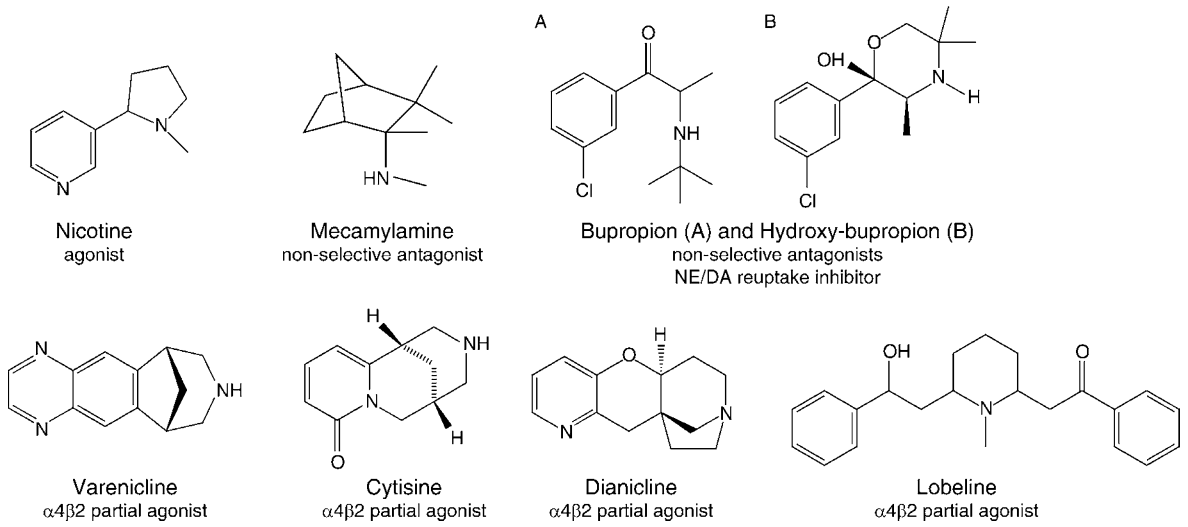


Nicotinic Agonists and Antagonists. Fig. 4. Schematic overview of the predominant central nAChR subtypes that are targets for the treatment of the central nervous system (CNS) disorders discussed in this chapter. Examples of CNS areas that are modulated by nAChRs are cortex (CTX), prefrontal cortex (PFC), hippocampus (HIPP), thalamus (THAL), locus coeruleus (LC), ventral tegmental area (VTA), nucleus accumbens (NAcc), striatum (STR), and spinal cord. Medicinal chemistry efforts targeting CNS disorders attempt to minimize activity at peripheral nAChR subtypes such as α1βδε (muscle) and α3β4 (ganglionic) that control a variety of critical physiological functions. Note that the figure is not inclusive of all nAChR subtypes expressed in the body; additional receptor subtypes not shown could represent therapeutic targets or mediate adverse events.

nonalcohol-dependent, heavy-drinking smokers. Additionally, one week of varenicline pretreatment significantly reduced alcohol consumption, attenuated alcohol craving, and increased the likelihood of remaining completely abstinent during an ad libitum self-administration period. Although these data came from a small study of short duration, they provide support for further clinical trials on the effects of α4β2 nAChR partial agonists on drinking behavior. Given the uncertainty over which nAChR subtypes mediate the effects of alcohol, studies on compounds with different nAChR subtype selectivity might provide clues for the potential of other nAChRs as targets for alcohol dependence treatments.

Depression

The cholinergic–adrenergic theory of ► depression states that overactivation of nAChRs by ACh contributes to the development and exacerbation of depressive symptoms. This hypothesis is supported by the well-established association between depression and nicotine and quitting smoking, the weak nAChR antagonist properties of most antidepressants, and the preclinical antidepressant-like activity of compounds that reduce nAChR activity. Clinical observations that the nonselective nAChR antagonist mecamylamine improves the antidepressant response in treatment-resistant depressed patients further strengthen the idea that reducing nAChR activity results in antidepressant effects (Shytle et al. 2002).



Nicotinic Agonists and Antagonists. Fig. 5. Structures of nicotine and nAChR ligands discussed for nicotine and alcohol dependence.

While nonselective nAChR antagonists block all central nAChR subtypes, selectively reducing the activity of nAChRs thought to contribute to depressive symptoms could result in better antidepressant efficacy and/or improved side-effect profiles. Decreasing α4β2 and/or α7 nAChR signaling can be achieved via receptor blockade using selective antagonists, via receptor desensitization using selective partial agonists, or by the action of negative allosteric modulators. As discussed earlier, partial agonists can potently desensitize nAChRs and could thus have antidepressant activity at low concentrations associated with desensitization (Picciotto et al. 2008).

Results from preclinical studies in animal behavioral models have demonstrated antidepressant-like activity for the antagonists mecamylamine (nonselective), methyllycaconitine (MLA, α7 selective), and dihydro-β-erythroidine (DHβE, α4β2), and the α4β2 selective partial agonists varenicline, cytisine, and ispronicline (TC-1734, AZD-2389) (Fig. 6). In contrast, the full agonists nicotine (Fig. 5), RJR-2403 (α4β2 selective; Fig. 6), and PNU-282987 (α7 selective; Fig. 6), were devoid of antidepressant-like activity.

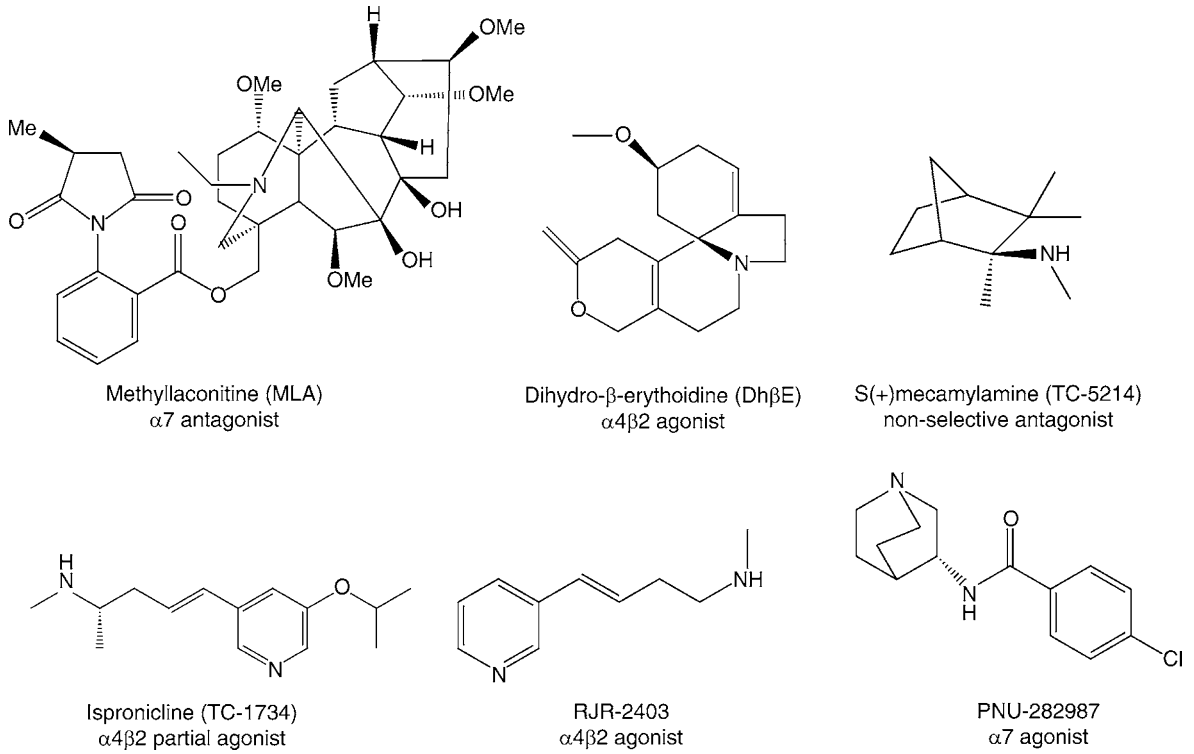
Combined with antidepressants, nAChR antagonists and partial agonists show synergistic effects in animal depression models. Mecamylamine potentiates the activity of both ▶ tricyclic antidepressants and selective serotonin reuptake inhibitors (▶ SSRI), co-administration of nicotine also enhances the effects of antidepressants, consistent with the potent desensitization activity of nicotine. Additionally, co-administration of a low dose of varenicline significantly enhances the effect of the SSRI ▶ sertraline.

The potential of nAChR antagonists and partial agonists as an antidepressant-augmentation strategy is supported by clinical data in treatment-resistant patients with major depressive disorders. Results from a small pilot study suggested that adding mecamylamine to antidepressants significantly decreases depressive symptoms, while a larger study found that co-administration of ▶ citalopram and mecamylamine improves depressed mood and irritability. Further clinical studies are now being conducted with the (+) enantiomer of mecamylamine, TC-5214, which showed robust effects as an augmentation therapy in treatment resistant patients in a large phase 2a study. Finally, in a small open label study, administration of the partial agonist varenicline to smokers on a stable antidepressant regimen significantly improved depression scores over eight weeks starting at week 2 of treatment.

While the available preclinical and clinical data support the notion that selective nAChR ligands may have antidepressant effects via antagonism or desensitization of α4β2 and possibly α7 nAChRs, large blinded studies with selective nAChR ligands are needed to demonstrate the validity of this approach.

Cognitive Deficits

Nicotine improves aspects of attention and memory in both laboratory animals and humans. The high prevalence of smoking in individuals with mental disorders has led to the speculation that nicotine use may be a form



Nicotinic Agonists and Antagonists. Fig. 6. Structures of nAChR ligands discussed for depression.

of self-medication to ameliorate some of the cognitive symptoms (► Cognitive Enhancers, ► Cognitive Enhancers: Novel Approaches) associated with disorders such as schizophrenia and ADHD. Beyond the adverse health effects of tobacco use, nicotine is not well suited as a therapeutic agent owing to its ► pharmacokinetic properties and poor toleration, especially among nonsmokers. Therefore, a number of selective nAChR ligands are being investigated as potential therapies for psychiatric and neurodegenerative disorders (Cincotta et al. 2008; Rusted et al. 2000).

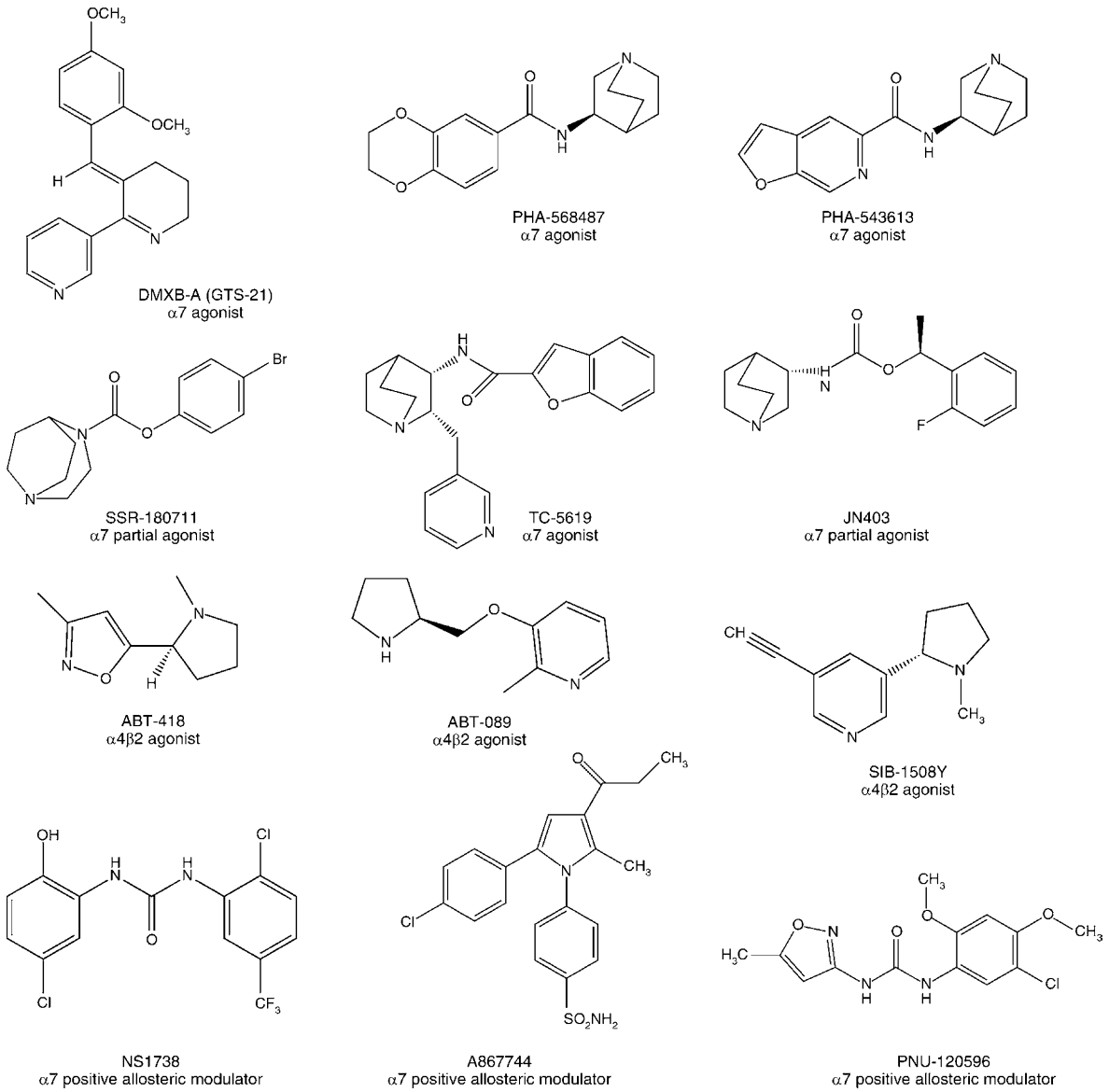
The largest effort has centered on the α4β2 and α7 nAChRs. These subtypes are the most prevalent among brain nAChRs; they influence cognitive function in preclinical models (► Rodent Tests of Cognition) and have been associated with both psychiatric and neurodegenerative disorders. However, recent data suggest that ligands targeting α6* nAChRs may be useful pharmacotherapies for diseases involving dopamine dysfunction.

The following sections address the major psychiatric and neurodegenerative disease areas, where nicotinic ligands have been proposed and/or tested for clinical benefit. It should be noted that the physiologic roles of individual nAChR subtypes is highly complex and far from being comprehensively understood. In addition, disease state and ligand exposure can substantially alter the number and type of nicotinic receptors expressed in various brain regions. Given these complexities, it is likely that ligands targeting an individual nAChR subtype may be beneficial for more than one disease.

Alzheimer's Disease ► Alzheimer's disease (AD) is characterized by the accumulation of neuritic ► plaques, ► neurofibrillary tangles, neuronal loss, and progressive deterioration of memory and cognitive function. Decreased levels of α4β2 nAChRs have been correlated with disease progression. This relationship, coupled with the importance of α4β2 nAChRs in cognitive function, has made this receptor subtype an attractive therapeutic target for AD, and several selective compounds have advanced to clinical trials. As the other major nAChR in the mammalian brain, the α7 receptor has also been the focus of extensive preclinical research. Activation of α7 nAChRs has been linked to cognitive enhancement, and disruption of α7 nAChR gene expression or function impairs cognitive performance and attention. Substantial drug discovery and development efforts with α7 nAChR agonists as potential treatment methods for impaired cognition in neurodegenerative diseases are ongoing.

Ispronicline (TC-1734 or AZD-3480; Fig. 6), an α4β2-selective partial agonist, significantly improved several cognitive measures for ► attention and ► episodic memory after 10 days of treatment in healthy volunteers, and induced ► Electroencephalography patterns associated with increased attention and vigilance. Similarly, ispronicline improves cognitive function in elderly subjects with age-associated memory impairment. Initial reports on the efficacy of ispronicline in patients with AD have been mixed, but improvements in some endpoints, such as the "Mini-Mental State Examination," have been reported.

The selective α4β2 nAChR agonist ABT-418 (Fig. 7) demonstrates positive effects in attention and in a ► delayed matching-to-sample task performance in aged monkeys. Transdermal application in patients with AD results in dose-dependent improved ► verbal learning, ► memory, and reaction time, some of which are qualitatively and quantitatively similar to those seen in acute



Nicotinic Agonists and Antagonists. Fig. 7. Structures of nAChR ligands discussed for cognitive defects (Alzheimer's disease (AD), schizophrenia, and attention-deficit/hyperactivity disorder (ADHD)) and neuroprotection for neurodegenerative diseases (Parkinson's disease (PD)).

trials with ACh-esterase inhibitors. Interestingly, consistent with animal studies, AD patients also show dose-related decreases in anxiety and fear, suggesting that this agent may also have ► anxiolytic effects.

DMXB-A (3-(2,4-dimethoxy)benzylidene-anabaseine, GTS-21; Fig. 7) was the first α7 nAChR agonist to undergo clinical testing for AD. Initial studies in healthy volunteers indicated positive effects on reaction time, correct detection during digit vigilance, word and picture recognition, memory, immediate and delayed word recall, and performance speed in numeric and spatial working memory tasks. However, DMXB-A is a very weak agonist at α7 nAChRs, and potent antagonist at α4β2 nAChRs. These characteristics, combined with suboptimal pharmacokinetic properties, have given rise to the search for new α7 nAChR agonists. Several pharmaceutical companies are advancing α7 nAChR partial and full agonists to clinical trials, e.g., TC-5619, SSR-180711, JN403 (Fig. 7), ABT-107, EVP-6124, AZD-0328, and R3487 (MEM3454; structures not disclosed). On the basis of publicly available information, the α7 nAChR partial agonist R3487 (MEM3454) appears to be currently ahead, with ongoing Phase 2a trials in AD and schizophrenia showing promising results. Significant progress has been made with the design of α7 nAChR allosteric modulators that are active in preclinical models, such as PNU-120596, NS-1738, A867744, (Fig. 7), and other compounds with undisclosed structures, and initial clinical evaluation is anticipated in the near future.

Schizophrenia Interest in specifically targeting α7 nAChRs to treat cognitive deficits in ► Schizophrenia was stimulated by evidence linking this receptor to deficits in auditory gating, a common ► Endophenotype associated with schizophrenia. Auditory gating is a form of sensory filtering whereby the amplitude of an auditory evoked potential is reduced if immediately preceded by a similar auditory tone ("prepulse"). Impairments in this filtering process are thought to lead to excessive sensory input, and result in poor performance in measures of attention. ► Single nucleotide polymorphisms (SNPs) in the gene encoding the α7 nAChR subunit (CHRNA7), and reduced levels of the encoded protein in patients with schizophrenia, further implicates α7 nAChR dysfunction as a contributing factor to this disease.

Although the clinical testing is still in the early phases, initial reports on the efficacy of α7 nAChR agonists for treating cognitive symptoms in schizophrenia are encouraging. For example, the α7 nAChR agonist DMXB-A (Fig. 7; see section "► Alzheimer's disease"), tested in a small ► double-blind study in patients with schizophrenia, normalized auditory gating and improved performance on a Neuropsychological Status (RBANS) scale and an attention subscale, with larger effect sizes than seen for nicotine or atypical antipsychotics in previous studies (Freedman et al. 2008). The effect of several doses of the α7 partial agonist MEM 3454 (also under investigation for cognitive improvement in AD; see section "► Alzheimer's disease") is currently being evaluated in a Phase 2 clinical study for cognitive impairment associated with schizophrenia. However, the development of some α7 nAChR agonists, e.g., PHA-568487 and PHA-543613 (Fig. 7), was halted in Phase 1 owing to safety concerns.

► Attention-deficit Hyperactivity Disorder Stimulant medications were introduced more than 60 years ago to treat the motor overactivity, impulsivity, and inattentiveness associated with ADHD, and remain one of the main treatment options. Though highly effective against these core symptoms, stimulants often do not fully address the cognitive impairments associated with ADHD that are increasingly recognized as key factors in long-term outcomes, including academic and occupational success. Therefore, there is growing interest in developing nonstimulant medications with reduced abuse liability that can also address the cognitive aspects of ADHD. The development of nAChR ligands as potential treatments has been largely driven by the cognition-enhancing properties of nicotine and other nicotinic ligands (Wilens and Decker 2007). As with other cognitive disorders, ADHD patients use tobacco products at a higher rate than the general population, suggesting that nicotine may alleviate symptoms of ADHD. Indeed, when tested in clinical settings, nicotine has consistently demonstrated beneficial effects on disease symptom rating scales as well as on the measures of cognitive function. However, the ► Adverse Effect of nicotine, predominantly gastrointestinal and cardiovascular effects, preclude the broad use of nicotine to treat ADHD.

Three nicotinic compounds with selectivity for α4β2* nAChR subtypes have been evaluated in clinical efficacy and safety studies in ADHD patient populations. ABT-418 (Fig. 7) is a high-affinity ligand that displays full agonist activity at α4β2* nAChRs in vitro and specificity versus α3-containing ganglionic nAChRs. In a three-week study, transdermal ABT-418 was associated with a significantly higher proportion of subjects demonstrating moderately to significantly improved scores on the Clinical Global Impression scales versus placebo. ABT-418 was generally well tolerated with nicotine-like side effects (adverse effects), including dizziness and nausea.

A related nicotine analog ABT-089 (pozanicline; Fig. 7) also has high binding affinity and selectivity for

the α4β2* receptor subtype, but very low efficacy at heterologously expressed α4β2* nAChRs. Interestingly, ABT-089 stimulates [^{3}H]-DA release in brain slices and synaptosomal preparations with full efficacy when compared with nicotine. This difference between heterologous and native nAChR affinities suggests that ABT-089 may interact with additional nAChR subtypes, e.g., receptors containing α4, α6, β2, or β3 subunits (Yang et al. 2009). In a placebo-controlled clinical trial, ABT-089 significantly improved spatial ▶ working memory, attention, hyperactivity, and ▶ impulsivity on an adult ADHD Rating Scale, and was well tolerated with no observed dose-limiting adverse events. Finally, it was recently reported that the selective α4β2 nAChR partial agonist ABT-894 (structure not disclosed) that is also in development for pain, showed positive results in a Phase 2 study in adult ADHD patients with comparable efficacy to ▶ atomoxetine.

Neuroprotection for Neurodegenerative Diseases

Selective nAChR agonists potentially represent a promising novel class of agents to treat neurodegenerative diseases (Rusted et al. 2000). AD is characterized by the presence of plaques containing ▶ amyloid-beta (Aβ) in the brain, which presumably contribute to neurodegeneration. Though there are conflicting reports in the literature, evidence suggests that Aβ can interact directly with α4β2- and α7-containing nAChRs, resulting in a functional blockade of these receptors. However, other reports suggest that some forms of Aβ can actually activate both α7 and non-α7 nAChRs. Although it appears that modulation of α7-containing nAChRs offers protection to neurons against Aβ-induced toxicity, the nature of these interactions and their relevance to AD need to be further investigated.

There is, however, substantial preclinical evidence that nAChR activation is neuroprotective against non-Aβ toxicity induced by a variety of insults in AD. Although multiple nAChR receptor subtypes are likely involved, neuroprotection seems to be mediated mainly via α7 nAChRs. Activation of α7 nAChRs protects in vitro cell and slice preparations against ethanol toxicity and cell death; cultured neurons against glutamate-induced ▶ excitotoxicity; and hippocampal slices against oxygen and glucose deprivation. To date, there are no clinical study reports on the potential neuroprotective effects of selective nAChR ligands in AD.

Compelling epidemiologic evidence exists for an inverse relationship between tobacco use and incidence of ▶ Parkinson's Disease (PD), with smokers of the longest duration and highest daily consumption at the lowest risk of developing the disease. Though many interpretations for this relationship have been made, it seems unlikely to result from genetic factors for either PD or smoking. Indeed, the preponderance of data suggests that a component of tobacco, likely nicotine, offers a biological protection against neurodegeneration of dopaminergic neurons (Quik et al. 2008).

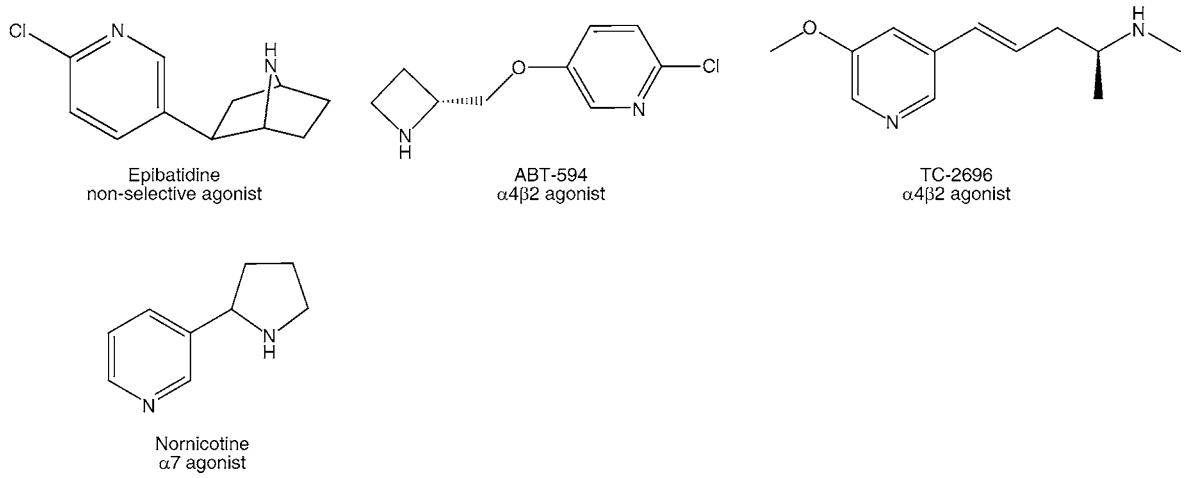
A hallmark feature of PD is loss of nigrostriatal dopamine function. Two nAChR populations are largely responsible for nicotine-evoked dopamine release in striatum: α4β2- and α6*-containing nAChRs. Though both populations appear to regulate dopamine release from the dopaminergic terminals, α6* nAChRs are more sensitive to nigrostriatal damage induced in animal models, generally paralleling other indices of nigrostrial degeneration. Declines in α4β2 nAChRs are also observed with disease progression, but this receptor population appears to be less sensitive than α6* nAChRs. Thus, targeting nAChRs appears to be a promising approach to protect against further nigrostriatal damage and to offer symptomatic relief by enhancing dopamine outflow.

Several small clinical studies have evaluated the effect of nicotine administered via smoking and/or NRT gum on the motor symptoms of PD (▶ Anti-Parkinson Drugs). However, evidence for the improvement of patients' status in these trials was at best modest and, in most cases, absent. Similarly, at least one clinical study has reported that the α4β2 agonist SIB-1508Y (Fig. 7) did not improve PD symptoms.

Although it is tempting to speculate that selective activation of α6* nAChRs may provide a greater opportunity for symptomatic relief, it is unclear if the progressive loss of the dopaminergic neurons that express this nAChR subtype would limit the therapeutic benefit for PD, especially in the later stages of the disease.

Pain

Preclinical pharmacologic studies have established that nicotine and several natural nicotinic compounds have analgesic effects that are attenuated by mecamylamine pretreatment. One example is the frog alkaloid epibatidine (Fig. 8), which has received much attention as an extremely potent analgesic that binds with high affinity to several nAChR subtypes (Arneric et al. 2007). Involvement of α4β2-containing nAChRs in nociception is suggested by their presence in regions that modulate pain perception, and increased inhibitory GABAergic tone in the spinal cord (an analgesic mechanism) following α4β2 activation. Other nAChR subtypes may also be involved in the pain response, but have not yet been investigated in the same detail. In this respect, it is interesting to know that the nicotine metabolite nornicotine (Fig. 8), which is



Nicotinic Agonists and Antagonists. Fig. 8. Structures of nAChR ligands discussed for pain.

reported to have analgesic activity, has an affinity for α7 nAChRs.

Since neither nicotine nor epibatidine can be used clinically owing to safety concerns at analgesic doses, synthetic nAChR agonists are being pursued as analgesics and most research has focused on selective α4β2 agonists. The α4β2 nAChR agonist ABT-594 (Fig. 8) is structurally related to epibatidine with similar analgesic potency, but its development was not pursued owing to limited tolerability. Similarly, the development of two other selective α4β2 nAChR agonists, TC-2696 (Fig. 8) and TC-6499 (structure not disclosed), which had shown analgesic efficacy in preclinical pain models, was halted because of lack of efficacy and an insufficient therapeutic index. More promising is a second-generation α4β2 full agonist, ABT-894 (structure not disclosed), which is currently under development for neuropathic pain.

While the clinical evidence for analgesic efficacy of selective α4β2 nAChR ligands is still limited, the possibility remains that the activity at other nAChR subtypes contributes to analgesic efficacy.

Conclusion

Our increased understanding of nAChR pharmacology and how agonists, partial agonists, and antagonists modulate the function of these receptors has led to the discovery of a large number of selective ligands that are being used either as tools for exploring the role(s) of nAChR subtypes or are in the preclinical or clinical stage of development as potential new pharmacotherapies. Several compounds represent promising new treatments for disorders in which nAChRs are thought to participate. However, the fact that to date very few nAChR ligands have been approved for clinical use illustrates the tremendous challenge of developing selective nicotinic compounds as novel medications without major side effects. The high degree of homology between the different receptor subtypes calls for a better knowledge of their function and distribution throughout the body and for the finding of subtype-selective compounds. In addition, high selectivity is essential for an acceptable side-effect profile to avoid interactions with peripheral muscle and ganglionic nAChR subtypes associated with cardiovascular, gastrointestinal, and respiratory adverse events. Clearly, progress in the development of novel drugs that target nAChR subtypes is dependent on the design and discovery of highly selective ligands with sufficient potency and adequate pharmacokinetic properties to have efficacy at doses at which selectivity is maintained.

Acknowledgment and Disclosure

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Cross-References

▶ Acetylcholine
▶ Adverse Effect
▶ Agonist
▶ Alcohol Abuse and Dependence
▶ Alzheimer's Disease
▶ Antagonist
▶ Anti-Parkinson Drugs
▶ Antidepressants
▶ Attention Deficit Hyperactivity Disorder

- ► Cognitive Enhancers
- ► Cognitive Enhancers: Novel Approaches
- ► Dopamine
- ► Efficacy
- ► Electroencephalography
- ► Endophenotype
- ► Nicotine
- ► Nicotine Dependence and Its Treatment
- ► Nicotinic Receptor
- ► Parkinson's Disease
- ► Partial Agonist
- ► Rodent Tests of Cognition
- ► Schizophrenia
- ► SSRI

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Nicotinic Receptor

Synonyms

nAChR

Definition

A subtype of acetylcholine receptors that respond to the alkaloid nicotine. They consist of ligand-gated ion channels. The two main groups are the muscle-type nicotinic receptors that are located in smooth and skeletal muscle cell membranes and the neuronal nicotinic receptors located in the plasma membranes on neurons of the CNS.

Cross-References

- ► Nicotine
- ► Nicotinic Agonists and Antagonists

NIDA IRP

- ► Addiction Research Center

Nightmares

- ► Parasomnias

Nimetazepam

Definition

Nimetazepam is a benzodiazepine that has anxiolytic, sedative, and anticonvulsant properties. It has a moderately long duration of action due to an elimination half-life of 14–30 h and conversion to the active benzodiazepine metabolite ► nitrazepam. Like most

similar compounds, nimetazepam is subject to tolerance, dependence, and abuse.

Cross-References
► Anxiolytics
► Benzodiazepines

Nitrazepam

Synonyms
1,3-Dihydro-7-nitro-5-phenyl-2H-1,4-benzodiazepin-2-one; Mogadon

Definition
Nitrazepam is an ► anxiolytic drug of the benzodiazepine class. It is a nitrobenzodiazepine and like other benzodiazepines, in addition to its anxiolytic properties, it is a hypnotic drug with sedative, amnestic, anticonvulsant, and muscle-relaxant effects. It is long-acting, lipophilic, and is metabolized in the liver by oxidation. It acts as a full agonist at benzodiazepine receptors in the brain, enhancing binding of ligands for $GABA_A$ receptors. It has ► abuse potential and is associated with a typical benzodiazepine ► withdrawal syndrome.

Cross-References
► Abuse Liability Evaluation
► Benzodiazepines
► Declarative and Non-Declarative Memory
► Driving Under Influence of Drugs
► Insomnia
► Sedative, Hypnotic, and Anxiolytic Dependence
► Social Anxiety Disorder
► Withdrawal Syndromes

Nitrites

Synonyms
Volatile nitrites

Definition
Nitrites are volatile compounds that are subject to abuse by inhalation. The first of these to see widespread use was amyl nitrite, an antianginal medication sold in ampules. The ampules were "popped" open and the contents inhaled, hence they were often referred to by illicit users as "poppers." Because they were available without a prescription in many areas in drug stores, supplies were easy to obtain. In many areas, restrictions were placed on amyl nitrite ampule sales that limited their availability. Almost immediately, commercial products containing other volatile nitrites such as butyl nitrite and cylohexyl nitrite were sold in sexual paraphernalia and video stores as room "odorizers." Nitrite vapors have a distinct smell not unlike the odor of one of the first products of this type named *Locker Room*. Other commercial nitrites adopted names associated with their use in sexual activity, such as Thrust, Ram, and Hardware. "Odorizers" and "aromas" are still widely available on the Internet and claim to contain nitrites, but their actual contents are not clear.

Cross-References
► Inhalant Abuse

Nitrous Oxide

Definition
Nitrous oxide is a widely abused inhalant than is used in medicine and dentistry for anesthesia. It is a gas at room temperatures and is sold under compression in cylinders. Soon after the discovery of nitrous oxide, its euphorigenic effects were noted and it became known as "laughing gas" and was used in minstrel shows where local dignitaries would agree to become intoxicated and behave abnormally for the delight of the audience. Another source of nitrous oxide is as a propellant in certain aerosols such as those for whipping crème. Nitrous oxide canisters for whipped crème dispersers became known as whippets and are subject to abuse. Nitrous oxide is usually directly inhaled from balloons or plastic bags that have been filled with the gas. The effects are almost instantaneous with the result that users can fall over and harm themselves or others.

Cross-References
► Inhalant Abuse

NK2

► Neurokinin A

NK3

► Neurokinin B

NKA

► Neurokinin A
► Tachykinins

NKB

► Neurokinin B
► Tachykinins

NMDA Receptors

Synonyms
N-Methyl-D-aspartate receptor

Definition
NMDA (N-methyl-D-aspartate) receptors are a class of receptors for the excitatory neurotransmitter ► glutamate. They are composed of four subunit proteins (two NR1 plus two NR2 subunits) that assemble together to generate a channel permeable to sodium, potassium, and calcium ions. The receptors are important for normal cognitive function and targets of some neuroactive steroids.

Cross-References
► Alcohol
► Anticonvulsants
► Antidepressants
► Antipsychotic Drugs
► Premenstrual Dysphoric Mood Disorder

NMS

► Neuroleptic Malignant Syndrome

NNH

► Numbers-Needed-to-Harm

NNT

► Number Needed to Treat

Nociception

Definition
The neural process of signaling tissue damage or chemical irritation that is perceived as pain or itch. Nociceptors (receptors responding to noxious stimuli) initiate the process by responding to mechanical, thermal, or chemical stimuli. Nociceptors then send afferent impulses to the spinal cord and brain, leading to the perception of pain.

Cross-References
► Analgesics
► Antinociception Test Methods
► Opioids

Nomifensine

Synonyms
Merital®

Definition
Nomifensine is a drug that blocks dopamine and norepinephrine transporters and was once marketed as an antidepressant. It has pharmacological properties similar to amphetamine and cocaine, but has fewer effects on serotonin systems than amphetamine or cocaine.

Cross-References
► Antidepressants
► Motor Activity and Stereotypy

Non-Benzodiazepine Agonists

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Synonyms
Z-drugs

Definition
The non-benzodiazepine hypnotics that work by selectively affecting γ-aminobutyric acid-A ($GABA_A$) receptors include a structurally dissimilar group of

substances, such as the cyclopyrrolone agents zopiclone and eszopiclone, the imidazopyridine derivative zolpidem, and the pyrazolopyrimidine compounds zaleplon and indiplon (Monti 2004).

Pharmacological Properties

Zolpidem was synthesized by Synthélabo Recherche in the early 1980s, and its therapeutic potential for the treatment of sleep disorders was recognized soon after.

Preclinical studies have shown ▶ zolpidem to exhibit sedative, anticonvulsant, and myorelaxant activities. However, zolpidem is more potent in suppressing locomotor activity (sedative effect) than pentylenetetrazol convulsions (anticonvulsant activity), and rotarod performance (muscle relaxation) in rats. In contrast to zolpidem, the ▶ benzodiazepine hypnotics produce a sedative effect with doses that are similar or greater than those producing anticonvulsant or myorelaxant effects.

In relation to the effects of zolpidem on sleep, a spectral analysis of sleep ▶ electroencephalograms in curarized rats has revealed that its power density in nonrapid eye-movement (NREM) sleep (▶ NREM sleep) is predominantly increased in the low frequency band (1.0–4.0 Hz). Moreover, in freely moving animals, zolpidem has been found to augment the duration of NREM sleep and to reduce ▶ wakefulness. The effect endured during subchronic administration with no rebound occurring after abrupt withdrawal. On the other hand, variable results have been reported in regard to rapid-eye-movement (REM) sleep (▶ REM sleep). In this respect, an increase and a reduction of REM sleep has been described in rats recorded during the light period (Monti et al. 2008).

Zopiclone was synthesized by Rhône-Poulenc Recherches in the early 1970s. Eszopiclone, the dextrorotatory enantiomer of racemic zopiclone, has a single chiral center with an S(+)-configuration.

Preclinical studies have shown ▶ zopiclone to exhibit sedative–hypnotic, anticonvulsant, myorelaxant, antiaggressive, and anticonflict activities. With regard to the sedative–hypnotic activity, zopiclone decreases locomotor activity, reduces waking, and increases slow wave sleep in the rat. Spectral analysis of the electrocorticogram after zopiclone administration has shown an increase of power density in the 2.0–4.0 Hz (delta), and the 12.0–16.0 Hz (beta) bands in the rat. Eszopiclone shares the sedative–hypnotic properties of zopiclone, whereas the (R)-enantiomer has no hypnotic activity (Carlson et al. 2001; Monti and Pandi-Perumal 2007).

▶ Zaleplon was synthesized by American Cyanamid Laboratories in the 1980s, and has been evaluated for its potential sedative, muscle relaxing, and anticonvulsant activity in mice and rats. Zaleplon has been shown to reduce locomotor activity and to produce motor deficits in the rotarod and grid tests. In addition, the pyrazolopyrimidine derivative blocked electroshock-, pentylenetetrazole-, and isoniazid-induced convulsions. In a ▶ drug discrimination procedure using rats trained to discriminate the benzodiazepine agonist ▶ chlordiazepoxide, zaleplon produced partial substitution for chlordiazepoxide at doses that significantly reduced response rates.

Both sedative and discriminative stimulus effects of zaleplon were antagonized by the benzodiazepine antagonist ▶ flumazenil (Sanger et al. 1996).

Zaleplon increased slow wave sleep and the relative electroencephalographic power density in the delta frequency band of rats prepared for chronic sleep recordings. REM sleep values showed no significant changes.

Indiplon originated in the 1980s at American Cyanamid's Laboratories. Indiplon inhibits locomotor activity, rotarod latency, and vigilance measures in the rat over a dose range consistent with its sedative activity. Indiplon is active in the Vogel test of anxiety in rat and, in addition, produces deficits in the passive avoidance and the ▶ delayed nonmatch to sample paradigms in rodents, both currently used as measures of learning and memory (Foster et al. 2004).

Mechanism of Action

▶ GABA is the most important inhibitory neurotransmitter in the mammalian brain and localizes to approximately 30% of central nervous system synapses.

The ▶ $GABA_A$ receptor is the site of action of cyclopyrrolone, imidazopyridine, and pyrazolopyrimidine derivatives. These different classes of ▶ hypnotic drugs modulate GABAergic function through different GABA receptor subtypes, defined by the subunits that participate in the receptor assembly. Most $GABA_A$ receptors consist of α, β, and γ subunits which contain multiple isoforms or variants: α_1–α_6, β_1–β_3, and γ_1–γ_3. Zolpidem, zaleplon, and indiplon preferentially bind α_1-containing subtypes (Ator and McCann 2005). Similar to the benzodiazepine hypnotics, zopiclone and eszopiclone bind at all $GABA_A$ subtypes. Notwithstanding this, the cyclopyrrolones might have more selectivity for certain subunits of the $GABA_A$ receptor (Sanger 2004).

$GABA_A$ receptors have been analyzed by gene knockout strategies. The sedative/hypnotic activity of benzodiazepines (including flunitrazepam and diazepam) has been shown to be dependent on the integrity of the α_1 subunit. On the other hand, the anxiolytic, anticonvulsant, myorelaxant, ataxic, and withdrawal effects depend upon their predominant affinity for the α_2- and α_3-containing

receptors. The finding that zolpidem, zaleplon, and indiplon have more selectivity for the α_1 subtype could tentatively explain the difference in effects on sleep architecture and the lower incidence of adverse events such as rebound insomnia, tolerance, dependence, and abuse.

Pharmacokinetics

The ► pharmacokinetics of zolpidem has been investigated in healthy adults and in elderly patients. Zolpidem is rapidly absorbed and extensively distributed to body tissues, including the brain. It has a bioavailability of approximately 70%, and is extensively bound to plasma protein. Peak plasma concentrations are attained 30–60 min after a single therapeutic dose of 10 mg, and the terminal-phase elimination half-life amounts to 2.6 h in healthy adults. Zolpidem is metabolized in the liver by a number of ► cytochrome P450 isoenzymes, but predominantly CYP 3A4, to inactive metabolites. The major routes of metabolism are oxidation and hydroxylation. After oral administration, zolpidem metabolites are largely excreted in the urine.

The metabolic clearance of zolpidem is reduced in elderly patients, resulting in increases in maximum plasma concentration, area under the concentration curve, and terminal-phase elimination half-life, the latter amounting to 2.9 h (Monti and Monti 2006).

Administration of zopiclone 7.5 mg orally at night is rapidly absorbed. It has a bioavailability of 75% and a time of occurrence of maximum plasma concentration of 1.6 h. The compound undergoes oxidation to the *N*-oxide metabolite, which is pharmacologically less active, and demethylation to the inactive *N*-demethyl-zopiclone. The ► elimination half-life for zopiclone and its *N*-oxide metabolite ranges from 3.5 to 6.0 h (Monti and Monti 2006).

Eszopiclone is rapidly absorbed and extensively distributed to body tissues. It is weakly bound to plasma protein. Peak plasma concentrations are attained 1.0–1.6 h after a single therapeutic dose of 3 mg, and the terminal elimination half-life amounts to 6.0 h. Eszopiclone is also extensively transformed in the liver to the *N*-oxide (less active) and the *N*-desmethyl (inactive) derivative. After oral administration, eszopiclone is predominantly excreted in the urine, primarily as metabolites. Less than 10% of the compound is excreted in the urine as parent drug.

The metabolic clearance of zopiclone and eszopiclone is reduced in elderly patients, resulting in increases in maximum plasma concentration and terminal elimination half-life. The latter is approximately 9.0 h in elderly patients who are being treated with eszopiclone (Monti and Pandi-Perumal 2007).

Zaleplon is rapidly and almost completely absorbed following oral administration of a 10 mg dose. The compound undergoes significant first-pass hepatic metabolism after absorption. As a result, its bioavailability amounts to only 30%. It attains maximum plasma concentration in approximately 1 h and has a terminal elimination half-life of 1.0 h. Zaleplon is primarily metabolized by aldehyde oxidase, and all of its metabolites are pharmacologically inactive (Hurst and Noble 1999).

Indiplon is rapidly absorbed following oral administration of a 15 mg dose. The derivative reaches a maximum plasma concentration at <1 h and has a terminal elimination half-like of 1.5 h. Indiplon undergoes demethylation and deacetylation to the inactive *N*--desmethylindiplon and *N*-deacetylindiplon metabolites (Madan et al. 2007).

Clinical Uses

Various populations have been included in the studies that assessed the efficacy and safety of the non-benzodiazepine hypnotics: subjects with transient ► insomnia, non-elderly and elderly patients with chronic primary insomnia, and patients with secondary or ► comorbid insomnia.

Zolpidem has been shown to be effective in improving sleep induction (reduction of sleep latency) at the recommended dose of 10 and 5 mg in non-elderly and elderly patients, respectively. In addition, subjective assessments and ► polysomnographic measures have shown that zolpidem improves sleep maintenance (reduction of wake time after sleep onset and the number of awakenings, and increase of total sleep time). However, the improvement of sleep maintenance was restricted in several studies to the first part of the night. This has led to the development of a modified-release formulation that provides extended plasma concentrations beyond four hours after administration. The available evidence tends to indicate that modified-release zolpidem is effective for the treatment of chronic primary insomnia characterized by difficulties with sleep onset and sleep maintenance at the recommended dose of 12.5 and 6.25 mg in adult and elderly patients, respectively Monti and Monti (2006).

Zopiclone has been studied in adult insomniac patients in clinical trials and sleep laboratory studies using objective measurements of sleep variables. In all these studies zopiclone 7.5 mg reduced the time to onset of sleep, the number of nocturnal awakenings, and increased total sleep time. The hypnotic drug also improved the quality of sleep. In controlled studies, elderly insomniac patients slept significantly better during treatment with zopiclone 3.75–7.5 mg than with placebo.

The subjective perception of improved sleep following eszopiclone 2 or 3 mg treatment has been demonstrated in

studies of up to 6 months' duration. In these studies, the drug significantly reduced sleep onset latency, the number of awakenings, and wake time after sleep onset, whereas total sleep time and quality of sleep were increased in non-elderly and elderly patients. Sleep laboratory studies of the effects of eszopiclone have confirmed the drug's clinical efficacy in subjects with chronic primary insomnia. Eszopiclone, unlike benzodiazepine hypnotics, does not significantly alter values corresponding to slow wave sleep and REM sleep (Monti and Pandi- Perumal 2007).

Zaleplon 10 mg was superior to placebo in decreasing latency to persistent sleep in normal adults experiencing transient insomnia.

Zaleplon 10–20 mg and 5–10 mg significantly reduced time to sleep onset in adult and elderly outpatients with chronic insomnia, respectively. Generally, a significant difference from placebo on total sleep duration was not demonstrated.

The efficacy of immediate-release indiplon (10 or 20 mg) was determined in adult patients with chronic primary insomnia. Compared with placebo, indiplon significantly reduced the latency to persistent sleep. Similar findings were obtained after administration of immediate-release indiplon (5 or 10 mg) to elderly patients with chronic primary insomnia. Modified-release indiplon administered to adult (20 and 40 mg) and elderly (15 mg) patients with chronic primary insomnia reduced sleep-onset latency, the number of awakenings and wake time after sleep onset, and increased total sleep time (Neubauer 2005).

Cross-References

- ► Benzodiazepines
- ► Electroencephalography
- ► Insomnias
- ► Pharmacokinetics

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Non-Invasive Neuro-Imaging

- ► Magnetic Resonance Imaging (Functional)
- ► Magnetic Resonance Imaging (Structural)

Nonorganic Insomnia

Synonyms

ICD-10

Definition

Nonorganic insomnia (ICD-10) is a condition of unsatisfactory quantity and/or quality of sleep, which persists for a considerable period of time, including difficulty falling asleep, difficulty staying asleep, or early final wakening.

Cross-References

- ► Insomnia
- ► Sleep

Non-Rapid Eye Movement Sleep

Synonyms

NREM sleep

Definition

NREM sleep is characterized by EEG brain waves that are slow with high voltage. Blood pressure is low, breathing and heart rate are regular and slow. NREM sleep is

subdivided into stages of increasing depth of sleep leading to REM sleep (NREM 1, 2, and 3/4). About 80% of sleep is NREM sleep. In the rat, it is identified by the presence of high-voltage slow cortical waves interrupted by low-voltage fast electroencephalographic activity, whereas slow-wave sleep distinguishes as continuous high-amplitude slow frontal and occipital waves combined with a reduced electromyogram.

Cross-References
► Electroencephalography

Nonselective Blockade

Definition
The blockade of several or all types of receptor roughly equally.

Nonspecific Memory Impairment

► Delay-Independent Deficit

Nonsteroidal Anti-Inflammatory Drugs

Synonyms
NSAIDS

Definition
Nonsteroidal anti-inflammatory drugs are a group of compounds that have anti-inflammatory, analgesic, and antipyretic actions. The prototype in this group is aspirin.

Cross-References
► Analgesics

Nootropics

Definition
Non-stimulant drugs that may improve cognitive function in the elderly.

Cross-References
► Classification of Psychoactive Drugs
► Cognitive Enhancers: Role of the Glutamate System
► Cognitive Enhancing Drugs: Neuroscience and Society

Noradrenaline

Definition
A neurotransmitter and member of the catecholamine family, otherwise known as norepinephrine.

Cross-References
► Norepinephrine

Nordazepam

► Benzodiazepines

Norebox

► Reboxetine

Norepinephrine

Synonyms
Noradrenaline

Definition
Norepinephrine is a ► catecholamine neurotransmitter that is synthesized from tyrosine via dopamine. In the brain, it arises almost exclusively from a single circumscribed region in the brain stem, referred to as the *locus coeruleus*. It is involved in arousal and sleep, emotion-related processes, the processing of sensory and spatial information, and other higher cognitive functions dependent on the ► prefrontal cortex. Outside the brain, norepinephrine is produced in postganglionic sympathetic neurons, and is released into the blood from the adrenal glands and contributed to the "fight-or-flight reaction"; its main physiologic actions include constriction of small blood vessels (leading to increased blood pressure),

increased heart rate, relaxation of smooth muscle, and release of glucose from energy stores.

Cross-References
► Beta-Adrenoceptor Antagonists

Norepinephrine Transporter

Synonyms
NET

Definition
This is the plasma membrane-bound protein that is responsible for removing norepinephrine from the synaptic cleft, transporting it back into the noradrenergic neurons from which it originated, thereby terminating its signaling activity on postsynaptic neurons. This is a target for classes of medications (including ► psychostimulants) used in the treatment of depression and attention-deficit/hyperactivity disorder.

Nortriptyline

Definition
Nortriptyline is a ► tricyclic antidepressant with a tertiary amine chemical structure. One of the earlier tricyclics to be developed, it acts by inhibiting the reuptake of norepinephrine. It is a metabolite of amitriptyline. While its primary use is in the treatment of depression, it is also used in lower doses to treat migraine headache and as an aid for smoking cessation, for which it is considered as a second-line treatment. Side effects are typical for tricyclic antidepressants and include sedation, cardiovascular, and anticholinergic effects.

Cross-References
► Amitriptyline
► Antidepressants
► Tricyclics

Novel Antipsychotics

► Second and Third Generation Antipsychotics

Novel Object Recognition

Synonyms
Novelty preference test

Definition
A recognition test that is often used for psychopharmacological studies in rodents. In a typical test, animals are first allowed to explore two objects within an environment for a specified period of time. After a delay, a second session is carried out in which one of the original objects has been replaced by a new one. During the second session, the animals are reintroduced into the environment and allowed to explore the objects that are present. Animals that spend more time exploring the novel object, relative to the old object, are said to recognize the old one.

Cross-References
► Rodent Models of Cognition

Novel Word Learning

► Verbal and Non-Verbal Learning in Humans

Novelty Preference Test

► Novel Object Recognition

NR2B

Definition
One of four possible NR2 subunit proteins (A-D) that, along with NR1 and possibly NR3 subunits make up the NMDA receptor tetramer. NR2 subunits confer distinct functional and pharmacological properties to NMDA receptors, including their sensitivity to Mg^{2+} block and the kinetics of opening and closing of the ion channel.

NREM

► Parasomnias

NREM Sleep

► Non-Rapid Eye Movement Sleep

NSAIDS

► Nonsteroidal Anti-Inflammatory Drugs

Nuclear Magnetic Resonance

Synonyms
Magnetic resonance

Definition
Nuclear magnetic resonance (NMR) refers to a physical resonance phenomenon that is observed when atomic nuclei in a static magnetic field absorb energy from a radio frequency field (or oscillating magnetic field) applied at the resonant frequency of the nuclei. The phenomenon of NMR has been used in a variety of scientific techniques, including magnetic resonance imaging (MRI).

Cross-References
► Magnetic Resonance Imaging (Functional)
► Magnetic Resonance Imaging (Structural)

Nucleus Accumbens

Synonyms
NAcc

Definition
The *nucleus accumbens* is a small brain region located in the ventral striatum. It is a major projection area (terminal field) for dopaminergic neurons located in the ventral tegmental area of the midbrain. It is thought to play an important role in many behavioral and psychological processes, including ► reward-related behavior, incentive motivation, memory processing and habit formation, and in dopamine-mediated psychotic symptoms in ► schizophrenia. It has been implicated in the reinforcing effects produced by various natural stimuli such as food, water, and sexual opportunity, as well as by ► drugs of abuse. In addition, it receives projections from the ► prefrontal cortex that may mediate the impulsivity associated with compulsive drug taking.

Cross-References
► Impulse Control Disorders

Number Needed to Treat

Synonyms
NNT

Definition
The number of patients that need to be treated in order for one to obtain a benefit that is attributable to active treatment and not placebo. It is a measure used in evidence-based medicine and epidemiology measure to assess the efficacy of interventions. The lower the number needed to treat, the more effective the intervention. Maximum efficacy is achieved when NNT = 1.

Cross-References
► Randomized Controlled Trials

Numbers-Needed-to-Harm

Synonyms
NNH

Definition
Number-needed-to-harm (NNH) is a clinically useful measure for the difference between treatment groups regarding a negative outcome, such as all-cause discontinuation, relapse, or number of patients with significant weight gain. It denotes the number of patients that need to be exposed to a treatment until one additional negative event of interest occurs in excess of the rate in the comparator group. The NNH is calculated by subtracting the percent rate of the comparator group from the percent rate of the active treatment group and dividing the difference by 1. An NNH of below 10 is generally considered clinically meaningful.

Cross-References
► Number-Needed-to-Treat
► Randomized Controlled Trials

O

OB Protein

► Leptin

ob/ob Mouse

Synonyms

Lep^{ob}/*Lep*^{ob} mouse

Definition

The *ob/ob* mouse is a genetically mutated *mouse* in which the mutation causes no production of the hormone leptin. The *ob/ob mouse* is extremely obese and has many of the metabolic defects including hyperphagia, hypometabolism, hyperinsulinemia, and infertility.

Cross-References

► Hyperphagia
► Transgenic Organism

Obsessions

Synonyms

Obsessive ruminations; Repetitive thoughts

Definition

Obsessions are persistent ideas, thoughts, impulses, or images that are experienced as intrusive and inappropriate and that cause marked anxiety or distress. They are not simply excessive worries about real-life problems. The person usually attempts to ignore or suppress them with some other thought or action. The person recognizes that the obsessional thoughts, impulses, or images are a product of his or her own mind. At some point during the course of the disorder, the person has recognized that the obsessions are excessive or unreasonable (**Note:** this does not necessarily apply to children (► Obsessive–Compulsive Anxiety Disorder in Childhood). The obsessions cause marked distress, are time consuming (>1 h/day), or significantly interfere with the person's normal routine, occupational or academic functioning, or usual social activities or relationships.

Cross-References

► Obsessive–Compulsive Anxiety Disorder

Obsessive Ruminations

► Obsessions

Obsessive-Compulsive Anxiety Disorders

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Definition

► Obsessive-compulsive disorder (OCD) is a common, debilitating illness that was considered untreatable until the 1960s. Since then, a relatively narrow range of pharmacotherapies has been found to be effective: clomipramine in the 1960s, selective serotonin re-uptake inhibitors SSRIs (► SSRIs and related compounds) in the 1980s, and adjunctive ► antipsychotic drugs in the 1990s (Fineberg and Gale 2005). The current standard of care is to offer either ► cognitive behavior therapy (CBT) or medication first line (NICE 2006). The form of CBT that has been most effective in OCD is *exposure and response prevention* (Drummond and Fineberg 2007). Whereas recognizing the importance of all aspects of management, we focus here on pharmacological approaches to treatment.

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Role of Pharmacotherapy

OCD and the Serotonin Hypothesis

Reports that ▶ clomipramine, the 3-chloro analog of the tricyclic imipramine, but not other ▶ tricyclic antidepressants (including desipramine, ▶ imipramine, ▶ nortriptyline, and ▶ amitriptyline), relieved obsessive-compulsive symptoms directed early OCD pharmacotherapy research. Clomipramine differs from other tricyclic antidepressants by its marked potency for blocking ▶ serotonin reuptake, generating a hypothesis that serotonin might be involved in OCD pathophysiology. Although clomipramine is a powerful serotonin reuptake inhibitor (SRI), its active metabolite has noradrenergic properties. However, additional studies favorably compared the more serotonin-selective SSRIs (▶ SSRI and related compounds) with the noradrenergic tricyclic desipramine as well as ▶ monoamine oxidase inhibitors (MAOIs) such as ▶ phenelzine. Despite this apparently selective pharmacological response, we understand little about the role of serotonin in the etiology of OCD or the mechanisms by which SSRIs (SSRI and related compounds) exert anti-obsessional effects (Fineberg and Craig 2008). Indeed, although SRIs are usually essential for OCD pharmacotherapy, because clinical response is not always satisfactory, we devote the latter portion of this essay to pharmacological approaches to SRI nonresponders.

Evaluating ▶ Treatment Response and ▶ Remission (Fineberg et al. 2007) in OCD

The pivotal rating instruments for measuring OCD severity and treatment response or remission in OCD include the ▶ Yale-Brown Obsessive-Compulsive Scale (Goodman et al. 1989) (Y-BOCS) and the ▶ Clinical Global Impression Scales (CGI) (Guy and editor. ECDEU Assessment Manual for Psychopharmacology 1976). Treatment response and remission rates in acute-phase OCD trials (lasting around 12 weeks) of SSRIs (SSRI and related compounds) rarely exceeded 60% and 45%, respectively, emphasizing the incomplete effect of these treatments over the short term in OCD.

Clomipramine in Acute Phase Treatment Trials

Several positive ▶ double-blind placebo-controlled trials conclusively established clomipramine as an effective treatment for OCD. Efficacy was demonstrated using as few as 14 patients, emphasizing the potency of the effect. The introduction of large-scale multi-center controlled studies enabled drug interventions to be assessed in reasonably heterogeneous groups of patients with OCD (Fineberg and Gale 2005). Two such trials, involving 238 and 263 subjects, specifically excluded comorbid depression to prevent it from confounding the outcome. Significant advantages for the clomipramine ($\leq$300 mg) group emerged by the first or second week and benefits accrued up to the 10 week endpoint. Under clomipramine, Y-BOCS scores decreased by roughly 40% (compared with 5% under placebo) and correlated with similar improvements in social and emotional well-being. It is important to investigate OCD *with* comorbid depression as up to 2 out of 3 individuals with OCD are depressed when they seek treatment. Depression in OCD is profoundly impairing (Heyman et al. 2006). Of the few studies that looked at this comorbidity, most used clomipramine, which was found to significantly reduce obsessional symptoms, though the effect on depression was often not reported.

SSRIs in Acute Phase Treatment Trials

▶ Fluvoxamine (including slow-release formulation), ▶ fluoxetine, ▶ sertraline, ▶ paroxetine, ▶ citalopram, and ▶ escitalopram have demonstrated efficacy against placebo in large-scale studies. Small-scale SSRI (SSRI and related compounds) studies, including only around 20 patients, were also positive, again suggesting a potential effect. Fluvoxamine was effective both in the presence and absence of depression. Moreover, in depressed cases of OCD, superiority for fluvoxamine over desipramine was reported for both Y-BOCS and Hamilton Depression Scale scores, highlighting the importance of treating co-morbid OCD with an SSRI (SSRI and related compounds). ▶ Venlafaxine, despite acting as an SRI at lower-dose levels, has not been found effective versus placebo.

SRIs in OCD – Which Dose?

Clomipramine has not been subjected to multiple-dose comparator trials, though fixed doses as low as 75 mg were found to be effective. Higher doses are associated with greater frequency of unwanted effects (described here). Two multicenter trials found that clomipramine dosed up to 300 mg was clinically effective. In the UK, the maximal SPC dose is 250 mg. ECG and plasma level monitoring is recommended if doses above this level are prescribed. Combined plasma levels of clomipramine plus desmethylclomipramine 12 h after the dose should be kept below 500 ng/mL to minimize the risk of seizures and cardiac conduction delay.

Apart from fluvoxamine, the SSRIs (SSRI and related compounds) have been subjected to placebo-controlled fixed-dose analysis in OCD trials. Fluoxetine – 60 mg, paroxetine – 60 mg, and escitalopram – 20 mg appeared the most effective when compared with the lower fixed doses of active drug in acute-phase studies, but the

superiority for 60 mg citalopram appeared only on secondary analyses, at the same time the sertraline study was unable to distinguish a dose–response relationship, possibly owing to design problems related to that study. An extended placebo-controlled study of escitalopram demonstrated enduring superiority for the 20 mg over the 10 mg dose lasting for 16 weeks. In a 12-month fixed-dose placebo-controlled fluoxetine trial in SSRI-responders, only the 60 mg dose protected against relapse. Thus, higher SRI doses appear the most effective for OCD. Though fast upward titration may produce earlier responses, long-term benefits of this approach are not established and may lead to a greater burden of side effects. Expert consensus currently favors moderated doses in the first instance, with upward titrations to maximum should symptoms persist (NICE 2006). Table 1 illustrates target doses recommended by the American Psychiatric Association for OCD.

Patients should be advised at the outset of treatment that the response to SSRI (SSRI and related compounds) or clomipramine is slow and gradual and the anti-obsessional effect takes several weeks to develop. A trial of at least 12 weeks at the maximum tolerated dose with careful assessment is advisable before judging its effectiveness.

Adverse Effects: SSRIs Versus Clomipramine

SSRIs (SSRI and related compounds) appear safe and well tolerated to the maximal SPC dose limits, according to the placebo-referenced OCD trials, which reported adverse-event-related withdrawal rates of around 5–15%. SSRIs (SSRI and related compounds) may be associated with initially increased nausea, nervousness, insomnia, somnolence, dizziness, and diarrhea. Sexual dysfunction, including reduced libido and delayed orgasm, affects up to 30% individuals. Three controlled studies compared the clinical effectiveness of different SSRIs (SSRI and related compounds), and the results were not strong enough to support the superior efficacy of any compound.

► Pharmacokinetic variation may be relevant for deciding which SSRI (SSRI and related compounds) needs to be prescribed. Fluoxetine, paroxetine, and to a lesser extent sertraline inhibit the P450 isoenzyme CYP 2D6, which metabolizes tricyclic antidepressants, antipsychotics, anti-arrythmics, and beta-blockers. Fluvoxamine inhibits both CYP 1A2 and CYP 3A4, which metabolize warfarin, tricyclics, ► benzodiazepines, and some antiarrhythmics. Citalopram and escitalopram are relatively free from hepatic interactions, and may therefore have an advantage in the elderly and physically unwell. Fluoxetine has a long ► half-life, and fewer discontinuation effects, which can be advantageous if treatment-adherence is poor. It has also been extensively used in pregnancy and generally shown to be safe.

In contrast, clomipramine is commonly associated with typical "tricyclic" effects such as dry mouth and constipation, produced by anticholinergic blockade, sedation, and weight gain, resulting from antihistaminic (H_1) binding (► histaminic agonists and antagonists) and orthostatic hypotension, caused by alpha-adrenergic blockade. Nausea, tremor, impotence, and anorgasmia also occur with clomipramine (as with other SRIs) and are probably mediated by serotonin. Sexual performance is impaired in up to 80% of patients. Compared with the SSRIs (SSRI and related compounds), clomipramine is

Obsessive-Compulsive Anxiety Disorders. Table 1. SRIs in OCD; usually prescribed dosages (From Koran 2007).

	Starting dose (mg/day)[a]	Usual maintenance dose (mg/day)	Occasional maximum dose prescribed (mg/day)[b]
SRIs[c]			
Citalopram	20	40–60	80–120
Escitalopram	10	20	40–60
Fluoxetine	20	40–60	80–120
Paroxetine	20	40–60	80–100
Sertraline	50	100–200	200–400
Fluvoxamine	50	100–300	300–450
Clomipramine	25	100–250	–

[a]In the elderly and in some individuals there may be a need to initiate the medication at half this dose to minimize side effects
[b]In cases of treatment resistance with no or mild side effects and in rapid metabolizers
[c]SRIs appear equally efficacious in treating OCD. SSRIs are safer and better tolerated than clomipramine and therefore should usually be chosen first line (NICE 2006)

also associated with a greater risk of potentially dangerous side effects including seizures (up to 2%) and prolongation of the cardiac ► Q-T interval. These risks increase at dosages exceeding 250 mg/day. Intentional overdose with clomipramine can thus be lethal and needs to be borne in mind when prescribing for OCD, in view of the increased suicide risk associated with the illness (Guy 1976). Comorbidity between ► bipolar disorder and OCD has been reported in up to 30% cases. SSRIs (SSRI and related compounds) are less likely than clomipramine to precipitate mania, but mood stabilizing medication is still advised to mitigate the risk (Koran 2007).

Which SRI First-Line?

Clinical effectiveness depends on a balance between efficacy, safety, and tolerability. Several studies, including placebo-controlled, head-to-head comparator studies and a meta-analytic review (NICE 2006), have demonstrated this, whereas the SRIs appear equally efficacious in treating OCD. SSRIs (SSRI and related compounds) are safer and better tolerated than clomipramine, and therefore should usually be chosen first-line.

Long-Term Effectiveness

OCD is a chronic illness and so treatment needs to remain effective over the longer term. Studies have shown that placebo-referenced gains accrue for at least 6 months and according to open-label follow-up data, for at least 2 years. The SRI-response is characteristically partial, particularly in the first few weeks. An uncontrolled study followed-up fluvoxamine-treated patients with severe OCD for 6–8 years. By the end of the study, responder rates of 60% were reported and 27% of patients had entered remission. However, the majority of patients had required further treatment (either medication or CBT) in the intervening years, suggesting that long-term treatments may be required to maintain efficacy. Results from an extended double-blind placebo-controlled escitalopram study showed that the responder rate has increased to 70% after 24 weeks of continuous SSRI, and 40% of these individuals achieved remission, suggesting a more favorable outcome with sustained treatment. Consistent findings were reported from an open-label trial where 320/468 (78%) cases achieved clinical response status and 45% cases achieved remission after 16 weeks escitalopram.

Thus, first-line treatments can lead to remission or clinically meaningful improvement in around 45 or 75% of cases, respectively, in clinical trial populations. Benefits increase gradually with ongoing treatment and treatment continues to be effective over the longer term. It is important to give some time for the treatment effect to develop and also not to discontinue, reduce dose levels, or change the drug prematurely. Indeed, studies looking at the effects of discontinuing SRIs under double- blind, placebo-controlled conditions showed a rapid and incremental worsening of symptoms in most people who switched to placebo. Therefore, treatment probably needs to be continued for patients to remain well.

Relapse Prevention

The question as to whether continued SRI treatment protects against relapse may be investigated using a ► relapse prevention study design. Table 2 systematically records the peer-reviewed relapse-prevention studies in OCD. Studies of fluoxetine and sertraline found that ongoing SSRI was associated with continued improvement in Y-BOCS scores and quality of life measures up to 12 months of open-label treatment. In the fluoxetine study, only patients remaining on the highest dose (60 mg) showed significantly lower relapse rates, implying an ongoing advantage for staying at the higher dose levels. Large-scale studies of paroxetine and escitalopram clearly demonstrated a significantly better relapse outcome for those remaining on the active drug over the 6-months double-blind

Obsessive-Compulsive Anxiety Disorders. Table 2. Double-blind studies of relapse prevention in adults with OCD.

Drug	Duration of treatment prior to randomization (weeks)	Number in randomization phase	Duration of follow-up after randomization (weeks)	Relapse rates
Fluoxetine	20	71	52	PBO=pooled FLUOX, PBO > 60 mg FLUOX
Sertraline	52	223	28	PBO=SERT (Acute worsening of OCD symptoms: PBO >SERT) (Dropout due to relapse: PBO > SERT)
Paroxetine	12	105	24	PBO > PAR
Escitalopram	16	320	24	PBO > ESC

discontinuation phase: 59% and 52% relapsed on placebo compared with 38% on paroxetine (20–60 mg) and 24% on escitalopram (10–20 mg), respectively. The risk of relapsing on placebo was more than double than that on SSRI.

Taken together, these data emphasize the importance of maintaining SSRI (SSRI and related compounds) at an effective dose level (NICE 2006), and argue against discontinuation even after one year. Protection is not complete, however, with roughly one quarter of cases becoming unwell despite adherence to treatment, highlighting the need for better long-term therapies.

Treatment of SRI-Resistant OCD

It is advisable to delay changing medication until an adequate trial of 12 weeks at the maximally tolerated dose has been attempted. There is a shortage of evidence to support drug-switching when compared with extending treatment with the same drug for a longer time. In one review, 11–33% of patients not responding to the first SRI were reported to show clinically meaningful response to a second drug, with decreasing likelihoods for subsequent changes (Fineberg et al. 2006). According to meta-analyses, factors linked with ▶ SRI-resistance include early onset, longer duration, more severe illness, and poor response to previous therapy. Few studies have investigated pharmacological treatments for SRI-resistant OCD using adequately controlled trial conditions.

Increase SRI Bioavailability

One strategy has been to increase the dose of SSRI (SSRI and related compounds) beyond SPC limits (Table 1). Citalopram (160 mg) and sertraline (400 mg) were helpful in small, open-label case studies of resistant OCD. Another study randomly assigned patients to sertraline (250–400 mg) and reported an improved Y-BOCS response when compared with those who remained within SPC dose limits, and high-dose sertraline was well tolerated. Risks are greater for increasing doses of clomipramine owing to its inherent toxicity; ECG and plasma monitoring is advisable above doses of 250 mg/day and other strategies are usually preferable.

Altering the mode of drug delivery may be another way to gain control of severe intractable OCD. A double- blind study showed intravenous clomipramine to be effective. Six out of 29 patients with refractory OCD were classed as responders after 14 daily infusions when compared with none in the placebo group. The superiority of intravenous citalopram observed during an open-label trial requires substantiation under double-blind conditions.

Change to ▶ SNRI

There are few rational alternatives to SRIs for first-line treatment. Two small open-label studies suggested that patients not responding to one or more SRIs might benefit from a change to venlafaxine. However, a double-blind, prospective study was negative.

Add ▶ Antipsychotic Drugs to SRI

There have been no positive trials using antipsychotics as monotherapy, though growing evidence supports their use as adjunctive treatment with SRIs. Placebo-controlled studies of adjunctive antipsychotic drugs have been limited by methodological shortfalls including small size, focus on acute treatment, and lack of consensus on definitions of treatment-resistance or response. ▶ Haloperidol, ▶ risperidone, ▶ olanzapine, and ▶ quetiapine have been found beneficial and between 18% and 64% of individuals responded. So far, there have been no long-term studies or fixed-dose trials in OCD, though treatment is usually started at low doses and increased cautiously subject to tolerability (e.g., 0.25–0.5 mg haloperidol, titrated slowly to 2–4 mg). One study reported a high level of relapse following open-label discontinuation, hinting that the antipsychotic may need to be continued to remain effective. This finding needs further confirmation. A meta-analysis suggested that patients with comorbid tic disorders were particularly responsive to adjunctive antipsychotic drugs (Bloch et al. 2006). Efficacy in OCD supports a theoretical link between OCD and ▶ Tourette's syndrome, for which antipsychotic drugs constitute the first-line treatments. Second-generation antipsychotics (▶ second- and third-generation antipsychotics) affect a broader range of neurotransmitters and may be preferred because of their more benign side-effect profile. Interestingly, emergent obsessions have been reported during the treatment of ▶ schizophrenia with second- generation antipsychotics (▶ second- and third- generation antipsychotics). It is unclear why dopamine antagonists work when added to SRIs but do not seem to have anti-obsessional properties when used alone or in OCD associated with schizophrenia.

Novel Pharmacotherapies

Novel treatments have been tested in resistant OCD, but few show promise (reviewed in (Fineberg and Craig 2008)). There is no convincing evidence that augmentation with ▶ lithium, ▶ buspirone, pindolol, ▶ clonazepam, desipramine, or St. John's Wort are beneficial. Monotherapy with oxytocin and ▶ naloxone have also failed to produce benefit. A small study suggested oral ▶ morphine augmentation was shown to be effective

when compared with placebo. A number of lines of research, from neuroimaging to genetics are converging to suggest that abnormal glutamatergic transmission may be important in OCD. These findings have led to a number of trials involving drugs that modulate ► glutamate such as riluzole, ► memantine, ► topiramate, and D-cycloserine. To date, these are mainly at the stage of case reports and open-label series. Other compounds with initial positive results warranting further study include inositol and D-► amphetamine.

Conclusion

SRIs have a rapid onset of effect and a broad spectrum of actions. SSRIs (SSRI and related compounds) offer advantages over clomipramine in terms of safety and tolerability and usually constitute first-line treatments. Higher doses usually offer greater benefits and gains continue to accrue for weeks and months. Ongoing treatment protects against relapse for most patients. For SRI-resistant cases, the strongest evidence supports adjunctive antipsychotic drugs. Their long-term effects remain unclear. Increasing the dose of SSRI (SSRI and related compounds) or switching SRIs are rational alternatives.

Cross-References

► Antidepressants
► Antipsychotic Drugs
► Bipolar Disorder
► Cognitive Behavior Therapy (CBT)
► Histaminic Agonists and Antagonists
► Lithium
► Monoamine Oxidase Inhibitors
► Q-T Interval
► Schizophrenia
► Second- and Third-Generation Antipsychotics
► SNRI
► SSRIs and Related Compounds

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Obsessive-Compulsive Anxiety Disorders in Childhood

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Synonyms

Childhood-onset obsessive-compulsive disorder; Pediatric-onset obsessive-compulsive disorder

Definition

Obsessive-Compulsive Disorder (OCD) is currently classified as an anxiety disorder (► Anxiety Disorders) in ► DSM-IV. OCD is typically characterized by both ► obsessions and ► compulsions. Obsessions are repetitive, unwanted, intrusive thoughts, images, or impulses.

Compulsions are repetitive physical or mental acts an individual feels driven to perform in a characteristic, stereotyped way, usually to relieve the anxiety or discomfort associated with depression. Typical symptoms of OCD include contamination obsessions and cleaning compulsions (i.e., fear of germs and compulsive hand washing), forbidden thoughts (i.e., obsessions about harm coming to self or others, sexual, or religious obsessions), hoarding, and symmetry (i.e., the need to have things symmetrical, ordered, arranged) (Bloch et al. 2008). These obsessions and/or compulsions must be severe enough to cause significant distress or impairment or be time-consuming (take up more than 1 h a day). Typically, patients with OCD have insight that their obsessions and compulsions are excessive and unreasonable, but feel driven to perform them by intolerable anxiety and discomfort caused by the obsessions.

OCD is generally considered to have a bimodal distribution in terms of age of onset, with a presence of 1–3% throughout the lifespan. The first incidence peak occurs around puberty and the second occurs in early adulthood. Across the life cycle, symptoms of OCD are similarly expressed; however, there are several important differences between pediatric and adult-onset OCD. Pediatric-onset cases of OCD have a male predominance (unlike adult-onset OCD cases, which are female predominant), have a stronger family history of OCD, and have higher rates of comorbid ►Attention-Deficit Hyperactivity Disorder and ►tic disorders. They are also more likely to experience a remission of their OC symptoms compared with adult-onset OCD. The specific content of obsessions and compulsions also differ across age ranges. Children with OCD have much higher rates of aggression obsessions (such as fear of a catastrophic event, and fear of harm coming to self or others) and tend to have poor insight (being unable to recognize their obsessions and compulsions as excessive and unreasonable). Adolescents with OCD have a higher proportion of obsessions with sexual and religious themes, whereas cleaning and contamination OCD symptoms are quite prevalent across all age ranges. Patients with OCD and comorbid tics have a significantly higher rate of intrusive, violent, or aggressive thoughts and images, sexual and religious preoccupations, concerns with symmetry and exactness, hoarding and counting rituals, and touching and tapping compulsions. Also common in patients with OCD and comorbid tics, are compulsions designed to eliminate a perceptually tinged mental feeling of unease, coined in the literature as "Just Right" perceptions.

The age threshold that differentiates pediatric-onset OCD from adult-onset OCD is not clearly defined in the scientific literature, as investigators differentiate the two groups with puberty or at age 16 or 18. The pharmacological and behavioral treatments for OCD are remarkably similar across the lifespan. The combination of pharmacotherapy with selective-serotonin reuptake inhibitors (►SSRI's and Related Compounds) (SSRIs) and cognitive-behavioral therapy (CBT) (POTS 2004) are most common. There are slight differences in pharmacological management and behavioral techniques to treat pediatric-onset OCD that appear more important when the child is younger.

Role of Pharmacology

SSRIs are the pharmacological treatment of choice for obsessive-compulsive disorder. The number needed to treat (►Number needed to treat) (NNT) with SSRIs to induce a clinical treatment response, as defined by a 25–35% reduction in CY-BOCS scores, has ranged from 4 to 6 in double-blind, placebo-controlled studies (Compton et al. 2007). Based on cumulative studies, SSRI pharmacotherapy will lead to an average of a 6.5–9 point decline in CY-BOCS ratings and an average 30–38% reduction in symptom severity. In OCD, improvement with SSRI pharmacotherapy commonly continues to occur up to 2–3 months after initiation of treatment. In adulthood OCD, a recent meta-analysis has demonstrated that higher doses of SSRI pharmacotherapy are more effective than lower dose treatments (Bloch et al. 2009). No fixed-dose SSRI trials exist in pediatric-onset OCD to demonstrate if this phenomenon is similar in children. OCD patients with comorbid tics appear less likely to respond to SSRI pharmacotherapy than those without comorbid tics (March et al. 2007). Table 1 depicts the typical starting and target doses of SSRI pharmacotherapy in children and adults with OCD.

Compared to other medications used to treat child psychiatric conditions, SSRIs are generally well tolerated in children. Children, however, appear slightly more sensitive to initial treatment and dose increases than adults. Gastrointestinal disturbance, headache, fatigue, and insomnia are common side effects of SSRI medications. These side effects are ephemeral and commonly occur at the initiation of treatment or at an increase in dose. Often, with continued treatment with the same dose, these side effects can disappear. Sexual side effects, including decreased sexual desire, pleasure, or performance, are all common dose-dependent side effects of SSRIs. Sexual side effects are a common, often unmentioned cause of medication noncompliance in adolescents and adults. It is, therefore, important to outline these possible sexual side effects to adults and adolescents and inform them

Obsessive-Compulsive Anxiety Disorders in Childhood. Table 1. Recommended dosing for serotonin reuptake inhibitors in OCD.

Medication	Starting dose (in mg)		Target dose (in mg)	
	Children	Adults	Children	Adults
SSRIs				
Fluoxetine	5–10	20	10–80	40–80
Fluvoxamine	12.5–25	50	50–300	100–300
Sertraline	12.5–25	50	50–200	150–250
Paroxetine	5–10	10–20	10–60	20–60
Citalopram	5–10	20	10–60	20–60
Escitalopram	2.5–5	10	5–30	20–40
TCAs				
Clomipramine	12.5–25	25	50–200	100–250

that they are not permanent. The sexual side effects disappear with SSRI discontinuation and often simply with a dose reduction.

Behavioral activation and suicidal ideation are less common but more severe side effects of SSRI pharmacotherapy. The Food and Drug Administration issued a "► black-box warning," stating that these medications were associated with an increased risk of suicidality when utilized in pediatric populations. This warning was based on a meta-analysis of 24 placebo-controlled trials in children with depression, anxiety disorders, and ADHD (Bridge et al. 2007). The ► meta-analysis found a 2% increase in the risk of suicidal ideation with treatment of SSRIs, which is equivalent to a relative risk of 2. There were no completed suicides that occurred in any of these trials. Subsequent meta-analyzes have suggested that this increased risk of suicidal ideation appears restricted to only pediatric patients with depression and that the risk/benefit profile of SSRIs appears better in pediatric anxiety disorders (Bridge et al. 2007). Based on this warning, the FDA currently advises clinicians to see a child weekly for 4 weeks after starting SSRIs, and monthly thereafter.

Behavioral activation is a syndrome associated with SSRI use that is characterized by hyperactivity, giddiness, insomnia, and agitation. These symptoms can sometimes involve mania, irritability, and aggression. Behavioral activation appears to be more associated with ► tricyclic antidepressant use and pharmacological treatment at a younger age (Martin et al. 2004).

Clomipramine, a tricyclic antidepressant with primarily serotonergic properties, was the first antidepressant the FDA approved for the treatment of pediatric OCD. A meta-analysis of pharmacotherapy trials for pediatric OCD found, using meta-regression techniques, that ► clomipramine was superior to the selective-serotonin reuptake inhibitors in the treatment of pediatric OCD, and the different selective-serotonin reuptake inhibitors currently used to treat OCD were roughly equivalent (Geller et al. 2003). These meta-regression results, however, should be interpreted with caution, considering that no studies have directly compared the efficacy of clomipramine to other selective-serotonin reuptake inhibitors in children with OCD. Studies comparing these agents in adults have found no significant differences. Clomipramine, due to its worse side effect profile compared to SSRIs, is no longer used as an initial pharmacological treatment for OCD. Clomipramine has higher rates of somnolence, gastrointestinal upset, and weight gain than SSRIs. Clomipramine also has anticholinergic effects, reduced seizure threshold, and arrhythmogenic side effects. Due to the potential arrhythmogenic properties of clomipramine, a baseline electrocardiogram and a detailed screening for a personal and family history should be undertaken in all patients before the initiation of pharmacotherapy. Guidelines for unacceptable EKG indices for use of clomipramine have been issued by the FDA, and are as follows: (1) PR interval >200 ms; (2) QRS interval >30% increased over baseline or >120 ms; (3) blood pressure greater than 140/90; (4) heart rate >130 bpm or (5) QTc >450 ms. Despite these concerns, clomipramine remains a valuable treatment option for children who do not respond to initial pharmacotherapy with one or more selective-serotonin reuptake inhibitors. Clomipramine is now utilized mainly as monotherapy for OCD patients who have not responded to two SSRI trials of adequate dose and duration, or as an augmentation agent to SSRIs in low doses. When using clomipramine as an augmentation agent, clinicians need to be vigilant for the onset of the ► serotonin syndrome.

Approximately half of the children placed on SSRI pharmacotherapy will fail to respond despite optimum pharmacologic treatment. If CBT has not been offered and conducted, it should be done so at this point. In adults with OCD, as many as 25% of initial nonresponders may respond if treated with another SSRI or clomipramine. Other options for augmentation include antipsychotic augmentation or augmentation with ► glutamate modulating agents.

No controlled trials of antipsychotic augmentation exist for children with OCD. A meta-analysis of placebo-controlled trials of adults with treatment-refractory OCD, has demonstrated that these agents are effective (Bloch et al. 2006). The NNT to induce a clinically significant treatment response (35% reduction in Y-BOCS ratings) in adults with OCD was 4.5 (95% CI: 3.2–7.1). ► Neuroleptic augmentation appears particularly effective in OCD patients suffering from comorbid tics (NNT = 2.3). This result is not surprising since antipsychotics are the most effective medications in treating tic disorders. The doses of neuroleptic medications used to augment SSRIs are traditionally much lower than those used to treat psychosis and aggression in children. Lower doses are preferred due to the increased sensitivity of children with TS and OCD to these medications and the CYP2D6-based pharmacologic interactions these medications have with many SSRIs. Children with OCD appear particularly prone to the metabolic side effects associated with ► antipsychotics. The restriction of antipsychotic augmentation is, therefore, advisable only for children with comorbid tics or severe functional impairment despite adequate treatment with SSRIs and behavioral therapy.

Riluzole is a glutamate modulating agent that is approved by the Food and Drug Administration for neuroprotection in the treatment of amyotrophic lateral sclerosis, also known as Lou Gehrig's disease. Riluzole is postulated to affect glutamate neurotransmission by reducing presynaptic glutamate release and by increasing glial cell reuptake of glutamate. Uncontrolled studies of both adults and children have provided encouraging data of efficacy. A case series of six children with treatment-refractory OCD at NIMH found four treatment responders (Grant et al. 2007). Case series of treatment-refractory adults demonstrated a 57% response rate and treatment gains that maintained for at least 2 years of follow-up (Pittenger et al. 2006). Riluzole's potential efficacy is yet to be demonstrated in any blinded or placebo-controlled trials. Although quite well-tolerated by most patients, riluzole's widespread use is limited by its potential hepatotoxicity. Riluzole use requires monitoring of liver function tests every 3 weeks for the first 3 months of treatment.

Role of Nonpharmacological Therapies

Cognitive behavioral therapy is a first-line treatment for pediatric-onset OCD. The NNT for CBT in pediatric-onset OCD is 2.6 (95% CI: 1.7–4.2) to induce a treatment-response (POTS 2004). CBT for children with OCD is based on exposure and response prevention. In CBT for OCD, the therapist must first examine and take a detailed history of a child's specific OCD symptoms. Symptom checklists, such as those that accompany the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS), Children's Y-BOCS, and Dimensional Y-BOCS are useful in these efforts. Then the therapist, working with the child and his/her parents, develops a hierarchy of exposures, both direct and imaginary, to trigger the anxiety associated with obsessions of OCD (i.e., touching a toilet seat for a child with contamination concerns, or imagining a parent in a car accident for a child with fears of harm coming to others). The therapist then enters into a contract with the child and parent to work on completing these exposures over a set time frame, usually a period of a couple of months. Next, the therapist engages in the specific exposures with the child (and sometimes the parents) over the next few treatment sessions, asking the child to agree not to engage in his/her compulsions in response to the anxiety produced. During exposures, the child reports his/her level of anxiety using subjective units of distress (SUDS), an anxiety thermometer. The child and parent are given similar exposure assignments to complete after each session. With increased duration of exposure and subsequent exposure, the child's anxiety lessens (without performing the compulsions), helping him/her to overcome the OCD. Most CBT treatment manuals for children with OCD are freely available, and additionally include techniques such as relaxation therapy, to help children deal with stress and anxiety. The manuals may also include exercises to illustrate other tenets of CBT. For example, they may help the child to recognize cognitive distortions common in OCD, such as overestimation of risk, all-or-nothing thinking, overcoming the need for certainty, and recognizing excessive feelings of responsibility or guilt. CBT is as effective as any pharmacological intervention for OCD, and should be utilized before pursuing less evidence-based augmentation strategies for OCD.

Conclusion

SSRIs and CBT are effective treatments for pediatric-onset OCD. The combination treatment of both SSRIs and CBT is more effective than either treatment alone. Although many children with OCD respond to submaximal doses of SSRI pharmacotherapy, it is important to pursue an SSRI trial of adequate dose, (maximal tolerated dose), and

duration (2–3 months) before progressing to augmentation therapies. Antipsychotic augmentation appears to be a particularly effective strategy for OCD patients with comorbid tics. Riluzole augmentation is an emerging treatment for OCD that may be effective for some patients. While there are several effective treatment options for OCD, there is still a great need for treatments that work better and faster.

Cross-References

- ▶ Adolescence and Response to Drugs
- ▶ Antidepressants
- ▶ Antipsychotic Drugs
- ▶ Anxiety Disorders
- ▶ Attention Deficit Hyperactivity Disorder
- ▶ DSM-IV
- ▶ SSRI's and Related Compounds
- ▶ Tic Disorders

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Obsessive–Compulsive Disorder

Synonyms

Obsessive–compulsive neurosis; OCD

Definition

Obsessive–compulsive disorder (OCD) is a disabling psychiatric disorder that usually pursues a chronic course and is characterized by recurrent unwanted thoughts obsessions and/or physical acts compulsions that are severe enough to be time consuming, cause marked distress or significant impairment. At some point during the disorder, the obsessions or compulsions are recognized to be excessive or unreasonable (DSM1V). If another DSM-IV Axis I disorder is present, the content of the obsessions or compulsions is not restricted to it. Nor is the disturbance due to the direct physiological effects of a substance or a general medical condition.

Cross-References

- ▶ Compulsions
- ▶ DSM1V
- ▶ Obsessions

Obsessive–Compulsive Neurosis

▶ Obsessive–Compulsive Disorder

Occasion Setting with Drugs

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Synonyms

Drug as cues; Drug discriminative stimulus; Drug facilitator; Drug modulator; Drug occasion setter

Definition

Occasion setting is a form of hierarchical learning involving associative and nonassociative processes. Occasion setters are discrete stimuli or contexts that disambiguate

Pavlovian and/or operant relations. In cases where stimuli or responses are "sometimes" associated with biologically relevant events, occasion setters can provide discriminant information that resolves the ambiguity of the antecedent. Drug states are internal contexts that can predict positive relationships between stimuli/responses and outcomes (feature-positive occasion setters) or negative relationships between stimuli/responses and outcomes (feature-negative occasion setters). Traditionally, occasion setters are considered nonassociative because their ability to influence behavior does not depend on a direct association with the antecedent or biologically relevant events, but can "transfer" to novel responses and situations.

Impact of Psychoactive Drugs

Introduction

In a standard ► Pavlovian (classical) conditioning experiment, the investigator establishes a relation between two stimuli. In a typical study involving rodents, one stimulus might be a tone or a light (termed ► conditioned stimulus [CS]) that is repeatedly paired with a more motivationally relevant stimulus such as food, water, drug, etc. (termed ► unconditioned stimulus [US]). Sometimes, the CS–US pairing occurs only in a particular situation or when some other stimulus is present. The stimulus that disambiguates when the CS will be reinforced is often referred to as a feature-positive occasion setter. Under these conditions, the CS evokes a ► conditioned response (CR) only when the feature is present. Alternatively, the feature might indicate when the CS will *not* be reinforced. In this case, the stimulus is referred to as a feature-negative occasion setter, and conditioned responding during the CS is withheld or inhibited. Many drugs have interoceptive (subjective) properties that function as stimuli capable of guiding learned behaviors. These interoceptive properties can be conceptualized as polymodal contextual (situational) cues in which the stimulus elements reflect the complex neurobiological action of that drug. As such, a drug state can function either as a feature-positive or as a feature-negative occasion setter disambiguating when a CS–US relation will or will not be in force, respectively. Drugs such as ► bupropion, ► caffeine, ► chlordiazepoxide (CDP), ► cocaine, D-► amphetamine, ► ethanol, ► flumazenil, indorenate, ► nicotine, ► methamphetamine, ► morphine, ► pentobarbital, ► rimonabant, ► sertraline, and Δ-9 tetrahydrocannabinol (THC) appear to function as feature-negative and/or feature-positive occasion setters.

Example Tasks

The occasion-setting function of drug states has been described in a variety of paradigms using a range of CS types, as well as appetitive and aversive USs. For the sake of brevity, we will focus the present discussion on two variants: discriminated ► conditioned taste aversions (DTA; Jarbe and Lamb 1999) and discriminated ► goal tracking (DGT; Palmatier and Bevins 2008). In DTA studies, the drug state sets the occasion in which a taste CS would or would not be followed by a noxious or aversive event, often lithium chloride-induced illness. Subjects are provided repeated access to a novel taste CS. During half of these conditioning trials, the taste CS is accessed in the drug state; during the remaining trials, the taste CS is accessed after a ► placebo injection (nondrug state). Following access to the CS, the illness-inducing US or placebo (no US) is administered. The CR is typically defined as avoidance of the taste CS. In DTA studies, drug states are most often trained as positive features – the taste CS is followed by illness when it is accessed in the drug state, and the same tastant is followed by a placebo injection when it is accessed in the nondrug state. Subjects learn to avoid the taste CS when it is presented in the drug state, but readily consume the CS in the nondrug state. Because the feature-positive drug state occasions taste-illness pairings in this task, it is sometimes referred to as a "danger cue." In this paradigm, drug states can also serve as negative features, which set the occasion in which the taste will not be followed by illness and are sometimes referred to as "safety cues" (see Skinner et al. (1995) and Hallmarks of Occasion Setters for more information).

In DGT studies, the drug feature sets the occasion on which a CS will or will not be followed by a rewarding US, typically food or sucrose solution. In this task, a brief auditory or visual stimulus (CS) is presented both in the drug state and the nondrug state (placebo). If the drug state is a positive feature, then the CS presentations that occur in the drug state are followed by access to the US; the same CS is presented in the nondrug state, but the US is withheld (Palmatier and Bevins 2008). Conversely, when the drug state serves as a negative feature, the US follows the CS after placebo injection and the US is withheld after drug injections (Bevins et al. 2006). In these studies, the CR is goal tracking, which reflects anticipatory approach to a location where the appetitive US has occurred previously (e.g., head entries into the receptacle where sucrose is delivered).

The concept that the internal milieu can provide a context with discriminant properties is not limited to drug states. Davidson and his colleagues (Davidson 1998) have

argued that internal contexts of hunger and satiety might function as occasion setters. In one notable study, hunger and satiety contexts were used to set the occasion for when a rat would receive a shock (US) in a particular chamber (CS). Rats were able to use an internal state to determine when a shock would occur, and the occasion-setting function of the hunger/satiety state transferred to other chambers that were associated with shock, but not to chamber CSs that were never associated with shock. Based on these and other findings, Davidson (1998) has argued that the occasion-setting function of the internal milieu could explain why more appetitive behaviors are exerted when food stimuli are presented in "hunger" states relative to "sated" states.

Hallmarks of Occasion Setters

An important aspect of occasion setting is ascertaining whether the feature's influence on behavior depends on a direct relationship with the US. Occasion-setting features typically have a perfect positive or negative correlation with the US, meaning that they may function only as simple conditioned excitors (feature-positive) or ► conditioned inhibitors (feature-negative) rather than occasion setters. Determining whether a feature is an occasion setter or a simple excitor/inhibitor often demands manipulating its relationship to the US and then a test to examine whether the manipulation has altered the feature's ability to increase or decrease responding evoked by the CS. If the feature functions only as a conditioned excitor or inhibitor, then this manipulation is expected to abolish its ability to modulate CS-evoked responding.

In the DGT task, the drug states (amphetamine, nicotine, and CDP) trained as positive features increased responding to a CS paired with sucrose (Palmatier and Bevins 2007). In the nondrug state, the CS evoked very little conditioned responding. To investigate whether these drug states increased responding because they served as simple CSs (i.e., direct association with US), we changed the relation between the drug state and the US. Each feature underwent an ► extinction treatment – rats were repeatedly exposed to the drug in the absence of the US. The discrete exteroceptive CS was never presented on these extinction trials. In subsequent tests, all three drug states still increased responding evoked by the CS. This finding suggests that the drug states functioned as occasion setters (nonassociative) rather than simple conditioned excitors (associative).

A second hallmark of occasion setters is their transitive nature; a feature that sets the occasion for one CS–US association can often transfer its discriminant function to another CS. Transfer of occasion setting normally involves a novel combination of features and CSs after the subjects have been trained on multiple discriminations. For example, we recently trained two drug states (nicotine and CDP) as positive features for two different CSs in the DGT task. A noise CS was followed by sucrose after nicotine injections, and a light CS was followed by sucrose after CDP injections. After placebo injections, the light and noise were presented but were never followed by sucrose. Following training on both discriminations, rats were tested on different combinations of drug features and CSs. As expected, nicotine and CDP facilitated responding to the CSs which typically occurred in those drug states. However, each drug also facilitated responding to the CS which had occurred in the *other* drug state. Neither CS evoked conditioned responding when presented after injection of a novel drug (i.e., amphetamine), and neither feature facilitated responding to a novel CS (Palmatier and Bevins 2008). In DTA procedures, positive drug features ("danger cues") typically transfer their facilitative function in a less specific manner. Skinner et al. (1998) have demonstrated that these danger cues will inhibit consumption of the taste CS as well as novel and familiar tastants that have never participated in an occasion-setting discrimination. They have argued convincingly that positive drug features in the DTA paradigm may set the occasion for associations between consummatory responses and the illness-inducing US (Skinner et al. 1998).

Recall that in the case of feature-negative training, conditioned responding evoked by the target CS in the drug state is significantly attenuated relative to the nondrug state. To our knowledge, transfer of negative occasion setting with drug features has not been investigated. This may be because researchers in this area suspect that negative drug features are functioning as simple conditioned inhibitors (Bevins et al. 2006; Skinner et al. 1995). The theoretical and, hence, the therapeutic implications could be significant if a drug state could acquire inhibitory properties. To gather convincing evidence for inhibitory conditioning to the interoceptive effects of a drug, one must show that a drug trained as a negative feature passes the summation and retardation tests of conditioned inhibition. In the ► summation test, the putative-conditioned inhibitor will also inhibit conditioned responding to an excitatory CS that has been trained independent of any occasion-setting function. For the ► retardation test, subsequent acquisition of an excitatory conditioned response to the negative feature will be impaired (retarded) relative to controls. Morphine trained as a negative feature in the DTA task ("safety signal") passes the summation test. That is, avoidance of a separately trained saccharin CS was diminished across repeated

extinction sessions in the presence of morphine that was previously trained as a negative feature indicating that vinegar solution would not be paired with illness (Skinner et al. 1995). A retardation test has not been conducted using the DTA procedures, nor has either the retardation or summation test been used within the DGT task. Thus, the field awaits a definitive demonstration as to whether a feature-negative drug state inhibits conditioned responding through direct inhibitory properties.

Significance and Application

Training the interoceptive effects of a drug as an occasion setter requires a discrimination to be made at least between the drug and nondrug state. Of course, as indicated earlier the discrimination is more specific than a mere presence vs. absence of an altered internal state. Given this pharmacological specificity in control of conditioned responding, these Pavlovian drug discrimination tasks have been used as a complement to the operant-drug discrimination task that uses drug ► discriminative stimuli to help elucidate the neuropharmacological processes underlying the subjective effects of a drug (Kreiss and Lucki 1994; Reichel et al. 2007).

Although clear advances have been made in understanding drug states as occasion setters, the role of such factors in addiction and other health-related behaviors and their therapeutic implications have yet to be fully realized. Regardless, we expect their importance to be high given the demonstrations that learning can alter the functional impact of the drug state. A salient example described earlier is the transfer (substitution) of occasion-setting function to a pharmacologically unrelated drug, only when the drugs share a common learning history – that is, trained as feature-positive occasion setters with different target CSs. Another example is the alteration of the psychomotor effects of stimulant drugs depending on whether there has been a training history with a positive or negative drug feature (Reichel et al. 2007). Briefly, rats were trained with ► methamphetamine as the occasion setter. For one set of rats, methamphetamine served a feature-positive occasion setter indicating when a brief light was paired with sucrose. The other set of rats had methamphetamine indicate when the light was not reinforced (i.e., feature-negative occasion setter). Following acquisition of the discrimination were intermixed substitution tests in which the cocaine and bupropion were tested. Substitution tests indicated that bupropion and cocaine had methamphetamine-like stimulus effect. More interestingly, from the current discussion's perspective is that the typical stimulant effects of these two drugs were significantly blunted if rats had methamphetamine trained as a negative feature. Much more research is needed to know the generality, extent, and mechanism(s) of this effect. Regardless, a well-documented behavioral effect of cocaine and bupropion was affected by training methamphetamine as a negative feature.

The significance of occasion setting by drug states is critical to the study of drug addiction. The widespread acceptance of associative learning processes in addictions is reflected by their inclusion as a critical component in bio-behavioral models of drug dependence (e.g., Koob and Le Moal 2008). However, the role ascribed to associative learning in most models is best described as simple and elemental. One cannot assume that for drug-dependent individuals all "drug-cues" are followed by rewarding drug effects each time they are experienced. For example, a smoker may be exposed to stimuli (i.e., cigarette packaging) that have a history of pairing with the reinforcing effects of nicotine. However, in many circumstances (i.e., in public buildings, offices, hospitals, filling stations) the effects of nicotine may be unattainable. In these cases, the contextual stimuli probably modulate the meaning of the CS (cigarette packaging). Given the frequently observed comorbidity between the drug dependence disorders (e.g., alcoholism and smoking), it is critical that we expand the role of learning processes in addictions and further examine the role of occasion setting by drug states and other contexts. These principles undoubtedly extend to other forms of addiction (e.g., gambling), other impulsive and compulsive behaviors (e.g., eating; see Davidson 1998), as well as pain management and cancer treatment.

Cross-References

► Addictive Disorder: Animal Models
► Blocking, Overshadowing, and Related Concepts
► Classical (Pavlovian) Conditioning
► Conditioned Drug Effects
► Conditioned Place Preference and Aversion
► Conditioned Taste Aversions
► Discriminative Stimulus
► Drug Discrimination
► Instrumental Conditioning
► Rodent Models of Cognition

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OCD

► Obsessive-Compulsive Anxiety Disorders in Childhood
► Obsessive–Compulsive Disorder

Octreotide

Synonyms
Sandostatin; SMS201-995

Definition
Octreotide is an octapeptide, the first somatotropin release-inhibiting factor (SRIF) receptor agonist in the clinic. Octreotide is used to treat acromegaly, some GIT disorders, and primarily a number of tumors in the gastroenteropancreatic tract. Octreotide has high affinity for sst2 and sst5 receptors.

Cross-References
► Somatostatin

Oculomotor Tasks

► Eye Movement Tasks

Odd-Ball ERPs

► P300

Off-Label Use of Drugs

Definition
The label is a document about a drug, which is approved by governmental "regulatory" agencies, such as the Food and Drug Administration (FDA) in the US and the European Medicines Agency (EMEA) in the EU. The label is the source for the package insert. The label includes the drug's approved indications, that is, the conditions, diseases, disorders, that can be treated with the drug. Off-label use refers to the practice of using a drug for the treatment of a disease or condition that is not listed on its label, or used in such a way that is not described in the label (e.g., in higher doses). Synonyms of off-label are extra-label use, nonapproved use or unapproved use. Off-label prescription raises legal and ethical issues. Some countries ban or restrict off-label use of drugs. Insurance companies may reject the reimbursement claims for off-label prescriptions. In case of unexpected side effects/adverse events of the drug treatment (unexpected adverse events are those, which are not described in the label), the manufacturer holds no responsibility as it is the case with prescriptions based on the label. Regulations may mandate that even evidence-based scientific speech violated the law if manufacturers were involved and the information concerned off-label uses.

6-OHDA

► 6-Hydroxydopamine

Olanzapine

Definition
Antipsychotic drug of the second generation, atypical category with combined dopamine D2/serotonin2 receptor blocking properties.

Cross-References
► Second and Third Generation Antipsychotics

Old Antipsychotics

► First-Generation Antipsychotics

Old Neuroleptics

► First-Generation Antipsychotics

Older Anticonvulsants

► First-Generation Anticonvulsants

Oligophrenia

► Autism Spectrum Disorders and Mental Retardation

Olton Maze

► Radial Arm Maze

Ontogenesis

► Ontogeny

Ontogeny

Synonyms

Morphogenesis; Ontogenesis

Definition

Describes the origin and the developmental history of an organism from the embryo to its mature form (adult). The term is opposed to "phylogeny" which denotes the evolutionary history of a species.

Open-Field Test

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Definition

Test consisting of scoring the behavior of a rodent that has been forced into a novel arena. Enables detection of effects of drugs on anxiety behavior, activity, and memory.

Principles and Role in Psychopharmacology

History

In 1934, Hall (1934) designed the open-field test to assess "emotionality" in rats. The procedure consists in introducing an animal into a new arena from which escape is prevented by walls (Walsh and Cummins 1976). Hall's apparatus consisted of a brightly lit circular environment (thereafter termed as "open field") of about 1.2 m diameter closed by a wall of 0.45 m high. Rats were placed individually in the open field and their behavior was recorded for 2 min, during daily repeated trials. In some cases, rats were tested after 24 or 48 h of food deprivation. Hall observed that rats exhibited increased locomotion when food was deprived, and also, surprisingly, some rats did not eat, in spite of the high alimentary motivation related to the food deprivation: these animals were termed "emotional." When compared with non-emotional rats, they displayed increased thigmotaxis (i.e., they walked in the outer ring of the apparatus, always maintaining a tactile contact with the walls via their vibrissae); these emotional rats also exhibited higher levels of defecation and micturation (Fig. 1).

Procedure

The procedure is generally based on the forced confrontation of the rodent with the open field, but in some cases

Open-Field Test. Fig. 1. A mouse in a circular open field – Dimensions of the arena: 40 cm diameter and 30 cm high.

animals have also been allowed free access to the arena from their familiar nest.

In this free confrontation situation, rodents will generally show avoidance for the brightly lit environment: before entering the arena, the animal will show risk assessment postures directed toward the open field. This is a first argument indicating that the open field may be a stressful situation. In case of forced confrontation, the animal is placed in the apparatus and the following behavioral items are recorded, usually during five min: locomotion, frequency of rearing or leaning (sometimes termed vertical activity), and grooming. Increase of time spent in the central part, higher ratio of central/total locomotion, or decrease of the latency to enter the central part are indications of reduced anxiety-like behavior. Therefore, experimenters are not measuring the effects of the factors they are interested in on exploration, as is sometimes claimed, but the effects on the reaction of the subjects to a stressful event. Additionally, other parameters may be measured, including physiological, neural, or endocrinological ones. For example, using telemetry, it has been shown that the forced confrontation to the open field induces increased heart rate, further indicating that the animal is in a stressful situation. Immunohistological experiments, allowing measuring of the activation of various brain areas via c-fos, have shown that exposure to the arena induces activation of several structures belonging to the limbic system, such as the ► hippocampus, the ► amygdala, or the bed nucleus of stria terminalis, further suggesting that the rodent is stressed. This is accompanied by an activation of some hypothalamic nuclei, including the paraventricular nucleus. Finally, open-field exposure also induces a rise of plasma corticosterone, which is the main stress hormone. Taken together, this indicates that forced exposure to the open field induces a complex response, characterized by a specific behavior associated with physiological, endocrine, and neural modifications all suggesting that the animal has been stressed.

Utilization

The open-field test is now one of the most popular procedure in behavioral neuroscience (see Belzung 1999; Prut and Belzung 2003), and is used to assess the effects of different factors on anxiety-like behavior, including the action of ► anxiolytic drugs, brain lesions, or genetic invalidation. In fact, it has become a convenient procedure to measure not only anxiety-like behaviors but also activity, enabling to detect sedation (decrease of activity) or hyperactivity. It can also be used to assess learning and memory. Several versions of the apparatus have been designed, differing in shape of the environment (circular, square, or rectangular), lighting, presence of objects within the arena, and so on. Utilization of this apparatus has been extended to a great number of species including not only farm animals such as calves, pigs, lambs, rabbits, but also other species including invertebrates such as honeybees and lobsters. In fact, stressful experience in the open field is triggered by two factors: individual testing (the animal is separated from its social group) and forced novelty (the animal is subjected to an unknown environment, with no ability to turn back to its home cage or to predict the outcome of this confrontation; further, the arena is very large relative to the animal's home cage or natural environment consisting in small galleries). These two factors may respectively be interpreted as stressful only in gregarious species and/or in species that show fear of open spaces into which they are forced. This is precisely the case with rodents that live in groups and in small underground tunnels. This is of course not the case in species such as lambs or cows that live in large fields.

Interpretation Bias

Behavior of rodents in the open field depends on several sensorial modalities, with a main involvement of tactile factors. Indeed, mice without vibrissae no longer display thigmotaxis, as they lose tactile contact with the walls. One must thus emphasize the possibility of misinterpretation of data related to effects of some treatments on the sensorial characteristics of the animals. As already indicated, exploration can be increased by some factors including food or water deprivation: it is therefore very important to verify that a given treatment does not act on such variables, before concluding the possible anti-stress effects. Finally, open-field behavior also depends on lighting conditions and upon the light–dark cycle (because exploration and food patrolling is increased during the animal's high-activity period, i.e., at the beginning of the dark phase) so that it may be relevant to ensure that a treatment does not modify internal clock-related behaviors and test the treatment under different lighting conditions.

Assessment of Drug's Effects on Anxiety Behavior

Using this device, the effects of different treatments have been investigated, mainly in the field of behavioral genetics (18% of the studies investigating the effects of targeted mutation of a given gene on anxiety-like behavior have been conducted using this device, a percent rising to 26%

for mutants of the serotoninergic system) and in the one of psychopharmacology. Concerning this last aspect, one may notice that many different drugs have been investigated in this situation, including compounds not only with effective or potential anxiolytic-like effects (► benzodiazepines, ► serotonin ligands, ► neuropeptides) but also compounds with psychostimulant (► amphetamine, ► cocaine), sedative (► neuroleptic), preictal (the state characterizing the prostration state induced by some epileptogenic drugs) activity or amnesic effects. An increased locomotion or time spent in the central part of the device without any modification of total locomotion has been interpreted as an anxiolytic-like effect while the contrary, which is a decrease of these variables, is associated with ► anxiogenic-like effects. Increased total locomotion (i.e., an increase of central and peripheral locomotion, in the same proportions) can be interpreted as hyperactivity while decreased rearing and locomotion are related to sedation or to postictal prostration. Concerning anxiety-like activity, the effects of three categories of drugs have been investigated, including compounds acting on the ► $GABA_A$ pentamer (not only benzodiazepine receptor ligands but also $GABA_A$ receptor agonists, ► barbiturate and ► neurosteroid ligands), serotoninergic-acting drugs such as ligands of the different 5-HT receptors or inhibitors of the serotonin transporter, and the effects of neuropeptidergic ligands (CRF, corticotropin-releasing factor; CCK, ► cholecystokinin; NK, neurokinin; neuropeptide Y). Interestingly, the open field is able to detect the anxiolytic-like effects produced by compounds effective in normal anxiety behavior, such as classical benzodiazepines and 5-HT_{1A} receptor agonists, while it lacks sensibility for the anxiolytic action of atypical benzodiazepines such as ► alprazolam or for the anxiolytic action of chronic antidepressants such as ► Selective Serotonin Reuptake Inhibitors, that display efficacy in some anxiety disorders such as panic, obsessional–compulsive disorder, social phobias, and post-traumatic stress disorder. It is to be emphasized here that benzodiazepines and 5-HT_{1A} receptor agonists do not increase exploration as it is sometimes claimed; they act by reducing the stress-induced inhibition of exploration. Further, this device detects the effects of these compounds on anxiety-like behavior, and not on anxiety. Indeed, anxiety-like behavior is only one component of the anxiety-like response, which also includes expressive reactions (e.g., the vocal expression such as ► ultrasonic distress calls), physiological alterations (modifications in body temperature, heart rate, arterial pressure), as well as cognitive/subjective aspects.

Assessment of Drug's Action on Locomotion (Sedation and Hyperactivity)

Concerning the ability to detect sedation, for example, after administration with high doses of benzodiazepines, ethanol, or neuroleptics, an important point to consider is that the free exploration situation is much more sensitive to the sedative effects of a treatment when compared with the forced situation. Indeed, in order to detect sedative effects, two-fold higher doses should be used in the forced situation. This can be explained by the fact that the forced confrontation imposes the experimenter to take the animal out of its home cage, which may induce awaking of an animal that would have been sleeping in its home cage. One may also mention the fact that the effects of a sedative treatment on rearing appear at lower doses than the ones on locomotion, indicating that this parameter is more sensitive. Sedative-like effects have to be distinguished from the preictal prostration that can be observed after administration of some proconvulsive treatments. The phenomenological features of these two behaviors may seem identical, as animals exhibit a reduced exploration in both cases. Therefore, when reduced exploration is seen, the experimenter has always to be very prudent in the interpretation of data. Further, reduced exploration can also be observed if the rodent is freezing; but in this case, the experimenter will observe a very different posture, the rodent showing a tonic immobility, while when sedated displays a nontonic immobility.

Hyperactivity can also be detected using this device. ► Hyperactivity never corresponds to increased exploration. Indeed, after treatment with ► psychostimulants, the animal will show elevated locomotion, sometimes close to stereotypy (as it may repeat the same locomotion pattern several times) with reduced exploratory items (no sniffing, few rearing).

Assessment of Drug's Effects on Learning and Memory

The open field has also been used to detect the effects of some treatments on learning and memory. Three different processes can be assessed in this case: ► habituation, object recognition, and ► spatial memory. To test habituation, one can compare the behavior of the rodent during the first 5 min with the ones of the last 5 min of a 15-min session, enabling to detect the effect of a treatment on short-term habituation. Alternatively, one can confront a rodent to several 5-min sessions, separated by inter-trial intervals of some hours or several days. In this case, one can distinguish the effects of a given treatment on encoding from its effects on consolidation or restitution, depending upon the injection schedule. When testing

object recognition using an open field, the subject is usually first introduced in the arena during a 5-min session. After an inter-session delay, the animal is further subjected to the open field, which now contains two identical objects. During a third session, the rodent is again introduced in the device, which contains one object identical to the one it has been confronted before and another one that is different. Higher exploration of the new object indicates that the animal has been able to remember the object it had seen before and is therefore considered an index of recognition memory. Pharmacological treatments can be tested either to detect promnesic/amnesic effects, or to counteract the stress-induced decline in learning and memory (e.g., ► antidepressants are able to restore a stress-induced decline in object recognition). Finally, this situation can also be used to detect the effects of drugs on spatial memory. In this case, the rodent is confronted to the arena containing three identical objects, placed in a precise spatial configuration; (e.g., a line) and after a delay, it will again be introduced in the device, with the same objects, placed, for example, in a triangular configuration. In this case, exploration of all objects that had been declining after habituation will start again. This process can be altered with pharmacological treatments such as, for example, anticholinergic drugs.

Conclusion

In conclusion, the open field is a very popular and useful device, not only enabling detection of effects of drugs on anxiety behavior, but also action of pharmacological compounds on sedation, hyperactivity, learning, and memory.

Cross-References

► Anxiety: Animal Models
► Anxiety Disorders
► Benzodiazepines
► Habituation
► Phenotyping of Behavioral Characteristics
► Translational Research

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Open-Label

Definition

Open-label is a method of research in which the identity of the treatment is known by both the researchers administering the treatment and the subjects involved in the study.

Cross-References

► Impulse Control Disorders

Operant

Definition

A class of activities, all of which produce a common effect on the environment. A typical example is pressing a lever. The different forms of behavior that result in lever depression are members of the operant class.

Operant Behavior in Animals

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Synonyms

Instrumental behavior; Instrumental performance; Purposive behavior

Definition

Operant behavior in animals encompasses activities that are influenced by their consequences. More precisely, the future likelihood of such behavior is a function of the history of consequences for that behavior. Particular classes of activities that are influenced by their consequences are called ► operants. For instance, any form of behavior that successfully results in the depression of a lever by a rat would be considered as part of the operant "lever pressing." Effective consequences are divided into two categories, those that make the behavior more likely in the future and those that make it less likely. The former are called ► reinforcers or reinforcing stimuli (akin to the everyday word "rewards") and the latter are called punishers or punishing stimuli. Reinforcers and punishers are further subdivided into two subcategories, positive and

negative. Positive reinforcers increase the subsequent probability of behavior if they are presented as a consequence, for example, presenting food to a hungry rat after it presses a lever, whereas negative reinforcers make behavior more likely when they are removed as a consequence, for example, when pressing a lever turns off an irritating loud noise. Positive and negative punishers therefore exert their effects upon presentation and removal, respectively. Behavior that is increased by experience with consequences is said to be reinforced and the process is called ► reinforcement. Conversely, decreasing behavior by means of consequences is called ► punishment. The effective consequences are functionally defined. For example, reinforcers are defined by three features. One, an operant has a consequence. Two, the operant subsequently becomes more probable. Three, the increase is due to the consequential relationship, not to the mere presentation of the consequence (e.g., consider trying to reinforce crying in a baby by pinching it when it cries). Punishment is analogously defined, the only difference being that the operant becomes less likely. Operant behavior in animals is used to model willful, voluntary behavior in humans. When consequences occur regularly (see next), either naturally (as when a door moves when pushed) or as a result of deliberate planning (as when an experimenter arranges that a lever press results in food presentation) and the behavior is affected by that relationship, it is often said that a ► contingency of reinforcement is evident.

Impact of Psychoactive Drugs

Principles and Use in Psychopharmacology

The basic techniques for establishing and studying operant behavior in animals were developed in large part by B. F. Skinner and his colleagues in the 1940s through the 1960s (see Skinner 1938). They have become a signature part of the armamentarium of psychopharmacology. Operant techniques play a prominent role in ► drug discrimination, drug ► self-administration, and ► behavioral economics. They are also used to study drug effects on sensory processes and on cognitive processes such as choice, timing, learning, and memory, as well as emotional responses such as anxiety and stress (Mazur 2006). Most of these applications of the techniques involve two important processes that characterize operant behavior. Those are (1) ► stimulus control, or discrimination (Nevin 1973), and (2) *intermittent reinforcement* via ► schedules of reinforcement (Ferster and Skinner 1957; Zeiler 1977). Before discussing these two processes, however, it is necessary to describe the conditions required to establish operant behavior.

There are two main methods for establishing operant behavior. The first is called free-operant acquisition, and the second is called shaping. In both, animals are generally studied, one at a time, in relatively barren environments. Usually, the animal is placed in a comparatively small space (sometimes called a Skinner box) outfitted with a device that the animal can move, such as a lever for a rodent or nonhuman primate or a lighted disk that can be depressed by a rodent or avian. Also available is an apparatus that permits delivery of a consequence, for example, a bit of food. In free-operant acquisition of lever pressing, for instance, the animal is initially habituated to the enclosure and it learns where the food is delivered. The experimenter then arranges the apparatus so that when the lever is initially pressed, for whatever reason, the food is immediately delivered. Under appropriately controlled conditions, the lever press is soon followed by many others and the behavior has been established for further study. The second method, shaping, can be used to establish behavior such as lever pressing, but also can be used to engender behavior that is extremely unlikely to occur if one simply waits. Shaping is also called the method of successive approximations, which provides a good description of how the procedure works. One reinforces successive approximations to the final activity. For example, suppose one wanted to train a rat to press a panel on the ceiling of its Skinner box. The first approximation might be providing a reinforcer when the rat walks to a place under the panel. Once that behavior has been established, reinforcement might then be made to depend on lifting a forepaw off the floor. The next approximation might be two paws off the floor, followed by requiring the paws to be progressively, at each step in the process, farther off the floor until the paws touch the panel.

Once operant behavior has been established it can be subjected to ► *extinction*, wherein the activity no longer results in the previously arranged consequence. Of course, the usual result of extinction is that the behavior becomes less probable over time.

Most often, operant behavior is studied under *free-operant* conditions. That is, the experiment is arranged such that after each instance of an operant, the animal is in position immediately to engage in the activity again, and the activity itself is generally of low effort and takes little time to execute. There are circumstances, however, in which the opportunity to perform the operant is limited, for example, by the use of a retractable lever. Such arrangements are usually used to study phenomena that are best examined with procedures in which independent trials can be arranged, and are called discrete-operant preparations. They are often used to study processes such as remembering and choice.

There are two characteristics of conditioned operant behavior that play a very large role in how such behavior is used in psychopharmacology. The first is that operant behavior can be brought under stimulus control, or in everyday parlance, it can be used to study discrimination among stimuli. The second is that operant behavior, once established, can be maintained with intermittent consequences. These two arrangements are often combined to produce relatively complex behavior to use when studying psychopharmacological agents.

To study discrimination using operant behavior, one needs to establish at least two different programs of reinforcing (or punishing) consequences, each associated with a distinctive circumstance. As a simple example, consider a monkey which has been trained to press a lever that results in intravenous injection of ► cocaine. To establish stimulus control one could arrange that a tone be on when pressing the lever is effective and that when the tone is off, pressing the lever results in presentation of nothing. If the monkey comes to press the lever when the tone is on and not when the tone is off, it indicates that the monkey can tell the difference between tone and no tone, that is, it can discriminate between the two stimulus circumstances. One could, by reducing the loudness of the tone, systematically determine how loud the tone needs to be for the monkey to be able to discriminate it. One could also test tones of other frequencies in order to test the degree to which the learning of the initial discrimination extends to other tones. All these, and many other processes, can be arranged so that the effects of psychoactive drugs on the behavior can be assessed.

Stimulus control can also be used to permit study of multiple activities. For example, one could in one stimulus circumstance (e.g., color of a light) study behavior that results in positive reinforcement, and when a different stimulus is present, study behavior that results in negative reinforcement. Simply by changing the stimulus, either kind of behavior can be "on call" for examination, and it can be accomplished in individual animals.

The "experiment" about discrimination summarized earlier would likely not be conducted exactly as described, but instead would probably involve intermittent reinforcement. That is, instead of reinforcing every lever press when the tone is on, only some presses would be reinforced. Two related experimental advantages accrue to the use of intermittent reinforcement. One, relatively large samples of behavior, often on the order of hundreds or even thousands of instances of an activity, can be generated in a single experimental observation period or session. Two, because of the large number of instances engendered it is possible to use frequency or rate of behavior as a measure, and that measure can vary over a very wide range of values, from near zero to hundreds per minute, yielding a potentially sensitive index.

Intermittent consequences can be arranged in myriad ways, with the various arrangements called ► *schedules of reinforcement*, which essentially are rules that describe which instances of behavior (usually called responses) will result in reinforcement. Schedules of reinforcement, interestingly, can have substantial influences on how a psychopharmacological agent acts. For example, in an influential experiment, Dews (1955) discovered that the schedule can influence whether a drug enhances or decreases a particular activity. In his study, pigeons pecked a lighted disk to earn access to food. In one condition, every 50th peck resulted in food presentation; in another, the first peck, after 15 min had elapsed, was followed by the opportunity to eat. Sodium ► pentobarbital was administered to birds under either condition. The surprising result was that a dose of the drug that greatly decreased pecking under the latter circumstance resulted in increases under the former. That is, depending on the reinforcement schedule, the drug acted as either a stimulant or depressant, for the same activity, key pecking, and for the same reason, to get food. Many other examples of interactions between reinforcement schedules and drug effects exist (e.g., Kelleher and Morse 1968). A final advantage of using intermittent reinforcement is that accumulated research indicates that under a wide variety of particular reinforcement schedules for free-operant behavior, reproducible temporal patterns and rates of behavior can be reliably established in individual animals (Ferster and Skinner 1957).

A final characteristic of operant behavior, especially as employed in the laboratory, is concerned with conditions that alter the effectiveness of consequences. Such factors are called motivational operations or ► establishing operations (Michael 1993). For example, to make food more effective as reinforcement, one often makes the animal hungry by not letting it eat for some time prior to the experimental test. Negative reinforcers, such as loud noises or irritating electric shock, are often made effective by their mere presentation, but how well they function depends also on their intensity and duration, both of which may be considered establishing operations.

Cross-References

► Abuse Liability Evaluation
► Active Avoidance
► Antinociception Test Methods
► Anxiety: Animal Models
► Behavioral Economics

- ▶ Behavioral Tolerance
- ▶ Breakpoint
- ▶ CANTAB
- ▶ Conditioned Reinforcers
- ▶ Contingency Management in Drug Dependence
- ▶ Decision Making
- ▶ Discriminative Stimulus
- ▶ Drug Discrimination
- ▶ Extinction
- ▶ Fixed Ratio
- ▶ Go/No-Go Task
- ▶ Instrumental Conditioning
- ▶ Intracranial Self-Stimulation
- ▶ Learned Helplessness
- ▶ Passive Avoidance
- ▶ Primate Models of Cognition
- ▶ Progressive Ratio
- ▶ Punishment Procedures
- ▶ Rate-Dependency Theory
- ▶ Rodent Models of Cognition
- ▶ Schedule-Induced Polydipsia
- ▶ Self-Administration of Drugs
- ▶ Short-Term and Working Memory in Animals
- ▶ Timing Behavior

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Operant Chamber

Definition

Experimental apparatus to record the behavior of animals. The quintessential operant chamber is the "Skinner Box" designed by B.F. Skinner (1904–1990) to study instrumental behavior in animals, which typically has two response levers (for a rat) or pecking keys (for a pigeon), arranged side by side on one of the walls, and a method for delivering reinforcers (such as a dispenser of food or liquid). Modern chambers, which are controlled by computer, may have alternative operandi, such as poke holes or touch screens, and a variety of optional stimuli, including visual, auditory, and olfactory.

Operant Conditioning

Definition

Operant conditioning is the use of environmental consequences of reinforcement and punishment to modify the occurrence and form of behavior. The strength and frequency of a response can be controlled by the schedule of reinforcement and the contingent presentation of reinforcing or punishing stimuli. Hedonic properties such as pain and pleasure are often attributed to such stimuli but do not enter into their definitions, which are based upon observed changes in behavior such as the acquisition of new patterns of simple or complex behavior or the suppression of existing behaviors.

Cross-References

- ▶ Instrumental Conditioning
- ▶ Operant Behavior in Animals

Operant Response

Definition

An operant response is a behavior that acts on the environment and is modifiable by its consequences. When behavior is modified by its consequences, the probability of that behavior occurring again may either increase (in the case of reinforcement) or decrease (in the case of punishment).

Opiate

Definition

This term is now mostly historical ("opioid" is now more commonly used) but strictly refers to drugs derived directly from opium. This includes morphine (the major

alkaloid in opium), codeine, and thebaine. Drugs derived by chemical modification of morphine and codeine are also sometimes referred to as opiates. These include heroin, oxymorphone, and oxycodeine.

Cross-References
► Opioids

Opioid

Definition
Any drug or endogenous substance that acts on classical opioid receptors (mu-, delta-, or kappa-receptors).

Opioid Addiction

► Opioid Dependence and Its Treatment

Opioid Analgesics

Synonyms
Narcotic analgesics; Narcotics

Definition
This is a group of natural and synthetic substances that have morphine-like pharmacological properties that are brought about through their actions on opioid receptors. Morphine is derived from the opium poppy (*Papaver somniferum*). Opiates are a group of naturally occurring compounds including ► morphine and related opium alkaloids; the name originally indicated their derivation from opium and they were also known as analgesics, because of their ability to relieve pain. The term "opioid" was later applied to synthetic substances with morphine-like effects but which were not from opium and had distinct chemical structures. The label opioid analgesic is now used to include all of these substances, regardless of whether they are of natural, synthetic, or semisynthetic origin.

Cross-References
► Mu-Opioid Agonists
► Opioids
► Tolerance

Opioid Antagonist

Definition
Opioid antagonist is a class of medication that binds to the opioid receptors in the brain, effectively blocking the effects of opiates (e.g., heroin, morphine, etc.). Examples of this class of medication include ► naloxone and ► naltrexone.

Cross-References
► Alcohol Abuse and Dependence
► Impulse Control Disorders
► Opioids

Opioid Dependence and Its Treatment

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Definition

Opioid Dependence
Opioid dependence is a medical condition characterized by an individual's preoccupation with and strong desire to take opioids coupled with persistent drug-seeking behavior. It involves a sense of compulsion to consume the psychoactive substance, an inability to stop using it or to control the mode of drug-taking behavior. Obtaining the drug takes on high priority and the condition is frequently accompanied by psychiatric comorbidity and multiple substance abuse, resulting in numerous social, psychological and biological problems. These include high risk behavior such as prostitution and drug-related crime, an increased risk of obtaining infectious diseases such as hepatitis and HIV through shared use of needles and sexual activity, leading to an increased mortality rate; accidental deaths by fatal overdose and suicides also contribute to these. According to the ► DSM-IV-TR (*Diagnostic and Statistical Manual of Mental Disorders*, 4th edn, text revision) clinical guidelines, three of the six following characteristics must be fulfilled for a definite diagnosis of dependency (American Psychiatric Association 2000).

1. The individual shows a sense of compulsion or strong desire to take the drug
2. The individual has difficulty in controlling drug-taking behavior in terms of its onset, termination, or levels of use

3. Stopping or reducing drug use results in a physiological withdrawal state with the characteristic ► withdrawal syndrome for the substance; or use of the same (or a closely related) substance with the intention of relieving or avoiding withdrawal symptoms
4. Evidence of ► tolerance, such that increased doses of the drug are required to achieve the effects originally produced by lower doses
5. Progressive neglect of alternative pleasures or interests because of drug use, increased amount of time necessary to obtain or take the drug or to recover from its effects
6. Persisting with drug use despite clear evidence of overtly harmful consequences, such as harm to the liver, depressive mood states or impairment of cognitive functioning

Role of Pharmacotherapy

Opioids: Psychopharmacology and Receptors

Definition of Opioids

Opioid (meaning "similar to opium") is a collective term for a group of heterogeneous natural and synthetic substances displaying morphine-like properties that unfold their actions on opioid receptors located in the brain, the spinal marrow and peripheral organs such as the intestinal tract.

There are different subdivisions and groups of opioids: *Exogeneous opioids* may be divided into three groups:

1. *Natural opioids* referred to as "opiates" are substances that naturally occur in the opium poppy; examples are morphine, codeine and thebaine. In terms of their chemical property they are alkaloids and can be extracted from the milk of the opium poppy (*Papaver somniferum*). ► Morphine is considered the prototype opioid.
2. *Semisynthetic opioids* such as ► hydromorphone or heroin are derived from natural opioids through a chemical process.
3. Numerous *fully synthetic opioids* have been produced pharmaceutically to exploit their analgesic effects for medical purposes, at the same time trying to minimize side effects. ► Fentanyl, ► tramadol and ► methadone are examples of these.

► *Endogenous opioids* are opioid peptides (endorphins, endomorphines and enkephalins) that are naturally present in the human body and play a role in stress reactions and pain suppression.

Opioids can be consumed intravenously, orally, sublingually, nasally and by smoking.

Opioid agonist drugs have their main indication in the treatment of pain; other less prominent indications include suppression of coughing and sleep induction, hence the name "narcotic" drug. In the treatment of severe cases of diarrhea the constipation induced by opioids can be a therapeutic measure. In addition, opioid maintenance therapy is considered the standard therapy for opioid dependence.

Opioid Receptors

At present, three different ► G-protein-coupled receptors at which opioids unfold their action are known. They are referred to as the delta (δ), kappa (κ) and mu (μ) receptors. A fourth receptor, the nociceptin/orphanin FQ (N/OFQ) receptor, has been postulated and is subject to investigation. Most opioid drugs produce their effects by acting as agonists at the μ receptor, although some also act at the κ receptor, whereas the therapeutic potential of the δ receptor is still unclear. Located in the brain, the spinal marrow and in peripheral organs such as the intestinal tract, receptors are activated by opioid agonists that initiate central and peripheral effects through the production of G-proteins. The fact that different receptors mediate different profiles of responses may be explained by their differing distributions throughout the central nervous system (Brunton et al. 2007).

Central effects can include analgesia, euphoria, sedation, muscular rigidity, anxiolytic effects, cramps, hypothermia, miosis, respiratory depression, antitussive effects, antiemetic effects, lowering of blood pressure and bradycardia. Peripheral effects can be obstipation, delayed emptying of the stomach, disturbance of the bile flow, urinary retention and the inhibition of labor.

Development of Opioid Dependence

Biological Factors

Despite their original intended purpose as therapeutic agents, their highly addictive nature fostered by initial euphoria and strong physical withdrawal make opioids a candidate for abuse. An estimated total of eight million people worldwide abuse opioids and the use continues to increase. The illicit abuse of opioids and opioid dependence are a major public health problem worldwide. In recent years, an increased rate of abuse and dependence on opioids has been noted in Eastern European countries, whereas a decrease has been reported for the West, possibly due to more frequent drug trafficking across the European Balkan route.

Opioid-induced euphoria, described by opioid dependents, is mainly attributable to the effects of the neurotransmitter ▶ dopamine, which is released from dopaminergic neurons that exert their mechanism of action in the nucleus accumbens, located in the forebrain. Even a single exposure of morphine produces an effect on dopamine neuron activities and a desensitization of opiate receptors. Repeated exposure to morphine induces substantial adaptive changes in cellular and synaptic functions in the mesocorticolimbic system. These mechanisms are likely to be part of the neurobiological basis for the development of ▶ dependence.

Another biological determinant critical to addictive potential is the speed at which a drug crosses the ▶ blood-brain barrier. Heroin, for instance, penetrates the brain more rapidly than morphine because it is more lipid-soluble, accounting for subjective reports that following intravenous administration, the euphoric experience is particularly intense.

Opioids are among the most potent drugs with regard to ▶ physical dependence and withdrawal. When administration of the drug is discontinued or an antagonist is given, a withdrawal or abstinence syndrome is manifest, characterized by diarrhea, vomiting, fever, chills, cold sweats, muscle and bone aches, muscle cramps and spasms, restless legs, agitation, gooseflesh, insomnia, nausea, watery eyes, runny nose and nightmares.

Psychosocial Factors

There is a strong overlap between ▶ comorbid mental disorders such as borderline and antisocial personality disorder, ▶ attention deficit disorder (ADHD), ▶ post traumatic stress disorder (PTSD), affective disorders and the development of opioid dependence. Predictors for the development of opioid dependence include a history of sexual or physical abuse, cohabitation with an opioid dependent partner, and an upbringing in an environment permissive to substance abuse.

With regard to gender, men dominate in the prevalence of opioid dependence, though the gender gap is narrowing and women show a younger age of initial use and a faster progression to addiction. Further gender-specific differences are that opioid-dependent men are more likely to stay employed than women, while women tend to receive more social welfare and engage in prostitution. However, men are more prone to engage in general drug-related crime and drug dealing. Though women have a faster progression to treatment, they have a lower retention rate due to gender specific barriers such as higher stigmatization, intimate partner violence, fear of losing custody of their children and a higher rate of comorbid affective disorders. Treatment settings designed for a predominantly male population cannot adequately accommodate for gender specific social factors affecting women.

Consequences of Opioid Dependence

Somatic comorbidities generally result from poor standards of living and high- risk sex behavior and needle sharing; poor dental status, high rates of infectious disease such as HIV and hepatitis, endocarditis and abscesses are the consequence. Studies have shown that women have a higher risk for HIV infection than men because of higher impulsivity and exposure to health-compromising situations including homelessness, condom nonuse and exchange of sex for money and/or drugs (Gowing et al. 2008). Furthermore, suicide, accidental death and overdose contribute to a mortality rate 13–17 times higher than the general population, with slightly higher rates for men.

Treatment of Opioid Dependence

Though opioid dependence is a chronic reoccurring illness, individually tailored comprehensive treatment can allow patients to lead normal lives. There are three main branches of treatment: withdrawal/detoxification, opiate-antagonist maintenance and opioid agonistic maintenance treatment. Currently, the most effective treatment for opioid dependence is opioid agonist maintenance therapy (Amato et al. 2008).

Withdrawal/Detoxification – Drug-free

Medically assisted detoxification is successful only when it is seen as the first step in a series of behavioral interventions and counseling. Withdrawal alone will result in the same outcome with regard to relapse as having no treatment at all. Detoxification can be handled in different ways, for instance in an outpatient setting, where gradual ▶ buprenorphine taper is an option, whereas inpatient detoxification programs proceed faster and usually involve administration of ancillary medication such as clonidine, or its further development ▶ lofexidine. There is no conclusive evidence to show that either outpatient or inpatient treatment is more effective (Day et al. 2005).

Ultrarapid detoxification is a treatment in which ▶ naltrexone is administered to patients under deep sedation or anesthesia; because of a high risk of cardiopulmonary complications, this practice is not recommended.

Opiate-Antagonist Maintenance

Naltrexone is a long-acting pure opiate receptor antagonist that is used in rehabilitation programs to ensure abstinence from opioids and should be prescribed only

to addicts who have already been detoxified, to prevent relapse. Patients should be opioid free for at least 3 days before receiving naltrexone, as it can lead to unintentional rapid detoxification in heroin addicts, precipitating massive withdrawal symptoms.

Opioid Maintenance Therapy

Agonist maintenance therapy is considered first line treatment in opioid dependency and leads to statistically significant reductions in illicit opioid use, risk behavior related to drug use such as injecting and sharing injecting equipment, and an improvement in social and psychological quality of life (Amato et al. 2008; Gowing et al. 2008). The most widely used replacement, ▶ methadone, shows a statistically superior effect in reducing heroin use and retaining patients in treatment, compared to medication-free programs (Mattick et al. 2002).

Proper medication-assisted treatment of opioid dependence should ensure that patients do not experience any withdrawal symptoms, or feel drugged or high during a time period of 24 h; the medication used should be present in the blood in levels sufficient to maintain normalcy over a 24 h period.

With regard to dosage regimen, drug-to-drug interactions must be taken into consideration. Opioid drug-to-drug interactions can, for example, occur with CNS depressant drugs such as ▶ benzodiazepines or ▶ alcohol and are additionally frequently evoked by a combination with substances that inhibit or induce the activity of the cytochrome P450 enzyme system. Metabolism, poor absorption, changes in urinary pH, concomitant medications or drug abuse, diet, physical condition, pregnancy and vitamins may influence medication levels and the rate of elimination (Payte et al. 2003).

Special target populations may require additional planning in therapeutic dosing regimens. In the case of opioid-dependent pregnant women, changes in metabolism due to enzyme induction usually require a gradual dose increase or split-dosing around the third trimester. The benefits of methadone maintenance during pregnancy compared to detoxification have been well established. Detoxification is usually associated with relapse and marked fluctuations of serum methadone levels, both of which are unfavorable to fetal outcome.

Psychosocial Treatments in Addition to Pharmacological Therapy

In the treatment of opioid dependence, ideally, behavioral interventions and a comprehensive all-round approach with a multidisciplinary team including social workers, should accompany psychopharmacological treatment. Psychosocial interventions can include different psychotherapeutic methods such as cognitive behavioral therapy (CBT), interpersonal therapy, subliminal stimulation, supportive-expressive therapy and contingency management approaches such as voucher incentives. However, a review of the literature shows that adding psychosocial interventions such as counseling, social work and psychotherapy to maintenance therapy on a random basis has limited beneficial effect on retention rate, opiate use or psychiatric symptoms. The only overall benefit of psychosocial support pertains to an improvement of the number of participants still abstinent at follow-up (Amato et al. 2008).

An important aspect when evaluating the effectiveness of treatment, however, is that a chronic relapsing disease like opioid dependence should have outcome criteria that take its nature into account. For instance, effect measurement should be done during treatment and not after discharge, especially when acute relapse episodes remain untreated.

Substances Available for Maintenance Treatment

Examples of medications commonly used for maintenance treatment are methadone, buprenorphine, ▶ buprenorphine–naloxone and the comparatively less frequently used ▶ l-alpha-acetyl-methadol (▶ LAAM) and ▶ slow-release morphines (▶ SROMs).

Methadone

Methadone is a full μ receptor agonist and is the oldest, most common, and widely used substance for substitution treatment. It is a racemate available in tablet form, as an injection, or as oral solution.

Methadone has been used internationally since 1965 and is the best studied substance available for opioid maintenance in terms of clinical effectiveness (Clark et al. 2002). It has been comprehensively shown that methadone is an effective treatment in reducing illicit opioid consumption, reducing high risk behavior such as needle sharing and increasing rates of treatment retention (Mattick et al. 2002). It has been demonstrated that higher dosages of methadone maintenance medication lead to improved outcome in terms of treatment retention and decreases in illicit opioid use.

For methadone maintenance treatment (MMT) the medication is administered orally; concentrations in serum reach a peak level 3–5 h after administration; it has a ▶ half-life of 24–36 h (Brunton et al. 2007). Side effects can be increased sweating, mood swings, depression, lack of energy, weight gain, edema, loss of libido and prolonged QTc time in the ECG.

Combined use with other substances that can influence the QTc time in the ECG such as ► antipsychotics, antiarrhythmics, antibiotics, ► tricyclic antidepressants and antifungal medication should be avoided whenever possible. Cardiac safety recommendations include obtainment of cardiac histories, a pretreatment ECG and follow-up ECGs within 30 days and annually. Other interactions involve diuretics, antibiotics, antihypertensives, HIV medicines and other antiviral medicines, other narcotic medications and drugs against epilepsy; interactions may lead to increase in serum concentration and overdose.

Buprenorphine

Buprenorphine is a partial μ-opioid-receptor agonist and a κ-receptor antagonist that was first marketed in the 1980s as an analgesic. For opioid maintenance therapy, comprehensive treatment experience has been available in Europe and Australia since the mid-1990s and in the United States, the American Food and Drug Administration approved buprenorphine and a buprenorphine/naloxone combination product, in 2002. Because of its partial antagonism, buprenorphine counteracts the effects of concomitant opioids taken by the patient and, unlike other opioids, does not produce tolerance. It has less severe withdrawal effects than methadone, making discontinuation easier (Gowing et al. 2006).

In a systematic review, buprenorphine was found to be inferior to methadone in terms of suppressing heroin consumption and retention rates in treatment when both were administered at adequate dosages (Mattick et al. 2008). However, buprenorphine is safer than methadone, especially for patients with coexistent benzodiazepine dependence, as side effects such as respiratory depression develop only to an uncritical degree even after extreme overdosing and it has lower dependence-liability. The treatment of buprenorphine overdose with naloxone needs special medical observation because of the tight receptor binding of buprenorphine.

Buprenorphine is administered as a sublingual tablet. Resorption takes place through the oral mucosa. Peak serum levels are reached after 1–3 h, after which it remains effective in the body for up to 48 h. Because of this long duration of action, dosing intervals of two days are optional. Side effects can include nausea, vomiting, drowsiness, dizziness, headache, itch, dry mouth, meiosis, orthostatical hypotension, difficulty with ejaculation, decreased libido, urinary retention, and constipation.

When patients are induced on buprenorphine, caution should be taken because, due to its ► partial agonist/antagonist activity, it may precipitate significant withdrawal symptoms if the first dose is administered too soon after the intake of other opioids.

Buprenorphine–Naloxone Combination Tablet

The buprenorphine–naloxone combination tablet is a further development of buprenorphine invented with the intention of reducing intravenous misuse of the medication. Naloxone has low oral bioavailability and so does not influence the mechanisms of buprenorphine action when taken orally. However, when buprenorphine/naloxone combinations are dissolved and injected intravenously, opioid agonist actions are blocked by naloxone and can, depending on which drugs have been misused previously, precipitate unpleasant and dysphoric symptoms of opioid withdrawal. Buprenorphine–naloxone combination tablets contain buprenorphine with naloxone at a ratio of 4:1. The buprenorphine–naloxone combination tablet should not be administered to pregnant and nursing women, as naloxone exposure may alter fetal and maternal hormonal levels.

LAAM (L-alpha-acetyl-methadol)

LAAM is a derivative of and has a similar mode of action as methadone. It was first approved in the USA in 1993 and in several European countries in 1997. The most significant difference between the two substances is that LAAM has a longer duration of drug effect, lasting up to 72 h; therefore it can be administered every 2–3 days. The plasma half-life is only 14–37 h, but the substance is metabolized into two active metabolites, nor-LAAM and dinor-LAAM, which have a half-life of 24–38 h and 66–89 h respectively. All three substances exert their mechanisms of action on the μ-receptor; however, nor-LAAM is five times as potent as the others. It may be more effective at reducing heroin dependence than methadone, but it is associated with adverse effects such as cardiac arrhythmias and QTc prolongation, some of which may be life-threatening. Following ten cases of death caused by LAAM, it was withdrawn from the market in Europe on the recommendation of the European Agency for the Evaluation of Medicinal Products (EMEA). In the USA, the US FDA has recommended that LAAM should not be used as first line therapy.

Slow Release Oral Morphine – SROM

Morphine on its own is not recommendable for maintenance therapy as it has low oral bioavailability, a half-life of only 2–3 h, and a very short time of drug effect. SROMs are a group of pure opiate-agonists that are products of morphine (i.e., morphine sulfate and morphine hydrochloride) with retarded release characteristics. SROMs are

available as tablets (i.e., morphine hydrochloride) or capsules containing micro-granular compounds (i.e., morphine sulfate) and may be more tolerable than methadone in terms of side effects or as an option for patients with an inadequate suppression of withdrawal symptoms under methadone. SROMs hold the advantage of having a longer half-life and time of drug effect lasts up to 24 h. They can therefore normally be administered once daily, except to "fast metabolizers" who need at least twice daily administration. They hold the disadvantage that urine toxicology will not detect a concomitant consumption of heroin because morphine is a metabolite of heroin.

Intravenous misuse of SROMs can lead to an increased risk of pulmonary embolism, attributable to the wax particles that are briefly liquefied in the cooking process and then solidify again in the body. Patients maintained on SROM must be warned about misusing the substance and examined for signs of needle puncture. The use of SROMs for opioid maintenance treatment is registered only in some European countries but international interest is rising.

Conclusion

Internationally, opioid maintenance therapy has been proved doubtlessly and conclusively as the most effective treatment for opioid dependency. It reduces illicit opioid use, lowers mortality rate and criminal behavior, and leads to improved health and social conditions of chronic opioid-dependent individuals by increasing rates of retention in treatment. The nature of opioid dependence as a psychiatric disorder needs to be considered carefully and psychosocial interventions may accompany medical treatment if indicated.

After declining for several years, new demands for the treatment of opioid dependence are on the rise in Europe and, from a public health stand point, the availability of treatment needs to be improved further. Treatment coverage worldwide could change for the better in the light of the recent approval of office-based treatment in the USA, where, in contrast to Europe and Australia, both continents with a long-lasting tradition in office-based opioid maintenance treatment, only specialized addiction clinics could provide treatment until recently.

Cross-References

- ▶ Buprenorphine
- ▶ Buprenorphine–Naloxone
- ▶ Detoxification
- ▶ L-alpha-acetyl-methadol
- ▶ Methadone
- ▶ Morphine
- ▶ Naltrexone
- ▶ Opiate
- ▶ Opioids
- ▶ Slow-Release-Morphine

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Opioid Maintenance Treatment

Definition

Opioid maintenance treatment is an evidence-based treatment where patients with opioid dependence are provided with opioid agonistic replacement medication. Proper medication-assisted treatment of opioid dependence should effect that patients do not experience any withdrawal symptoms, or feel drugged or high during a time period of 24 h.

Opioids

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Synonyms

Opiates

Definition

The term opiate refers to drugs extracted from opium, i.e., morphine and codeine, whereas an ▶ opioid is any drug or endogenous agent that acts as an ▶ agonist or ▶ antagonist on one of the three major (classical) opioid receptors.

Pharmacological Properties

Opium that contains the principal ▶ opiate, morphine, has been used for its powerful pain relieving (analgesics), somnorific, and euphoric properties since antiquity (Brownstein 1993). Since the discovery of opioid receptors in 1972 and the first ▶ endogenous opioid peptides in 1975 much has been learned about the anatomy and function of opioid actions. However, much remains to be discovered about the function of endogenous opioids and opioid drugs in specific populations of neurons and neural systems. In addition to therapeutically valuable actions on the sensory and affective components of pain, opioids also produce profound effects on neural systems involved in respiration, reward and learning, and many other behavioral and physiological processes. Current knowledge of these systems is summarized in the following sections.

Endogenous Opioid Peptides

The general distribution of opioid peptides was reported soon after the discovery of ▶ enkephalins in 1975 (Khatchaturian et al. 1983). Genes encoding four endogenous opioids and opioid-related peptide precursors have since been identified in the mammalian genome, and the products of all but one act as agonists on the classical opioid receptors: ▶ mu (μ- or MOR, aka OP_3, MOP), delta (δ- or DOR, aka OP_1, DOP), and ▶ kappa (κ- or KOR, aka OP_2, KOP) ▶ receptors. As with other peptide hormones and neurotransmitters, the final active peptides are cleaved at dibasic amino acid sites from large polypeptide precursors by processing enzymes. The precursors such as pro-opiomelanocortin (POMC), preproenkephalin, and prodynorphin express the sequences for β-▶ endorphin, enkephalins, and ▶ dynorphins, respectively. POMC contains a single copy of β-endorphin (which can be lyzed to shorter, potentially active endorphin fragments) along with other biologically important hormones/neurotransmitters including the major ▶ stress hormone, adrenocorticotrophic hormone (ACTH). Preproenkephalin encodes multiple copies of two enkephalin pentapeptides, leucine-enkephalin and methionine enkephalin (longer active peptides can be found in some tissues). Prodynorphin contains the sequences of α-neoendorphin, dynorphin-A and dynorphin-B, as well as "big dynorphin," which is the uncleaved sequence of dynorphin-A and dynorphin-B (the dynorphin A and B peptides are separated by one pair of basic amino acids in prodynorphin).

All the endogenous opioid peptide families described above contain a canonical N-terminal amino acid sequence, N-Tyr-gly-gly-phe, followed by one to 26 other amino acids. The extended amino sequences, which vary in length in different cells, confer differential selectivity among the three major opioid receptors as well as potentially modifying susceptibility to degradation by peptidase enzymes such as "▶ enkephalinase" (EC 3.4.24.11). It should be noted that deletion (des-tyr) or chemical modification of the N-terminal tyr (N-acetylation occurs for a substantial proportion of the β-endorphin from the pituitary) renders all opioid peptides inactive at opioid receptors. These peptides subserve endocrine (e.g., β-endorphin from the pituitary; pro-enkephalin from the adrenal medulla) and paracrine (opioid peptides are expressed in the immune system;) functions in addition to their well known effects on the nervous system.

The most recently discovered opioid-related peptide family, orphanin-FQ or nociceptin (usually denoted N/OFQ), is distantly related to prodynorphin but contains an N-terminal Phe rather than Tyr. It is the endogenous ligand of the orphan opioid receptor Opioid-receptor-like-1 (ORL1, aka NOP, NOR). It has high affinity and selectivity for ORL1 but interacts very weakly with the KOR (see below). The N/OFQ-ORL1 system is not widely considered to represent an "opioid-system" because classical opioid drugs and endogenous opioids do not interact significantly with ORL1. It is therefore not considered in detail here.

Two additional endogenous opioids (endomorphin 1 and endomorphin 2) have been purified from mammalian tissue. Although these tetrapeptides are very selective for MOR and can be visualized in neurons immunohistochemically (which is not proof of presence), no genomic sequences encoding endomorphin 1 and

endomorphin 2 have been identified; so their physiological relevance will remain uncertain until a biological synthetic mechanism is identified.

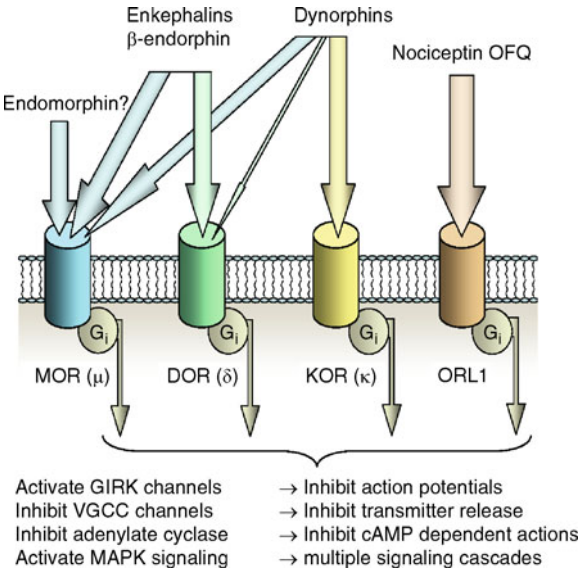
Opioid Receptors

MOR, DOR, and KOR opioid receptor types were first identified using pharmacological approaches. σ (sigma)-Opioid receptors also were proposed, but structural and pharmacological studies indicate that ► σ-receptors are not part of the opioid family. Three independent genes encoding MOR, DOR, and KOR have been identified, firmly establishing that these are the three principal opioid receptors. Soon after the isolation of these genes a fourth opioid-receptor like (ORL1) sequence was identified by homology screening of cDNA libraries for sequences resembling the other receptors. The biochemistry and regulation of opioid receptors are extensively reviewed elsewhere (e.g., Waldhoer et al. 2004). Briefly, the amino acid sequences of all opioid receptors (and ORL1) are about 60% identical with each other. They belong to a small subfamily of G-protein coupled receptors (► GPCR) that includes the ► somatostatin receptors. Multiple RNA ► splice variants have been identified, in particular MOR1A, B, and C (the biological relevance of other putative splice variants is uncertain). The B and C variants differ in the amino acid composition at the C-terminus and affect receptor regulatory events such as receptor distribution, ► internalization, and recycling rates but have little or no influence on drug selectivity. Opioid receptor subtypes, such as μ_1 and μ_2 receptors, also have been proposed, but they remain tentative. Splice variants of DOR or KOR may explain differential pharmacology of proposed receptor subtypes (e.g., putative δ1 and δ2 receptors), but these have not yet been established. Formation of ► hetero-oligomers between different opioid receptor types could also explain experimental results claiming existence of opioid receptor subtypes. As for other GPCRs, oligomer formation of opioid receptors appears to be obligatory for membrane expression and function (Milligan and Bouvier 2005). While homo-oligomers are probably the most commonly formed and appear to explain most opioid pharmacology in vivo, there is growing biochemical and pharmacological evidence that different subtypes of opioid receptors can form hetero-oligomers in isolated experimental systems and perhaps in vivo.

Interaction of Opioids with Opioid Receptors

Some authors have attempted to ascribe three distinct signaling systems to the three different opioid peptide families matching them respectively with the three receptor types. This is incorrect because each opioid peptide family can interact with more than one receptor type, as summarized in Fig. 1. Among the three peptide groups and receptors, the dynorphin-KOR pair is the best candidate to be defined as a distinct signaling system because dynorphin is the only endogenous opioid that interacts significantly with KOR. However, dynorphins are also potent MOR agonists and can potentially be metabolized to shorter and less selective dynorphin fragments (including leucine-enkephalin), which interact potently with both MOR and DOR. It should also be noted that early studies suggesting that enkephalins are the endogenous ligands for DOR were premature because they were subsequently shown to be nearly equi-effective agonists at both MOR and DOR.

A large number of small, organic molecule agonists for opioid receptors have been developed since the first isolation of morphine from opium in 1806 and synthesis of heroin in 1898 (Brownstein 1993). Nearly all of the small molecule agonists in clinical use are selective for MOR although experimental opioid agonists selective for DOR and KOR have been developed. A more limited



Opioids. Fig. 1. Selectivity profiles of the major endogenous opioids for the different opioid receptors are shown with thickness of the arrows indicating relative selectivities or potencies for MOR (blue), DOR (green), KOR (yellow) and ORL1 (orange). All endogenous opioids except nociceptin/OFQ (which is not generally considered an opioid) can act as agonists at more than one opioid receptor type. All opioid receptors couple to Gi proteins to modulate the major signaling mechanisms shown.

range of small molecule antagonists exists, although some of these commercially available antagonists display high receptor type selectivity. Most commercially available small molecule opioids have the advantage that they readily penetrate the central nervous system following systemic injection. However, some have been specifically developed to avoid crossing the ▶ blood-brain barrier (e.g., methylnaloxone). The optimal selection of an opioid for a given experimental purpose depends on a number of considerations, so recommendation of particular drugs for an opioid receptor type is beyond the current scope. The major pharmacological societies provide and regularly update comprehensive guides to the most appropriate selective agonists and antagonists for each receptor. These include The International Union of Basic and Clinical Pharmacology (IUPHAR) (http://www.iuphar-db.org/index.jsp) and the British Pharmacological Society (http://www3.interscience.wiley.com/journal/122206250/issue).

Opioid Receptor Signaling and Regulation

As shown in Fig. 1, all opioid receptors when activated by an agonist transduce intracellular signals via activation of inhibitory G-proteins. The major consequence of opioid receptor activation in neurons is inhibition in both cell bodies and nerve terminals. Downstream signaling includes modulation of many biochemical and gene regulatory cascades – a full description of which is beyond the current scope (see however, Williams et al. 2001; Waldhoer et al. 2004). Briefly, while subtle variations occur among the specific G-proteins activated by different receptor types (and perhaps hetero-oligomers), all opioid receptors activate Gi-proteins, which leads to the release of GTP bound active Giα subunits and Gβγ subunits from the receptor. The major immediate consequence (within ~50 ms of receptor activation) is inhibition of neuronal excitability via Gβγ subunit inhibition of ▶ voltage-gated calcium channels (VGCCs; particularly $Ca_V2.2$–2.3) and activation of ▶ G-protein coupled inwardly rectifying potassium channels (GIRKs) in the local membrane. Inhibition of VGCCs in nerve terminals can contribute to inhibition of neurotransmitter ▶ release probability upon invasion of action potentials. Other ionic channels and biochemical effects (e.g., inhibition of ▶ cAMP formation) also contribute to presynaptic inhibition. Free Gβγ subunits may also activate (more slowly) components of protein kinase cascades. Giα-subunits inhibit most isoforms of adenylate cyclase that are expressed in many types of neurons. Other cascades are modulated by the opioid receptor trafficking and internalization that occurs after activation in an agonist dependent manner (Waldhoer et al. 2004). It should also be noted that many of these mechanisms can contribute to the cellular and ▶ synaptic plasticity of signaling that are associated with ▶ tolerance, ▶ physical dependence, and ▶ addiction following chronic opioid treatment (Williams et al. 2001).

The complexity produced by multiple opioid receptor types and signaling mechanisms requires that opioid actions and adaptations in different neural systems be determined on a case by case basis. While the direct effects of opioids on cell bodies and synapses are almost invariably inhibitory, activation of neural systems can be the net outcome when the dominant opioid effect is localized to inhibitory interneurons and synapses. For example, MOR activation in the ▶ ventral tegmental area enhances ▶ dopamine release because MOR are located on inhibitory interneurons that synapse on dopaminergic neurons. This type of disinhibition is common to opioids. Thus, localization of opioid receptors to a particular structure provides little information about function without an understanding of the local cellular circuitry.

Opioid Receptor Distribution

Opioid receptors are found throughout the central and peripheral nervous systems. Some of the peripheral tissue locations such as the guinea pig ileum and mouse vas deferens are well known because of their use for many decades as assays for opioid receptor activity. Opioid receptor expression in the gut largely accounts for constipation, a major side effect of MOR agonists. Opioid receptors are also found on primary afferent nociceptors and immune cells (Stein et al. 2003).

MOR, DOR, and KOR can be found from the cerebral cortex to the spinal cord. The distribution of opioid receptors revealed by in situ hybridization, ligand binding, and immunohistochemsitry (Mansour et al. 1995) is so extensive that describing the many brain structures with receptors is more tedious than useful. This point is highlighted by a list of the structures in which opioid receptors have been reported (Table 1). High levels of MOR and KOR are found from the cerebral cortex to the dorsal horn of the spinal cord. DOR distribution also is extensive, but more limited than MOR and KOR. However, recent studies showing that DOR are mobilized by environmental stimuli (Cahill et al. 2007) indicate that DOR have a much broader distribution than previously thought. For example, chronic administration of morphine or prolonged stress stimulates the movement of DOR in the periaqueductal gray (PAG) from intracellular stores to the plasma membrane. Although previous studies did not report DOR in the PAG, functional membrane receptors can be found under these conditions. Thus, the

Opioids. Table 1. Location and density of opioid receptors in the rat CNS.

Structure	MOR	DOR	KOR
Amygdala	High	High	High
Anterior olfactory nucleus	High	Medium	Low
Arcuate nucleus	–	–	Medium
Bed nucleus stria terminalis	Medium	Medium	High
Caudate-Putamen	High	High	High
Cortex	High	High	Medium
Dorsal tegmental nucleus	Medium	–	Low
Globus pallidus	Low	Low	Low
Hippocampus	High	–	–
Hypothalamus	Low	Low	High
Inferior colliculus	High	Low	Medium
Interpeduncular nucleus	High	High	High
Islands of Calleja	Low	High	High
Locus coeruleus	High	–	Medium
Lateral reticular nucleus	Low	–	Low
Septum	High	Medium	Medium
Mammillary nucleus	High	–	Medium
Nucleus accumbens	High	High	High
Nucleus diagonal band	Medium	Medium	High
Nucleus reticularis gigantocellularis	Low	–	Low
Nucleus tractus solitarius	High	Low	High
Olfactory bulb	High	High	Medium
Olfactory tubercle	Low	High	High
Parabrachial nucleus	High	–	Medium
Paraventricular hypothalamus	–	–	High
Periaqueductal gray	Medium	–	Medium
Pituitary gland	–	–	High
Pons	–	Medium	–
Preoptic area	Low	Low	High
Presubiculum	High	High	Low
Raphe dorsalis	Medium	–	Medium
Raphe magnus	Medium	–	Low
Raphe medius	Medium		Low
Sensory nucleus trigeminal	Low	–	–
Spinal trigeminal nucleus	High	–	Medium
Spinal dorsal horn	High	Low	Medium
Spinal ventral horn	Low	–	Low
Substantia nigra	High	Low	Low
Supraoptic nucleus	–	–	Medium
Superior colliculus	High	Low	Medium
Thalamus	High	Medium	High
Zona incerta	–	–	Medium

Opioids. Table 2. Synthetic pathways for POMC.

Cell body location	Terminal locations
Pituitary gland	Pituitary gland
Arcuate nucleus	Periventricular gray
	Hypothalamic nuclei
	Medial preoptic area
	Medial septum
	Bed nucleus of stria terminalis
	Amygdala
	Periaqueductal gray
	Raphe nuclei
	Parabrachial nuclei
	Nucleus reticularis gigantocellularis
	Nucleus tractus solitarius
	Dorsal motor nucleus of the vagus nerve
Nucleus tractus solitarius	Medullary regions
	Parabrachial nuclei
	Spinal cord

intensity and distribution of DOR labeling is more extensive than that is revealed in Table 1.

Endogenous Opioid Distribution

One would expect the distribution of ▶ endogenous opioids to match closely the distribution of opioid receptors. There is much overlap, but a clear one-to-one relationship between opioid terminals and receptors is not always evident. Of course, endogenously released opioids may also act by ▶ volume transmission and therefore have a greater spatial range of influence than a single point to point synapse (see Williams et al. 2001). Opioids derived from POMC are synthesized in just a few sites, but the terminal fields of these neurons are widely dispersed (Table 2). By contrast, neurons that produce opioids from proenkephalin and prodynorphin tend to be local interneurons (Khachaturian et al. 1993). These neurons are found throughout the central nervous system (Table 3).

Opioids. Table 3. Location of neurons containing proenkephalin and prodynorphin.

Structure	Proenkephalin	Prodynorphin
Amygdala	Interneurons	Interneurons
Bed nucleus of stria terminalis	Interneurons	
Cerebral cortex	Interneurons	Interneurons
Dorsal tegmental nuclei	Interneurons	
Globus pallidus	Interneurons	Terminals
Hippocampus	Interneurons	Interneurons
Hypothalamus	Interneurons	Interneurons
Inferior colliculus	Interneurons	
Interpeduncular nucleus	Interneurons	
Lateral geniculate nucleus	Interneurons	
Lateral reticular nucleus	Interneurons	Interneurons
N. reticularis gigantocellularis	Interneurons	
Nucleus tractus solitarius	Interneurons	Interneurons
Parabrachial nuclei	Interneurons	Interneurons
Periaqueductal gray	Interneurons	Interneurons
Paraventricular nucleus		Interneurons
Periventricular thalamus	Interneurons	
Preoptic area	Interneurons	
Raphe nuclei	Interneurons	Terminals
Septum	Interneurons	
Spinal dorsal horn	Interneurons	Interneurons
Striatum	Interneurons	Interneurons
Substantia nigra	Interneurons	Terminals
Superior colliculus	Interneurons	
Supraoptic nucleus		Interneurons
Trigeminal nucleus	Interneurons	Interneurons
Vestibular nuclei	Interneurons	

Behavioral Effects of Opioids

Given the wide distribution of opioid peptides and receptors, it is not surprising that opioids influence many behaviors. These include the inhibition of pain (analgesia), reward and addiction, mood, eating and drinking, sexual activity, sedation, thermoregulation, cardiovascular function, respiration, gastrointestinal transit, and nausea (Bodnar 2008). Most of what is known about these behavioral effects is derived from studies in which opioid drugs are administered. Administration of opioid receptor antagonists have almost no effect on ongoing behavior indicating that tonic release of endogenous opioids has a negligible impact on behavior in most circumstances but more subtle effects have been determined from gene knockout studies (Kieffer and Gaveriaux-Ruff 2002). For example, administration of the opioid receptor antagonist naloxone does not enhance pain sensations except when used to reverse environmentally induced antinociception or to precipitate ► withdrawal from chronic opioid administration. A full description of the range of behaviors linked to opioids would require an entire book (Bodnar 2008). This section provides a brief description of a few key opioid receptor-mediated effects and identifies the brain structures contributing to these effects. Given that the primary medical use of opiates is the inhibition of pain, the role of opioids in pain inhibition will be highlighted. Opiates also are widely abused so the role of opioids in reward and addiction will be described briefly.

Analgesia

Administration of agonists for all three of the primary opioid receptors (MOR, DOR, and KOR) has been shown to produce analgesia, and this has been confirmed by extensive gene knockout studies (Kieffer and Gaveriaux-Ruff 2002). However, the best and most commonly used opiates for the treatment of pain act almost exclusively via the MOR receptor. Morphine, heroin, and other derivatives such as meperidine (Demerol), ► fentanyl, and ► codeine are common MOR receptor agonists with potent analgesic effects.

MOR agonists (and to some extent DOR and KOR agonists) produce analgesia via both inhibiting ascending pain transmission and activating descending pain modulatory pathways. MOR agonists produce profound analgesia when applied directly to the spinal cord (used clinically in humans) because MOR is expressed on both the nerve terminals of nociceptive afferent nerves and primary transmission neurons in the dorsal horn of the spinal cord. The principal descending pathway through which MOR agonists produce analgesia runs from the PAG to rostral ventromedial medulla (RVM) to dorsal horn of the spinal cord (Fields 2004). Direct application of a small concentration of morphine into any one of these sites in the rat inhibits nociception throughout the body. Opioids in these regions inhibit tonically active ► GABAergic neurons by activation of GIRK channels and direct inhibition of GABAergic synapses (Williams et al. 2001). The natural function of this system is to produce analgesia in response to ► fear or stress. Fear appears to activate the nociceptive modulatory system in the PAG via a projection from the ► amygdala. Although the source of PAG opioids for fear-induced antinociception is not known, both intrinsic enkephalin containing neurons

and β-endorphin terminals arising from the arcuate nucleus could contribute. With chronic treatment, repeated morphine inhibition of GABAergic neurons in the ventrolateral PAG, but not the RVM produces tolerance to the analgesic effects. Although tolerance is associated with a number of changes in MOR signaling, the specific mechanisms underlying tolerance to opioids are only partially known. In humans and other animals, the analgesic effects of morphine tend to be greater in males compared to females. Variations in the number of MOR, particularly in the PAG and the magnitude of morphine analgesia across the estrus cycle, suggest that estradiol influences the function of MOR.

Direct administration of morphine to many other brain regions also has been shown to inhibit pain in laboratory animals. For example, activation of MOR in the ► amygdala, nucleus submedius, or nucleus cunieformis produce ► antinocieption by activating the PAG. In addition to these central effects, MOR, DOR, and KOR receptor agonists attenuate pain by inhibition of primary afferents at the site of injury (Stein et al. 2003).

Reward and Addiction

Opioids, like other ► drugs of abuse (e.g., cocaine, amphetamine, ethanol) increase the release of dopamine in the ► nucleus accumbens (Le Moal and Koob 2007) and have been subject to animal models of addiction (► addictive disorders: animal models). The most commonly abused opiates, morphine and heroin, increase dopamine release in the nucleus accumbens by disinhibiting dopaminergic neurons in the ► ventral tegmental area. MOR and DOR agonists are thought to inhibit tonically active GABAergic neurons in the ventral tegmental area which activates dopamine neurons projecting to the nucleus accumbens. Direct opioid inhibition of ► nucleus accumbens neurons also contributes to the rewarding effects of opioids. Other brain structures that contribute to the reinforcing effects of opioids include the amygdala and bed nucleus of the stria terminalis.

Although the reinforcing effects of opioids are probably linked to many behaviors that are necessary for survival (e.g., food, sex, social interactions), this system also leads to opioid abuse and addiction. Addiction typically starts as a result of the euphoric effects of opioids, but is maintained by dysregulation of endogenous opioid signaling (Le Moal and Koob 2007). Removal of opioid administration results in intense ► craving and withdrawal, which leads to further abuse. The rewarding effects of opioids are specific to MOR and DOR. KOR agonists inhibit dopamine release in the nucleus accumbens and produce aversion.

Cross-References

► Addictive Disorders: Animal Models
► Analgesics
► Blood-Brain Barrier
► Opioid Dependence and Its Treatment
► Somatostatin
► Synaptic Plasticity

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Opportunity Cost

Definition

Time allocated to the pursuit of reward at the expense of forgoing alternate activities, such as exploration, grooming, and resting.

Cross-References

► Intracranial Self-Stimulation

Opposite Effect

► Effect Inversion

Optical Isomers

► Stereoisomers

Optogenetics

Definition

A set of methods that use engineered light-activated channels to selectively manipulate neuronal activity in genetically defined neuronal subsets with millisecond temporal precision.

Oral Self-Administration

► Drug Taste Preference Conditioning

Orexigenic

Definition

Systems or endogenous factors that provoke and/or sustain eating events.

Cross-References

► Appetite Stimulants

Orexigens

► Appetite Stimulants

Orexins

► Hypocretins

Organic Brain Syndromes

Definition

Organic brain syndrome is a broad term that refers to diseases (usually not psychiatric disorders) that cause mental dysfunctions. Examples of diseases causing organic brain syndrome are: brain trauma, stroke, infections of the central nervous system, dementia, tumor, kidney, liver, or endocrine diseases, and vitamin deficiency.

Organizational Effects of Hormones

Definition

Relatively permanent effects of hormones on structure and function of the body. Often there is a critical period of development during which these organizational effects can take place. The most important critical periods are during fetal development and puberty.

Cross-References

► Sex Differences in Drug Effects

Orphenadrine

Synonyms

N,N dimethyl-2[α-(o-tolyl)benzyloxy]ethylamine HCl or citrate

Definition

The main indications of orphenadrine are painful musculoskeletal conditions and cramps. It is an anticholinergic, and possibly also an analgesic. It may be used in Parkinson's disease to treat drug-induced extrapyramidal symptoms.

Cross-References

► Antimuscarinic Anticholinergic
► Anti-Parkinson Drugs

Orthosteric Site

Definition

A site of a receptor in which the endogenous ligand binds to produce its effects.

Osmotic Minipump

Definition

Device made to slowly deliver pharmacological compounds (e.g., subcutaneously, lower back, over 2–4 weeks) and to

avoid repetitive injection schedules. It is a miniature infusion pump for the continuous dosing of laboratory animals as small as mice and young rats. This minipump provides researchers with a convenient and reliable method for controlled agent delivery *in vivo*.

Othello Syndrome

► Delusional Disorder

Ovary or Testis

► Gonads

Overconsumption

► Hyperphagia

Overshadowing

Synonyms

Cue competition

Definition

The reduction in associative learning that is produced by the presentation of a more salient competing conditioned stimulus. This is an effect seen in classical (Pavlovian) conditioning and a constraint on the general importance of temporal coincidence as the sole determinant of new learning.

Cross-References

► Classical (Pavlovian) Conditioning

Oxazepam

Definition

Oxazepam is an active metabolite of diazepam formed, during the breakdown of ► diazepam and similar drugs. As a member of the benzodiazepine class of drugs, it has typical actions and side effects for that class. Like ► lorazepam, it is metabolized by glucuronidation and has an intermediate time course of action. In addition to its anxiolytic effects, it is sometimes used in the treatment of alcohol withdrawal.

Cross-References

► Abuse Liability Evaluation
► Alcohol Abuse and Dependence
► Benzodiazepines
► Declarative and Non-Declarative Memory
► Driving Under Influence of Drugs
► Insomnia
► Sedative, Hypnotic, and Anxiolytic Dependence
► Social Anxiety Disorder
► Withdrawal Syndromes

Oxazolam

Definition

Oxazolam is a prodrug (precursor) for the benzodiazepine desmethyl-diazepam (nordazepam) and is itself a metabolic product of other benzodiazepines. It has anxiolytic, sedative, and anticonvulsant properties.

Cross-References

► Anxiolytics
► Benzodiazepines

Oxcarbazepine

Definition

Oxcarbazepine is used primarily as an antiepileptic drug to control seizures in patients. However, it has gained utility in various mood disorders including anxiety, depression, bipolar disorder, as well as in the management of neuropathic pain and migraine. Oxcarbazepine is structurally similar to an older antiepileptic ► carbamazepine, and like carbamazepine works by reducing excessive or inappropriate excitability of nerve cells that normally occurs in conditions such as epilepsy and neuropathic pain.

Cross-References

► Anticonvulsants
► Bipolar Disorder
► Mood Stabilizers

2-Oxopyrrolidin-1-Acetamide

► Piracetam

Oxprenolol

Synonyms

RS)-1-[2-(allyloxy)phenoxy]-3-(isopropylamino)propan-2-ol

Definition

Oxprenolol is a nonselective ► β-adrenoceptor antagonist but with some intrinsic sympathomimetic activity. It is lipophilic so, unlike many of its class, it penetrates readily to the brain and exerts central effects. It is mainly used for the treatment of angina pectoris, abnormal heart rhythms and high blood pressure, and occasionally in the treatment of somatic anxiety. Typical side effects include headaches.

Cross-References

► Anxiolytics

Oxybate

Synonyms

Gamma-hydroxybutyrate; GHB; Sodium 4-hydroxybutyrate

Definition

Although it is a central nervous system depressant, oxybate is thought to be useful in the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy, and may also be used to for pain and fibromyalgia. It is often illegally sold and abused, especially by young adults in social settings such as nightclubs.

Cross-References

► Abuse Liability Evaluation
► Hypersomnias

Oxycodone

Definition

Oxycodone belongs to the opiate (narcotic) analgesic medication class. It is used to relieve moderate to severe pain. Oxycodone is also available in combination with acetaminophen, aspirin, and ibuprofen. The use of oxycodone can lead to dependence.

Cross-References

► Addiction
► Analgesics
► Dependence
► Opioids
► Pain
► Tolerance

Oxymorphone

Synonyms

14-Hydroxy-dihydromorphinone

Definition

Oxymorphone is a semisynthetic opioid narcotic. It is used in the treatment of chronic pain and is available in an extended-release formulation allowing 24 h management of pain in patients suffering from chronic long-term pain. Like morphine, it has the potential to lead to abuse and long-term dependence on the drug, and can lead to physical dependence.

Cross-References

► Analgesics
► Opioid Dependence and Its Treatment
► Opioids
► Physical Dependence

Oxytocin

Synonyms

Love drug; Love hormone; Pitocin; Syntocinon

Definition

Oxytocin is a nine amino acid ► neuropeptide (nonapeptide), synthesized in the magnocellular neurosecretory cells of the ► hypothalamus and released both within the brain and from the posterior pituitary gland into the bloodstream. Oxytocin exerts peripheral actions that promote uterine contractions and the milk let-down reflex and is also increasingly recognized for its central effects that can lead to lasting changes in social behavior, mood

and emotion in many mammalian species. Recent studies show that intranasal administration of oxytocin can modify social cognition, social memory, interpersonal behavior, and associated brain activation in human subjects.

Cross-References

- ► Ecstasy
- ► Neuroendocrine Markers for Drug Action
- ► Social Behavior

P

P3

► P300

P300

Synonyms
Odd-ball ERPs; P3

Definition
The P300 refers to a positive EEG voltage deflection seen around 300 ms after the presentation of a novel stimulus. It can be recorded using stimuli of any sensory modality but most commonly in the auditory domain. The simplest paradigm used to elicit the P300 involves presenting repeated simple auditory tones of a given frequency every second or so. The P300 is generated when a tone of a different frequency is presented randomly at a rate of around 1 in 10 of the more common tones. It is observed by comparing the event-related potentials, time locked to the presentation of the tones, generated by the "frequent" versus the "rare" frequencies. It is seen most prominently over the parietal lobe. Unlike ► mismatch negativity, subjects need to be consciously attending to the stimuli. The presence, magnitude, topography, and time of this signal are often used as metrics of cognitive function in decision-making processes.

Cross-References
► Event-Related Potentials

P450

► Cytochrome P450

Pain

Definition
The sensory perception associated with actual or potential tissue damage.

Pain-Relievers

► Analgesics

Pair-Feeding

Definition
A procedure used in animal studies to control for decreases in food intake associated with chronic drug exposure that involves providing a control group with only as much food daily as is consumed by the drug-treated experimental group.

Palatability

Definition
A subjective measure of the acceptability and pleasantness of food. It implies a property of "being acceptable to the taste or mouth," with a sufficiently agreeable flavor for eating and pleasing to taste. It embraces the hedonic evaluation of a food resulting from its sensory properties, modified in relation to energy needs, past experience and learning, and the quantity of food consumed within a meal. Palatability may be inferred from the intensity and persistence of ingestion (palatability response). High-palatability foods tend to be energy dense, with high fat and carbohydrate content. It is an important determinant of caloric intake and can overwhelm processes of satiation;

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the greater the palatability of food, the more likely it is that overconsumption will occur.

Cross-References

- ▶ Appetite
- ▶ Hunger
- ▶ Hyperphagia

Paliperidone

Synonyms

9-hydroxyrisperidone

Definition

Paliperidone is a second-generation antipsychotic medication indicated for the acute and maintenance treatment of schizophrenia. It acts as a dopamine D2 and serotonin 5-HT_{2A} antagonist. It is the 9-hydroxymetabolite of risperidone with which it shares many pharmacological properties. An extended release formulation of paliperidone allows for once-daily dosing, results in lower peak plasma levels and hence less side effects, and thereby limits the need for dose-titration that is otherwise required at the start of treatment with risperidone.

Cross-References

- ▶ Antipsychotic Drugs
- ▶ Antipsychotic Medication: Future Prospects
- ▶ Risperidone
- ▶ Schizophrenia
- ▶ Second- and third-generation Antipsychotics

Panic

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Definition

The aim of this entry is to describe the pharmacological treatment of one of the most common anxiety disorders: panic disorder. We have focused on antidepressants (ADs), especially on ▶ serotonin selective reuptake inhibitors (SSRIs), which have been found to be effective in treating panic disorder and are the first-line treatment with regard to their efficacy and safety. The other ADs are listed along with the other pharmaceutical classes with their indications, side effects, and implementation issues.

Role of Pharmacotherapy

Introduction

▶ Panic Disorder is one of the most common anxiety disorders in the general population with a lifetime prevalence of 4.7% (Kessler et al. 2005). It is often disabling, especially when complicated by agoraphobia, and is associated with functional morbidity and reduced quality of life. The disorder is also costly for individuals and society, with increased use of health care and absenteeism.

Role of Pharmacotheraphy

Medications have been known to be useful in the treatment of panic disorder for over 30 years, with the first description of efficacy of the ▶ tricyclic antidepressant imipramine for blocking ▶ Panic Attacks by Donald Klein in 1964. Many studies have recorded the efficacy of most ADs in panic disorder. ▶ Benzodiazepines are the other effective medication currently available. The aim of pharmacotherapy should be to eliminate panic attacks, if possible, because partial response often results in continued avoidance of frightening situations and impairment in social functioning. However, the goal of treatment should also be to reduce or eliminate associated anticipatory anxiety, phobic avoidance, and other symptoms due to co-morbid conditions such as major depression and to improve global functioning. Medications from several classes have been shown to be effective.

Treatments

Serotonin Selective Reuptake Inhibitors (SSRIs)

Efficacy The efficacy of SSRIs in the treatment of depression is now very well documented, and they have also been found to be effective in treating panic disorder. Their efficacy and safety render them the first-line treatment for this condition. Each of the six SSRIs (▶ fluoxetine, ▶ paroxetine, ▶ sertraline, ▶ fluvoxamine, ▶ citalopram, and ▶ escitalopram) has demonstrated its effectiveness in ▶ randomized clinical trials.

Meta-analyses and reviews focusing on several of these agents have reported medium to profound effects compared with placebo and have confirmed that this efficacy may be maintained for up to 1 year (Otto et al. 2001). Therapeutic response in panic disorder seems to be a class effect, which

is common to all the SSRIs, with no evidence of differential long-term efficacy within the class.

Side Effects The main side effects of SSRIs are headache, irritability, nausea and other gastrointestinal complaints, insomnia, sexual dysfunctions, increased anxiety, jitteriness, drowsiness, and tremor. They can be prescribed to patients with prostatic hypertrophy or narrow-angle glaucoma according to the absence of clinically significant anticholinergic effects.

► Discontinuation reactions have been associated with all the major classes of AD. They are reported to occur particularly with compounds having short ► elimination half-lives (for SSRIs, e.g., paroxetine) and can mimic the reappearance of the underlying disorder. These discontinuation symptoms may vary in nature and severity. They begin shortly after stopping the drug. Discontinuation reactions last between 1 day and 3 weeks with a rapid reversal on restarting the original drug. Tapering of antidepressant use is the most common preventive strategy.

Implementation Issues Patients suffering from panic disorder tend to be more sensitive to SSRIs side effects than depressed patients; hence, the treatment must be started at lower doses than those used in depression (half dose or less). After a few days, according to efficacy and tolerance, doses must be progressively increased to the same or greater levels than those used in depressive disorders. The onset of action is usually 2–8 weeks. There is no clear evidence about what should be the optimal length of treatment, but classically, treatment should be pursued until 6 months after the remission of symptoms (McIntosh et al. 2004).

Tricyclic Antidepressants

Efficacy ► Imipramine and ► clomipramine have been the most extensively studied of the tricyclic ADs and both have demonstrated efficacy in treating panic disorder. Other tricyclic ADs that have shown some evidence of efficacy include desipramine, ► doxepin, ► amitriptyline, and ► nortriptyline (for review see Cox et al. 1992). One meta-analysis concluded that there were no significant differences between SSRIs and tricyclic ADs in terms of efficacy or tolerability in short-term trials for panic disorder treatment (Otto et al. 2001). Another meta-analysis comparing paroxetine and imipramine concluded that paroxetine is better tolerated than imipramine and should be the first-line treatment (Wagstaff et al. 2002).

Side Effects All tricyclic ADs have common side effects such as anticholinergic effects (dry mouth, constipation, difficulty urinating, increased heart rate, and blurred vision), increased sweating, sleep disturbance, orthostatic hypotension, fatigue, cognitive disturbance, weight gain, and sexual dysfunction. Prostatic hypertrophy or narrow-angle glaucoma are contraindications for these molecules. Cardiac function should be carefully monitored.

Implementation Issues For the same reasons as with SSRIs, it is recommended that tricyclics be started at doses lower than those for patients with ► depression. For example, imipramine should be started at only 10 mg/day and gradually increased up to a minimal dose of 75 mg/day.

The duration of treatment should be the same as with SSRIs, and it is recommended that the dose be tapered before stopping.

Benzodiazepines

Efficacy ► Alprazolam and ► clonazepam (high-potency benzodiazepines) have been studied more extensively than low-potency benzodiazepines and have shown to be more effective for the specific treatment of panic disorder. The primary advantage of using benzodiazepines is rapid relief from anxiety and panic attacks. As already mentioned, ADs have a delayed therapeutic onset (Moroz 2004).

Side Effects The disadvantages of benzodiazepines include sedation, ataxia, slurred speech, cognitive clouding, interaction with alcohol, physiological dependence, and the potential for a ► withdrawal syndrome. The prescription of benzodiazepines in elderly patients must be carefully weighed against the risk of oversedation, falls, and cognitive impairment due to the decreased elimination of these compounds.

Implementation Issues Because of its short duration of action, alprazolam generally must be administered in three to five daily doses. Clonazepam, which has a longer duration of action than alprazolam, can generally be administered twice a day. Clonazepam is reported to have less abuse potential than alprazolam, and is found to be easier to taper during discontinuation owing to its longer half-life. Very few studies have empirically evaluated dose requirements. Thus, it is recommended to slowly increase the doses according to the efficacy/tolerability ratio. There are very few data indicating the optimum length of treatment with benzodiazepines, but short-term treatment is recommended to minimize the risk of ► tolerance and ► dependence.

Furthermore, benzodiazepines can be helpful when AD treatment is initiated and when a rapid onset of therapeutic effect is desired. They can also help to improve the short-term tolerability of SSRIs by blocking the jitteriness and exacerbation of panic sometimes observed when initiating treatment with an AD. Benzodiazepines can also be useful to "top up" the patient's treatment on an as-needed basis for sudden and unexpected decompensation or short-term psychosocial stressors. However, benzodiazepines are associated with a worse outcome in the long term than AD treatment (McIntosh et al. 2004).

Other Antidepressants

Venlafaxine ►Venlafaxine is a member of the dual serotonin–norepinephrine reuptake inhibitor (►SNRI) class of AD and received approval for panic disorder in the USA. A number of ►open-label and ►double-blind studies have demonstrated the effectiveness of venlafaxine immediate-release (IR) and extended-release (ER) formulations for the treatment of panic disorder. One study published in 2007 compared venlafaxine ER with paroxetine in the treatment of panic disorder with or without agoraphobia, demonstrating that both venlafaxine and paroxetine are more effective than placebo and are well tolerated. Both fixed doses of venlafaxine ER (75 and 150 mg/day) demonstrated efficacy and tolerability that were comparable with each other and with paroxetine at 40 mg/day. The most common side effects reported for venlafaxine were sweating, dry mouth, dizziness, anorexia, tremor, constipation, diarrhea, and somnolence (Pollack et al. 2007). Discontinuation reactions have been described for venlafaxine. These reactions are very similar to those with SSRIs. The same strategy of decreasing the doses very slowly should be used before stopping the treatment.

Nefazodone and Trazodone A retrospective analysis and two open-label trials reported that nefazodone may be effective in the treatment of panic disorder. Furthermore, nefazodone is reported to have a better side-effect profile than other ADs, with no weight gain or sexual dysfunction.

Two studies with ►trazodone found disparate results. One single-blind study reported that patients improved significantly compared with placebo, but a double-blind study comparing imipramine, alprazolam, and trazodone showed trazodone to be less effective than imipramine or alprazolam.

Mirtazapine A double-blind randomized controlled study with only 27 panic patients showed no statistical difference between ►mirtazapine and fluoxetine. Four open-label trials reported also the effectiveness of mirtazapine in panic disorder. The average dose is 30 mg/day and the most frequently reported side effects are weight gain, initial drowsiness, and constipation (Ribeiro et al. 2001).

Reboxetine ►Reboxetine is a selective norepinephrine reuptake inhibitor reported to be more effective than placebo in a double-blind randomized controlled trial. However, in a single-blind study, reboxetine appeared to be less effective than paroxétine in the treatment of panic disorder. The adverse events reported most frequently with reboxetine are insomnia, constipation, and dry mouth (Bertani et al. 2004).

Monoamine Oxidase Inhibitors

Efficacy In fact, there are no studies proving that the classical irreversible ►MAO inhibitors are effective in treating panic disorder specifically; however, six earlier pre-DSM III studies showed efficacy in the phobic anxiety of individuals with panic-like symptoms. Two studies with reversible inhibitors of MAO A (RIMAs), one a double-blind comparison of brofaromine with clomipramine and the other, an open study of brofaromine, showed antipanic and antiphobic efficacy. No medication in the RIMA class is currently approved for use in USA, but at least one drug, moclobemide, is widely used in Europe and Canada despite the lack of clear evidence of its efficacy (for review see Bandelow et al. 2008).

Side Effects The disadvantages of the MAO inhibitors make them second- or third-line treatments for panic disorder; these include orthostatic hypotension, weight gain, sexual dysfunction, and dietary restrictions (low tyramine diet), with the potential for a tyramine-induced hypertensive crisis. They should be prescribed by physicians with experience in monitoring MAOI treatment. The RIMAs appear safer, with lessened potential for side effects, and do not require adherence to a tyramine-free diet.

Other Agents

Anticonvulsants ►Anticonvulsants, such as ►valproate, ►carbamazepine, and levetiracetam, have demonstrated preliminary evidence of efficacy in the treatment of panic disorder, but with side effects such as gastrointestinal dysfunction, weight gain, dizziness, nausea, sedation, and alopecia (for review see Bandelow et al. 2008).

Levetiracetam is an anticonvulsant, currently approved by the US Food and Drug Administration for the adjunctive treatment of partial-onset seizures in patients with epilepsy. In an open-label, fixed-flexible dose study, 18 patients were treated with levetiracetam for 12 weeks. Of the 13 patients completing the study, 11 were rated "very much" or "much" improved on the CGI-I. For most patients, clinical benefits were apparent after only 1–2 weeks of treatment. The tolerance was good with minimum side effects.

Antipsychotic Medications There is no evidence that conventional antipsychotic medications are effective in the treatment of uncomplicated panic disorder. ► Second-generation antipsychotics such as ► aripiprazole and ► olanzapine appear to be effective as an augmentation strategy in the treatment of SSRI-resistant panic disorder, but in open–label studies or case reports only.

Recommendations and Conclusion

Unless otherwise indicated, an SSRI should be offered as a first-line treatment. When a medication is started, the efficacy and side effects should be reviewed within 2 weeks and again at 4, 6, and 12 weeks. At the end of 12 weeks, an assessment of the effectiveness of the treatment should be made and a decision taken to continue or consider an alternative intervention. If there is no improvement after a 12-week course of a first SSRI, another SSRI or an SNRI may be considered. SNRIs tend to be used as a second-line therapy after SSRIs fail to improve panic or in patients who cannot tolerate them. The tricyclics have the disadvantages that make them second- or third-line treatment now. If there is no improvement after another 12-week course, an AD from the alternative classes should be offered or a strategy adopted for augmenting SSRIs with benzodiazepines, other ADs, or atypical neuroleptics could be tried. There is no evidence that will allow the clinician to predict which of the three broad intervention groups (pharmacological, psychological, or self-help) will be effective for an individual patient, based on duration of illness, severity of illness, age, sex, gender, or ethnicity. In the same way, there is no evidence that will allow the clinician to predict which AD will be effective. Treatment choice depends on patients' characteristics (such as previous response or contraindication), the evidence-base supporting its use, and patient and physician preference. If the patient shows improvement on AD treatment, medication should be continued for at least 6 months after the optimal dose is reached, after which the dose can be tapered. There is no clear published evidence about what is the optimal length of treatment with medication (NICE 2004).

The response rate to pharmacotherapy approaches 70%, but many studies clearly show that discontinuation of medication results in relapse with rates of 25–50% recorded within 6 months, depending on various studies. The strategy for patients not responding to the first SSRI is not well documented with placebo-controlled studies; and the notion of resistance still needs to be clearly defined.

Cross-References

► Agoraphobia
► Antidepressants
► Anxiety: Animals Models
► Benzodiazepines

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Panic Attack

Definition
Panic attacks are sudden, discrete periods of intense anxiety, mounting physiological arousal, fear, and discomfort that are associated with a variety of somatic, cognitive, and behavioral symptoms. The onset is typically abrupt and may have no obvious triggers.

Cross-References
► Agoraphobia
► Panic
► Panic Disorder

Panic Disorder

Definition
This disorder is characterized by recurrent unexpected panic attacks followed by at least 1 month of persistent concerns about additional attacks (i.e., anticipatory anxiety), worry about the implications or consequences of the panic attack or significant changes in behavior (e.g., avoidance) related to the attacks. Panic attacks are not better accounted for by a ► comorbid mental disorder and are not normally due to the direct physiological effects of a substance or general medical condition. Depending on whether criteria are also met for ► agoraphobia, panic disorder with or without agoraphobia is diagnosed.

PANSS

Synonyms
Positive and negative scale for schizophrenia

Definition
PANNS is a scale for the measurement of positive, negative, and general schizophrenic symptoms.

Papaveretum

Definition
Papaveretum is a preparation containing three of the principal opium alkaloids: ► morphine, papaverine, and ► codeine. One of the first available analgesic formulas, papaveretum is now relatively uncommon due to the more widespread availability of simple and synthetic opioids. Papaveretum continues to be used primarily as a preoperative sedative, but also for moderate to severe pain. In comparison with morphine, papaveretum has fewer gastrointestinal side effects and little abuse potential as IV administration at low doses produces severe headaches in most individuals. An additional component, noscapine, was removed from the formula in 1993 due to potential genotoxic effects.

Cross-References
► Analgesics
► Opioids

Paracetamol

Cross-References
► Analgesics

Paracodeine

► Dihydrocodeine

Paradoxical Effects

Definition
Paradoxical effects refer to results from various measures that may lead to apparently contradictory conclusions. For example, drugs of abuse can condition both approach and avoidance behaviors. The same drug (at the same dose and animal) appears to have both rewarding and aversive effects.

Paralogism

Definition
Distorted argumentation.

Paramagnetic

Synonyms
Paramagnetism

Definition
Paramagnetic refers to having the property of being attracted to magnetic fields. It is a form of magnetism that occurs only in the presence of an externally applied magnetic field.

Cross-References
► Magnetic Resonance Imaging (Functional)

Paramagnetism

► Paramagnetic

Paranoia

► Delusional Disorder

Paranoid Delusions

► Delusional Disorder

Paranoid Psychosis

► Delusional Disorder

Parasomnias

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Synonyms
Arousal disorders; Catathrenia; Confusional arousals; Exploding head syndrome; Nightmares; Rapid eye movement disorder; RBD; Sleep enuresis; Sleep paralysis; Sleep related dissociative disorder; Sleep related eating; Sleep terrors; Sleepwalking

Definition
The class of sleep disorders known as Parasomnias (L. *Para*=next to; *Somnus*=sleep) includes some of the most unusual, challenging, fascinating, and potentially instructive of all behavioral disorders. These are clinical disorders characterized by abnormal behavioral or physiological events, usually unpleasant or undesirable, which accompany sleep-specific sleep stages or sleep/wake transitions (American Academy of Sleep Medicine 2005; American Psychiatric Association 2000; see Table 1). Parasomnias are associated with central nervous system (CNS) activation, increases in skeletal muscle activity, and autonomic nervous system (ANS) changes. The immediate consequences of parasomnias include the possibility of sleep disruption and physical harm to affected individuals. Parasomnias can also lead to poor health and psychosocial consequences. Because parasomnias tend to run in families, it has long been suspected that genetic factors are involved in their pathophysiology (Hublin and Kapiro 2003).

Clinical Diagnosis and Evaluation
Experienced sleep physicians can often diagnose parasomnias with a few simple questions. More detailed clinical diagnoses of parasomnias involve collecting a thorough

Parasomnias. Table 1. Parasomnias. (Modification of American Academy of Sleep Medicine 2005.)

Disorders of arousal
1. Confusional arousals
2. Sleepwalking
3. Sleep terrors
Parasomnias usually associated with REM sleep
1. REM sleep behavior disorder
2. Recurrent isolated sleep paralysis
3. Nightmare disorder
Other parasomnias
1. Sleep-related dissociative disorders
2. Sleep enuresis
3. Sleep-related groaning (catathrenia)
4. Exploding head syndrome
5. Sleep-related hallucinations
6. Sleep-related eating disorder
7. Sleep talking (Somniloquy)

clinical history from the patients and family. Formal overnight ► polysomnography (PSG) is limited to those patients whose behaviors are violent or extremely bothersome to other individuals or which cause significant physical damage. Additionally, the final PSG assessment may include a more detailed montage to rule out other potential confounding factors (such as nocturnal seizures, obstructive sleep apnea (OSA), nocturnal panic attacks, or ► rapid eye movement (► REM) behavior disorder).

Parasomnias can be broadly and conveniently classified based on the state from which they arise – events that occur during *REM sleep*, nonrapid eye movement (NREM) sleep, or both sleep states.

Non-REM (NREM) Parasomnias

Disorders of arousal during ► NREM sleep include the following: sleepwalking, sleep terrors, and confusional arousals. Thought to occur because of the instability of slow-wave sleep (SWS), arousal disorders are not presumed to be an *all-or-none* phenomenon, but rather a continuum of behaviors involving reestablishment of full alertness, orientation, judgment, and self-control, and/or a rapid alternation between sleep and waking states (Mahowald and Schenck 2005a).

Confusional Arousals

Similar to sleepwalking and sleep terrors, confusional arousals are brief and incomplete arousals that typically begin during SWS. The aroused individual typically looks confused. A confusional arousal or behavior differs from sleepwalking in that the affected patient does not leave the bed. Inasmuch as the episodes generally follow arousals from SWS, they most commonly occur during the first one-third of the night. However, such arousals can also occur in other NREM sleep stages and/or during the later part of the night. Common examples include sitting up in bed and making simple vocalizations or picking at bedclothes. Confusional arousals are often seen in children not only from nocturnal sleep but also from diurnal naps. The term *sleep drunkenness* has also been used to describe such confusions inasmuch as the episodes, especially those following arousal upon arising in the morning, are often accompanied by disorientation, impaired cognition, and behavioral disturbance.

Approximately 10–20% of children and 2–5% of adults report a history of confusional arousals. In adults as well as children, ► anxiety, sleep deprivation, fever, and endocrine factors (e.g., pregnancy) can increase the frequency of episodes. Other precipitating factors include the consumption of ► alcohol and/or other hypnotics, antihistamines, ► lithium, and potentially other medications that tend to elevate the arousal threshold. In adults, primary sleep disorders (e.g., apnea or periodic leg movement syndrome) can also exacerbate such conditions.

Sleepwalking

Sleepwalking (somnambulism), which is initiated during SWS and generally occurs within the first one-third of the sleep period, consists of a series of complex, elaborate motor behaviors and results in walking during a state of altered consciousness. Sleepwalking occurs in 10–20% of children and 1–4% of adults. Most prevalent in children between 5 and 10 years of age and less so with advancing age, sleepwalking events range from subdued to elaborate. These events can include the unlocking of doors, dressing, and even driving. Typical episodes can last from 15 s to 30 min, with recall often being sketchy to absent the next day. During the somnambulistic state, there is an absence of dreaming. The affected individual's eyes are open and behavior may be clumsy. When awakened, the sleep walker typically responds with simple phrases and noninsightful mentation ("had to talk to John Doe"). Frequent sleepwalking in adults may be associated with violent or dangerous activity and warrants treatment. Sleepwalking patients are generally neurologically normal. The presence of other contributing sleep disorders should be investigated and ruled out prior to a final diagnosis.

Sleep Terrors (Night Terrors, Pavor Nocturnus)

Sleep terrors are also characterized by arousals from SWS. They are less common than sleepwalking, occurring in 5% of children and 1–2% of adults. A night terror starts with an incomplete arousal from SWS and is often associated with ANS activation and reports of frightening imagery. A typical event might terrify the patient, who often emits an abrupt piercing scream, accompanied by autonomic and behavioral manifestations of intense fear. The events are often associated with agitation, sweating, hyperpnea, and tachycardia. Episodes typically occur in the first one third of the night, with the patient having no or very little recall of the event the next morning. Witnesses tend to be more distressed by the events than patients. Children who present with sleep terrors often grow out of them. Events may be precipitated by such stressors as alcohol use, psychological strain, sleep deprivation, and shift work. Adults presenting with sleep terrors should be assessed for ► comorbid psychiatric disorders.

Treatment of Arousal Disorders

Once an arousal disorder is assessed and properly diagnosed, a treatment plan can be developed. The structure and sequencing of the plan should take into account the nature and severity of the symptoms. Management of arousal disorders, especially in children, should primarily

involve education. Patients and parents should understand that arousal disorders in children generally do not require intervention and that the symptoms will minimize with time. Although stress may be a factor in disorders of arousal, it should not be the clinician's first assumption.

Proper clinical management involves the recommendation of good sleep hygiene including refraining from alcohol and drugs. Further, the patient should keep a consistent sleep/wake schedule, and take steps to reduce bedroom light and noise. Sleep deprivation should be avoided. The environment should be kept safe (e.g., mattress on the floor, locks on doors, use of alarms) when necessary. Scheduled awakenings (on a regular basis awakening the patient 15 min before each usual arousal) have been shown to be effective. Table 2 lists common safety recommendations. Stress management skills, psychotherapy, and hypnosis have also been found useful. Pharmacological treatment becomes necessary when arousal events are frequent, put the family or patient at a risk of being harmed, or disturb the family life. ► Benzodiazepines (BDZs, used continuously or as needed) and ► tricyclic antidepressants have been successfully used in treatment, though controlled trials are lacking (Table 3).

In summary, because all the above episodes occur during NREM sleep, it is difficult to arouse the individuals from the episodes. When aroused, patients can be confused or even aggressive with subsequent amnesia for the episode. Dreaming is often absent in these episodes, although the patient may occasionally report vague and fragmented dreams. Further, all three arousal disorders can co-exist, making them difficult to distinguish from one another.

Parasomnias Usually Associated with REM Sleep

REM-Sleep Behavior Disorder

REM-sleep behavior disorder (RBD) is characterized by vigorous motor activity, which typically occurs during REM sleep and thus in the absence of muscle atonia. RBD often consists of injurious dream-enactment motor activity associated with vivid dreaming. REM sleep behavior disorder is symptomatically complex, often involving behaviors that are dangerous to the affected patient, or to his/her bed partner, and vivid dream imagery that is almost always unpleasant. REM behavior disorder is more frequent in males and usually occurs in the middle-aged or elderly. Although the exact prevalence of RBD in the general population is unknown, it is estimated to be 0.5% (Ohayon et al. 1997). Patients exhibiting such complaints should seek a thorough evaluation by a sleep specialist. RBD can be idiopathic or related to underlying neurological conditions (e.g., synucleinopathies). It is thus advisable that patients undergo a thorough physical examination for the purpose of identifying any comorbidities that might interrupt REM sleep (Ferini-Strambi et al. 2005). Acute RBD can be induced by medications (► monoamine oxidase inhibitors, serotonin reuptake inhibitors, and tricyclic antidepressants), alcohol, and BDZ withdrawal.

As was suggested for disorders of arousal, recommendations for therapy should emphasize the safety of the patient and his/her bed partner as paramount considerations. The patient and his/her bed partner should sleep in separate beds until events are controlled. Patients usually respond well to ► clonazepam (0.5–2.0 mg) or ► temazepam (15–45 mg). ► Melatonin, ► levodopa, and ► pramipexole have also been reported to be useful in some cases. See Table 4 for the minimum diagnostic criteria for RBD on a PSG.

Parasomnias. Table 2. List of safety suggestions for violent or disruptive parasomnias.

Install alarm systems to alert when someone has left the room or house
Sleep in a separate bed from bed partner
Place mattress on floor
Remove obstructions from room
Remove coat hooks from door
Cover windows and glass doors with drapes
Lock doors with a double cylinder lock
Light outside hallways
Place gates at top of staircases and in doorways

Sleep Paralysis

Sleep paralysis occurs when there is a persistence of REM muscle atonia into wakefulness. Although eye movements and respiratory activity remain intact, somatic movements are not possible. Episodes of sleep paralysis may often accompany a residual dream-related fear or with anxiety when a patient realizes that movement is not possible. Although the episodes may last one to several minutes, they often can be terminated by an external stimulus (e.g., touch). Patients with infrequent episodes should refrain from sleep deprivation and alcohol, but further treatment (beyond reassurance) is generally not required. For recurrent episodes, evaluation for depression or other psychiatric conditions with the potential for producing sleep disturbance is warranted.

Nightmares

Nightmares are frightening dreams that can awaken the sleeper from REM sleep. Although they may occur at any part of the night, they predominantly occur during the final

Parasomnias. Table 3. Pharmacological treatment of parasomnias. (Adapted from Winkelman 2005.)

Medication	Effective dose range (mg)	Appropriate patient population	Possible side effects
Non-REM parasomnias			
▶ Diazepam	5–10	Can be effective for ST	Rebound insomnia on discontinuation. May induce SRED
▶ Clonazepam	0.5–2.0	Can be effective for SW and ST and SB	Daytime somnolence, cognitive dysfunction
▶ Imipramine	10–300	Can be effective for ST	Anticholinergic effects
▶ Paroxetine	20–40	Can be effective in SW, ST, and PTSD	Nausea
▶ Melatonin	3–15	Has been effective in SW and ST.	Not FDA approved, daytime somnolence
Sleep-related eating disorders			
▶ Topiramate	25–400	First- or second-line therapy	Paresthesias, cognitive dysfunction
▶ Pramipexole	0.125–0.5	May be effective	Nausea
Clonazepam	0.5–2.0	May be effective	Worsening of amnesia with event, daytime somnolence
REM-related parasomnias			
Clonazepam	0.5–2.0	First-line treatment for RBD	Daytime somnolence, cognitive dysfunction
Melatonin	3–15	Has been effective in RBD	Not FDA approved, daytime somnolence
Pramipexole	0.5–1.0	Reported to help RBD	Nausea, daytime somnolence
▶ Tricyclic Antidepressants	Variable	May suppress nightmares	Anticholinergic side effects.
▶ Prazosin	1.0–5.0	Effective for PTSD, and nightmares	Worsens cataplexy in narcoleptics
Other parasomnias			
Clonazepam	0.5–2.0	May be useful for SB and SRDD	Daytime somnolence, cognitive dysfunction
▶ Quetiapine	50–200	May be useful for SRDD	May cause tarditive dyskinesia
Clonidine	0.3	May be useful for SB	
▶ Venlafaxine	37.5–150	May be useful for RISP	May exacerbated RLS.

SW sleepwalking; *ST* sleep terrors; *SB* sleep bruxism; *RBD* REM sleep behavior disorder; *PTSD* posttraumatic stress disorder; *SRDD* sleep-related dissociative disorder; *RISP* recurrent idiopathic sleep paralysis

Parasomnias. Table 4. Minimum diagnostic criteria of RBD based on polysomnographic (PSG) variables. (American Academy of Sleep Medicine 2005.)

The suggested criteria include:
1. PSG abnormality during REM sleep: REM sleep without atonia; elevated submental EMG tone or excessive phasic submental or limb EMG twitching
2. Documentation of abnormal REM sleep behaviors during PSG studies (prominent limb or truncal jerking; complex, vigorous, or violent behaviors) or history of injurious or disruptive sleep behaviors
3. Absence of EEG epileptiform activity during REM sleep

one-third of the night where REM sleep is more prominent. Recall of a nightmare is generally vivid and detail-oriented. Nightmares are often associated with predominant emotions such as fear or anxiety; however, feelings of anger, sadness, and embarrassment may also occur. Although more commonly seen in children, adults also report having nightmares, with stress and antidepressant or antihypertensive medications often being implicated as causal factors. Nightmare disorder, the experience of recurrent nightmares, can be idiopathic or related to an underlying condition such as psychological trauma or psychopathology (e.g., posttraumatic stress disorder, affective disorders). Frequent

nightmares can lead to disturbed sleep onset latency, awakenings, restless sleep, insomnia, and a lower overall quality of life. Imagery rehearsal therapy has shown promising results in the treatment of nightmares. Patients are taught to "change the dream any way (he) wishes" and imagine the new dream for 5–20 min daily. Though more commonly used to treat hypertension, prazosin has also been found effective as a routine treatment (Lancee et al. 2008).

Other Parasomnias

A host of other parasomnias, many of which are related to medical and/or psychiatric dysfunctions, have been described in the literature. Some require specific medical intervention, whereas others only require reassurance.

Sleep-Related Dissociative Disorders

Sleep-related dissociative disorders are commonly divided into three categories: dissociative identity disorder, dissociative fugue, and dissociative disorder not otherwise specified. During these states (which can vary in duration from minutes to hours), patients commonly have disturbances in consciousness, memory identity, and environmental awareness. Nocturnal re-enactments range in severity, and include episodes such as binging on high caloric sweets, acting out past physical and sexual abuse, driving an automobile, or eating uncooked foods. Patients generally lack memory of the event.

Patients often have histories of psychopathology or report past experiences of sexual, physical, and/or emotional abuse. A full psychological evaluation is recommended and no single treatment approach is accepted as the most effective in this population. A combined pharmacotherapy and psychotherapeutic approach is likely to be most effective. Treatment approaches most likely to succeed should focus on any underlying psychiatric disorders. Pharmacotherapy should similarly address the potential presence of depression and/or anxiety. Psychotherapy should be directed at tension management and reduction of stimuli that tend to provoke dissociative experience.

Sleep Enuresis

Sleep enuresis is characterized by recurrent involuntary voiding that occurs during sleep. Although bedwetting is considered normal for some ages, it becomes pathological when it occurs at least twice weekly during sleep in patients who are 5 years of age or older. Primary enuresis patients, those who have never been consistently dry during sleep, may have a neurological impairment or a deficient release of vasopressin. Secondary enuresis patients have had periods of remaining dry during sleep at least 6 months' duration. Enuresis has been linked to a number of factors including urinary tract infection, diabetes mellitus, epilepsy and other neurological disorders, and psychological stress. Treatment recommendations include reassurance and, especially in children, positive reinforcement for achieving goals. Patients should refrain from taking liquids late in the evening. Behavioral conditioning treatments such as bell and pad alarms have been found useful. Desmopressin has been used in some to reduce urine production. Tricyclic antidepressants (desipramine or imipramine) have also been found to be beneficial for short-term management.

Catathrenia (Sleep-Related Groaning)

Catathrenia is a rare form of parasomnia (Siddiqui et al. 2008). Often most disturbing to bed partners or family members, a typical episode is characterized by a prolonged groan, which is accompanied with an expiration of oronasal flow. Although catathrenia episodes predominantly occur during REM sleep, they can in some cases occur during NREM sleep (Siddiqui et al. 2008). Evaluation should include a PSG to rule out any comorbid sleep disorders (e.g., OSA). Catathrenia is not known to be associated with any apparent medical and/or psychiatric illnesses and it traditionally does not respond to pharmacotherapy. Reassurance is traditionally the treatment of choice.

Exploding Head Syndrome

Patients suffering from what has been termed as exploding head syndrome report being awakened by the sensation of a loud, explosion-like bursting sound in the head. Subjects may describe having a nonobjective auditory experience, with intensities ranging from a painless loud bang to more subtle loud sounds. Typically, these experiences occur just as they are falling asleep. Although the experience is usually painless, patients occasionally note a small jab of pain with the sound. The subjective explosions are often exacerbated by sleep deprivation or personal stress, and treatment recommendations emphasize reassuring the patient that these events are benign in nature.

Sleep-Related Eating Disorder (SRED)

Sleep-related eating disorder involves partial arousals from sleep where patients engage in involuntary eating and drinking. Patients have limited or no memory of events, and foods consumed can consist of peculiar combinations or even inedible/toxic substances such as coffee grounds, cake mixes, frozen or uncooked products, and eggshells or cleaning materials. Patients may have unexplained weight gain and morning anorexia. SRED has a higher prevalence in patients with a history of eating disorders or sleepwalking. Certain medications have also been reported to induce SRED (e.g., ▶ zolpidem, anticholinergics, and lithium). Patients should be evaluated for comorbid sleep disorders

such as periodic limb movements and obstructive sleep apnea. Topiramate and dopaminergic medications have been found effective for some patients.

Sleeptalking (Somniloquy)

Sleeptalking refers to the utterance of speech or sounds during sleep without simultaneous subjective detailed awareness of the event. Occurring during Stage 2, SWS or REM sleep, sleeptalking is the most common during the first half of the night. Episodes are exacerbated by stress, new medications, acute medical illness, or a comorbid sleep disorder. Simple sleeptalking generally does not require intervention unless another sleep disorder is suspected. If treatment is required, patients are counseled to follow proper sleep hygiene and reduce exacerbating factors such as alcohol and sedatives.

Sexsomnia

Sexsomnia (*somnambulistic sexual behavior*) is characterized by abnormal sexual behaviors during sleep, with patients having little to no memory of the event. The characteristic features of sexsomnia include sexual arousal accompanied by autonomic activation (e.g., nocturnal penile tumescence, vaginal lubrication, nocturnal emission, and dream orgasm). Many patients who have a history of sleepwalking and comorbid sleep disorders should be evaluated. Patients are advised to obtain adequate sleep on a regular basis.

Forensic Implications

Violent behaviors may occur during the sleep period and can occur without the conscious awareness by affected individuals. These sleep-related behaviors, which have been reported in 2% of the population, can occasionally have significant forensic implications (Mahowald and Schenck 2005b). Prominent legal cases involving murder, assault, or apparent suicide have occasionally been linked to disorders of arousal, RBD, psychogenic dissociative states, or sleep-related seizures. As an appreciation of such linkages is being increasingly acknowledged, sleep medicine clinicians are becoming more frequently involved in these cases as expert witnesses. It is thus in their professional interest to become informed of the medical and legal implications, where assumption of intentionality in aberrant behavior is involved. Further study is necessary to understand the true prevalence of these disorders, how to best diagnose and treat them, and how to protect others around the patient.

Conclusion

Parasomnias are often considered as the most fascinating category of sleep disorders. The associated phenomena, often distressing to those who experience them, have been well described behaviorally, but remain poorly understood in terms of their mechanisms. Parasomnias are common nocturnal events that can occur at any stage of sleep. Often a full or extended montage EEG set-up accompanied by video–audio PSG is necessary for proper diagnosis of this disorder. Genetic epidemiological studies reveal that the parasomnias often run in families. While genetic susceptibility of some parasomnias has been confirmed, not all variants of the disorder demonstrate a clear linkage. Further research into the interplay between gene–environment interactions and other potential environmental causes needs to be undertaken to understand the exact nature of such disorders. The clinician and patient should work together to tailor the treatment to each patient, and to reduce the risk of injury, increase the safety of family members, and to increase the patient's quality of life.

Cross-References

- ▶ Benzodiazepines
- ▶ Delirium
- ▶ Hypnotics
- ▶ Insomnias
- ▶ Sedative, Hypnotic, and Anxiolytic Dependence

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Pargyline

Synonyms
Methylbenzylpropynylamine; N-Methyl-N-2-propynylbenzylamine

Definition
Pargyline is an irreversible inhibitor of monoamine oxidase used for the treatment of depression with selectivity for MAO-B. It is less effective than ► tricyclic antidepressants and its interactions with dietary amines lead to serious toxicity. For example, foods such as cheeses that contain tyramine must not be consumed. It can also interact dangerously with other drugs including tricyclic antidepressants. Its use is now very limited, mainly to cases of depression that do not respond to newer antidepressants such as the inhibitors of the reuptake of serotonin and norepinephrine. Other side effects include hypotension, sedation, and weight gain.

Cross-References
► Antidepressants
► Monoamine Oxidase Inhibitors

Parkinson's Disease

Synonyms
PD

Definition
A neurodegenerative disease of adulthood and aging, characterized by neuropathology, including ► Lewy body formation and cell death, in the dopaminergic neurons of the *Substantia nigra* in the ventral mesencephalon; dopamine denervation in the striatal forebrain targets of these neurons (in particular, the caudate nucleus and putamen); the resulting syndrome is characterized by motor symptoms of ► akinesia, difficulty in initiating movements, rigidity, resting tremor, and with cognitive impairments in a significant subset of patients. Parkinson's disease is most usually modeled in experimental animals by neurotoxin-induced lesions of the midbrain dopamine neurons.

Paroxetine

Synonyms
Aropax; Paxil; Seroxat

Definition
Paroxetine is an antidepressant that inhibits potently and specifically serotonin reuptake (SSRI). It was introduced in 1992. It is mainly used in the treatment of ► major depression, ► social anxiety disorder or social phobia, ► generalized anxiety disorder, ► post-traumatic stress disorder, ► panic disorder, ► obsessive–compulsive disorder, and sometimes of migraine. It is claimed to be as effective as older tricyclic antidepressants, but with a more favorable side-effect profile. Its major side effects are nausea, sleep disturbances, decreased libido, and possible weight gain. The most serious concern with paroxetine treatment is the emerging risk for suicidal ideation and behavior in some adolescents and adults that led to the recommendation not to prescribe it for children. There continues debate about the seriousness of symptoms upon discontinuation of paroxetine.

Cross-References
► Antidepressants
► SSRIs and Related Compounds
► Tricyclic Antidepressants

Partial Agonist

Definition
Partial agonists bind to and activate a receptor, but are not able to elicit the maximum possible response that is produced by full *agonists*. The maximum response produced by a partial agonist is called its intrinsic activity and may be expressed on a percentage scale where a full agonist produced a 100% response. A key property of partial agonists is that they display both agonistic and antagonistic effects. In the presence of a full ► *agonist*, a *partial agonist* will act as an ► antagonist, competing with the full *agonist* for the same receptor and thereby reducing the ability of the full agonist to produce its maximum effect. The balance of activity between agonist and antagonist effects varies from one substance to another, according to their intrinsic activities, and is also influenced by the test system used to measure their effects. Weak partial agonists are those compounds, possessing low intrinsic activity, that are able to produce only a small percentage of the total response produced by an agonist and which act predominantly as antagonists. Strong partial agonists may come close to mimicking the maximum effects of a full agonist and may display only weak antagonistic ability. When the test system under study has a large receptor

reserve, weak partial agonists show greater agonist activity then when the system has a small receptor reserve.

Cross-References

► Agonists
► Antagonists
► Inverse Agonists

Partial Reinforcement

► Relative Validity

Passive Avoidance

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Synonyms

Emotional learning and memory; Instrumental aversive conditioning

Definition

Passive (or inhibitory) avoidance: An aversive (emotional) conditioning paradigm in which the subject learns to associate a particular context with the occurrence of an aversive event (e.g., an electrical shock, the unconditioned stimulus [US]). Passive avoidance behavior of rodents is defined as the suppression of the innate preference for the dark compartment of the test apparatus (or stepping down from an elevated platform) following exposure to an inescapable shock. Thereby, the passive avoidance task combines Pavlovian contextual ► fear conditioning with the expression of an instrumental response, the avoidance of entering a particular (punished) area of the training context.

Principles and Role in Psychopharmacology

Theoretical Background

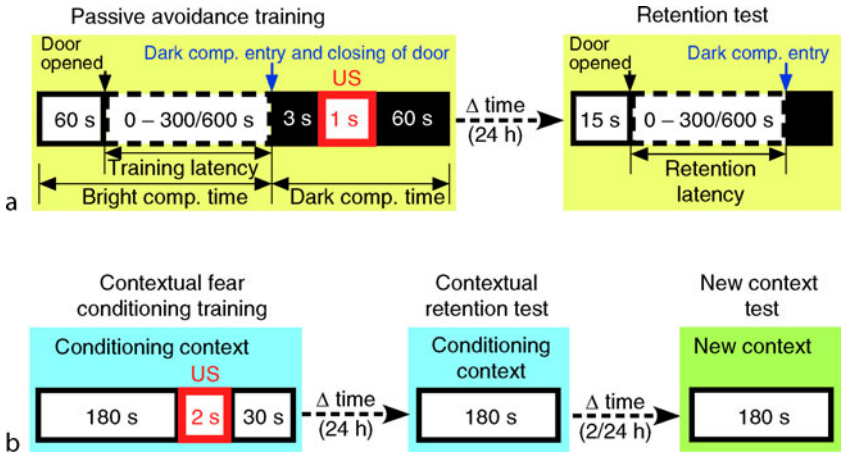
Analyses of learning experiments demonstrated very early that in conditioning certain relationships are established between particular external events, e.g., stimuli and/or responses. Psychological learning theory distinguishes between classical and instrumental aversive conditioning based on the different ways (contingencies) by which the aversive event (the ► unconditioned stimulus; US) is related to the ► conditioned stimulus (CS) and the unconditioned response (UCR). Instrumental (aversive) conditioning refers to contingencies in which the behavior of the subject determines whether or not the US will occur (Ögren 1985). In ► active avoidance paradigms, the rat has to perform a discrete response of a low probability, e.g., running from one side of a two-compartment box to the other when a discrete stimulus, e.g., the conditioned stimulus (CS) is presented in order to escape or avoid the US. In the passive avoidance task the animal learns to suppress a motor response to avoid exposure to the test area (context) associated with or predictive of the aversive event, such as a dark compartment of the passive avoidance apparatus that is normally preferred over the brightly illuminated compartment. Thereby a conflict situation is created.

Analyses of avoidance learning indicate that it involves different processes. Initially, presentation of the US results in a learned emotional state (e.g., ► conditioned fear), involving Pavlovian classical conditioning followed by the acquisition of the discrete, adaptive behavioral responses, the escape or avoidance response. The adaptive response requires for its association temporal contiguity between the US and the sensory stimulus or context used as the CS. Typical examples of the experimental sequence of passive avoidance and fear conditioning are presented in Fig. 1.

More recent theories on aversive learning have focused on the cognitive processes by which the animal acquires information about its experimental context. The cognitive interpretation of passive avoidance suggests that this paradigm is based on place learning involving the hippocampus (see below).

Passive Avoidance Tasks

Several varieties of passive avoidance tasks exist such as step-down or step-through avoidance. Passive avoidance is a learning task based on associative ► emotional learning (Ögren 1985), similar to contextual fear conditioning (Fendt and Fanselow 1999; LeDoux 2000). Unlike active avoidance tests, passive avoidance tests do not use an explicit CS. Instead, the training context serves as CS. Contextual stimuli are important for optimal ► retention performance. Changes in training context or internal stimuli, e.g., time of testing will impair retention performance.



Passive Avoidance. Fig. 1. Experimental sequences for passive avoidance experiments (**a**) and contextual fear conditioning (**b**) with training and retention tests with information on the duration of subintervals as used in previous studies. Blue arrows (**a**) indicate when the instrumental response occurs, i.e., the active choice of transferring from the bright into the dark compartment. In contrast, in fear conditioning the fear response is commonly quantified on the basis of visually observed or computer-derived freezing as index of active suppression of ongoing behavior. The test in the new context serves as control to determine the specificity of the fear response elicited by the distinct stimuli provided in the conditioning context. US = unconditioned stimulus (foot shock); comp. = compartment. (Modified from Ögren et al. 2008.)

Step-Through Passive Avoidance (Inhibitory Avoidance)

The step-through task is a one-trial emotional memory task combining fear conditioning with an instrumental response, e.g., the active choice of an animal to avoid entering the dark compartment associated with an aversive event (Ögren 1985). The passive avoidance task differs from the typical fear conditioning experiment in which training and testing occur in a one-compartment box. The rodent placed in the apparatus is exposed to one or several foot shocks (shock intensities 0.5–0.8 mA). Memory retention is measured as the degree of suppression of motor behavior quantified on the basis of ▶ freezing.

The typical step-through passive avoidance test is conducted in a two-compartment box with one bright and one dark compartment connected by a sliding door. The subject is placed in the bright compartment and will after a defined time interval gain access to the dark compartment. When entering the dark compartment (training latency), the door will be closed and the subject will be subjected to a brief aversive stimulus (US; foot shock intensities in mice around 0.2–0.4 mA) that will lead to the formation of an association of the dark compartment with the US. For the retention test (usually 24 h after training) the animal is returned in the bright compartment with the sliding door open. The animal has now the option to avoid or enter the dark compartment by discriminating the bright (safe) from the dark (unsafe) compartment. The rapid acquisition of not making a response indicates that the test involves learned inhibition rather than loss of an innate response tendency. Usually one trial, i.e., one exposure to the inescapable shock is sufficient to suppress the innate preference of the rodents for the dark chamber of the apparatus. The acquisition of passive avoidance is measured either as a significant increase of the step-through latency compared to training latencies or as the decrease of the time spent by the subjects inside the dark chamber. Thus, the passive avoidance procedure has the advantage of simplicity in that both the safe and the noxious compartment are clearly defined as well as the correct adaptive response that is to refrain from entering the dark compartment.

Step-Down Passive Avoidance

In the step-down passive avoidance task the subject is placed on an elevated platform from which it can step down onto the floor below, mainly a shock grid. When stepping onto the floor, the animal will be subjected to one or several ▶ aversive stimuli (US; foot shock) that will lead to the formation of an association between the shock and the context resulting in avoidance or delay to step down when returned to the platform in the retention test. Unlike the step-through passive avoidance procedure, the retention test is performed in the original (punished)

context similar to fear conditioning. This feature may lead to a substantial amount of contextual freezing, which is rarely observed in the step-through task. Another important issue relates to the compartment size, i.e., the space available for exploration in a one-compartment box. It is recommended to offer sufficient space for exploration instead of having systems with minimal compartment size from which animals instantly transfer when moving. Step-down passive avoidance tasks are more sensitive to changes in locomotor activity than step-through passive avoidance tasks particularly if the platform is small. Drug-induced or lesion-induced alterations in locomotor activity may confound the actual avoidance response.

Since the majority of passive avoidance investigations are based on the use of step-through avoidance paradigms, the following sections will focus on this task.

Procedural and Experimental Parameters

In the available literature there is quite a range of different procedures and experimental designs. Procedural differences have considerable consequences for passive avoidance performance and variability in results. Therefore, important aspects of different procedures are briefly summarized in Table 1. Different passive avoidance systems exist that are customized or available from different vendors. It is important that they fulfill certain hardware/software requirements for flexible use ideally with convenient software controls as indicated in Table 1.

Some pre-experimental procedures have considerable effects on the results. Handling by the experimenter has been shown to reduce variations between animals in the passive avoidance task probably by lowering the adverse effects of acute stress (Madjid et al. 2006). Another procedural modification, which reduces variations in results, is to allow the animal to explore both compartments for a short time (e.g., 1 min) 1 h before the actual passive avoidance training. However, this procedure may result in ▶ latent inhibition, e.g., reduced transfer latency, if the pre-exposure to the dark compartment is too long, if it occurs 24 h before training or if the strain of mice or rats is particularly sensitive to pre-exposure (Baarendse et al. 2008).

The most critical parameters in passive avoidance are the shock intensity and its duration. The avoidance response shows a very steep increase in the transfer latency with increasing shock intensity (Fig. 2). Thus, even small variations in intensity can change passive avoidance performance. Therefore, it is important to determine shock thresholds in all experiments, since large species and strain variations exist. To be able to study both enhancement and impairment of passive avoidance memory in the same experiment, different shock intensities can be used.

To enable demonstration of facilitatory effects on drugs on passive avoidance retention, a mildly aversive electrical current can be used while a strong current can be employed to explicitly study impairment of passive avoidance retention. This procedure provides a sufficiently wide for impairment and blockade of impairment when combining agonist and antagonist treatment (Fig. 3). An alternative approach is to use very long training latencies, e.g., up to 900 s, to have a sufficient dynamical range, or to combine it with pre-exposure (latent inhibition).

In addition, a wide range of retention measures is generally observed as a sign of large inter-individual variability. Therefore, larger group sizes (generally $n=12–16$/group) are required to achieve required statistical power unless profound drug effects are observed. Statistical analysis may have to be performed with nonparametric analysis of variance (ANOVA) using the Kruskal-Wallis test followed by the Mann-Whitney U test for pair-wise comparisons due to deviations from normal distribution of individual data and large group variances or responses exceeding maximum transfer latencies (cut-off latencies).

Handling of animals just after training can reduce the retention latency considerably. Particularly in mice, it is important that they can remain in the dark compartment of the passive avoidance apparatus for at least 30 s before being removed and transferred to their holding or home cage. Thus, the animal has to be given sufficient time to process the training context. In fear conditioning, exposure to the shock instantly after placement in the conditioning context leads to the "immediate shock deficit" in rats and mice, i.e., the absence of contextual conditioning. Thus, contextual information requires sufficient processing time to form an aversive association indicating the importance of the temporal relation of CS and US for associative learning. This is achieved by the initial confinement to the bright compartment. Another important rationale for the 30-s delay after US exposure is to avoid that mice form an aversive association of the US with the handling procedure (removal from the compartment after the US exposure).

Neural Systems

The nature of contextual stimuli which are critical for associative learning in the passive avoidance are not well characterized. It seems likely that passive avoidance, similar to contextual fear conditioning, depends on multisensory associations rather than unisensory associations. The relative role of sensory cues representing the CS is not known at present. Sensory afferents are required for the

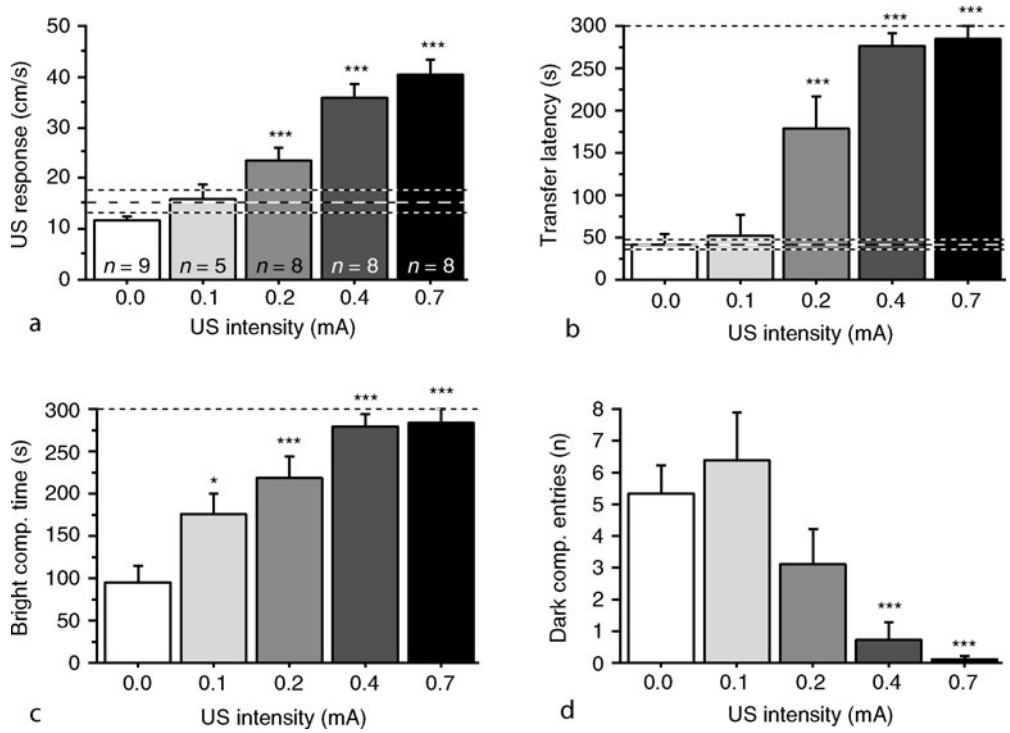
Passive Avoidance. Table 1. Important experimental features in passive avoidance experiments.

Apparatus:	Compartment sizes (larger compartments allow for movements irrespective of lack of transfer) Door size and visibility (larger doors promote faster transfer during training) Light intensity differences between compartments (should be profound, e.g., 10–100-fold difference) Door mechanism (a guillotine door falling on a mouse that is not yet completely in the dark compartment may act as US) Shocker with sufficient sensitivity (ideally >0.1 mA increments) and range (e.g., 0–1 mA)
Pre-experimental procedures:	Housing (single or group) and transfer (short vs. long) to the experimental room (arousal affecting the actual training and testing) Pre-exposure(s) before training, timing of pre-exposure (to reduce data variability), risk of latent inhibition Handling (to reduce variability in training latencies) Timing of drug treatment (pre- vs. post-training, pretest, state-dependent learning)
Experimental procedures:	Timing of retention testing (from short-term [1 h] to long-term memory [24-? h]; remote memory [>7 days] is hardly explored) Test duration (cut-off time: e.g., 300 s vs. 600 s) US intensity range used: low for facilitation vs. high for impairment Current: constant vs. scrambled shock (generally scrambled shocks are more effective) Extinction tests based on repetitive testing (with/without forced exposure to the dark compartment)* Waiting/delay time before access to the dark compartment is provided (e.g., 60 s during training, 15 s during testing)* Delay between dark compartment entry and US exposure to avoid escaping to the bright compartment*
Experimental parameters:	Transfer latencies detection (full transition when the animal is in the dark compartment with all four feet) Transitions between compartments (detection based on center of gravity may record transitions in mice during stretch-attend postures while exploring the door; this is not ideal for automated analysis) Total time spent per compartment US response assessment (important to avoid misinterpretations based on altered nociception) Activity measurements (some hypoactive and neophobic mouse strains such as A/J are unsuited for passive avoidance experiments despite implying to be good learners; therefore it is sometimes recommendable to include non-shocked controls) Time of testing (fluctuations in passive avoidance response throughout the circadian cycle have been reported in rats)
Statistical considerations:	Group sizes (normally n = 8/group is minimum, ideally n = 12–16/group) Parametric (ANOVA) and nonparametric data analyzes (Kruskal-Wallis and Mann-Whitney U test) (depending on the normal distribution of individual data [group variance] or skewed data because of maximum latency cut-off)

*These parameters have not been systematically investigated

detection of the different stimuli provided in the passive avoidance test environment from tactile to visual cues, nociceptive pain receptors for US detection and possibly also olfactory cues. Besides processing in the thalamus (except for olfactory information), higher brain centers are involved for ►encoding, ►consolidation, and ►extinction. The ►amygdala, the ►hippocampus, and the various cortical areas are part of the neural network that subserve passive avoidance learning (Baarendse et al. 2008; Burwell et al. 2004; McGaugh 2004; Ögren et al. 2008).

A number of studies have shown that passive avoidance depends on hippocampal function and its ►NMDA-receptors. Thus, infusion of the NMDA-receptor antagonists, AP5, into the dorsal hippocampus of mice profoundly impairs passive avoidance retention (Baarendse et al. 2008). Also neurotoxic lesions of the corticohippocampal circuitry (perirhinal, postrhinal, and entorhinal cortex) cause profound deficits in passive avoidance learning (Burwell et al. 2004). These results indicate that the passive avoidance task requires processing of spatial information about the test environment.



Passive Avoidance. Fig. 2. Passive avoidance performance in male C57BL/6J mice as a function of US intensity using multiple measures. US responses (activity) were measured during training and compared to baseline activity (**a**). In the retention test, transfer latencies (**b**), the total time spent in the bright compartment (**c**), and number of entries into the dark compartment (**d**) were analyzed as a function of US intensity (US duration: 2 s). The basal exploratory activity in the initial 180-s period of exploration in the light compartment is indicated as dashed horizontal line (dotted lines: ±SEM) in panel a. The dashed horizontal line (dotted lines: ±SEM) in panel b indicates the mean training latency. Dotted lines at 300 s in panels b and c denote the cut-off time in the retention test. Error bars indicate SEM. comp. = compartment; *$p < 0.05$ and ***$p < 0.001$ vs. 0.0 mA control group (based on Mann-Whitney *U* test for panel b).

The passive avoidance task differs from spatial tests such as the ► Morris water maze both with regard to sensitivity to parahippocampal lesions and modulation of cholinergic mechanisms, suggesting that these two spatial tasks differ in their dependence on processing of polymodal sensory information (Burwell et al. 2004; Ögren et al. 2008). Finally, it should be noted that mice with hippocampal dysfunction may acquire passive avoidance, although suboptimally, using a hippocampus-independent strategy (see Baarendse et al. 2008).

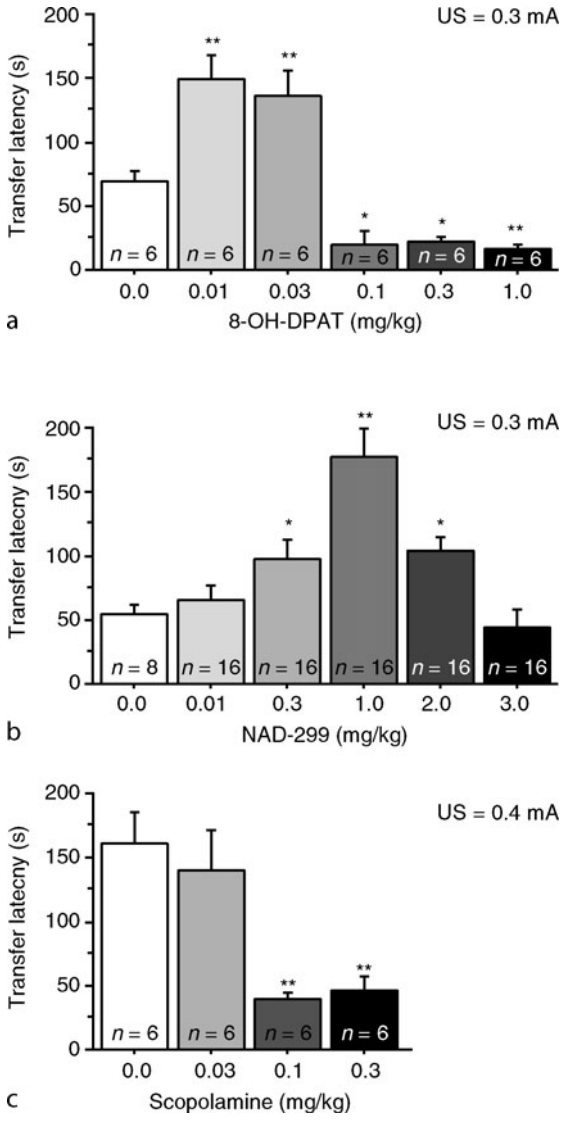
A large body of literature points at the crucial role of the amygdala, a heavily innervated assembly of many different subnuclei that are essential for aversive learning (LeDoux 2000; McGaugh 2004). Among these subnuclei, the basolateral nucleus plays a major role in the convergence of CS and US for associative learning. The basolateral nucleus of the amygdala is connected to the central nucleus of the amygdala. Outputs from the central nucleus of the amygdala are essentially responsible for the expression of fear responses. This network triggers behavioral adjustments indicative of learning and memory through motor control and concomitant autonomic and endocrine adjustments via efferent pathways. The efferent pathways are specific for certain response domains but subserve both learned and innate responses. These brain areas include hypothalamic and various brain stem areas that will not be discussed here.

Application of Passive Avoidance in Neuropsychopharmacology

Passive avoidance is one of the most frequently used animal tests for studying learning and memory mechanisms and to identify compounds modifying cognitive processes. This task is often a first-line test in

pharmaceutical companies. The task has also a prominent role in neuroscience research focusing on the role of neurotransmitters and molecular signals in learning and memory processes. An accumulated body of work has characterized the major multiple neurochemical systems and some of its molecular components which mediate or modulate this type of learning (Ögren et al. 2008). Research already in the 1970–1980s showed a significant role of cholinergic transmission in storage and retrieval of information. Thus, the nonselective muscarinic receptor antagonists such as ► scopolamine, when injected prior to passive avoidance training, were found to cause a dose-dependent impairment of passive avoidance retention (Bartus et al. 1982). Subsequent studies showed that administration of cholinomimetic drugs such as the acetylcholinesterase inhibitor ► physostigmine could partially antagonize the deficit caused by scopolamine. These findings formed part of the cholinergic hypothesis of geriatric memory dysfunction (Bartus et al. 1982) that provided the rationale for introducing ► cholinesterase inhibitors as anti-dementia drugs. A number of studies have also demonstrated a significant role for brain serotonin in passive avoidance learning. Both increases and decreases in brain 5-HT transmission have resulted in passive avoidance deficits (Ögren et al. 2008) probably reflecting the involvement of multiple 5-HT receptors in this task (Misane and Ögren 2000). However, through the use of 5-HT receptor subtype-specific ligands, such as selective 5-HT_{1A} receptor agonists and antagonists, the role of 5-HT in passive avoidance has been more thoroughly investigated (see Fig. 3). With passive avoidance as the major behavioral test it has been possible to distinguish the modulatory action of pre- and post-synaptic 5-HT_{1A} receptors in cognitive function (Ögren et al. 2008). Based on these findings, the 5-HT_{1A} receptors have emerged as an important target for drugs acting in psychopathologies characterized by mood disorders and disturbances in emotional memory (Ögren et al. 2008).

A major problem in the analysis of drug effects in passive avoidance is that drug-induced changes in emotionality, motivation, or brain chemistry may be part of the training context. ► State-dependent learning refers to the situations in which retention is poor for rodents when the drug state during learning and retention differs. This means that information acquired under the drug state can only be retrieved when the animal is in the same drug state. Analyses of state-dependent learning can be an important tool by which to assess nonspecific effects on performance from associative learning mechanisms. The research design in passive avoidance



Passive Avoidance. Fig. 3. Passive avoidance performance based on transfer latencies in the retention test in male NMRI mice as a function of drug treatment using different shock (US) intensities during training as indicated. The full 5-HT_{1A} agonist 8-OH-DPAT (**a**) facilitates at the low-dose range (0.01–0.03 mg/kg) and impairs at high-dose range (≥0.1 mg/kg). The selective 5-HT_{1A} antagonist NAD-299 (**b**) facilitates passive avoidance retention latencies in the dose range of 0.3–2 mg/kg. The muscarinic acetylcholine receptor antagonist scopolamine (**c**) impairs passive avoidance retention at 0.1 and 0.3 mg/kg. US duration was 1 s. Retention latency cut-off was 300 s. All drugs were injected either subcutaneously 15 min (a and b) or 40 min before training (**c**). Error bars indicate SEM; *$p < 0.05$ and **$p < 0.01$ vs. 0.0 mg/kg control group. (Modified from Madjid et al. 2006).

experiments should always include a test group receiving the same treatment at both training and test.

Advantages and Limitations of Passive Avoidance Experiments

The advantage with the passive avoidance procedure is that it is a single-trial task and it produces similar results in both mice and rats. Unlike multitrial tasks, single-trial tasks allow for a precise timing of drug injections either before or after training, or before the retention test. It is, therefore, possible to dissect out the possible contributions and effects of drug interventions on encoding, consolidation, and retention (memory retrieval and expression). Since the retention tests can be performed at variable time intervals after training, ▶ short-term (STM) and long-term memory (LTM) can be assessed separately. However, since subsequent tests are confounded by prior experiences, an animal can only be tested once. Post-training administration provides the opportunity for studying the endogenous modulation of memory consolidation.

There are also drawbacks with this one-trial task, including large inter-subject variability (discussed above) and different sensitivity to the shock exposures. The memory-strength (retention) is influenced by many factors including the mental state at the time of learning, emotional reactivity and responses to stress hormones (McGaugh 2004). Experimental manipulations that cause changes in locomotion, pain perception or anxiety states can also confound measures of memory. Information on these behavioral domains is important to rule out alternative explanations rather than altered cognitive function(s).

Attenuated pain perception by pharmacological or genetic manipulations with analgesic effects may render a low US ineffective as punisher, thereby preventing passive avoidance learning. Knowledge about the US responsiveness (see Baarendse et al. 2008) is crucial to rule out passive avoidance impairments because of lack of US salience/perception. Since the US is given in the dark compartment, quantification is hardly possible unless the passive avoidance system used can detect the activity of experimental animals in the dark compartment. It is useful to install photo beams that transmit through the black walls or using infrared cameras for video tracking. At least the US reactions (e.g., vocalization and jumping) of the animals should be visually observed and noted by the experimenter to exclude a potential lack of perception.

There is often a general assumption that enhanced anxiety-like behavior is associated with increased fear (avoidance) responses. Although this cannot be ruled out, there is at this moment no clear evidence that this assumption is valid (Madjid et al. 2006). On the contrary, studies using different strains of mice show that the DBA/2J strain which are more anxious than the C57BL/6J strain, show reduced passive avoidance learning compared to C57BL/6J mice (Baarendse et al. 2008). In conclusion, despite their limitations, passive avoidance paradigms have turned out to be very useful in analyzing the neurochemical and molecular basis of cognition.

Perspective

Passive avoidance tests have been used in research for more than 6 decades. The success of this behavioral test is probably based on the fact that it exploits adaptive behavioral mechanisms critical for survival and shaped through evolution. Moreover, the passive avoidance task is very flexible and allows for investigation of a large number of cognitive domains in neuropsychopharmacology and related disciplines. Yet, the full potential of this task in studying memory mechanisms is still not always well perceived in the research community. The advent of advanced passive avoidance systems will allow a much more penetrating analysis of domains of cognition with relevance for psychopathology such as latent inhibition and extinction of passive avoidance responses. In addition, the integration of additional measures such as neural responses and autonomic adjustments with passive avoidance will open up new avenues for an integrative analysis of avoidance behavior Therefore, it is suggested that the passive avoidance task has an important place in both current and future neuroscience research.

Cross-References

- ▶ Amygdala
- ▶ Anxiety
- ▶ Associative Emotional Learning
- ▶ Conditioned Fear
- ▶ Consolidation
- ▶ Encoding
- ▶ Extinction
- ▶ Fear Conditioning
- ▶ Hippocampus
- ▶ Latent Inhibition
- ▶ Pavlovian Fear Conditioning
- ▶ Punishment Procedures

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Passive Immunization

Definition

Administration of purified drug-specific antibodies produced in some other species (e.g., rabbits, mice) or in vitro. Primary advantages of this approach are the ability to achieve necessary serum concentrations of antibody virtually immediately and precise control of the antibody dose to allow study of dose–response relationships and the effects of high antibody concentrations that ca not be achieved via vaccination. Main disadvantages of passive immunization are that it requires relatively frequent injections to maintain antibody levels and is relatively expensive compared to vaccination.

Patch Clamp

Definition

Patch-clamp recording denotes a variety of electrophysiological recording modalities that exploit the property of a glass recording electrode to form an electrically tight seal (patch) against the cell membrane.

The patch-clamp technique can be used to study the opening and closing of single or multiple ion channels in mainly excitable cells. Measurements require a tight seal (gigaohm-seal) between a glass pipette, filled with an intracellular solution and a Ag/AgCl wire, and the membrane of a target cell. Various approaches can be used to yield differential data. For example, whole-cell patch clamping is used to measure the activity of ion channels across the entire surface of a cell whereas cell-attached, inside-out or outside-out patches can be used to monitor either single channel activity or massed activity of the section of membrane attached to the electrode. Inside-out patches are particularly useful for studying how cytosolic events affect ion channel activity.

Cross-References

► Intracellular Recording

Pathological Gambling

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Synonyms

Compulsive gambling; Gambling addiction; Impulsive–compulsive gambling; Problem Gambling

Definition

Pathological gambling (PG) is classified as an ► impulse control disorder (► ICD) characterized by persistent and recurrent maladaptive ► gambling behavior and resulting in impaired social and/or occupational functioning (► DSM-IV-TR; American Psychiatric Association 2000). An essential feature of ICDs is the diminished ability to resist drives or urges to perform behaviors that may be harmful; consistently, individuals with PG frequently score high on measures of impulsivity. While classified as an ICD, PG shares many similarities with substance dependence. Of the ten diagnostic criteria that characterize PG, four resemble symptoms commonly observed in ► substance dependence including an intense preoccupation with gambling, repeated or unsuccessful attempts to stop or cut down, and aspects of tolerance and withdrawal (American Psychiatric Association 2000). Other similarities between PG and substance use disorders include clinical characteristics (e.g., higher prevalence rates in men compared to women) and courses (e.g., earlier age of onset in men, higher rates in adolescence, and lower rates in elderly adults), and an observed telescoping phenomenon in women (i.e., shorter duration between onset of gambling and the report of a gambling problem in women compared to men). Additionally, like substance dependence, individuals with pathological gambling experience cycles of ► abstinence and ► relapse.

In this sense, some have likened gambling to a nonchemical or "behavioral" addiction.

Role of Pharmacotherapy

Both psychotherapeutic and pharmacological treatments have been investigated in the treatment of PG. Effective psychotherapies have utilized behavioral (e.g., aversion therapy, in vivo and imaginal exposure, skills training) and/or cognitive (e.g., cognitive restructuring, problem solving) and motivational (e.g., motivational enhancement) techniques to address maladaptive gambling behaviors and thought patterns (Brewer et al. 2008). As with studies of psychotherapies, relatively few systematic, controlled, and adequately powered trials have investigated pharmacotherapies for PG.

Axis I and Axis II disorders often co-occur with PG (Ibanez et al. 2001); therefore, it is clinically relevant to consider treatment approaches based on types of co-occurring disorders (e.g., alcohol or drug use disorders, bipolar disorders, anxiety disorders, or major depression). Given the proposed mechanisms of action of specific psychotherapies and pharmacotherapies, it is also important to consider specific neurobiological aspects of PG (e.g., opioid system, serotonin system) when considering treatments. This chapter will focus on findings from placebo-controlled studies and cite references that review these and other studies. For additional information about specific studies, readers are encouraged to see the original sources cited in the review articles.

Opioid System

► Endogenous opioids and opioid receptors in the brain may mediate reward, urges, and hedonia. Controlled studies of opiate antagonists such as ► naltrexone and nalmefene have yielded particularly promising results. Opiate antagonists bind to opioid receptors, influencing the release of gamma-aminobutyric acid (► GABA) and subsequent dopaminergic neurotransmission from the ► ventral tegmental area (VTA) to the ► nucleus accumbens (NA) and the ventral pallidum. In this way, opioid antagonists are hypothesized to modulate the tension and/or pleasure that individuals with addictive and impulsive behaviors report feeling and are believed to help suppress urges that may lead to impulsive behaviors.

Naltrexone. Naltrexone, a long-acting opioid receptor antagonist, has been investigated in the treatment of disorders where urges are indicated as a predominant symptom including bulimia nervosa, ICDs, disorders with associated self-injurious behaviors, and various substance use disorders including alcohol and opioid dependence. Findings from such studies remain mixed, as naltrexone has not demonstrated consistent efficacy in reducing urges across all disorders. However, the success of naltrexone in treating addictive disorders (including FDA-approval for the treatments of opioid and alcohol dependence) has led to the investigations of PG (Brewer et al. 2008).

In a 12-week ► double-blind, ► placebo-controlled trial, 83 individuals with PG underwent a week-long, single-blind placebo lead-in and were randomly assigned to receive a flexible dose of either naltrexone (mean end-of-study dose of 188 mg/day) or placebo (Brewer et al. 2008). Thirty eight individuals were removed from the analyses for multiple factors (e.g., placebo responders, intolerable side effects, inability to keep study schedule) leaving 45 participants. Individuals who received naltrexone showed significant improvement on all three measures of gambling compared to those who received the placebo. By study end, 75% of individuals in the active naltrexone group, compared to 24% of those in the placebo group, reported significant improvement in gambling symptoms, although there was also a significant improvement from baseline within the placebo group. The findings from the study are limited by the frequency of placebo response, drop out related to elevations in liver enzymes, and the exclusion of individuals with co-occurring Axis I disorders.

A second, 18-week, double-blind, placebo-controlled trial of naltrexone was conducted to replicate and extend earlier findings (Grant and Potenza 2008). Following a weeklong placebo lead-in, 77 individuals with PG were randomly assigned to one of three doses of naltrexone (50, 100, or 150 mg/day) or a placebo. Based upon naltrexone's proposed mechanism of action and previous findings suggesting it reduces self-reported urges to gamble, only participants who reported significant gambling urges were included in the study. While there were no significant differences in response between doses of naltrexone, naltrexone treatment compared to placebo was associated with reduced self-reported gambling urges, longer abstinence, and improved psychosocial functioning. Placebo response was also observed, although response in this group was substantially lower than in the naltrexone group. The findings were limited by the study's short-term duration. That is, while the present study employed longer treatment duration of 18 weeks, it did not assess treatment effects past this point. Despite this limitation, the findings suggest naltrexone may be useful in treating acute PG, particularly among individuals who report significant urges to gamble. In addition, the findings suggest that a high dose of naltrexone targeted in earlier studies might not be essential to observe clinical response.

Thus far, naltrexone is the only medication having shown efficacy in two or more double-blind, controlled studies. The studies support the safety and tolerability of naltrexone in the short-term treatment of PG. However, clinicians should remain aware of its dose-dependent hepatotoxicity (Grant and Potenza 2008). Continued research via large-scale, multi-center, controlled clinical trials would help to better clarify the utility of naltrexone in the treatment of PG.

Nalmefene. Nalmefene is a long-acting opioid receptor antagonist that shares proposed mechanisms of action with naltrexone and, like naltrexone, has been investigated in the treatment of ► alcohol dependence. Unlike naltrexone, nalmefene has not shown dose-dependent hepatotoxicity. To date, one multi-center double-blind, placebo-controlled trial has examined the efficacy and tolerability of nalmefene in the treatment of PG (Brewer et al. 2008). Two hundred and seven PG subjects were randomly assigned to one of three doses of nalmefene (25, 50, or 100 mg/day) or placebo and followed for 16 weeks. Individuals who received nalmefene demonstrated improvement across a range of gambling measures, and this difference was greater than changes observed in individuals receiving placebo. The findings were limited by high frequencies of subject drop out and placebo response. Despite these limitations, the findings suggest nalmefene may be an effective pharmacologic option for the short-term treatment of PG. While its lack of hepatotoxicity makes it an appealing alternative to naltrexone, clinicians should remain aware of the reported adverse effects of nalmefene (e.g., nausea, insomnia, dizziness), particularly at higher doses, and its limited availability due to limited indications for which it is approved.

As individual differences have been associated with opioid-antagonist-treatment response in alcoholism, outcome data from nalmefene and naltrexone trials were analyzed (Grant and Potenza 2008). A positive family history of alcoholism and strong gambling urges were positively associated with response to opioid antagonists. Younger age was positively associated with placebo response. Taken together, these studies support a role for opioid antagonists in treating PG. However, more controlled studies are needed, particularly ones of longer duration and in conjunction with behavioral therapies.

Serotonin System

► Serotonin systems have been implicated in various impulse control and ► compulsive disorders (e.g., PG, kleptomania, compulsive shopping, compulsive skin picking) with studies suggesting deficits in serotonergic functioning being associated with increased impulsivity (Brewer and Potenza 2008; Williams and Potenza 2008). Thus, serotonergic medications have been examined in treating PG.

Clomipramine. ► Clomipramine is a serotonin reuptake inhibitor (SRI). In an early case study with a 31-year-old female gambler, treatment with clomipramine was associated with a reduction in gambling symptoms and gambling behavior (Kim and Grant 2001). To date, no further clinical investigations of clomipramine in the treatment of PG have been published. As such, precise conclusions about its efficacy in treating PG cannot be drawn.

Fluvoxamine. The efficacy and tolerability of ► fluvoxamine, a selective SRI (SSRI), was initially examined in the treatment of 16 individuals with PG (Brewer et al. 2008). Participants entered an 8-week placebo lead-in phase, followed by an 8-week single-blind trial of fluvoxamine. Of the original 16 participants, 10 completed the medication trial with 7 of these considered treatment responders. Treatment with fluvoxamine (mean end-of-study active dose 220 mg/day) was associated with reductions in gambling-related thoughts and behaviors. In two of the three nonresponders (both with histories of cycling mood disorders), treatment with fluvoxamine appeared to exacerbate gambling behavior. The findings are limited by a small sample size, an open-label design, and thus the possible placebo effects.

A subsequent study involving 15 patients with PG further investigated the efficacy and tolerability of fluvoxamine (Brewer et al. 2008; Kim and Grant 2001). Individuals entered a 1-week placebo lead-in followed by a 16-week crossover trial of fluvoxamine and placebo with ten participants completing the trial. Treatment with fluvoxamine (mean end-of-study active dose of 195 mg/day) yielded greater reductions in gambling-related thoughts and behaviors as compared to placebo. A significant drug-by-phase interaction was observed in which differences between fluvoxamine and placebo were observed in the second but not in the first phase of the crossover trial, consistent with a more robust placebo effect in the first phase. The study was limited by a small sample size, short treatment duration, and the placebo effects.

In a pilot study investigating the efficacy of fluvoxamine treatment, 32 individuals with PG were enrolled in a randomized, double-blind, placebo-controlled study of fluvoxamine for a duration of 6 months (Grant and Potenza 2007). There were no observed differences in treatment outcomes between the fluvoxamine-treated and placebo-treated groups. Similar to other trials of fluvoxamine, the findings were limited by placebo response and a small sample size, and the latter factor may have precluded the identification of between-group differences.

A comparison study investigated the effectiveness of fluvoxamine to ► topiramate (Iancu et al. 2008). Topiramate is a medication hypothesized to mediate its therapeutic actions via influencing the mesolimbic dopamine system via GABAergic mechanisms and has shown promise in treating disorders characterized by poor impulse control. Thirty-one men with PG were randomly assigned to receive 200 mg/day of either topiramate or fluvoxamine for 12 weeks. Results demonstrated treatment completers in both groups responded positively to treatment, with 9/12 individuals in the topiramate group and 6/8 individuals in the fluvoxamine group reporting full remission of symptoms at the end of treatment. Greater drop out was observed in the fluvoxamine group relative to the topiramate group. Additionally, improvement in scores on the Clinical Global Impression (CGI) scale reached significance for individuals who received topiramate, but not for those who received fluvoxamine. These findings were limited by a lack of a placebo-control group, raters unblinded to treatment conditions, and a small sample consisting solely of men. Nonetheless, the findings suggest that topiramate is well tolerated and may prove useful in the treatment of PG.

Paroxetine. ► Paroxetine, another SSRI, has been investigated as a possible treatment for PG. In a double-blind, placebo-controlled study examining the efficacy and tolerability of paroxetine treatment in PG (Brewer et al. 2008), subjects were entered into a week-long placebo lead-in and then assigned to receive paroxetine or placebo for 8 weeks. Results revealed a greater reduction in gambling symptoms in the paroxetine group as compared to the placebo group; however, the results are limited by a small sample size with unequal numbers of men and women and a relatively short treatment course of 8 weeks. Still, the findings provided preliminary evidence to suggest paroxetine may be effective in the treatment of PG.

A larger 16-week, double-blind, placebo-controlled study was conducted across several sites in two countries to further examine the efficacy of paroxetine (Brewer et al. 2008). Seventy-six individuals with PG were entered into a week-long placebo lead-in followed by randomization to paroxetine or placebo treatment. Although a numerically larger percentage of paroxetine-treated patients were clinical responders as compared to placebo-treated subjects (59% vs. 48%, respectively, at 16 weeks), the difference did not reach statistical significance. While the findings did not replicate those of the earlier study, perhaps related to the substantial placebo response, the results suggest paroxetine is well tolerated.

As with opioid antagonists, individual differences may be important to consider for SRIs. Specific subgroups of individuals (e.g., those with depression or anxiety disorders) might respond preferentially to SRIs, and this possibility warrants further investigation. A subsequent analysis of individuals involved in the earlier-mentioned paroxetine trial investigated the relationship between measures of impulsivity and compulsivity with respect to treatment outcome. Although both impulsivity and compulsivity measures were associated with gambling severity at treatment onset, changes in gambling symptomatology correlated with changes in impulsivity during the course of treatment. No relationship was observed with respect to paroxetine treatment. These findings suggest that treatments that target impulsivity may be worth pursuing further in the treatment of PG.

Sertraline. To date, only one controlled trial of ► sertraline, another SSRI, has been conducted (Brewer et al. 2008). Sixty individuals with PG were treated in a double-blind, flexible-dose, placebo-controlled study for 6 months. Improvement was observed in both the sertraline and the placebo groups, with no statistically significant differences in outcome measures between the two groups at trial end. These findings were limited by a high placebo response and a relatively small sample.

Escitalopram. ► Escitalopram, another SSRI, is FDA-approved for the treatment of major depression and anxiety disorders. As PG and anxiety disorders often co-occur, escitalopram has been investigated in the treatment of individuals with PG and co-occurring anxiety disorders. Thirteen individuals were enrolled in an open-label 12-week trial of escitalopram (Brewer et al. 2008; Grant and Potenza 2007, 2008). Approximately 62% of individuals who completed the study experienced a 30% or greater reduction in both gambling and anxiety symptoms and were considered treatment responders. These individuals were then enrolled in an 8-week double-blind discontinuation. While no statistically significant worsening of symptoms was reported for those who had received escitalopram, the individual randomized to placebo reported a return of gambling and anxiety symptoms within 4 weeks.

While a preliminary pilot, these data demonstrate an association between open-label escitalopram and improvements on reported gambling and anxiety symptoms and quality of life, and suggest both gambling and anxiety may be addressed simultaneously during a course of pharmacologic treatment. The study is limited by a small sample size, lack of a placebo control group in the initial phase, lack of blinding in the initial phase, and a small number of individuals participating in the double-blind discontinuation phase.

In a recent open-label trial, 19 individuals with PG were enrolled in a 10-week course of escitalopram

following a 2-week observation period (Black et al. 2007). Improvement in gambling symptom severity, urges, and behaviors and decreases in money wagered and time spent gambling were observed. The drug was well tolerated with no dropouts attributed to side effects. The limitations of the study include a small sample size, lack of a placebo group, lack of blinding, and short treatment trial duration.

Nefazodone. Nefazodone, primarily a serotonin receptor antagonist, exhibits characteristics of a mixed noradrenergic/serotonergic reuptake inhibitor (NSRI). Fourteen PG subjects were enrolled in an 8-week open-trial flexible-dose investigation of orally administered nefazodone (Grant and Potenza 2007). Of the 12 completers, 75% were considered responders with significant reductions in episodes of gambling and time and money spent gambling per week. Limitations include lack of both a placebo-control group and double blinding.

Overall, findings from studies investigating medications that target serotonin systems are mixed, generating a complex picture. While case studies and open-trial investigations have demonstrated support for the utility of SSRIs and serotonin receptor antagonists, larger controlled trials have been less consistent. The findings suggest that SSRIs and serotonin antagonists may be effective for specific groups of PG subjects. More extensive and targeted research with careful characterization of subject groups (e.g., defined by co-occurring disorders) or specific individual differences (e.g., readily measurable clinical information in self-report, behavioral and genetic domains) is necessary to better clarify the role of serotonergic drugs in the short- and long-term treatment of individuals with PG.

Mood Stabilizers

► Bipolar disorder and PG share characteristics including impulsive behavior, risk taking, fluctuations in mood, and poor judgment (Iancu et al. 2008). Additionally, PG often co-occurs with bipolar disorders. Should the impulsivity in ► mania and related disorders on a bipolar spectrum possess similar underlying neurobiological mechanisms as the urges in PG, then drugs effective in the treatment of bipolar disorder may be helpful for individuals with PG.

Lithium. A medication typically used to treat manic states and mood lability associated with bipolar disorder, ► lithium has been investigated in the treatment of PG. An early set of case studies investigated the effectiveness of lithium carbonate to treat three individuals with compulsive gambling and found lithium to be well tolerated (Brewer et al. 2008). Findings suggest lithium treatment may have blunted the reported thrill individuals experienced when gambling and decreased the frequency of gambling. The results are considerably limited by the nature of the case studies, providing only preliminary support for the continued investigation of lithium to treat PG.

To date, only one double-blind, placebo-controlled trial of lithium has been conducted (Brewer et al. 2008). Forty individuals with PG and bipolar-spectrum disorders (predominantly bipolar II) were randomly assigned to receive sustained-release lithium or placebo for 10 weeks. Although no significant between-treatment differences were observed between groups on several self-reported gambling behaviors (number of gambling episodes per week, time spent gambling per episode, or money lost gambling), greater improvement was observed for individuals receiving lithium on measures of gambling-related thoughts and urges compared to individuals receiving placebo. Decreases in measures of mania over time paralleled decreases in measures of gambling. The findings were limited by the relatively short treatment duration and a small sample size. Nonetheless, the study supports the tolerability and efficacy of lithium in the short-term treatment of PG and co-occurring bipolar-spectrum disorders. It also highlights the need for researchers to identify clinically relevant subgroups of individuals with PG.

Valproate. ► Valproate is an anticonvulsant and mood stabilizer that has been used in the treatments of bipolar disorder and epilepsy. Based upon the success of valproate and other mood stabilizers to treat disorders with impulsive features (e.g., aggressive behavior, kleptomania, ► trichotillomania, and borderline personality disorder), it has been explored in the treatment of PG.

In a single-blind trial, 42 individuals with PG were randomly assigned to receive lithium or valproate for 14 weeks (Brewer et al. 2008). Both treatment groups demonstrated improvement on gambling-related measures and no significant between-group differences by the end of treatment. While limited by a lack of a placebo-control group, a small sample size, and single-blind design, the findings suggest valproate may work as well as lithium in diminishing gambling-related symptoms in PG.

Olanzapine. Traditionally used as an antipsychotic, ► olanzapine demonstrates mood-stabilizing properties, possibly mediated through dopamine and serotonin receptor antagonism, and thus has been investigated as a possible treatment for PG. Support for its proposed use in PG stems from its efficacy in the treatment of other ICDs such as trichotillomania and skin picking. Two controlled trials of olanzapine to treat PG have been conducted.

In a 12-week double-blind, placebo-controlled trial, 42 individuals with PG was randomly assigned to receive

olanzapine or placebo (Grant and Potenza 2008). Treatment with olanzapine was similarly efficacious as placebo. Olanzapine treatment was associated with discontinuation. Limitations included a relatively small sample and short-term duration. A 7-week, double-blind, placebo-controlled trial of olanzapine was conducted with a group of 21 individuals with video-poker-based PG (Grant and Potenza 2008). As with the other investigations, no significant between-group differences in outcome were observed. The study was limited by a small sample, consistently, solely of video-poker gamblers and the exclusion of individuals with co-occurring psychiatric disorders. Findings suggest that olanzapine may not be any more effective than placebo in the treatment of PG.

Carbamazepine. ► Carbamazepine is a mood stabilizer that is used to treat bipolar disorder and has shown some efficacy in treating ICDs. Support for the investigation of carbamazepine to treat PG comes from two sources: the proposed relationship between PG and bipolar disorder, and the implication that carbamazepine may dampen the impulsivity proposed to underlie PG (Black et al. 2008). A 10-week open-label study examined extended-release carbamazepine in a sample of eight individuals with PG and found the majority to be treatment responders with a reduction in gambling severity; almost half reported abstaining from gambling during the final month of treatment. The findings suggest the possible efficacy of extended-release carbamazepine in the treatment of PG, but should be interpreted with caution based upon the small sample size, the lack of blinding and a placebo-control group, and considerable treatment drop out.

Overall, studies investigating the effectiveness of mood stabilizers in the treatment of PG suggest some medications may reduce preoccupations with gambling, frequency of gambling, and amount of money wagered on gambling; however, not all mood stabilizers have demonstrated consistent efficacy. Therefore, it is important for research to evaluate further the efficacies and tolerabilities of specific mood stabilizers in the treatment of well-defined groups of PG subjects such as those with co-occurring bipolar disorders.

Glutamatergic Agents

N-Acetyl cysteine. Studies have suggested that extracellular ► glutamate within the nucleus accumbens may mediate reward-seeking behaviors by decreasing cravings. ► N-acetyl cysteine (NAC), a glutamate-modulating agent, is proposed to influence extracellular levels of glutamate leading to a stimulation of the inhibitory glutamate receptors. NAC has been found to reduce reward seeking in studies of cocaine dependent rats and craving in a study of individuals with cocaine addiction.

To date, only one study has examined the potential of NAC in the treatment of PG (Grant and Potenza 2008). Twenty-seven individuals with pathological gambling were entered into an 8-week open-label trial of NAC with treatment responders completing a 6-week randomized, double-blind discontinuation phase. Gambling symptoms improved in the majority of treatment completers during the treatment phase, with a trend toward a significant difference between individuals in the active vs. the placebo group at the end of the discontinuation phase (response percentages of 83.3 and 28.6% for the active drug and placebo groups, respectively). These findings suggest that there may be an effect that is attributable to the administration of the active drug, although the lack of a placebo control group in the initial phase limits the interpretation of the results. Additionally, the study was limited by a small sample size. The results preliminarily suggest modulation of the glutamate system may play an important role in the reward-seeking behavior observed in PG and that NAC may be effective in the treatment of PG.

Other Agents

Bupropion. As a reuptake inhibitor of dopamine and noradrenaline, ► bupropion is approved for the treatment of major depression and nicotine dependence, and in the latter condition reduces both smoking-related urges and withdrawal. Based on data that bupropion may be helpful in the treatment of ► attention deficit hyperactivity disorder (ADHD), proposed similarities between ADHD and pathological gambling, and bupropion's proposed mechanism of action, bupropion was investigated to test the hypothesis that it would target impulsivity and attentional deficits in individuals with PG (Iancu et al. 2008).

In an initial open-label trial, ten individuals with PG were prescribed a flexible dose of bupropion for 8 weeks (Brewer et al. 2008). The drug was well tolerated and significant improvements in gambling symptoms were observed. Study imitations include the open-label, unblinded design, small sample, and short treatment duration. A subsequent study examined the efficacy of bupropion, comparing it to that of naltrexone, in the treatment of PG (Brewer et al. 2008). Thirty-six men with PG were randomly assigned to receive either sustained-release bupropion or naltrexone for 12 weeks. The majority of individuals in both treatment groups responded well to treatment with comparable percentages of responders. The findings suggest that bupropion may be as effective as naltrexone in reducing gambling severity,

the frequency of gambling, and the amount of money spent on gambling. Study limitations include the lack of a placebo-control group, short duration of treatment, and small sample.

A later placebo-controlled trial was conducted in which 39 individuals with PG were randomly assigned to a 12-week course of bupropion or placebo (Iancu et al. 2008). Individuals receiving bupropion and placebo showed comparable improvement on short-term measures of gambling severity and placebo response was frequently observed. Study limitations include significant treatment drop out. Together, findings suggest that future treatment trials target specific subgroups of individuals with PG, such as those with co-occurring depression or nicotine dependence, disorders representing current indications for bupropion.

Summary

Findings from pharmacologic studies emphasize the potential for pharmacotherapies, with arguably the strongest data supporting the use of opioid antagonists, particularly among individuals with strong gambling urges and familial propensities for addiction. Other medications (e.g., glutamatergic agents such as NAC) also appear promising, whereas other drugs (e.g., SRIs) have shown mixed results and might be particularly helpful for specific subgroups. The interpretation of open-label studies should be circumspect, given frequent placebo responses in controlled trials and apparent failures to replicate initially promising open-label findings in randomized placebo-controlled trials. Pharmacotherapy trials thus far have been relatively short and highlight the need for large-scale investigations with longer treatment courses in order to better understand the potential long-term benefits and risks of these medications. Medications that have been tested can be conceptualized and grouped based upon their proposed mechanisms of action (e.g., opioid antagonists, SRIs, mood stabilizers), and individual differences (e.g., with respect to co-occurring disorders) and may be particularly relevant in selecting the most appropriate drug treatments for specific patients. Investigating potential benefits and risks of specific pharmacotherapies in conjunction with specific empirically supported psychotherapies represents an important next step.

Cross-References

- ► Impulse Control Disorders
- ► Mood Stabilizers
- ► Opioids
- ► Substance Use Disorders

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Patient-Controlled Analgesia

Definition

A method of pharmacological pain relief in which a patient initiates and controls delivery of the analgesic, typically by pressing a button on the PCA machine, which results in an infusion of a prescribed amount of the analgesic through an implanted intravenous catheter. There is a certain amount of time after each infusion during which no further infusions are possible.

Pavlovian Conditioning

Synonyms

Classical conditioning; Respondent conditioning

Definition

In its simplest form, Pavlovian conditioning typically involves the presentation of two stimuli; one is termed a conditioned stimulus (CS) and the other is termed an

unconditioned stimulus (US). The stimuli are often presented relatively close in time and independent of the subject's behavior. Conditioning is said to occur when one of the stimuli either comes to control a response it did not previously control or modify an ongoing behavior. In laboratory situations, the CS tends to be a relatively neutral stimulus such as an auditory, olfactory, tactile, or visual cue. The US tends to be a stimulus with motivational properties (food, water, sex, illness, drug, etc.). This setup tends to be for methodological convenience (i.e., easy to measure conditioning) rather than ecological relevance as stimuli with motivational effects readily function as CSs and occasion setters. Although most Pavlovian conditioning research involves repeated presentation of the CS and US, one trial conditioning is well documented.

Cross-References

- ▶ Active Avoidance
- ▶ Alcohol Preference Test
- ▶ Blocking, Overshadowing, and Related Concepts
- ▶ Classical (Pavlovian) Conditioning
- ▶ Conditioned Drug Effects
- ▶ Conditioned Place Preference and Aversion
- ▶ Conditioned Taste Aversions
- ▶ Conditioned Taste Preferences
- ▶ Latent Inhibition
- ▶ Occasion Setting With Drugs
- ▶ Passive Avoidance
- ▶ Pavlovian Fear Conditioning

Pavlovian Fear Conditioning

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Synonyms

Classical fear conditioning; Conditioned emotional response; Conditioned freezing

Definition

Pavlovian fear conditioning is a behavioral paradigm in which an initially neutral cue (the ▶ conditioned stimulus, ▶ CS), usually a tone, is paired with an aversive stimulus (the ▶ unconditioned stimulus, ▶ US), usually a footshock, that elicits a fear ▶ unconditional response (▶ UR). As a result of this pairing, subjects form an associative memory between the CS and US. Following training, when presented with the CS alone, the subject will exhibit a fear-▶ conditioned response (▶ CR), which is a defensive behavior related, but not identical to the UR. Aside from fear of the tone (▶ cued fear), subjects also come to fear the environmental context associated with shock administration (▶ contextual fear). In the standard paradigm, rodents are trained in fear-conditioning chambers and receive 1–10 tone-shock pairings over the course of 5–10 min. The rodents are returned to the conditioning chambers days or weeks later for a brief contextual fear test, which consists of placing the animals in the chambers for 5–10 min and observing fear behaviors. On a third day, cued fear is assessed in a novel context by presenting the animals with the training tone 1–3 times after a 2-min baseline period (Anagnostaras et al. 1999, 2000; Fanselow 1984; Maren 2008). This overall experimental scheme is often modified depending on the needs of the experimenters. ▶ Fear is an inferred psychological state, which serves to organize and coordinate various species-specific defensive responses necessary for survival. Many defensive responses can be studied during the contextual and cued fear tests, including increases in heart rate, blood pressure, respiration, analgesia, ulcers, glucocorticoid activation, muscle tone, skin conductance, and potentiated startle (Davis 1992). However, the most commonly assessed fear response in mice and rats is ▶ freezing behavior, because of convenience and reliability. Freezing is defined as the absence of all movements other than that required for respiration, and can be scored by observers using time-sampling, a stopwatch, or a variety of automated methods (Anagnostaras et al. 2000; Fanselow 1984).

Impact of Psychoactive Drugs

Neurobiology

As the neurobiology and behavioral psychology of Pavlovian fear conditioning are well understood, Pavlovian fear conditioning has become a valuable rodent model of both memory and anxiety in humans. Pavlovian fear conditioning depends on the convergence of CS and US information in the basolateral/lateral complex of the ▶ amygdala. The CS–US association may occur in the amygdala via a synaptic process like ▶ long-term potentiation (Rogan et al. 1997). Production of the fear response, following presentation of the CS or US, depends on the central nucleus of the amygdala, which coordinates the output of defensive responses through downstream connections with response-specific brain centers (Davis 1992; Maren 2003). For example, freezing and conditioned analgesia are generated by the periaqueductal gray matter, while potentiated startle is mediated by the nucleus

reticularis pontis caudalis. Thus, discrete cued fear is a reductionist model of associative memory that can be studied in the basolateral/lateral complex of the amygdala. Aside from the amygdala, contextual fear is dependent on the ▶ hippocampus; and this rodent paradigm has become a leading model of human ▶ declarative memory (Anagnostaras et al. 2001; Maren 2008). As with human amnesia, lesions of the hippocampus made shortly after conditioning (recent memory) produce a severe and selective deficit of contextual fear, whereas those made 1 month or more after training (remote memory) have little or no effect on contextual fear, a phenomenon known as temporally graded retrograde amnesia. This occurs because over time, contextual memories come to depend on cortical areas. Therefore, contextual fear conditioning can be used as a model not only for acquisition of declarative memories, but also for consolidation of those memories from a hippocampus-dependent to cortical-dependent state. In contrast, the amygdala remains important for both contextual and tone-fear conditioning for the life of the animal (Gale et al. 2004). Therefore, it is believed that the role of the hippocampus in fear conditioning is specifically to acquire a spatial or configural representation of context, which is then conferred to the amgydala for association with the shock (Anagnostaras et al. 2001).

Role in Pharmacological Screening

As a Model of Higher Level Cognition

Fear conditioning is an efficient model of higher level cognition for many reasons (Anagnostaras et al. 2000). First and foremost, conditioned freezing is an extremely reliable behavioral measure, and the equipment used is fairly standardized, compact, and readily available. Second, the neurobiology is well understood and internally controlled; it can dissociate hippocampus-dependent and -independent memory within the same subject. For example, a deficit observed in contextual and tone fear can be interpreted as affecting fear in general, whereas a deficit selective to contextual fear can be interpreted as likely to affect declarative memory. Third, it is rapidly acquired (1–10 tone-shock pairings in a 5–10-min period are commonly used) and lasts the lifetime of the animal. Because training is punctate and brief, it is highly suitable for studies that require the examination of memory a few minutes or hours after acquisition, or those requiring administration of an agent during training. Most other hippocampus-dependent memory paradigms, in contrast, require many hours and days of training. Fourth, it is very amenable to high-throughput screening, because of reliability, quick acquisition, and compact equipment that can be concentrated in a small lab space. Fifth, the procedures for mice and rats are quite similar and fairly interchangeable. This means fear-conditioning researchers can take advantage of the large behavioral and pharmacological database for rats, as well as the more novel database for genetically modified mice. Finally, fear conditioning has already been used extensively in rodents to model cognitive function and a large experiential database exists on the various caveats and procedures one can use.

Some uses of fear conditioning in pharmacological screening include toxicological assessment for amnesia or specific assessment of drugs to enhance memory. For example, researchers may administer a given treatment drug during fear-conditioning training to ensure that overall cognitive functioning remains intact. Fear conditioning can be similarly useful in screening for agents that may enhance memory acquisition or expression. This can be done in normal mice or rats if screening for general cognitive enhancers or in genetic models of memory defects, such as ▶ Alzheimer's disease or mental retardation. Fear conditioning has already proven valuable in this sense, and its high efficiency and comparable performance in mice and rats have lent to this value (Maren 2008).

A variety of ancillary measures can be taken during the fear-conditioning session which can be useful in addressing confounds or other concerns the experimenter may have. For example, locomotor activity is frequently assessed prior to the tone-shock pairing on the training day, as an indicator of overall activity. If a drug or mutation produces a large drop or increase in activity during this time period, it is likely it would do so on the open-field paradigm as well. Second, activity during the shock can be used as a gross measure of pain. If shock reactivity is abnormal this could suggest that the animals are unable to feel pain. All of these measures may be taken using automated equipment (Anagnostaras et al. 2000). Finally, freezing during the training period (known as post-shock freezing) can be used as a measure of initial acquisition. This could be particularly important in situations where animals show deficits in contextual and tone fear during testing, in order to show that the animals are actually capable of exhibiting the freezing response. Thus, fear conditioning offers many opportunities for control over various confounds that may present themselves.

As a Model of Anxiety Disorders, Especially Phobia

Pavlovian fear conditioning is also a prominent model of pathological fear, such as in ▶ anxiety disorders. Fear conditioning is a model for both etiology as well as treatment of pathological fear, especially phobia. Most often phobia is treated through exposure (or extinction) therapy, whereby the subject is repeatedly exposed to the cues associated with fear. In animals, this is most often

modeled through repeated presentations of the tone without any reinforcement. ▶ Extinction is effective but weaker than initial conditioning, and is thus subject to loss due to changes in conditions of testing (such as a context shift, known as renewal), or simply passage of time (known as spontaneous recovery). Thus, considerable effort has been made to develop extinction-enhancing drugs, which would be given during extinction training to make it more stable and robust. Among agents that have been discovered this way are D-cycloserine and cannabinoid agonists (Quirk and Mueller 2008). Fear conditioning can also be used to screen for drugs which reduce fear specifically, though this is less common than using unlearned fear tasks, such as the ▶ elevated plus maze. This is likely to change as fear conditioning continues to be adopted in pharmacological work.

Conclusion

Pavlovian fear conditioning, especially conditioned freezing, has become a valuable tool for modeling general cognitive function, especially declarative memory or pathological fear. It is also a model of learning and memory, in general. The simple and reliable nature of the paradigm lends itself to high-throughput applications, which can be followed up in secondary evaluation by additional memory or anxiety tests. Thus, Pavlovian fear conditioning is a tool of growing utility in pharmacological assessment.

Cross-References

▶ Amygdala
▶ Anxiety: Animal Models
▶ Classical Conditioning
▶ Consolidation
▶ Declarative and Nondeclarative Memory
▶ Fear Conditioning
▶ Hippocampus
▶ Learning & Memory: Molecular Mechanisms
▶ Long-Term Potentiation
▶ Reconsolidation

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Paxil

▶ Paroxetine

PCP

▶ Phencyclidine

PD

▶ Parkinson's Disease

PDD NOS

▶ Pervasive Developmental Disorder Not Otherwise Specified

PDE Inhibitors

▶ Phosphodiesterase Inhibitors

PDE3 Inhibitors

Definition

PDE3 inhibitors are drugs that inhibit phosphodiesterase3, which hydrolyzes cAMP. PDE3 is found in the heart and smooth muscles, but also throughout the brain.

There are two PDE3 inhibitors on the market; milrinone (Primacor) for the treatment of congestive heart failure and cilostazol (Pletal) for the treatment of intermittent claudication. Cilostazol is also in clinical development for the treatment of stroke.

Cross-References

- ▶ Congestive Heart Failure
- ▶ Intermittent Claudication
- ▶ PDE4 Inhibitors
- ▶ PDE5 Inhibitors
- ▶ Phosphodiesterase Inhibitors

PDE4 Inhibitors

Definition

PDE4 inhibitors are drugs that inhibit phosphodiesterase4, which hydrolyzes cAMP. PDE4 is found in a wide variety of tissues including lungs and smooth muscles. It is also present in brain structures such as the hippocampus, amygdala, and cortical areas. PDE4 inhibitors have clinical potential for the treatment of inflammatory disorders including asthma and chronic obstructive pulmonary disease. In addition, they could offer possible treatments for depression, Alzheimer's disease, or pain. However, up to now none of the developed PDE4 inhibitors has reached the market due to the emetic side effects including nausea and vomiting. One of the most explored PDE4 inhibitors is rolipram.

Cross-References

- ▶ PDE3 Inhibitors
- ▶ PDE5 Inhibitors
- ▶ Phosphodiesterase Inhibitors
- ▶ Rolipram

PDE5 Inhibitors

Definition

PDE5 inhibitors are drugs that inhibit phosphodiesterase5, which hydrolyzes cGMP. PDE5 is particularly present in smooth muscles of lungs and the corpus cavernosum. The PDE5 inhibitor sildenafil is on the market for the treatment of erectile dysfunction under the name of Viagra. In addition, sildenafil has been approved for the treatment of arterial pulmonary hypertension under the name of Revatio. Two other PDE5 inhibitors approved for the treatment of erectile dysfunction are vardenafil (Levitra) and tadalafil (Cialis).

Cross-References

- ▶ Erectile Dysfunction
- ▶ PDE3 Inhibitors
- ▶ PDE4 Inhibitors
- ▶ Phosphodiesterase Inhibitors
- ▶ Pulmonary Hypertension
- ▶ Sildenafil

Peak-Interval Procedure

Definition

Peak-interval (PI) procedure is a ▶ reproduction protocol that comprises two types of trials randomly intermixed: In fixed-interval trials, subject's responses are reinforced at the to-be-timed duration. In peak trials, subjects are required to respond at the appropriate time, but no reinforcement is available. The typical result is that the distribution of responses in peak trials is centered around the criterion duration, with a variance proportional to this criterion. In a variant of this procedure, the PI procedure with gaps, subjects are also presented with trials in which the to-be-timed duration is interrupted by a brief gap or retention interval in order to evaluate their short-term memory for time.

Cross-References

- ▶ Timing Accuracy

Pediatric-Onset Obsessive-Compulsive Disorder

- ▶ Obsessive-Compulsive Anxiety Disorders in Childhood

Pediatric Schizophrenia

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Synonyms

Childhood-onset schizophrenia; EOS; Early onset schizophrenia; Schizophrenia with onset during childhood and adolescence; Very early onset schizophrenia (VEOS)

Definition

The onset of ▶ schizophrenia before age 18 years, i.e., during childhood and adolescence. Early onset schizophrenia refers to cases with onset between age 13 and 17 years whereas very early onset schizophrenia or childhood-onset schizophrenia refers to onset before age 13 years.

Role of Pharmacotherapy

Nosology, Epidemiology, Phenomenology

The diagnosis of pediatric schizophrenia is made using unmodified criteria for adulthood-onset schizophrenia (i.e., onset at age 18 or older). The subtypes of schizophrenia are also identical in both groups. While the prevalence of childhood-onset schizophrenia (onset of psychotic symptoms before 13 years of age) is very low (approximately 1/100 cases of schizophrenia), approximately 12%–33% of individuals with schizophrenia have their illness onset between age 13 and 17 (Kumra et al. 2008). Current phenomenological, cognitive, genetic, and neuroimaging data strongly support continuity between pediatric and adult onset schizophrenia, suggesting similar neurobiological correlates and clinical deficits (Kyriakopoulos and Frangou 2007). Although the (yet unknown) etiology and pathophysiology of pediatric and adulthood schizophrenia are believed to be very similar, patients with pediatric onset schizophrenia seem to have a worse illness course that generally is characterized by greater chronicity and functional impairment compared to the adulthood-onset counterpart (Kumra et al. 2008). Whether this is related to direct biological effects or to the fact that the psychotic illness occurs at a time of critical developmental tasks, which disrupts the achievement of educational and social milestones, is unclear. However, due to the difference in outcomes, schizophrenia with onset before 18 years has been used as a distinct phenotype for genetic research in order to achieve greater homogeneity. Of note, however, patients with adulthood-onset schizophrenia also commonly experience varying degrees of developmental delays, psychosocial and educational problems, and functional decline during childhood or adolescence. Moreover, patients with pediatric and adulthood-onset schizophrenia frequently report "prodromal" psychotic symptoms and signs in childhood or adolescence. The ▶ schizophrenia prodrome often consists of depressive and negative symptoms as well as, attenuated psychotic symptoms (i.e., subthreshold forms of unusual ideas, suspiciousness, grandiosity, abnormal perceptions, and disorganized thought, speech or behavior) (Correll et al. in press).

The Evidence Base

To date, 14 randomized controlled trials (RCTs) (n = 1,155) have been completed in patients with pediatric schizophrenia (Kumra et al. 2008; Sikich et al. 2008). Six trials had a placebo comparator and evaluated the efficacy and safety of ▶ haloperidol (N = 1, n = 12), haloperidol and loxapine (N = 1, n = 75), ▶ aripiprazole (N = 1, n = 301), quetiapine (N = 1, n = 220), ▶ risperidone (N = 1, n = 160), and ▶ olanzapine (N = 1, n = 107), and one trial (n = 279) used a very low dose of risperidone (0.15–0.6 mg/day) as a pseudo-placebo comparator (N denotes the number of trials with each drug, n denotes the number of patients).

In addition to the placebo-controlled, three-arm study comparing haloperidol and loxapine (N = 1, n = 75), another seven trials (n = 275) compared antipsychotics head-to-head in youth with schizophrenia. These included a comparison of ▶ thiothixene and ▶ thioridazine (N = 1, n = 21), haloperidol, olanzapine, and risperidone (N = 1, n = 50, 52% schizophrenia spectrum psychosis, 48% affective spectrum psychosis), ▶ molindone, olanzapine, and risperidone (N = 1, n = 119), haloperidol and ▶ clozapine (N = 1, n = 21), clozapine and olanzapine (N = 2, n = 64), and olanzapine and ▶ quetiapine (N = 1, n = 50, 64% schizophrenia spectrum psychosis, 36% affective spectrum psychosis).

Efficacy

While the two underpowered studies from 1976 and 1984 involving ▶ first-generation antipsychotics (FGAs) did not significantly separate from placebo, there was a trend for greater improvement on the Clinical Global Impressions-Severity (CGI-S) scale in favor of haloperidol and loxapine in the one study, and a significant baseline to endpoint change in the Brief Psychiatric Rating Scale (BPRS) for haloperidol, but not for placebo (Kumra et al. 2008). By contrast, all of the ▶ second-generation antipsychotic (SGA) trials completed since 2005 showed significantly greater improvements on the primary outcome measure, the Positive and Negative Syndrome Scale (PANSS) for all doses that were studied. Overall, the numbers-needed-to-treat (NNT) for study defined response for aripiprazole, olanzapine, quetiapine, and risperidone range from 4 to 10. Based on the results from these placebo-controlled trials in pediatric schizophrenia, risperidone, quetiapine, olanzapine and aripiprazole were approved by the Food and Drug Administration (FDA) in the USA for use in adolescents age 13–17 years old, and aripiprazole was approved for use in adolescents age 15–17 years in Europe by the European Medicines Agency (EMEA). Moreover, after an official FDA hearing in June 2009, olanzapine and

quetiapine are expected to receive FDA approval in the USA for use in adolescents age 13–17 years with schizophrenia. Despite inadequate trial data for first-generation antipsychotics, haloperidol and thioridazine were grandfathered in, being indicated for adolescents with schizophrenia in the USA, and the dosing and use of several first-generation antipsychotics, mainly haloperidol, for adolescents with schizophrenia is mentioned in regulatory documents in some European countries.

Across the seven studies, comparing two FGAs, one FGA with one or two SGAs, or two SGAs with each other, the only significant group differences were found in favor of clozapine compared to haloperidol, regular dose olanzapine (up to 20 mg/day) and to "high"-dose olanzapine (10–30 mg/day) (Kumra et al. 2008; Sikich 2008). Since in all active controlled studies, the numbers of patients in individual study arms were very small, ranging from 8 to 41, a type-2 error cannot be excluded; yet the results of relatively similar efficacy results parallel data in adult schizophrenia.

Tolerability and Side Effects

Children and adolescents seem to be more sensitive to most antipsychotic adverse effects, including sedation, ► Extrapyramidal motor side-effects (except for ► akathisia), withdrawal dyskinesia, prolactin abnormalities, weight gain, and metabolic abnormalities (Correll 2008a). On the other hand, adverse effects that require a longer time to develop (e.g., diabetes mellitus) and that are related to greater medication dose and lifetime exposure (e.g., ► tardive dyskinesia) are less prevalent in pediatric samples. However, there is concern that these later onset adverse events are not seen because of short follow-up periods and that they may emerge in vulnerable patients prematurely in adulthood the earlier antipsychotics are started in childhood.

► Extrapyramidal Side Effects (EPS)

In general, children and adolescents are more sensitive than adults to Parkinsonian side effects associated with FGAs and SGAs (Correll 2008a). An RCT of 40 youths with psychotic disorders comparing haloperidol (mean dose: 5 mg/d), risperidone (mean dose: 4 mg/d), and olanzapine (mean dose: 12 mg/d) found substantial EPS not only with haloperidol (67%), but also with olanzapine (56%) and risperidone (53%), although haloperidol-treated patients reported more severe EPS (Sikich et al. 2004). In the Treatment of Early-Onset Schizophrenia-Spectrum (TEOSS) study, patients randomized to molindone (mean dose: 59.9 mg/day) required more frequent coadministration of an anticholinergic (45%) than patients randomized to risperidone (mean dose: 2.9 mg/day, 34%) or olanzapine (mean dose: 11.8 mg/day, 14%), even though patients on molindone were given prophylactic, blinded benztropine 0.5 mg bid (Sikich et al. 2008). Clozapine and quetiapine appear to be associated with relatively low EPS rates in pediatric patients. For aripiprazole and ► ziprasidone, EPS rates appear to increase with increasing dose.

Akathisia

Incidence rates of ► akathisia from placebo-controlled RCTs in pediatric schizophrenia have been reported for aripiprazole (5% for placebo, 5% in the 10 mg/day group, and 11.8% in the 30 mg/day group), risperidone (6% on placebo, 7% in the 1–3 mg/day group, and 10% in the 4–6 mg/day group), corresponding to NNH of 15 to no risk for aripiprazole 30 mg/day and 10 mg/day, respectively, and 25 to 100 for risperidone 4–6 mg/day and 1–3 mg/day, respectively (Correll 2008b). The relatively high akathisia rates for placebo, especially in the pediatric schizophrenia trials, suggest the potential presence of a relevant carryover effect from prior antipsychotic treatment or the possibility of withdrawal phenomena after a brief washout from antipsychotics and/or medications that can mitigate akathisia. In the TEOSS study, molindone, but not olanzapine or risperidone, was associated with a significantly greater rate of self-reported akathisia compared to risperidone and olanzapine (Sikich et al. 2008).

Withdrawal Dyskinesia

During FGA treatment, youths are at risk of developing withdrawal dyskinesia, yet, unlike in adults, dyskinetic movements are frequently reversible. Withdrawal dyskinesia rates appear to be lower with SGAs compared to FGAs, although a switch from an antipsychotic with strong D2 affinity (risperidone or aripiprazole) to one with less potent affinity (quetiapine or clozapine) may predispose to withdrawal dyskinesia (Correll 2008a).

► Tardive Dyskinesia (TD)

Long-term TD data in patients with pediatric schizophrenia are lacking. A meta-analysis of 10 studies lasting at least 11 months reported on TD rates in 783 patients age 4–18 (weighted mean: 10) years old. Most patients were prepubertal (80%), male (82%), white (79%), and only 3% had a schizophrenia spectrum disorder (Correll and Kane 2007). Across these studies, only three cases of TD were reported, resulting in an annualized incidence rate of 0.4%, which was approximately half of the rate found in a prior meta-analysis of TD rates in adults. However, it is unclear how much these data can be extrapolated to pediatric patients

with schizophrenia, as antipsychotic doses were low, and lifetime exposure was relatively short.

Weight Gain

Although pediatric data are still limited, youth with severe psychiatric disorders seem to be at increased risk for being overweight or obese, especially when exposed to antipsychotics for longer periods of time. Age-inappropriate weight gain is of particular concern in pediatric patients, due to its association with glucose and lipid abnormalities and cardiovascular morbidity/mortality. Reasons for weight gain are complex, including psychiatric illness, unhealthy lifestyle, and treatment effects. A review of pediatric data suggests that the weight gain potential of FGAs and SGAs follows roughly the same ranking order as found in adults, but that the magnitude is greater (Correll 2008a). Exceptions may be a greater relative weight gain propensity of risperidone, and a greater likelihood of aripiprazole and ziprasidone to not be weight neutral in subgroups of pediatric patients (Correll et al. 2009). For example, in an 8-week study, Sikich et al (2004) found a higher weight gain in young patients age 5–17 years with psychotic disorders taking olanzapine for 8 weeks (7.1±4.1 kg) than in those taking either risperidone (4.9±3.6 kg) or haloperidol (3.5±3.7 kg); all weight gain was severe and disproportionate to that expected from normal growth. Results from four 6-week studies in adolescents with schizophrenia suggest that the olanzapine group had the greatest risk for significant weight, risperidone and quetiapine were associated with intermediate risk, and aripiprazole showed the lowest risk. The respective numbers-needed-to-harm (NNH) for ≥7% weight gain was 4 for olanzapine, 7–8 for quetiapine, 8 for risperidone, and 25–34 for aripiprazole (Correll 2008b). However, the interpretation of weight gain results across various studies and agents is complicated by the effects of baseline weight, developmental stage and growth, past antipsychotic exposure, treatment duration and setting, comedications, etc., that varied across trials.

Metabolic Adverse Effects

Whereas in adults the link between antipsychotics and adverse metabolic effects, such as dyslipidemia, hyperglycemia, diabetes, and metabolic syndrome, has been established, the few pediatric studies which reported data have produced mostly negative results. Interpretation of these findings is limited by the small sample size, varying treatment histories, and inclusion of non-fasting blood assessments. Case reports of new-onset diabetes in antipsychotic-treated youths and the known link between weight gain and metabolic abnormalities suggest that youths are at least as liable to develop metabolic abnormalities as adults. However, in pediatric RCTs, so far, only olanzapine has been associated with significant increases in glucose, insulin, and lipids (Correll 2008a,b). Nevertheless, the lack of significant metabolic abnormalities in the other short-term RCTs despite mostly significant weight gain needs to be interpreted with caution, as the negative findings could be due to the short-term trial duration, lack of strict fasting assessments, and to order effects in patients with more extensive past antipsychotic exposure. A recent cohort study in 272 antipsychotic-naive youth (30.1% with schizophrenia spectrum disorders) confirmed that during the first 12 weeks of treatment, olanzapine has the greatest adverse effect on body composition, which was associated with significant worsening of fasting glucose, insulin, insulin resistance and all lipid parameters, except for HDL-cholesterol (Correll et al. 2009). By contrast, despite similar adverse effects on body composition, the metabolic effects differed across quetiapine, risperidone and aripiprazole. At least during the first 3 months of treatment, quetiapine was associated with a significant increase in most lipid parameters, whereas with risperidone lead only to a significant increase in triglycerides, and changes with aripiprazole remained non-significant. This suggests that in addition to indirect, weight-related metabolic changes, direct, weight-independent effects on glucose and lipid metabolism exist, at least for some antipsychotics.

Prolactin-related Side Effects

FGAs and SGAs can elevate prolactin levels, and these elevations appear to be accentuated in children and adolescents. Similar to adults, albeit at higher levels during adolescence, the relative potency of antipsychotic drugs in increasing prolactin is, roughly: ▶ paliperidone≥ risperidone>haloperidol> olanzapine≥ziprasidone> quetiapine≥clozapine>aripiprazole. To date, adequate long-term data are lacking to determine if hyperprolactinemia at levels found during antipsychotic therapy alters bone density, sexual maturation, or the risk for benign prolactinomas (Correll 2008a). Since aripiprazole is a partial D2 dopamine agonist, prolactin levels can decrease below baseline. To date, no adverse effects of low prolactin have been described in youth. Complicating the interpretation of the relevance of prolactin elevations in youth is the fact that sexual and reproductive system side effects related to prolactin levels are rarely directly inquired about, and youth might either not express these symptoms due to sexual immaturity or because they do not know what their normal levels of functioning ought to be.

Summary and Conclusion

Although still understudied, schizophrenia with onset in childhood and, especially, with onset in adolescence seems to be biologically and phenomenologically continuous with adulthood-onset schizophrenia, albeit being more often associated with poorer illness course and outcomes. Moreover, children and adolescents appear to be more sensitive to antipsychotic adverse effects than adults, at least compared to more chronically ill samples. As in adults, antipsychotics are more effective than placebo, with meaningful clinical effects. Moreover, also like in adults, differences in efficacy between antipsychotics seem to be much smaller and less predictable than differences in side effects and, thus, in effectiveness, which takes the short- and long-term side effect burden and treatment discontinuation rates into account. Based on this risk-benefit evaluation, it appears that second-generation antipsychotics might be preferable to first-generation antipsychotics to reduce the risk for EPS, TD, secondary negative symptoms, early treatment discontinuations and, possibly, relapse rates. However, since a number of second-generation antipsychotics are associated with significantly greater risks for age-inappropriate weight gain and metabolic abnormalities than mid and high potency first-generation antipsychotics, the neuromotor side effect advantages and related benefits are likely offset by the risk of longer-term health problems for those higher metabolic risk second-generation antipsychotics. Therefore, it appears that second-generation antipsychotics with the least risk for developmentally inappropriate weight gain and related or, even, direct metabolic abnormalities are to be considered first-line treatment options. In case these fail, higher cardiometabolic risk antipsychotics should be tried. Given the significant efficacy advantage of clozapine over first- and second-generation antipsychotics in pediatric onset schizophrenia similar to adulthood schizophrenia, clozapine should be considered for severely ill and treatment resistant youth with schizophrenia to improve outcomes and functioning, balancing its problematic side effect profile against its superior efficacy.

Cross-References

- ► First-Generation Antipsychotics
- ► Schizophrenia Prodrome
- ► Second-Generation Antipsychotics

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Pemoline

Synonyms

Magnesium pemoline

Definition

Pemoline is a psychostimulant that was used for the treatment of attention deficit hyperactivity disorder. It was less effective than methylphenidate and was withdrawn from the U.S. market due to liver toxicity. In earlier studies, it was found to produce small enhancements in selective aspects of learning and memory in human and animal subjects.

Cross-References

- ► Attention Deficit Hyperactivity Disorder
- ► Methylphenidate

Pentazocine

Definition

Pentazocine is a synthetic opioid with partial agonist–antagonist properties. It is used to treat mild to moderately severe pain. It can partially block effects of full opioid agonists such as ▶ morphine and heroin. It exists as one of two enantiomers: (−)-pentazocine is a ▶ κ-opioid receptor agonist while (+)-pentazocine is not but displays ten-fold greater affinity for sigma receptors. This action on sigma receptors may account for notable side effects that include hallucinations and other psychotomimetic effects. Apart from its analgesic effects, pentazocine has minimal clinical use. It is subject to abuse and dependence, although the severity is typically less than that for full opioid agonists. Some tablets are formulated to contain both pentazocine and naloxone to reduce abuse; the naloxone blocks opioid effects if the tablets are dissolved and injected, but allows analgesia to develop if they are taken orally.

Cross-References

▶ Morphine
▶ Naloxone
▶ Partial Agonists

Pentobarbital

Synonyms

Pentobarbitone; Sodium 5-ethyl-5-(1-methylbutyl) barbiturate

Definition

First synthesized in 1928, pentobarbital is a short-acting barbiturate used formerly in humans as a sedative/hypnotic and anxiolytic agent. Now it is used more commonly as an anesthetic in veterinary practice and as an anticonvulsant. Like other barbiturates, it acts at the $GABA_A$ receptor to enhance inhibitory neurotransmission but it also acts as an antagonist at glutamate receptors of the AMPA subtype, thereby reducing excitatory neurotransmission. It is now a regulated ▶ drug of abuse, partly because of its association with suicide and as an agent of euthanasia.

Cross-References

▶ Abuse Liability Evaluation
▶ Barbiturates
▶ Driving Under Influence of Drugs
▶ Insomnia
▶ Sedative, Hypnotic, and Anxiolytic Dependence

Pentobarbitone

▶ Pentobarbital

Peptidomics of the Brain

▶ Neuropeptidomics

Pergolide

Synonyms

8 β[(methylthio)methyl]-6-propylergoline monomethanesulfonate; LY127809

Definition

Pergolide is a centrally and long-acting D1 and D2 dopamine receptor agonist. It is believed to stimulate dopamine receptors in the nigrostriatal system. The compound also inhibits the secretion of prolactin and thus is used to treat hyperprolactinemia. Pergolide is generally used as an adjunctive treatment with ▶ levodopa/carbidopa for signs and symptoms of Parkinson's disease. However, the compound was withdrawn from the US market due to stimulation of $5\text{-}HT_{2B}$ receptors and the resulting heart valve problems (valvulopathies). In Europe, cabergoline and pergolide are contraindicated in patients with evidence of valvulopathies.

Cross-References

▶ Anti-Parkinson Drugs

Peri-Adolescent Psychopharmacology

▶ Adolescence and Responses to Drugs

Periciazine

▶ Pericyazine

Pericyazine

Synonyms

Periciazine

Definition

Pericyazine is a first-generation antipsychotic medication that acts as a dopamine D2 antagonist. Pericyazine is indicated for the treatment of schizophrenia and other psychoses, and for short-term adjunctive treatment of severe anxiety, psychomotor agitation, excited or violent states. It is a piperazine-phenothiazine derivative and like other similar agents, it produces drowsiness and sedation. hypotension is common when treatment is initiated.

Cross-References

- ► Antipsychotic Drugs
- ► First-Generation Antipsychotics
- ► Impulse Control Disorders
- ► Schizophrenia

Perinatal Exposure to Drugs

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Definition

Perinatal exposure to drugs involves exposure of the developing organism to substances of abuse or to psychotherapeutic compounds prior to birth and perhaps shortly thereafter. Such drug exposure typically occurs indirectly through maternal drug use, with the drug gaining access to the fetus via crossing the placenta to distribute in amniotic fluid and/or the fetal circulation, and to the infant via partitioning of the drug into milk during lactation.

Current Concepts and State of Knowledge

The prenatal and early ► postnatal period is often a sensitive period during which exposure to a variety of drugs may induce long-term alterations in brain function and behavior that are not evident with comparable exposures later in life. In recognition of this possibility, part of the testing process required for potential new therapeutic compounds in the United States involves assessment of each substance's developmental toxicity in pre-clinical studies (i.e., studies in laboratory animals) before the drug can be approved for initial (Phase 1) clinical trials (e.g., see Hodgson 2004). Initially spear-headed by studies of the ► fetal alcohol syndrome beginning in the mid-1970's, research examining the impact of maternal drug use during pregnancy and lactation has spread to encompass all major drugs of abuse. Through such studies, along with research examining the potential developmental neurotoxicity of environmental contaminants such as lead, consensus has been reached on a number of points. Some of these generalities will be briefly summarized here before highlighting consequences of perinatal exposure to several drugs of abuse.

Despite often necessary differences in assessment measures, generally comparable functional effects are often seen following perinatal drug/chemical exposure in humans and laboratory animals. During the first wave of research in ► developmental toxicology, there was appropriate concern as to whether findings obtained in laboratory animals would be comparable to those seen in human clinical studies. Careful examinations of across-species comparability of findings in animal models and clinical work, however, yielded notable across-species commonalities in the developmental toxicology of chemicals, ranging from ► alcohol, ► anticonvulsants, and ► methadone to environmental neurotoxicants such as lead and methylmercury, even though different measures were often necessary to assess particular functions (e.g., sensory or motor function, cognition, motivation, social behavior, etc.) in clinical studies versus research with laboratory animals (Stanton and Spear 1990). Additional evidence of general across-species comparability has continued to emerge with the escalation of research in this field over subsequent decades (e.g., Slikker et al. 2005; Slotkin 2008), despite challenges in attributing clinical findings to the focal drug per se versus other factors (stressful living environment, malnutrition, use of other drugs, etc.) that often co-occur with maternal drug use (see Fried 2002).

These findings lend credence to the use of animal models in studies of perinatal drug exposures. Such studies are important to confirm and extend clinical findings, anticipate other potential consequences of early drug exposure, determine the neural mechanisms underlying behavioral effects, and suggest potential therapeutic approaches. Yet, applicability of animal models is by no means assured. ► Pharmacokinetic differences are common across species, raising the importance of dose, route of administration and pattern of administration. Given the greater metabolic rate characteristic of small species such as rodents, higher doses may be necessary when using rodent models to produce drug levels in blood equivalent to those seen upon drug use in humans. Yet, too high a dose level may produce drug burdens that are out of the range associated with human exposures,

decreasing the potential relevance of findings obtained with the animal model. Other important considerations when developing animal models include controlling of possible drug-induced decreases in food intake and/or residual effects of drug exposure during pregnancy on subsequent maternal behavior – issues typically addressed via the use of ▶ pair-feeding and ▶ fostering procedures, respectively (e.g., see Spear and File 1996, for discussion and references for these and other control issues). Finally, although multiple offspring are commonly generated per litter when using rodent models of developmental toxicology, the evidence is clear that offspring from the same litter are not independent samples, and thus the assignment of more than one offspring/litter to a given experimental group markedly inflates the possibility of false positives.

Behavioral, hormonal, and neural alterations are typically induced at exposure levels well below those that induce major malformations or maternal toxicity (Adams et al. 2000). It is not surprising that at exposure levels high enough to induce maternal toxicity, chemical and other physiological consequences of that toxicity often exert multiple adverse effects on fetal development, including alterations in brain function and behavior. Yet, neurobehavioral effects are also evident in offspring at drug exposure levels lower than those necessary to induce maternal toxicity or signs of gross malformation in the offspring. The brain is unusually susceptible to disruption by drugs during its development, with drugs potentially affecting a variety of developmental processes, including neuronal migration and differentiation, glia proliferation, along with normal ontogenetic changes in cell adhesion, neural communication, energy utilization, and apoptosis (e.g., Goodlett and Horn 2001). Drug effects on ongoing developmental processes may extend well beyond the direct neural actions of that drug; for instance, perinatal exposure to ▶ nicotine alters not only cholinergic nicotine receptor function throughout life, but also influences the trajectory of development for a wide variety of neurotransmitter systems other than the cholinergic system (Slotkin 2008).

Observed consequences of perinatal exposures are not only drug- and dose-dependent, but also critically dependent on the timing of the exposure, and when and how functional consequences are assessed. Different portions of the brain develop at different times, and hence differ in the timing of their vulnerability to drug-induced disruption. Thus, consequences of developmental exposure to drugs are to some extent dependent on the timing of that exposure. Even as little as a one day difference in the timing of drug exposure can influence behavioral outcome, although generally speaking, the greatest vulnerability for structural damage occurs early in organogenesis, whereas functional impairments are most likely evident following drug exposure during mid- to late-organogenesis (See Spear and File 1996). When varying developmental stage during which drug exposure is given, it is important to note that ▶ altricial animals (such as laboratory rats and mice) are born at a less mature stage than humans. Hence, the ▶ prenatal period in rodents is approximately equivalent to the first and second trimesters of human pregnancy, with the first 10 days or so of postnatal life in rat approximating the third human trimester (see Spear and File 1996, for discussion and citations).

The timing during which functional consequences are assessed is also critical. Functional deficits often emerge well after termination of the drug exposure, and long after the drug and its metabolites have cleared the brain and body. Thus, developmental drug exposures are thought to alter the trajectory of normal brain development, changing future ontogenetic patterns in the emergence of brain neurocircuitry and function (see Slotkin 2008). Under some instances, deficits may be seen early in life and may recover thereafter, perhaps manifesting at some later developmental point (e.g., adolescence), during aging, or under stressful or challenging circumstances (Adams et al. 2000). In other cases, functional alterations may not be readily apparent until neural development is sufficiently mature to reveal underlying deficiencies. For instance, cognitive effects of prenatal exposure to marijuana are minimal during the infant and toddler stage, but do become progressively more evident as normally delayed ▶ executive function capacities emerge, with youth exposed prenatally to marijuana showing disruptions in certain aspects of executive function (e.g., attentional behavior; hypothesis testing) (Fried 2002).

The developmental toxicology of perinatal drug exposure is critically moderated by genetic background and the environment. The process of neural development is orchestrated by genes, with marked changes in the profile of genes expressed as development proceeds across different brain regions. Variants across individuals in the form of expression of particular genes (▶ gene polymorphisms) can increase vulnerability to adverse effects of perinatal drug exposures. Not all women who drink during pregnancy, for example, bear infants that meet the diagnostic criteria (i.e., growth deficiency, CNS disorders, and facial dysmorphic features) of fetal alcohol syndrome (FAS – e.g., see Mattson et al. 2001). Although timing and amount of alcohol use likely contribute to this variability,

the presence or absence of genetic variants that increase the vulnerability of the developing brain to developmental perturbations is also likely contribute. And, at the frontier of current research is the increasing recognition that perinatal drug exposure itself, like other environmental influences, may in turn alter developmental patterns of gene expression in specific brain regions through ▶ epigenetic regulation, exerting long-term effects on brain function through such "▶ developmental programming." Thus, exposure to drugs during the perinatal period provides an important component of the early environment of the developing organism that, along with other early experiences, may influence and be influenced by developmental patterns of ▶ gene expression (see Goodlett and Horn 2001). Consequences of perinatal drug exposure, like other adverse early experiences, may be moderated or exacerbated to some extent by environmental experiences as well. For instance, toddlers exposed to drugs prenatally have been found to be much more likely to exhibit secure attachment relationships if their mother had been abstinent since birth than if their mother continued to abuse drugs (Fried 2002).

Perinatal exposure to ▶ drugs of abuse often exerts lasting and drug-specific neurobehavioral effects. With some drugs of abuse, consequences for offspring may be immediate and obvious, and may resolve to some extent with time. The ▶ neonatal abstinence syndrome is a good example. That is, fetuses of drug-dependent mothers may themselves become addicted, and may undergo withdrawal following removal of their drug source (their mother) at birth. Such signs of withdrawal are most evident in neonates exposed prenatally to ▶ opiates such as heroin or methadone, and are characterized by transient hyperreactivity, irritability, feeding and sleep disturbances (see Spear 1997, for review and references). In contrast to these transitory effects, other consequences of perinatal exposure to drugs of abuse may be evident early in life and persist thereafter. Other consequences may not emerge until later, becoming manifest only when portions of the nervous system critical for expression of that function are sufficiently developed. To illustrate these effects of perinatal exposure to drugs of abuse, the focus will be on four drugs whose developmental effects have been particularly well studied: ▶ alcohol, ▶ nicotine, ▶ cocaine, and ▶ cannabinoids (including those in marijuana).

Cognitive effects. Cognitive deficits are a common sequela of perinatal drug exposure. Exposure to cocaine during development has been reported to impair performance of cognitive tasks in laboratory animals, and to lower IQ, impair language development, and disrupt cognitive function in children (e.g., Harvey 2004). Similarly, exposure to nicotine during development has been observed to induce deficits in cognitive function in both humans and laboratory animals (Slikker et al. 2005). Prenatal alcohol exposure has likewise been shown to disrupt learning and memory in animal studies, with FAS offspring also having difficulties learning both verbal and nonverbal problems, and showing deficits in certain aspects of memory performance (Mattson et al. 2001).

In studies of children exposed prenatally to marijuana, however, little sign of cognitive alterations were evident until the children approached school age. At this time, as non-exposed children began to exhibit increasing evidence of ability in various executive function domains, deficits in these functions began to emerge in children exposed prenatally to marijuana. Impaired ▶ executive functions persisted with age, and were particularly notable on measures of attentional capacity and abstract/visual reasoning. These alterations were not associated with alterations in global IQ scores (Fried 2002). Disruptions in attentional processes have also been reported following prenatal cocaine exposure in developmental studies of both laboratory animals and humans (Harvey 2004). Deficits in executive function also have been reported following heavy prenatal exposure to alcohol (Mattson et al. 2001).

Thus, although alterations in cognitive functions are a common outcome of perinatal drug exposure, the nature of those alterations seemingly differs with the drug of abuse. Indeed, from studies comparing cognitive function in offspring of mothers smoking cigarette versus marijuana during pregnancy, Fried (2002) concluded that in utero exposure to marijuana disrupts "top-down" executive functioning, whereas prenatal exposure to cigarette smoking was associated with alterations in certain basic perceptual abilities and fundamental cognitive skills – more consistent with dysfunction in "bottom-up" cognitive skills.

Increased later drug use/abuse. Human adolescents whose mothers used alcohol during pregnancy have been reported to exhibit early alcohol consumption and a greater propensity to abuse alcohol (Mattson et al. 2001). Indeed, there is some evidence that prenatal exposure to alcohol may exert a greater effect on later alcohol use/abuse than family history of alcohol abuse per se. Studies with laboratory animals have likewise generally observed that fetal or early postnatal exposure to ethanol enhances later intake of alcohol (Spear and Molina 2005). In laboratory animals, prenatal exposure to nicotine, as well as to cocaine, also has been reported to elevate levels of self-administration of the drug later in life beyond those

seen in non-exposed animals (see Harvey 2004; Slotkin 2008). Similarly, adolescents whose mothers smoked during pregnancy, regardless of whether their mothers continued to smoke during their childhood, were at increased risk for beginning to smoke and were more likely to relapse when they attempted to stop smoking (Slotkin 2008). Thus, there is considerable converging evidence across a number of drugs that perinatal exposure to a drug of abuse increases later risk for drug use and abuse.

Other behavioral alterations. Children exposed to alcohol prenatally (whether or not they meet the diagnostic criteria of FAS) are not only at risk for alcohol/drug abuse problems, but also are more likely than non-exposed children to exhibit other problem behaviors as well, including impulsivity, delinquency and hyperactivity, along with poor social and communication skills. Offspring exposed prenatally to marijuana smoke likewise have been reported to exhibit increased levels of delinquency, conduct disorder, hyperactivity and impulsivity (Fried 2002). ► Hyperactivity is also commonly reported following prenatal nicotine exposure in laboratory animals, as well as in children whose mothers smoked during pregnancy (Slikker et al. 2005). Such behavioral disorders are multifactorally determined, and hence could reflect alterations in a diversity of neural systems precipitated by perinatal exposure to these different drugs.

Neural alterations. Cognitive and behavioral alterations following perinatal drug exposures ultimately reflect drug-induced alterations in brain function. These effects are not global, but reflect alterations in specific brain regions that are typically drug-specific and are related to the timing of the exposure. For instance, fetal alcohol exposure was found in human imaging studies to exert particularly pronounced alterations in the corpus callosum, along with reductions in size of the caudate nucleus, cerebellum and hippocampus, findings reminiscent of those seen following prenatal ethanol exposures in laboratory animals (Mattson et al. 2001). The more invasive studies possible when working with animal models have revealed a rich variety of influences of perinatal drug exposure on the developing brain, including alterations in patterns of cell replication/differentiation, neural communication, signal transduction, cell death, gene regulation and so on (Goodlett and Horn 2001; Slikker et al., 2005). And, although observed neural alterations are sometimes highly selective to particular components of the neural systems normally targeted by action of that drug in adulthood, other neural systems are often impacted as well. For instance, in animal studies, prenatal cocaine exposure was found to uncouple D1 dopamine receptors, while leaving D2 receptor functioning largely unaffected. Long-lasting alterations in cortical cytoarchitecture were also evident in the cocaine-exposed offspring, and were suggested to reflect in part altered D1-receptor functioning and the resultant disruption in balance of D1 and D2 regulatory actions on neuronal development (Harvey 2004).

Conclusions

Perinatal exposure to drugs often exerts a long-term impact on brain function and behavior via alterations in the trajectory of neural development and its functional consequences. These effects are rarely global, but instead typically are drug-specific, dependent on the timing of exposure, and moderated by genetic background and early life experiences. Expression of drug-induced alterations also varies with assessment age and functions assessed. Among the consequences of perinatal exposure to drugs of abuse are increases in the propensity for later use/abuse of that drug, potentially contributing to a perpetuating and transgenerational cycle of drug use and abuse.

Cross-References

► Alcohol
► Alcohol Abuse and Dependence
► Cannabinoids
► Cannabis Abuse and Dependence
► Cocaine
► Cocaine Dependence
► Environmental Enrichment and Drug Action
► Epigenetics
► Foetal Alcohol Syndrome
► Impulsivity
► Neurotoxicity
► Neurotoxins
► Nicotine
► Nicotine Dependence and Its Treatment

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Peripheral Markers

Definition

Accessible markers mirroring physiopathologic processes of a disease. Usually, this term refers to markers of neuropsychiatric diseases, considering the difficulties involved in accessing directly into the CNS for studying the pathologic processes. Due to their availability, CSF and blood represent two major sources for identifying suitable peripheral markers of neuropsychiatric dysfunction.

Perospirone

Definition

Perospirone is a benzisothiazole derivative that belongs to the class of second-generation (atypical) antipsychotic drugs and is indicated for the treatment of schizophrenia. It has high-affinity antagonist activity at 5-HT_{2A} and D_2 receptors. It also displays partial 5-HT_{1A} agonist properties and some affinity for D_1, α_1-adrenergic and H_1 receptors, but has no appreciable affinity for muscarinic receptors. It has at least four active metabolites, but all of them have lower affinity for D_2 and 5-HT_{2A} receptors than the parent drug. It can induce extrapyramidal motor side effects and insomnia, but it displays low toxicity.

Cross-References

► Extrapyramidal Motor Side Effects
► Schizophrenia
► Second-Generation Antipsychotics

Perphenazine

Definition

Perphenazine is a first-generation antipsychotic medication that acts as a dopamine D2 receptor antagonist. It is a piperazine-phenothiazine derivative, also available as depot medication. Perphenazine is indicated for the treatment of schizophrenia and other psychoses, mania in bipolar disorder, and the short-term adjunctive treatment of severe anxiety, psychomotor agitation, excited or violent states. It can also be used as an anti-emetic drug. Extrapyramidal motor symptoms occur, especially dystonia especially at high doses.

Cross-References

► Antipsychotic Drugs
► Bipolar Disorder
► Extrapyramidal Motor Side Effects
► First-Generation Antipsychotics
► Schizophrenia

Persecutory Delusions

► Delusional Disorder

Perseveration

Definition

The antithesis of flexibility, perseveration is the term used to refer to responses or behavior that persist even when it is no longer beneficial and may even have a cost. Whenever a task involves an uncued switch, shift, or reversal, the subject will make errors until the new contingencies are learned. If the previously rewarded response persists despite a lack of reinforcement, it is perseverative. There are examples in the literature of the classification of errors made after a rule change as "perseverative" when a respondent persistently returns to making a previously rewarded response even after there is evidence that a

new response has been learned (errors up until this point being classified as "learning errors"). In this, more specific, use of the term, a statistical criterion is applied to make the classification. The term is also used to refer to the continuous repetition of thoughts and statements.

Cross-References

► Five-Choice Serial Reaction Time Task

Personality: Neurobehavioural Foundation and Pharmacological Protocols

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Definition

Personality represents the structuring of human behavior into major traits that reflect the activity of (1) motivational–emotional systems and (2) their underlying neurobiological networks. There is consensus on the existence of four major traits: extraversion, neuroticism, social closeness or agreeableness, and constraint or conscientiousness. We describe the psychological features of these four traits, and how pharmacological protocols have aided in defining their underlying neurobiology. Discussion of the relation of dopamine (DA), serotonin (5-HT), corticotropin-releasing hormone (CRH), and mu-opiate functioning within specific brain regions to the four major traits is provided.

Current Concepts and State of Knowledge

The Nature of Personality. In the early 1970s, a significant development occurred in reconceptualizing the nature of personality. Employing an evolutionary biology perspective, Gray (1973) proposed a new structure of human-motivated behavior defined as systems that evolved to adapt to stimuli critical for survival and species preservation. Such behavioral systems are fundamentally emotional systems that incorporate both a motivational state and emotional experience that is concordant with, and engages us with or disengages us from, rewarding or aversive critical stimuli. Furthermore, Gray hypothesized that each of these motivational–emotional systems is associated with its own network of brain regions and with specific neurotransmitters and neuropeptides that modulate the functioning of those networks. Within this framework, the mean functional properties of the relevant neurotransmitters–neuropeptides, influenced by genetics and experience, may underlie stable individual differences in the behavioral reactivity of such systems. This theoretical framework led Gray to suggest further that stable neurobiological individual differences in motivational–emotional systems form the foundation of higher-order traits of personality. These notions raised the possibility that one means of testing the neurobiological tenets of this theory is the use of pharmacological protocols, where pharmacological agents that act as agonists or antagonists of neurotransmitters are used to assess whether drug-induced modulations of specific neurotransmitters are associated with particular personality traits.

The Structure of Personality. The structure of personality is hierarchical in nature, where behavioral features are assessed by inventory items which, by use of factor analysis, are clustered into lower-order primary or facet scales, which in turn are further clustered into higher-order traits. The higher-order traits represent theoretical constructs that attempt to account for the coalescence of the lower-order traits. From Gray's theoretical framework, the higher-order traits reflect the activity of a specific motivational–emotional system, and the lower-order traits represent different behavioral patterns that intercorrelate because they are influenced similarly by the motivational–emotional system represented by the higher-order trait. Although numerous classificatory systems of personality exist, all tend to agree on four higher-order traits: extraversion, neuroticism, social closeness or agreeableness, and constraint or conscientiousness. The first three traits are thought to reflect the activity of specific motivational–emotional systems, whereas the fourth may reflect not a specific emotional system, but rather a general property of the central nervous system that affects the threshold for eliciting all types of emotional behavior.

Extraversion. Depue and Collins (1999) provided a comprehensive analysis of the trait of extraversion as reflecting the activity of one of Gray's motivational–emotional systems – behavioral approach based on in centive motivation. Both unconditioned and conditioned rewarding stimuli (positive incentive stimuli) activate a motivational system of incentive motivation, which energizes approach to a rewarding goal. Extraversion, then, would represent individual differences in the threshold for positive incentives to (1) facilitate an emotional state that supports approach behavior, including a positive

affective state of desire, strong, peppy, enthusiastic, excited, and self-confidence; and (2) elicit approach, forward locomotion, and engagement with rewarding stimuli.

Conceptualizing extraversion as based on incentive motivation, which is a behavioral system found at all phylogenetic levels of animals, allows for the drawing of an analogy between human personality patterns and the animal neurobehavioral research literature. Animal research demonstrates that behavioral facilitation reflecting the activation of incentive motivation is associated with the functional properties of the ▶ ventral tegmental area (VTA) ▶ dopamine (DA) projection system. Thus, just as extraversion emerges as a higher-order construct that incorporates a modulatory mechanism that operates across lower-order traits, the VTA DA projection system might also be considered a higher-order modulator of a neurobiological network that integrates behavioral functions associated with extraversion. Indeed, DA agonists or antagonists in the VTA or ▶ nucleus accumbens (Nacc), which is a major terminal area of VTA DA projections, in animals facilitate or markedly impair, respectively, incentive-elicited locomotor activity to novelty and food; exploratory, aggressive, social, and sexual behavior; and the acquisition and maintenance of approach behavior.

In humans, DA agonists, such as ▶ amphetamine, ▶ cocaine, and ▶ methylphenidate, also elicit facilitated motor activity, as well as both positive emotional feelings such as elation, and a sense of reward, and motivational feelings of desire, wanting, craving, potency, and self-efficacy (Canli 2006; Depue 2006; Depue and Collins 1999). Moreover, neuroimaging studies have found that, during acute cocaine administration, the intensity of a subject's subjective euphoria increased in a dose-dependent manner in proportion to cocaine binding to the DA uptake transporter (and hence DA levels) in the striatum.

A number of pharmacological protocols have been used to explore the relation of extraversion to DA functioning in humans. A widely used protocol involves use of a DA agonist-induced challenge of (1) variables that are known to be modulated by DA activation, such as hormones like growth hormone and prolactin, eye-blink rates, rate of switching between percepts (e.g., ascending vs. descending views of a staircase), motor velocity, positive affective reactivity, and visuospatial working memory; or (2) fMRI-imaged, DA-relevant brain regions during the performance of psychological tasks (Canli 2006; Depue 2006; Depue and Collins 1999). Such studies have consistently shown a strong, positive correlation between degree of DA-induced modulation of the variable in question and questionnaire-assessed extraversion, often accounting for over 40% of the observed variance.

Another important protocol is the use of a pharmacological agent that binds to specific DA receptors, where the level of competitive binding with natural DA, measured by ▶ PET scanning, is inversely related to the natural level of DA functioning. This protocol has been used to assess D2-like DA autoreceptor density. Since D2 autoreceptors are localized to the soma and dendrites of VTA DA neurons and provide one of the most potent inhibitory modulations of DA cell firing, reduced autoreceptor availability in the VTA region is related to increased DA cell firing and enhanced postsynaptic activation. Extraversion-like traits have been found to be inversely related (approximately −0.68) to D2 autoreceptor availability in the VTA region (e.g., Zald et al. 2008).

Finally, use of a pharmacological challenge protocol has recently been used in much more detailed ways to assess the nature of the relation of DA to psychobiological processes associated with extraversion. A major effect of DA release in the Nacc is to enhance the binding of (1) corticolimbic inputs to Nacc dendrites that carry information about the current context and (2) the magnitude of context-induced reward (Depue and Collins 1999; Depue and Morrone-Strupinsky 2005; Kauer and Malenka 2007). That is, DA plays an important role in binding contextual ensembles to the occurrence of reward, an important predictive function of the brain. As animal research has shown, enhanced state or trait DA functioning increases the binding of contextual cues to the experience of reward. Similarly, we have found that increasing levels of extraversion are strongly associated with the ability to bind together the experience of DA agonist (methylphenidate)-induced reward and contextual cues, as evidenced in DA modulated processes of motor velocity, positive affective reactivity, and working memory (Depue 2006).

These findings have relevance for the maintenance of drugs of abuse that activate DA release into the Nacc, which most do (Kauer and Malenka 2007). Indeed, DA-induced synaptic changes in the Nacc are likely to facilitate the formation of powerful and persistent links between the rewarding aspects of the drug experience and the multiple cues associated with that experience – that is, to facilitate long-lasting memories of the drug experience. In light of our findings discussed above, it may be that extraversion represents one modifier of the strength of drug (reward)-context conditioning, and hence of relapse rates.

Neuroticism. Adaptation to aversive environmental conditions is crucial for species survival, and at least two distinct behavioral systems have evolved to promote such adaptation. One system is fear (often labeled *Harm Avoidance* in personality literature), which is a behavioral

system that evolved as a means of escaping very specific and explicit aversive stimuli that are inherently dangerous to survival, such as tactile pain, predators, snakes, spiders, heights, and sudden sounds. There are, however, many aversive circumstances in which *specific* aversive cues do not exist, but rather the stimulus conditions are associated with an elevated *potential* risk of danger, such as darkness, open spaces, strangers, unfamiliarity, and predator odors. Conceptually, these latter stimuli are characterized in common by their unpredictability and uncontrollability – or, more simply, uncertainty.

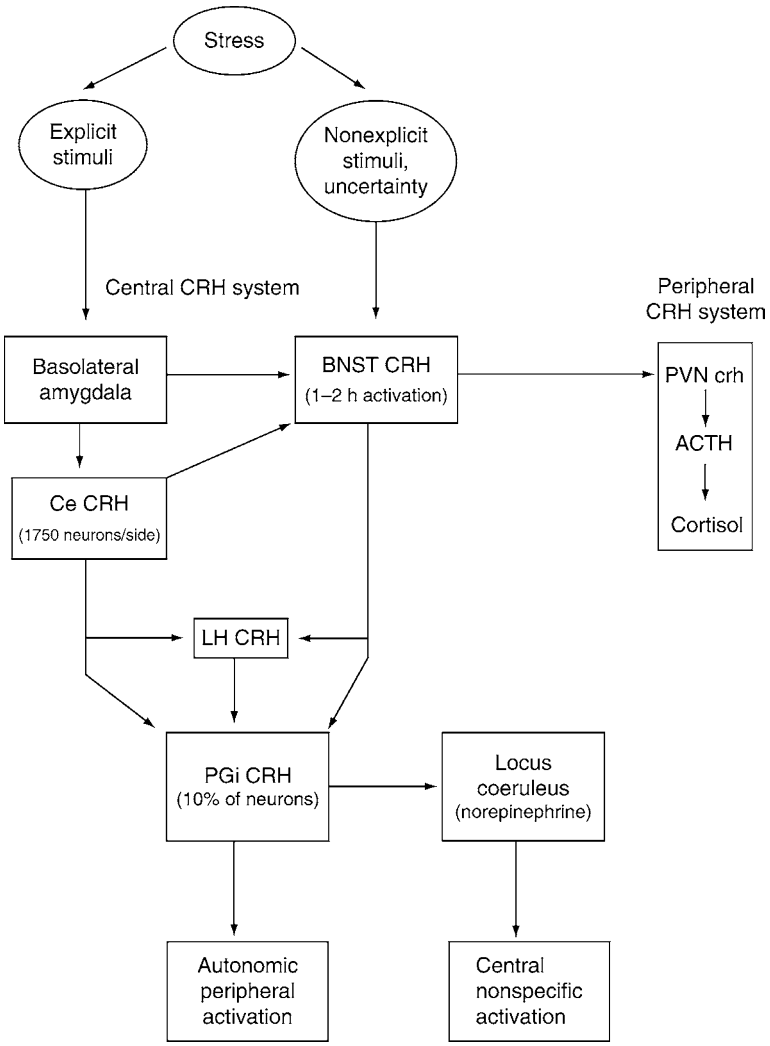
To adapt to these latter stimulus conditions, a second behavioral system evolved, *anxiety*, and it is this system that is thought to underlie the trait of Neuroticism. ► Anxiety is characterized by negative emotion or affect (anxiety, depression, hostility, suspiciousness, distress) that serves the purpose of informing the individual that, though no explicit, specific aversive stimuli are present, conditions are potentially threatening (White and Depue 1999). This negative affective state continues or reverberates until the uncertainty is resolved. It is the prolonged negative subjective state of anxiety that distinguishes its subjective state from the rapid, brief state of ► panic associated with the presence of a specific fear stimulus. The trait literature supports the *independence* of anxiety and fear, which as personality traits are completely uncorrelated, and are subject to distinct sources of genetic variation (White and Depue 1999).

The psychometric independence of fear and anxiety is mirrored in their dissociable neuroanatomy (Depue and Lenzenweger 2005; Davis and Shi 1999) and neurochemistry (White and Depue 1999; White et al. 2006). Whereas fear is dependent on output from the central nucleus of the ► amygdala to various brainstem regions, anxiety is subserved by outputs to similar brainstem regions from the bed nucleus of the stria terminalis (BNST), a structure that receives visual information via glutamatergic efferents from the perirhinal+basolateral amygdala (e.g., light–dark conditions) and parahippocampal+entorhinal+hippocampal (contextual and unfamiliarity stimuli) regions, as opposed to specific objects or sounds converging on the basolateral amygdala (Davis and Shi 1999; White and Depue 1999). The dissociation between fear and anxiety has also been found repeatedly with monoamine agonist challenge, such that trait fear but not trait anxiety predicts mood, cortisol, and physiologic responses to general monoamine challenge and to alpha-1 noradrenergic challenge, suggesting a role for ascending catecholamine systems in trait fear but not trait anxiety in humans (White and Depue 1999; White et al. 2006).

Animal research has demonstrated that naturally occurring chronic stress activates the central CRH system, which, as shown in Fig. 1, is composed of CRH neurons located in many different subcortical brain regions that modulate emotion, memory, and central nervous system arousal (Bale 2005; Depue and Lenzenweger 2005). Importantly, CRH neurons in the central amygdala induce prolonged elevated levels of CRH in BNST, which accounts for the potentially long endurance of anxiety as opposed to fear responses (Bale 2005). For instance, marked anxiety effects lasting longer than 24 h can be produced experimentally after three doses of CRH administered centrally over 1.5 h, but with no lasting effect on peripheral release of CRH from the ► hypothalamus. Anxiogenic effects and an aversion to a CRH-paired environment, both via CRH-R1 receptors, are dependent on intra-BNST administration of CRH. Furthermore, transgenic mice with elevated CRH-R1 (but not with R2) receptors in the central forebrain (but not peripherally in hypothalamus or pituitary), or conditional activation of CRH-R1 gene expression centrally, show extreme indications of anxiety. Thus, anxiety is a stress response system that relies on a network of central CRH neuron populations, in conjunction with the peripheral CRH system, that provide integrated responses (hormonal, behavioral, autonomic and central arousal) to a stressor, and in lateral BNST mediate prolonged anxiogenic effects and aversive contextual conditioning.

Pharmacological protocols used in exploring the psychobiology of extraversion have not been applied in human studies of anxiety, and so this type of research is sorely needed. One important avenue of this research would be the development of CRH-R1 antagonists that act centrally as anxiolytic agents. That such an approach may be significant is supported by a recent study of such an antagonist (antalarmin) in monkeys: Oral antalarmin impaired development and expression of contextual fear conditioning, and decreased stress-induced increases in anxiety behaviors, ACTH, cortisol, ► norepinephrine, epinephrine (i.e., HPA axis), CSF CRH concentration, and locus coeruleus neuronal firing (Habib et al. 2000).

One additional area of research is worth noting. A form of chronic stress reactivity is jointly correlated with the trait of neuroticism and a polymorphism in the promoter region of the gene that codes for the serotonin (5-HT) uptake transporter, creating two common alleles – long (l) and short (s). The s-allele is associated with (1) twice the risk of anxiety, depression, and suicide attempts in a context of childhood maltreatment and stressful life events; and (2) persistent enhanced amygdala activation to emotional stimuli – and thus persistent vigilance for threat, increased aversive conditioning to context, and negative thoughts and emotional memories. One important hypothesis is that, due to the significant



Personality: Neurobehavioural Foundation and Pharmacological Protocols. Fig. 1. CRH stress-response systems. Components of the central and peripheral corticotropin-releasing hormone (CRH) systems, which together coordinate emotional responses to stressful stimuli. Explicit stressful stimuli (e.g., predator cues, heights, tactile pain) are processed by the basolateral amygdala, whereas nonexplicit stressful stimuli (e.g., open spaces, context, darkness, strangers) are processed by the BNST. The basolateral amygdala activates Ce CRH neurons (about 1,750 neurons per hemisphere) which, together with nonexplicit stressful cues, release CRH in the BNST to produce prolonged neural activation in the BNST. In both cases, the Ce and/or BNST activate CRH neurons in the LH, which integrates and activates ANS activity in response to the stressor. In turn, Ce, BNST, and LH activation of the PGi (a major integrative nucleus in the rostroventrolateral medulla) CRH neurons (about 10% of PGi neurons) facilitate ANS activity via afferents to the spinal cord. The PGi CRH neurons also activate LC norepinephrine neurons, which project broadly to the CNS and elicit activation of all CNS regions. The peripheral CRH system is activated by the Ce and BNST CRH output neurons to the PVN. *Ce* central amygdala nucleus; *BNST* bed nucleus of the stria terminalis; *LH* lateral hypothalamus; *PGi* medullary paragiganticocellularis nucleus; *PVN* paraventricular nucleus of the hypothalamus; *ACTH* corticotropic hormone from the anterior pituitary; *CNS* central nervous system; *ANS* autonomic nervous system.

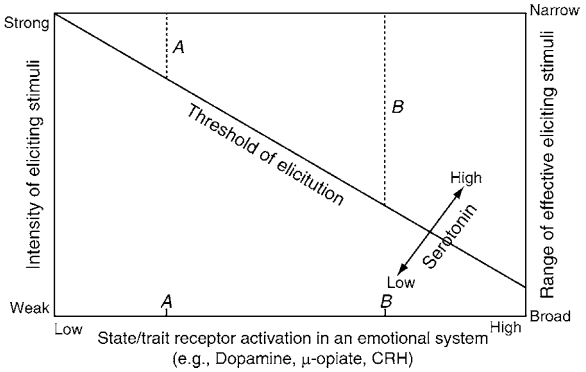
effects of 5-HT on early exuberant development of connectivity within forebrain regions, that the amygdala is less well modulated by emotion regulating regions such as the rostral anterior cingulate cortex. Indeed, these two regions show significantly less coherence in activity in s- versus l-allele individuals, accounting for ~30% of the variance in neuroticism scores (Pezawas et al. 2005). There has been little use of human pharmacological

protocols to explore the mechanisms of how 5-HT modulates stress reactivity, vigilance, and memory formation in these polymorphic conditions, again suggesting an area ripe for pharmacological exploration.

Social Closeness/Agreeableness. Social Closeness reflects the capacity of an individual to experience reward elicited by affiliative stimuli (e.g., soft tactile stimulation associated with grooming, caressing, and sexual intercourse). This capacity is reflected in the degree to which people value close relationships and spend time with others, as well as the desire to be comforted by others at times of stress. There has been very little human neurobiology research on the capacity to become attached to another person. While vole research has focused on the roles of oxytocin and vasopressin, genetic knockout studies have not demonstrated a *necessary* role for these ► neuropeptides in social bonding, suggesting that they may be affecting other variables that influence bonding, such as facilitation of sensory receptivity and subsequent acquisition of memories (Veenema and Neumann 2008). Human studies, on the other hand, are few, but some have used a promising pharmacological protocol: intranasally administered oxytocin is used to modulate short-term neural states and is then correlated with affective processes.

Noting that these neuropeptides do not mediate a sense of reward elicited by affiliative stimuli, we detailed a comprehensive role for mu-opiates in affiliative reward (Depue and Morrone-Strupinsky 2005). Recent primate research supports the *necessary* aspect of mu-opiates for social bonding (Barr et al. 2008). Practically no human pharmacological work has been done on mu-opiate mediation of affiliative reward, but the recent animal studies above are concordant with findings of regulation of human affective responses by limbic-opioid neurotransmission. They are also consistent with our results of enhanced human affiliative responses in individuals scoring high versus low in trait levels of social closeness, and with the elimination of those differences by use of the mu-opiate antagonist, ► naltrexone. Clearly, additional pharmacological work along these lines is strongly encouraged.

Constraint/Conscientiousness. Constraint is a poorly conceptualized personality trait, but is clearly related to a generalized behavioral impulsivity. Recent models of this behavioral profile have begun to clarify the nature of this trait (Depue and Collins 1999; Depue and Morrone-Strupinsky 2005). Elicitation of behavior can be modeled neurobiologically by use of a minimum threshold construct, which represents a central nervous system weighting of the external and internal factors that contribute to the probability of response expression (Fig. 2). We and others have proposed that constraint is



Personality: Neurobehavioural Foundation and Pharmacological Protocols. Fig. 2. Minimum threshold model. A minimum threshold for elicitation of a behavioral process (e.g., incentive motivation-positive affect, affiliative reward-affection, anxiety-negative affect) is illustrated as a trade-off function between eliciting stimulus magnitude (left vertical axis) and postsynaptic receptor activation in a neurobiological system (e.g., dopamine, mu-opiate, CRH) underlying an emotional trait (horizontal axis). Range of effective (eliciting) stimuli is illustrated on the right vertical axis as a function of level of receptor activation. Two hypothetical individuals with low and high *trait* postsynaptic receptor activation (demarcated on the horizontal axis as *A* and *B*, respectively) are shown to have narrow (*A*) and broad (*B*) ranges of effective stimuli, respectively, which influences the frequency of activation of the processes associated with a personality trait. Threshold effects due to serotonin modulation are illustrated as well.

the personality trait that reflects the greatest CNS weight on the construct of a minimum emotional response threshold. As such, constraint exerts a general influence over the elicitation of *any* emotional behavior. In this model, other higher-order personality traits would thus reflect the influence of neurobiological variables that strongly contribute to the threshold for responding, such as DA in the facilitation of incentive motivated behavior, mu-opiates in the experience of affiliative reward, and CRH in the potentiation of anxiety.

Functional levels of neurotransmitters that provide a strong, relatively generalized *tonic inhibitory* influence on behavioral responding would be good candidates as significant modulators of a response elicitation threshold, and hence may account for a large proportion of the variance in the trait of constraint. We and numerous others have suggested that 5-HT, acting at multiple receptor sites in most brain regions, is such a modulator (see review by Carver and Miller 2006). 5-HT modulates a diverse set of functions – including emotion, motivation,

motor, affiliation, cognition, food intake, sleep, sexual activity, and sensory reactivity, and reduced 5-HT functioning is associated with many disorders of impulse control (Depue and Lenzenweger 2005). Thus, 5-HT plays a substantial modulatory role that affects many forms of motivated behavior. Therefore, constraint might be viewed as reflecting a modulatory influence of 5-HT over the threshold of elicitation of emotional behavior (Fig. 2).

The variety of pharmacological protocols described above have been used extensively in animal research with 5-HT, and most show that reduced 5-HT functioning is indeed related strongly to a reduced threshold of emotional reactivity. However, such studies have been few in the human personality area, despite the fact that we found strong evidence for a role of 5-HT in constraint using a protocol of 5-HT-activation of prolactin secretion. Therefore, there is a strong need for additional pharmacological research on constraint to detail the manner in which 5-HT modulates emotional and cognitive processes associated with personality traits.

Conclusion

The use of pharmacological protocols to explore the neurobiological basis of higher-order personality traits is an underutilized research strategy. Clearly, such an approach has been quite informative with respect to the neurobiological nature of extraversion and neuroticism. However, pharmacological research on the nature of social closeness and constraint lags far behind. In particular, recent work suggests that a particularly powerful research strategy is the use of pharmacological protocols in defining the relation between behavioral processes and neurobiology in personality groups defined on the basis of genetic polymorphisms associated with DA, CRH, 5-HT, and mu-opiate systems.

Cross-References

- ▶ Aminergic Hypotheses for Depression
- ▶ Anxiety: Animal Models
- ▶ Arginine-Vasopressin
- ▶ Benzodiazepines
- ▶ Central Catecholamine Systems
- ▶ Conditioned Drug Effects
- ▶ Conditioned Place Preference and Aversion
- ▶ Corticotropin Releasing Factor
- ▶ Dopamine (DA) Uptake Transporter
- ▶ Emotion and Mood
- ▶ Impulse Control Disorders
- ▶ Impulsivity
- ▶ Neuroendocrine Markers for Drug Action
- ▶ Opioids
- ▶ Phenotyping of Behavioral Characteristics
- ▶ Receptors: Functional Assays
- ▶ Social Stress
- ▶ Trait Independence
- ▶ Traumatic Stress (Anxiety) Disorder
- ▶ Tryptophan Depletion

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Pervasive Developmental Disorder Not Otherwise Specified

Synonyms
Atypical autism; PDD NOS

Definition
PDD NOS is defined by severe and pervasive impairment in social reciprocity and either impairment in communication or stereotyped behavior, interests and activities. Individuals with this diagnosis cannot meet criteria for another Pervasive Developmental Disorder (autism, Rett's disorder, childhood disintegrative disorder, Asperger's disorder).

Cross-References
► Autism Spectrum Disorders and Mental Retardation

Pervasive Developmental Disorders

Definition
A group of lifetime neuropsychiatric disorders that cause disruptions in social interactions, disruptions in communication, and restricted interest and activities. This group of disorders includes autism, Asperger's disorder, pervasive developmental disorder not otherwise specified, Rett's disorder and childhood disintegrative disorder.

Cross-References
► Autism Spectrum Disorders and Mental Retardation

PET Imaging

► Positron Emission Tomography (PET) Imaging

Pethidine

Synonyms
Demerol; Meperidine

Definition
Pethidine is a synthetic, addictive opioid analgesic drug. Like other opioids, it can be used for treating moderate to severe pain but it has few unique indications. It has a rapid onset and short duration of action. Its analgesic effects are due to its action as an agonist at μ-opioid receptors. In accordance with this mode of action, it produces a morphine-like abstinence (withdrawal) syndrome and is subject to abuse and dependence. Pethidine also inhibits the dopamine and norepinephrine transporters, leading to psychomotor stimulant effects and a euphoric mood. Its efficacy as an analgesic is less than that of morphine and the side effects may be greater, due to the actions of a more toxic metabolite (norpethidine).

Cross-References
► Dependence Opioid Analgesics
► Opioids
► Withdrawal Syndromes

P-Glycoprotein

Definition
A 170 kD transmembrane glycoprotein from the superfamily of the adenosine triphosphate (ATP)-binding cassette (ABC) transporters that functions as ATP-dependent efflux pump able to extrude many classes of lipophilic and cationic chemicals. This protein is extensively expressed in intestinal epithelium, hepatocytes, renal proximal tubular cells, and in the luminal membrane of the endothelial cells of the BBB where it transports compounds out of the brain. P-glycoprotein (abbreviated as P-gp or Pgp) is also called ABCB1 (ATP-ABC subfamily B member 1), MDR1 (for multiple drug resistance).

Pharmacodynamic Tolerance

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Definition
Tolerance is a drug-induced reduction in subsequent drug effect. Pharmacodynamic tolerance refers to instances of tolerance that involve either (a) adaptive changes in

receptor binding, or (b) recruitment of processes that limit or oppose the effects of the drug on receptor-mediated signaling pathways.

Impact of Psychoactive Drugs

Overview

Tolerance refers to a phenomenon in which the potency and/or maximal effectiveness of a drug to produce some effect is reduced after a regimen of prior exposure to that drug. Tolerance may be expressed as a reduced effect produced by a given drug dose, a requirement for higher drug doses to sustain a given effect, or a rightward and/or downward shift in a drug dose-effect curve. Tolerance may result from a variety of different mechanisms. Pharmacodynamic tolerance refers to instances of tolerance associated with pharmacodynamic mechanisms that are described below. It can be distinguished from pharmacokinetic tolerance (tolerance related to processes of ▶ pharmacokinetics: drug absorption, distribution, metabolism, and excretion) and ▶ behavioral tolerance (tolerance related to whole-organism learning processes).

Pharmacodynamics is the study of drug action on a biological system, and pharmacodynamic mechanisms can be divided into two dissociable but complementary components of drug action: ▶ receptor binding and pharmacodynamic efficacy. Receptor binding quantifies the direct physical interaction between a drug and one or more target receptor(s). The degree of receptor binding produced by a given concentration of a drug is determined by the density of a given receptor type in a biological system (often expressed as ▶ Bmax; receptors per unit mass of tissue) and by the ▶ affinity of the drug for that receptor type (often expressed as Kd; the concentration of drug required to bind 50% of the receptor population). Pharmacodynamic efficacy describes the degree to which a drug activates, inactivates, or otherwise modulates signaling pathways coupled to a receptor. These signaling pathways originate with changes in receptor conformation/function and are transduced into downstream changes in intra- and intercellular biochemistry, physiology, and behavior. ▶ Agonists stimulate these pathways, ▶ inverse agonists reduce ▶ constitutive activity in these pathways, and ▶ antagonists have no effect on their own but block effects of agonists and inverse agonists. Pharmacodynamic tolerance can be mediated by drug-induced changes in either receptor binding or receptor-mediated signaling. Moreover, these mechanisms are not mutually exclusive to each other or to nonpharmacodynamic mechanisms of tolerance. Rather, tolerance to a given effect of a given drug may involve multiple mechanisms, and mechanisms that underlie tolerance to one effect of a drug may differ from the mechanisms underlying tolerance to another effect of that same drug or to other drugs.

Tolerance and Receptor Binding

One mechanism that may contribute to tolerance is a drug-induced change in the density of receptors to which a drug binds. Depending on the drug, either decreases in receptor density (receptor downregulation) or increases in receptor density (receptor upregulation) may contribute to tolerance. Thus, receptor downregulation can reduce the effects of an agonist by reducing the number of receptors available for agonist-induced stimulation. Conversely, receptor upregulation can reduce the effects of an inverse agonist or antagonist by increasing the number of constitutively active receptors or the number of receptors available for stimulation by endogenous neurotransmitter agonists. Examples of tolerance-associated changes in receptor density include the downregulation of ▶ cannabinoid CB1 receptors produced by chronic exposure to cannabinoid agonists such as Δ^9-tetrahydrocannabinol (Martin et al. 2004) and upregulation of dopamine D2 receptors produced by chronic exposure to antipsychotic dopamine D2 receptor antagonists such as ▶ haloperidol (Sibley and Neve 1997). The precise mechanisms that underlie drug-induced changes in receptor density vary as a function of such variables as the drug, treatment regimen and receptor type, and in many cases, these mechanisms remain unknown. However, the density of available receptors is determined by rates of ▶ gene expression, protein synthesis, receptor trafficking to and from the membrane, and degradation. Drug exposure may modulate each of these processes. One illustrative mechanism will be described below in the context of receptor desensitization.

It is also theoretically possible for tolerance to occur as a result of reduced affinity of a drug for its receptor; however, tolerance-associated reductions in affinity have usually not been observed. Chronic drug exposure may promote changes in the relative abundance of different receptor subtypes for which a drug has differing affinities (e.g., Wafford 2005), but this mechanism can best be conceptualized as a change in the relative densities of different receptor types rather than as a change in the affinity of the drug for a single receptor type.

Tolerance and Receptor-Mediated Signaling Pathways

Although changes in receptor binding may contribute to some forms of pharmacodynamic tolerance, mechanisms involving changes in receptor-mediated signaling appear to

be more commonly involved. The wide variety of signaling pathways associated with different receptor types creates a multitude of potential mechanisms whereby prior drug exposure can modulate subsequent drug effects. In general, these mechanisms have the effect of limiting or opposing the effects of the drug, and these mechanisms can act at the level of the receptor itself, the intracellular signaling pathways coupled to the receptor, or the intercellular neural circuits containing cells that express the receptor. Examples will be provided from the literature on tolerance to ► morphine and other ► opioids acting at the mu-opioid receptor (Christie 2008).

Drug binding sites on receptor proteins are coupled to proximal transduction mechanisms that consist of either separate domains of the receptor itself (e.g., ion channels in the case of ligand-gated ion channels) or separate proteins located immediately adjacent to the receptor (e.g., G-proteins associated with ► G-protein coupled receptors (GPCRs)). For example, mu-opioid receptors are GPCRs, and receptor-mediated signaling begins with agonist-induced interactions between the receptor and an adjacent G-protein to activate the G-protein and initiate multiple cascades of downstream neurochemical processes that affect ion channels, intracellular enzyme activity, and gene transcription. The drug-binding site and proximal transduction mechanism can be uncoupled in a process also referred to as receptor desensitization, and this process is thought to be especially important for drugs that act as direct agonists at a receptor. With mu-opioid receptors, agonist binding promotes the phosphorylation of the receptor by G-protein-coupled receptor kinases (GRKs) that recognize and phosphorylate amino acids on the intracellular C-terminus of the agonist-bound conformation of the receptor. Receptor phosphorylation itself may reduce the efficiency of G-protein activation by the receptor. In addition, the phosphorylated region of the receptor may also become bound by another protein called β-arrestin, which is thought to further obstruct the receptor's ability to interact with and activate the adjacent G-protein. As a result, the receptor is effectively uncoupled from the G-protein and other downstream signaling processes (Gainetdinov et al. 2004; Martini and Whistler 2007).

Another role of β-arrestin in the regulation of GPCRs like the mu-opioid receptor is to facilitate internalization by endocytosis. Specifically, the β-arrestin-bound receptor migrates to clathrin-coated pits in the cell membrane, and these pits are then invaginated and pinched off to form intracellular vesicles. Internalized receptors can then be destroyed (via degradation by proteases in lysosomes, a process that may contribute to receptor downregulation) or recycled to the membrane (via dephosphorylation of the receptor and subsequent fusion of the vesicle with the extracellular membrane). Through this latter mechanism, β-arrestins may contribute not only to the negative regulation of receptor signaling, but also to the resensitization of the receptor. Thus, it has been suggested that short-term desensitization, internalization, and recycling of receptors could prevent the development of longer-term tolerance mediated by the activation of compensatory adaptations in signaling pathways downstream of the receptor (Martini and Whistler 2007, see below). Furthermore, the interaction of internalized receptors with β-arrestins can result in signaling through alternative (non-G-protein mediated) pathways. Thus, roles of GRKs and β-arrestins in mediating acute drug action and tolerance are complex (Gainetdinov et al. 2004; Schmid and Bohn 2009). For example, the genetic knockout of the β-arrestin-2 subtype of β-arrestin increases sensitivity to some of morphine's effects (e.g., supraspinal antinociception), while decreasing sensitivity to other effects (e.g., constipation). Moreover, tolerance to the antinociceptive effects of morphine is attenuated in β-arrestin-2 knockout mice, whereas antinociceptive tolerance to more potent or efficacious opioids, such as etorphine or ► methadone, is unaffected by the loss of β-arrestin-2. Interestingly, antagonist-precipitated withdrawal after chronic morphine was also unaffected in β-arrestin-2 knockout mice. Overall, then, the roles of GRK/β-arrestin regulatory mechanisms in drug tolerance are likely to be multifaceted, and could in some cases mediate while in other cases oppose drug tolerance.

Reductions in drug effects can also be produced by a compensatory recruitment of intracellular opponent processes downstream from the receptor. For example, in many cell types that express mu-opioid receptors, agonist binding initiates a series of biochemical events that includes (1) activation of Gi/Go proteins, which (2) inhibit adenylyl cyclase, an enzyme that converts adenosine triphosphate (ATP) into cyclic adenosine monophosphate (cAMP), resulting in (3) reduced levels of cAMP and (4) reduced activity of protein kinase A (PKA), an enzyme that is activated by cAMP. This in turn results in (5) decreased phosphorylation of other downstream proteins, including membrane-bound ion channels that can influence short-term patterns of cell activity and transcription factors that can influence gene transcription and longer-term cell structure and function. Tolerance to the effects of a mu agonist can result from the regulation of any step in this pathway. For example, chronic exposure to mu-opioid receptor agonists may promote a compensatory upregulation in adenylyl cyclase, the enzyme normally inhibited by mu receptors (Nestler and Aghajanian 1997). This upregulation in adenylyl cyclase may be sufficient to offset the inhibitory effect

mediated by mu-opioid receptors and restore enzyme activity to basal, pre-drug levels despite continued drug presence.

In multicellular biological systems, opponent processes can be recruited not only in the cell that contains the receptor at which the drug acts, but also in other cells involved in circuits that mediate drug effects on physiology and behavior. Thus, to the degree that a drug produces a net change in activity of a downstream cell, opponent processes may be recruited to oppose the drug effect and shift cell activity back toward basal levels. As one example from the mammalian central nervous system, mu-opioid receptors are located on inhibitory interneurons that regulate the activity of a population of dopaminergic neurons collectively referred to as the mesolimbic dopamine system. The agonist-induced activation of these mu receptors inhibits the interneurons, and thereby disinhibits the dopamine neurons to increase dopamine release. This increased mesolimbic dopamine release is a shared property of many drugs of abuse, and it is thought to play a key role in the neurobiology of addiction. However, sustained increases in dopamine (produced by mu agonists or by other drugs of abuse) may then act on postsynaptic D1 dopamine receptors to promote synthesis in those neurons of the endogenous opioid peptide ▶ dynorphin, which can be released by recurrent collaterals that feedback onto the dopamine neurons. Dynorphin can then act at kappa opioid receptors on the dopamine neurons to inhibit further neural activation and dopamine release. Thus, mu agonists may activate dopamine neurons via one process, but this activated dopaminergic activity may then trigger a dynorphin/kappa opioid receptor-mediated opponent process that opposes further activation of dopaminergic neurons (Chartoff et al. 2006; Shippenberg et al. 2007).

It should also be noted that the recruitment of opponent processes may contribute not only to tolerance, but also to the expression of ▶ withdrawal syndromes and ▶ addictive disorders. Thus, when drug is present, the drug and its opponent processes oppose each others' effects in a dynamic balance that shifts the level of cell or circuit activity toward basal, predrug levels and results in the phenomenon of tolerance. However, when the drug is removed, the opponent processes are released from drug opposition, and the disinhibited opponent processes may then produce effects different from and often opposite to those originally produced by the drug. For example, withdrawal from a mu agonist may release both upregulated adenylyl cyclase activity within mu-receptor-containing cells and upregulated dynorphin release from downstream cells, and these disinhibited opponent processes may then contribute to physiological and behavioral signs of opioid withdrawal that contribute to opioid addiction (Christie 2008; Nestler and Aghajanian 1997; Shippenberg et al. 2007).

Cross-References

▶ Addictive Disorder: Animal Models
▶ Behavioral Tolerance
▶ Opioids
▶ Pharmacokinetics
▶ Receptor Binding
▶ Withdrawal Syndromes

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Pharmacodynamics

Definition

The processes through which drugs bring about their actions on living organisms. It is distinguished from pharmacokinetics that relates to the absorption, distribution, and metabolism of drugs.

Pharmaco-Ethology

▶ Ethopharmacology

Pharmacogenetics

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Synonyms

Pharmacogenomics

Definition

Pharmacogenetics (PGx) refers to the influence of genetic variations on drug responses. More specifically, it is the study of how ► polymorphic genes that encode the function of transporters, metabolizing enzymes, receptors, and other drug targets in humans and other animals are related with variations in responses to drugs, including toxic and therapeutic effects. PGx, which may be considered to be a subfield of ► ecogenetics, tends to be used interchangeably with ► pharmacogenomics, with the same imprecision that conflates "genetics" with "genomics."

Current Concepts and State of Knowledge

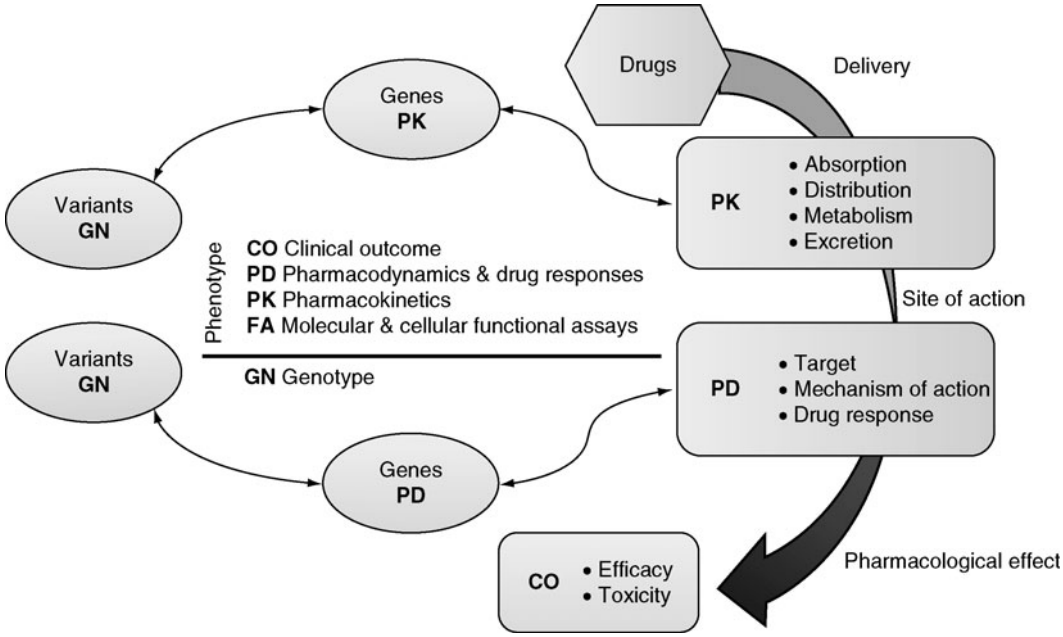
One thread of the origin of PGx dates back to the 1950s (see Box 1) when pharmacologists began to incorporate genetics into their studies of adverse drug reactions. Examples of classical PGx studies include the observations that at doses tolerated well by others, the muscle relaxant succinylcholine, the antimalarial drug primaquine and the antituberculosis drug isionazid induced life-threatening effects, such as respiratory arrest, hemolytic anemia and neuropathies, in some patients. By studying families and ethnic populations as well as through careful phenotyping, pharmacologists demonstrated that these unusual drug responses were inherited and due to certain enzyme variations controlled by single-genes. The understanding of the molecular genetic basis for the phenotypes came later, with the development of DNA technology (► Single nucleotide polymorphism testing and, more recently, ► haplotype testing) and in vitro molecular tests allowing the exact identification of the gene sequences responsible for variations in drug responses. The recent flourishing of genomics with development of new technologies such as microarrays has changed the focus of PGx from study of the effect of single gene sequence polymorphisms in two ways. First, the search has broadened to multiple genes (i.e., from monogenic to polygenic traits), and second, gene expression is now known to play an important role in affecting variations in drug responses. Indeed, modern PGx (pharmacogenomics) often uses a reverse approach, studying whether sequence variations and/or gene expression are in any way related to variations in drug response phenotypes (see methods).

The second thread antecedent to PGx can be traced to the field of behavioral genetics. Studies of behavioral responses to a variety of drugs, often in mice and rats, employed genetically varying populations and consistently found that different genotypes had characteristic, and widely varied, responses to many drugs. Starting in the late 1940s, this field also pioneered the use of selective breeding to create rat and mouse lines with extreme drug responses. The earliest systematic summary of this work was a monograph by Broadhurst (1978). Behavioral genetic studies now also incorporate ► genetically modified animals and the studies of gene-targeted mutant lines and selected lines have contributed much to our understanding in drug action, particularly in the addictions field.

Defining Pharmacogenetics

Pharmacology often divides drug's interactions with the body into their ► pharmacokinetic and ► pharmacodynamic aspects. Pharmacokinetics, sometimes described as what the body does to a drug, incorporates drug absorption, distribution, metabolism, and excretion. Pharmacodynamics, described as what a drug does to the body, involves receptor binding, post-receptor effects, and chemical interactions. Drug's pharmacokinetics and pharmocodynamics are both genetically and environmentally influenced. Genes contain information that determine the structure of proteins and any variations in the DNA sequence (mutation) may alter the expression or the function of proteins. DNA mutations that occur at a frequency of 1% or greater are termed polymorphisms. Polymorphisms in genes coding for a protein that carries a drug to its target cells or tissues may cripple the enzyme that activates a drug or aid its removal from the body, and thus may induce pharmacokinetic or pharmacodynamic variations leading to individual differences in the response to the drug (see Fig. 1).

The majority of pharmacogenetic studies have focused on drug metabolizing enzymes. For example, ► cytochrome P450 (CYP, P450) is a large superfamily of metabolizing enzymes. Within the CYP2 family, polymorphic CYP2D6 was one of the first and most important drug-metabolizing enzymes to be characterized at the DNA level. By using response to a "marker" drug (i.e., dextromethorphan), four phenotypes may be described: "poor metabolizers," "intermediate metabolizers," "extensive metabolizers," and "ultrarapid metabolizers." Ultrarapid metabolizers have multiple copies of the *CYP2D6* gene



Pharmacogenetics. Fig. 1. Schematic representation of how gene variants affect pharmacokinetic and pharmacodynamic factors resulting in potential modifications in the pharmacological effect of drugs (from http://www.pharmgkb.org).

expressed, and greater-than-normal CYP2D6 activity. Therefore, ultrarapid metabolizers may not achieve therapeutic levels with usual doses and may require several doses to show a response. On the other hand, poor metabolizers are at increased risk of toxicity from CYP2D6 substrate drugs (e.g., codeine). In addition to CYP2D6, polymorphisms have now been identified in more than 20 drug metabolizing enzymes in humans. Some of these polymorphisms show different distributions in racial groups and phenotypically relevant consequences from a clinical point of view (see Table 1). More recently, there has been increased recognition in the contribution of genetic variation in proteins involved in drug responses. For example, a polymorphism in the ▶ serotonin transporter protein that affects serotonin availability in brain has been reported to be associated with a predisposition to depressive illness as well as with therapeutic response to antidepressive or antipsychotic pharmacotherapy.

Box 1. Dates

1949: Initiation of first rat line selected for high alcohol consumption by J Mardones at the University of Chile (Mardones and Segovia-Riquelme 1983)
1950: Extensive characterization of mouse and rat genetic differences in response to psychoactive drugs.
1957: Delineation of the field of PGx by Motulsky (1957).
1959: Introduction of the term "PGx" by Vogel (1959).
1962: Definitive establishment of the field by Kalow's monograph (Kalow 1962).
1968: Demonstration by Vessel of the general importance of polygenic inheritance in metabolism of many drugs (Vessel and Shapiro 1968).
1990s: Introduction of the term "pharmacogenomics" with emergence of the Human Genome Project.

Methods

PGx may use a phenotype-driven or a genotype-driven approach for understanding the genetic contributions to variations in drug responses in humans and nonhumans. In the phenotype-driven approach (i.e., from phenotype to genotype), once a genetic contribution to the phenotype of interest has been confirmed (with family analysis, animal models analysis and/or linkage studies), genetic markers reliably associated with the phenotype are identified by genome-wide- and/or –candidate-gene approaches. Such studies must first identify the rough genomic locations of causative genetic variation. These locations are called quantitative trait loci (QTL), and QTL-analysis is the first step for identifying the subset of chromosomal areas containing genes responsible for the genetic variation in a specific trait, and to locate these areas on a genomic map. QTL analyzes have been widely used in animal models with inbred and recombinant strains of rats and mice, as well as in lines selectively bred for extremes in response to various

Pharmacogenetics. Table 1. Representative examples of the relation between genetic polymorphisms of drug-metabolizing enzymes with drug responses adapted from Weber (2008).

Gene	Polymorphism	Drug response
CYP2D6(L)	2–13-fold multiplication of gene	Failure to respond to nortryptyline; toxicity to codeine
CYP2C19	SNP truncates gene	Failure to respond to proton inhibitors and proguanil
CYP2C9	Two major SNPs (Arg-144-Cys) (Ile-359-Leu) impair metabolic efficiency	Toxicity to Warfarin and phenytoin
VKROC1	Promoter variants impair or enhance vitamin K reductase efficiency	Toxicity to, or lack of efficacy of Warfarin
ALDH2	SNP (Glu-487-Lys). This variant is highly prevalent in East Asian gene pools. Homozygotes are essentially 100% protected from developing alcoholism.	Impaired metabolism of ethanol, leading to high levels of acetaldehyde and many highly aversive effects. The drug disulfiram (Antabuse®) mimics the slow-metabolizing variant
TPMT	SNP (Pro-238-Ala)	Drug-induced bone narrow toxicity
NAT2	Multiple SNP	INH-induced peripheral neuropathy; susceptibility to bladder cancer from aromatic amine carcinogens
DPYD and DPD	Splice site mutation IVS14 + 1G > A	Severe 5-fluorouracil toxicity
TAA	Mutated promoter (TA7)TAA	Severe irinotecan toxicity
FMO3	SNP (Pro-153-Leu)	Psychosocial disorders resulting from inability to metabolize trimethylamine in foods
MDR1	MDR1 (C3435T)	Enhances therapeutic effect of antiretroviral drugs (efavirenz, nelfinavir) in HIV-infected patients
MRP2	Absence of functional MRP2	Dubin-Johnson syndrome

drugs. When chromosomal regions associated with the magnitude of the phenotype have been identified, the QTL initially span genomic regions containing dozens or even hundreds of genes. Fine-mapping can be carried out to refine the search, narrow the confidence intervals, and, finally, identify potential susceptibility genes. Eventually, candidate-genes remaining in the QTL interval are sequenced to identify the specific sequence variants associated with the phenotype. Alternatively, or additionally, in a genotype-driven approach (i.e., from genotype to phenotype), pharmacogeneticists characterize the functional significance of polymorphisms with high population frequency for a gene for which previous knowledge suggests that it could influence drug responses. In this approach, the development of genetically modified animals such as transgenic and knock-out mice has been particularly useful for investigating the direct effects of gene mutation on responses to drugs. In both approaches, analyses of gene expression are now commonly evaluated as well to identify candidate genes within each QTL.

Methods used for genotyping involve a series of molecular biological, physical, and chemical procedures used to distinguish among the alleles of a SNP or the measurement of the allele-specific products. PGx principally use methods applied in genetics and pharmacology but also borrow the knowledge and progress available in other fields such as bioinformatics. Because final proof of a quantitative trait gene (QTG) nearly always involves behavioral assessment of genetically modified animals, the tools of behavioral analysis are also employed.

Clinical Applications

The clinical consequences of Interindividual differences in drug responses are manifested in a variety of ways such as acute or delayed toxicity, unusual response, resistance to a drug or unwanted drug interactions (when combined with use of other agents). Adverse side effects of drugs represent a significant public health and economic problem, affecting more than 2 million people annually in the United States, including 100,000 deaths and costing more than $100 billion. The use of PGx in a clinical setting could reduce these costs, and help to determine the most appropriate treatment for individual patients according to their unique genetic make-up (personalized medicine). Indeed, identification of relevant polymorphisms known to affect drug effects could help treatment providers determine which available drugs would ensure maximum efficacy with minimal adverse effects.

However high expectations surrounding "personalized medicine" remain unfulfilled and only a few products have reached the market and clinical practice. One example is the DNA chip AmpliChip® (developed by Roche Molecular System Inc.) used for testing variations in expression of the CYP2D6 and CYP2C19 genes, which play a major role in metabolism. Another is the HER2 test which is used prior to prescribing Herceptin® to breast cancer patients. HER2 is the receptor for the epidermal growth factor which can stimulate cells to divide and grow. HER2 testing measures the number of copies of HER2 gene (*neu)* in each cell and/or the level of HER2 protein in the tumor sample. Only people showing HER2 gene amplification and overexpression are prescribed Herceptin®, which attaches to the HER2 protein, and stops human epidermal growth factor from reaching the breast cancer cells. A third is a test for variants of the enzyme thiopurine methyltransferease (TPMT) before prescribing thiopurine (i.e., antileukemic drugs such as 6-mercaptopurine and 6-thioguanine) for the treatment of acute lymphocytic leukemia. Genotype-based testing allows the identification of individuals showing a reduced TPMT enzyme activity. Because these people may show a toxic accumulation of thiopurine in the body responsible for bone-marrow suppression, they are not prescribed thiopurine drugs. Pharmacogenetic testing is currently used in only a limited number of teaching hospital and specialist academic centers.

Some genetic and non-genetic factors may explain why, despite the well- documented functional relevance of many-drug-metabolizing enzymes, the translation of PGx into clinical practice has yet to reap its benefits. First, drug responses are likely due to many genes, each bearing many polymorphisms. Identification of all these genes and polymorphisms is difficult and time-consuming, and would have to be performed before the selection of the right drug and the right dose for the individual patient. Second, genotyping is not sensitive to drug-drug interactions or to environmental factors, which can affect treatment response. For example, dietary intake may influence drug metabolism, as in the case of ► monoamine oxidase inhibitor (MOAI) drugs for the treatment of ► depression or ► Parkinson's disease. Patients using these drugs need to avoid food containing the amino acid "tyramine" (i.e., such as cheese and fish), because accumulation of this amino acid leads to a hypertensive crisis with headache and high blood pressure. This example shows how pharmacogenetic information alone will not predict the variation in efficacy or safety of a drug.

Besides enabling clinicians to select the most effective drugs for treatment of individuals, PGx could also be used for salvaging drugs that have been withdrawn from the market because of adverse drug reactions – so-called "drug rescue." Retrospective genotyping of clinical trial subjects could help to distinguish patients who were susceptible to an adverse response from those patients who showed benefit from the drug. Finally, PGx could also have an impact on the process of drug research and development, by helping to develop specific drug targeting proteins with variant structures resulting from the presence of genetic polymorphisms. Such research could assist pharmaceutical companies to develop more effective drugs with fewer side effects.

Currently, no countries have clinical practice regulations relating to PGx or pharmacogenomics. Such regulations, including prescription guidelines, testing, and usage labels, will be needed if the techniques are to be widely used. However, before regulation can be introduced to guide prescribing practices, the field needs more robust prospective data from well-designed studies.

Conclusion

PGx provides an experimental framework to understand variation in human drug responses as a function of inherited material. Recently, the field has experienced a period of rapid growth with the initiative of the human genome project. With the improvement and the wide availability of sequencing technology, the use of PGx in clinical practice is expected to increase.

Cross-References

► Delayed Onset of Drug Effects
► Ecogenetics
► Gene Expression and Transcription
► Genetically Modified Animals
► Pharmacokinetic
► Proteomics

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Pharmacogenomics

Synonyms
Pharmacogenetics

Definition
Pharmacogenomics can be defined as the study of variations of DNA and RNA characteristics as related to drug response. However, there is no consensus about the semantic differences between pharmacogenetics and pharmacogenomics, and these two terms tend to be used interchangeably. The history of usage generally parallels the development of the new field of genomics from the old field of genetics. The older term "pharmacogenetics" is now generally thought of as the limited study of single or few genes and their effects on interindividual differences in drug responses while the newer term "pharmacogenomics" is thought to refer to the application of genomic technologies to the study of drug discovery, pharmacological function, disposition, and therapeutic response.

Pharmacokinetics

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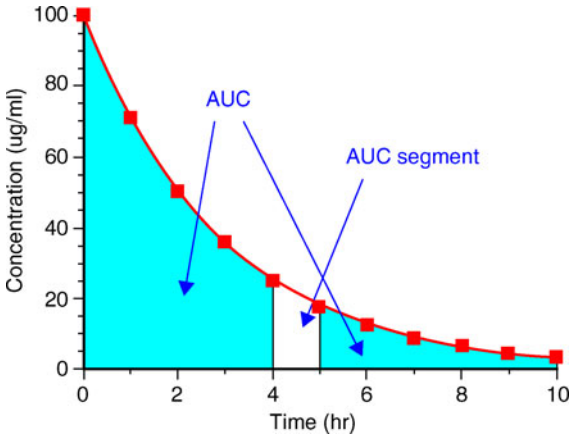
Synonyms
Kinetics; PK

Definition
Pharmacokinetics (in Greek "pharmacon" meaning drug and "kinetikos" meaning putting in motion and the study of time dependency) has been variously defined as the study of the relationship between administered doses of a drug and the observed blood (plasma or serum) or tissue concentrations. It is a branch of pharmacology that explores what the body does to a drug and hence concerns itself with the quantitation of drug absorption, distribution, metabolism and excretion (ADME).

Impact of Psychoactive Drugs
Despite the enormity of the pharmaceutical industry and the vast array of psychoactive substances used in an illicit manner, the mode of action of drugs in the body can be understood by reference to basic pharmacokinetic principals, assuming a linear relationship between blood and tissue (brain) exposure. Understanding the pharmacokinetic principles of a drug often explains the manner of its use and aids the clinician in a number of ways: in anticipating the optimal dosage regime; in predicting what may happen if the dosage regime is not followed; in responding to over dosing and; to monitor the consequences of harmful or dependent use.

Pharmacokinetic parameters describe how the body affects a specific drug after administration and explains how the variables such as the site of administration and the dose and dosage form in which the drug is administered can alter this response. Pharmacokinetic analysis is performed by noncompartmental (model-independent) or compartmental methods. Noncompartmental methods estimate the exposure to a drug by evaluating the ► Area Under the curve (► AUC) of a concentration-time graph. Compartmental methods estimate the concentration-time graph using kinetic modeling. Compartment-free methods are often more versatile in that they do not assume any specific compartmental model and produce more accurate results.

Noncompartmental Analysis
Noncompartmental pharmacokinetic analysis is highly dependent on the estimation of total drug exposure; most often estimated by AUC methods, using the trapezoidal rule, which is the most common area estimation method (Fig. 1).



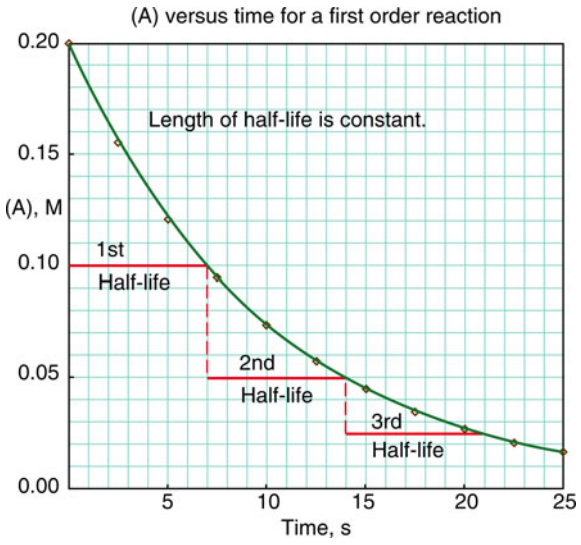
Pharmacokinetics. Fig. 1. Calculation of area under the curve (AUC) using the Trapezoidal Rule showing a linear plot of concentration of drug in plasma (Cp) versus Time showing AUC and AUC segment (http://www.boomer.org/c/p4/c02/c0208.html).

The AUC is very useful for calculating the total body clearance (► CL) and the ► apparent volume of distribution (see later). In the trapezoidal rule, the area estimation is highly dependent on the blood/plasma sampling schedule. That is, the more frequent the sampling, the closer the trapezoids to the actual shape of the concentration-time curve (Fig. 1). Intravenous administration of a developmental drug can provide valuable information on fundamental pharmacokinetic parameters, but may often be biased towards an apparent rapid peak plasma concentration and short lasting exposure when compared to oral administration.

Compartmental Analysis

Compartmental pharmacokinetic analysis use kinetic models to describe and predict the concentration-time curve. The advantage of compartmental to some non-compartmental analysis is the ability to predict the concentration at any time. The disadvantage is the difficulty in developing and validating the proper model. Compartment-free modeling based on curve stripping does not suffer this limitation. The simplest PK compartmental model is the one-compartmental PK model with IV bolus administration and ► first-order elimination kinetics, (Neligan 2009) where a constant fraction of the drug in the body is eliminated per unit time as shown in Fig. 2.

Pharmacokinetics is predominantly studied in a laboratory setting using advanced chromatographic technology (gas GC, or liquid ► HPLC) coupled to ► mass spectrometry (MS). This is because of the complex nature of the matrix (blood (or brain tissue extracts in animals)) to be analysed; the need for high sensitivity to detect low drug concentrations (10^{-6} to 10^{-9}g) and the long time-point data. Blank or $t = 0$ samples taken before administration are important in determining a baseline and ensure data integrity with such complex sample matrices. There is currently considerable interest in the use of very high sensitivity LC-MS-MS for micro dosing studies, which are seen as a promising alternative to animal experimentation.



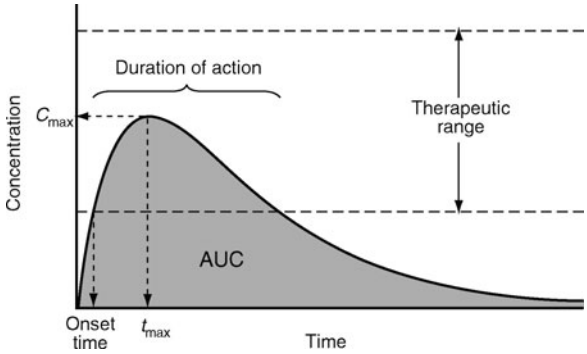
Pharmacokinetics. Fig. 2. First-order elimination for a drug (A) administered by the intravenous route showing elimination over time.

Population pharmacokinetics is the study of sources and correlates of variability in drug concentrations among individuals who are the target patient population receiving clinically relevant doses of a drug of interest. This methodology seeks to identify the measurable pathophysiologic factors that cause changes in the dose-concentration relationship and the extent of these changes. The industry standard software for population pharmacokinetics analysis is NONMEM.

A basic tenet of clinical pharmacokinetics is that the magnitudes of both desired response and toxicity are functions of the drug concentration at the site(s) of action (Rowland and Tozer 1995). Using this definition, "therapeutic failure" results when either the concentration of the drug at the site of action is too low, giving ineffective therapy, or is too high, producing unacceptable toxicity. For example, in drug treatment services, relapse and a return to illicit drug use has been frequently observed when the maintenance dose of ► methadone is too low to stop opioid withdrawal symptoms or ► craving for heroin. The concentration range in between these limits, the range associated with "therapeutic success" is often regarded as the "therapeutic window or range" (Fig. 3). However, these definitions are sometimes difficult to interpret for drugs that are not controlled by pharmaceutical regulations (► cocaine or ► cannabis or, ► MDMA) or are difficult to apply to drugs consumed without restriction (► alcohol and ► nicotine).

In practice, the measurement of a drug in the body is usually determined in blood or urine, because measurement of the drug concentration at the site of action is not easily achievable.

For some drugs with variable pharmacokinetics such as *Warfarin* (*Coumadin*), biological monitoring is required to ensure that the blood concentration of the drug is strictly maintained within the therapeutic window (normal reference range, Fig. 3). Warfarin used for preventing thrombosis and embolism (abnormal formation and migration of blood clots) interacts with



Pharmacokinetics. Fig. 3. Pharmacokinetic parameters describing a typical plasma concentration-time profile after an oral administration. C_{max} maximum concentration; t_{max} time to C_{max}; *AUC* area under the curve.

many common medications and some foods. Its activity has to be monitored by frequent blood testing for the international normalized ratio (INR) to ensure an adequate yet safe dose is taken. Other compounds, for example, *clozapine* have a risk of serious side effects. ▶ Clozapine is used principally in treating ▶ schizophrenia and also for reducing the risk of suicide in patients with chronic risk for suicidal behavior. Plasma concentration of clozapine and norclozapine need to be measured regularly in order to assess adherence to the dosing regime, prevention of toxicity, and in dose optimization.

The discipline of pharmacokinetics is concerned with the quantitation of the mechanisms of ▶ absorption. The process by which a drug enters the blood stream; ▶ distribution of an administered drug; the rate at which a drug action begins; the duration of the effect; the ▶ metabolism of the drug in the body and; the effects and routes of ▶ excretion of the drug and its metabolites. These processes together are commonly referred to as *ADME* (Jacobs and Fehr 1987). More recently biopharmaceutics has emerged as a new body of science that links traditional pharmacokinetics with pharmaceutics and the acronym *LADME* (http://en.wikipedia.org/wiki/Pharmacokinetics) has been used to describe the processes studied by biopharmacists. Essentially adding the term "▶ Liberation" to the well recognized ADME acronym.

Understanding Drug Effects

In order for a drug to exert its pharmacological effect, it must first gain entry into the body, be absorbed into the blood stream and transported to the site of action (usually in the brain for CNS active drugs). The intensity of effect of a drug is governed by two major factors:

- The concentration of drug at the site of action in the body; and
- The sensitivity of the target cells (i.e., the magnitude of their response to a given concentration of drug).

The Concentration of Drug at the Site of Action

The concentration of drug at the site of action in the body at any given time after administration is determined by both the size of the dose and the pharmacokinetics of the substance.

Liberation

Biopharmaceutics has brought to the fore the importance of the physicochemical properties of a drug, the dosage form (or design) and the route of administration, all of which are key parameters when considering drug "Liberation." Once administered, the drug must be liberated from its dosage form. Tablets and capsules may require disintegration (forming smaller particles) before dissolution and entry into the systemic circulation can occur. Similarly, the delivery of drug particulates into the lung from passive inhaler products is only achieved after "Liberation" of the drug from the formulation during inhalation activation. The science of drug formulation design has rapidly grown over the last decade and is a thriving discipline.

Drug Dissolution

Drug dissolution usually occurs in the stomach and is dependent upon gastric activity. Many factors influence the dissolution of tablets and capsules, including particle size, chemical formulation, the inclusion of inert fillers, and the outer coating of the tablet. It is not unusual, therefore for proprietary or generic preparations of a drug to have different dissolution characteristics and produce a range of plasma concentrations after oral administration. Dissolution characteristics of a dosage form are thus important considerations when interpreting pharmacokinetic data.

Absorption and Routes of Administration

As explained above, the extent and rate of absorption of a substance depends on the chemical properties of the drug itself and the way in which it is administered. The rate of absorption depends on the concentration of the drug, its degree of lipid solubility, the surface area of absorption, and the diffusion distance (i.e., the number of membranes it must cross before it reaches the bloodstream). Peak plasma concentration-time is the most widely used

general index of absorption rate; the slower the absorption, the longer period of time to reach peak plasma concentration.

There are four principle methods of drug administration: oral/ingestion, across mucous membranes, by inhalation, and by parenteral process (injection).

Oral (*by swallowing*): Drugs taken orally are generally absorbed primarily in the small intestine rather than in the stomach. The ▶ benzodiazepines comprise a large family of lipophilic drugs. ▶ Diazepam for instance, is rapidly absorbed, with peak concentration occurring within an hour for adults and, as quickly as, 15–30 min in children (Jenkins 2008). This route is characteristically slow and may be delayed by the presence of food in the digestive tract. The oral route may be ineffective for certain drugs because the acidity of the stomach renders them ineffective. Heroin provides a good example of the latter phenomenon. Drug users looking for an immediate or intense effect or "rush," avoid the oral route. Nonlipophilic (nonionized) compounds such as ▶ alcohol, readily cross cell membranes by passive diffusion and are easily and rapidly absorbed from the gut, particularly on an "empty" stomach.

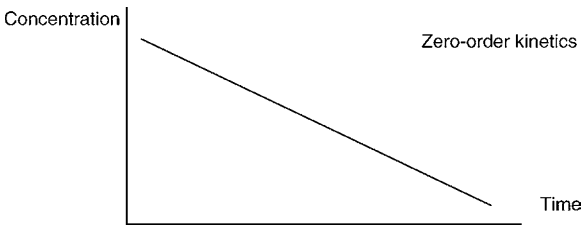
Transmucosal Absorption: Mucous membranes (that form the moist surfaces that line the mouth, nose, eye sockets, throat, rectum and vagina, etc) are thinner, have a greater blood supply and, are more permeable (lack keratin) compared with the epidermis (skin). For these reasons, absorption across mucus membranes is rapid and drugs (especially lipophilic compounds) are effectively absorbed into the bloodstream. ▶ Nicotine in the form of chewing tobacco and buprenorphine placed sublingually (under the tongue) is successfully absorbed through the mucous membranes of the mouth. Drugs can be administered rectally including aminophylline, a drug used in the treatment of bronchial asthma and tribromoethanol, an anesthetic. Drugs can also be absorbed by insuffalation (sniffing, snorting), which allows ▶ cocaine, ▶ ketamine amylnitrite and tobacco stuff to be absorbed across the mucous membranes of the nose and sinus cavities. Nasal administration (a preferred route for users of illicit substances) enables rapid absorption into the cerebrospinal fluid (CSF) and hence, the cerebral circulation. After nasal administration, the concentration of some drugs in the CSF may be higher than in plasma (Calvey 2007).

Inhalation: In the case of inhalation, a drug is absorbed into the bloodstream across the alveolar membranes of the lung. This occurs in gas form (e.g., the vapors of solvents), in fine liquid drops (heroin or cocaine), or in fine particles of matter suspended in a gas (e.g., aerosols or the smoke from tobacco or cannabis). For many drugs, inhalation is the most rapid method of absorption into the general circulation. Glue "sniffing" is actually an incorrect description; technically, glue vapors are inhaled and absorbed via the linings of the lung.

Parenteral (*Injection*): The term "parenteral" denotes those pathways through which drugs are injected directly into the body. There are three principle parenteral routes: subcutaneous, intramuscular, and intravenous. Subcutaneous injection ("skin popping" to street users) involves injecting the drug under the skin. The rate of absorption from the site of injection is slower than the intravenous injection, but faster than the oral route. Intramuscular injection involves deeper penetration of the drug into the body tissue. The drug is injected either in solution or in suspension directly into the muscle mass, where it is slowly absorbed into the bloodstream. Intravenous injection (popularly known as "mainlining") involves the direct injection of the drug into the veins. It is one of the fastest ways of getting a drug into the bloodstream and also allows relatively large amounts of a drug to be administered at one time. Intravenous drug administration poses the highest risk of toxicity and overdose (Wolff 2005).

Kinetics of Absorption The oral absorption of drugs often approximates first-order kinetics, especially when given in solution. Under these circumstances, absorption is characterized by an absorption rate constant, K_a, and a corresponding half-life. ▶ First-order kinetics depend on the concentration of only one reactant and a constant fraction of the drug in the body that is eliminated per unit time. The rate of absorption is proportional to the amount of drug in the body.

Sometimes a drug is absorbed essentially at a constant rate, called zero-order absorption. ▶ Zero-order kinetics is described when a constant amount of drug is absorbed (or eliminated) per unit time but the rate is independent of the concentration of the drug (Fig. 4). Zero-order kinetics explains the way in which alcohol is handled in



Pharmacokinetics. Fig. 4. Schematic representation of the absorption of a drug by zero-order kinetics.

the body and several other drugs at high dosage concentrations, such as phenytoin and salicylate (Neligan 2009).

The pharmacokinetic parameter linked to the passage of a drug into the systemic circulation is known as ► Bioavailability. It is a measurement of the amount of active drug that reaches the general circulation and is available at the site of action (although this parameter is difficult to establish for CNS active drugs, due to the need to cross the blood-brain barrier). It is expressed as the letter *F*.

It is assumed that a drug given by the intravenous route will have an absolute bioavailability of 100% or 1 ($F = 1$), while drugs given by other routes usually have an absolute bioavailability of less than one. *F*, is often calculated as the proportion of drug that reaches the systemic circulation after oral compared to IV administration. It is the fraction of the drug absorbed through non-intravenous administration compared with the corresponding intravenous administration of the same drug. The formula for calculating *F* for a drug administered by the oral route (p.o.) is given below.

$$F = \frac{[\mathrm{AUC}]_{\mathrm{po}} * \mathrm{dose}_{\mathrm{IV}}}{[\mathrm{AUC}]_{\mathrm{IV}} * \mathrm{dose}_{\mathrm{po}}}$$

F is measured by comparing the AUC for oral and i.v. doses from zero to the time point for which elimination is complete.

The calculation of *F* requires an intravenous reference, that is, a route of administration that guarantees the entire administered drug reaches the systemic circulation. Such studies come at considerable cost, not least because of the necessity to conduct preclinical toxicity tests to ensure adequate safety.

Bioavailability is usually calculated by determining the maximum (peak) plasma drug concentration (C_{max}), the time that it takes to reach the peak (T_{max}), and AUC. Plasma drug concentration increases according to the extent of absorption; the T_{max} is reached, when drug elimination rate equals absorption rate. Bioavailability determinations based on the C_{max} however can be erroneous because drug elimination begins as soon as the drug enters the bloodstream.

For drugs excreted primarily unchanged in urine (amphetamine), bioavailability can be estimated by measuring the total amount of drug excreted after a single dose. Ideally, urine is collected over a period of 7–10 elimination half-lives for complete urinary recovery of the absorbed drug.

The Distribution of Drugs in the Body

Once a drug is absorbed into the systemic circulation, distribution occurs throughout the body. The distribution for most drugs in the body is not even; some drugs bind to plasma proteins, while others are sequestered into adipose tissue, and a few have great affinity for bone tissue. Drugs must be highly fat soluble in order to enter the brain. Similarly, fat-soluble drugs can cross the placenta to affect the fetus; these same drugs are also found in the milk of lactating women.

Unevenness of distribution is a barrier to the accurate interpretation of the concentration of a drug in the body and complicates efforts to correlate blood concentrations with behavior. High blood drug concentrations are usually related to greater behavioral effects than low concentrations. However, some drugs (the barbiturates) have passed their peak plasma concentration before peak behavioral effects are seen. In the case of alcohol, some of the above differences do not apply, since alcohol crosses all barriers to distribute uniformly in total body water. Therefore, in the non tolerant individual blood alcohol concentrations are highly correlated with behavioral effects.

In pharmacokinetic terms, the ► Volume of Distribution (V_{D}) also known as the apparent Volume of Distribution is the parameter used as a direct measure of the extent of distribution. V_{D} is purely hypothetical and does not represent an actual physical volume inside the body. It is defined as the volume in which the amount of drug would need to be uniformly distributed to produce the observed blood concentration, by supposing that its concentration is homogeneous, i.e., the average tissue concentration is identical to that of the plasma. V_{D} is expressed as:

$$V_{\mathrm{D}} = \mathrm{dose}/\mathrm{C}_0\,(\text{initial concentration})$$

For example, after intravenous injection of 100 mg of a drug whose initial concentration, C_0, in plasma is 10 mg/L, the V_{D} would be 10 L. For a given drug, the knowledge of its desirable concentration in blood and V_{D} allows evaluation of the dose to administer.

It is possible for V_{D} to be close to a recognizable volume, such as plasma volume (~0.05 L/kg), extracellular fluid (~0.2 L/kg), or total body water (~0.7 L/kg). This would happen if the drug is uniformly distributed in one of these "compartments," but this is rare. Indeed, when a drug binds preferentially to tissues at the expense of plasma (a drug that is highly lipophilic), the plasma concentration will be extremely low (e.g., methadone, Δ^9-tetrahydrocannabinol). This will result in a large V_{D}, that may be larger than the actual volume of the individual itself (>1 L/kg) e.g., digoxin. A large V_{D} implies wide distribution, or extensive tissue binding, or both.

The V_{D} is thus a mathematical method for describing how well a drug is removed from the plasma and distributed to the tissues. However, V_{D} does not provide

any specific information about where the drug is or whether it is concentrated in a particular organ. V_D may be increased by renal failure (due to fluid retention) and liver failure (due to altered body fluid and plasma protein binding). Conversely V_D may be decreased in dehydration.

The ► distribution phase is so called, because distribution determines the early rapid decline in plasma concentration. However, changes in plasma concentration reflect primarily movement within, rather than loss from the body. In time, equilibrium is reached between the drug present in tissue and that in plasma, and eventually plasma concentration reflects a proportional change in the concentrations of drug in all tissues and hence in the body. At this stage decline in drug concentration is only due to the elimination of drug from the body (elimination phase). Two pharmacokinetic parameters describe the elimination phase, the V_D (as described above) and the biological or ► elimination half-life.

The elimination half-life of a drug is the time taken for the plasma concentration as well as the amount of drug in the body to fall by one half and is usually denoted by the abbreviation $t_{1/2}$. Knowledge of the $t_{1/2}$ is useful for the determination of the frequency of administration of a drug (the number of intakes per day) and to calculate the desired plasma concentration. Generally, the $t_{1/2}$ of a particular drug is independent of the dose administered (Table 1).

The Elimination of Drugs from the Body

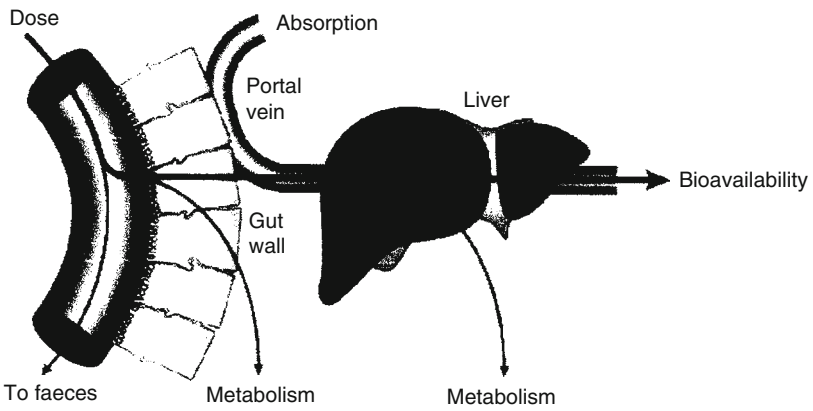
Elimination occurs by metabolism and excretion. Some drugs are eliminated via the bile and others in the breath, but for most drugs the primary route of excretion occurs via the kidneys.

Metabolism: Drugs are eliminated from the body in both changed and unchanged states: that is, part of the drug eliminated is chemically identical to the drug which was administered, and part has been changed (metabolized). The proportion of a drug dose eliminated in a particular state is determined by the nature of the drug, the dose, the route of administration, and the physiological characteristics of the user. The excretion of unchanged psychoactive drugs via the urine or faeces is generally inefficient because of their high fat solubility. As a result, fat-soluble substances are metabolized into water-soluble products that can be readily excreted by the kidneys and/or the intestines (Fig. 5).

Drugs are metabolized by specialized proteins called enzymes, which act as catalysts in the metabolic reaction. Most drug metabolism occurs in the liver, although enzymes in the kidneys, gut, lungs, and blood may also aid in the process. In the liver, there are two types of enzymes: microsomal (insoluble) drug metabolizing enzymes, and cytoplasmic (soluble) metabolizing enzymes (which metabolize alcohol and similar drugs). The conversion of a fat-soluble drug to a substance that has sufficient water solubility for efficient excretion may involve several sequential chemical reactions, each step rendering the molecule slightly more water soluble than before (Feldman et al. 1997). Thus many metabolites are often derived from the same parent drug (for example, there are at least 25 known metabolites from tetrahydrocannabinol (THC), the main psychoactive ingredient of cannabis).

Pharmacokinetics. Table 1. Plasma elimination half-life for a selection of different compounds.

Substance	Half-life	Notes
► Diazepam (Valium)	20–50 h	Rapid absorption and fast onset of action with peak plasma concentration achieved 0.5–2 h after oral dosing. Active metabolite desmethyldiazepam has a half-life of 30–200 h
► Carbamazepine	18–60 h	Carbamazepine exhibits auto induction: it induces the expression of the hepatic microsomal enzyme system CYP3A4, which metabolizes carbamazepine itself
► Haloperidol	14–36 h	Fifty times more potent than chlorpromazine. Rapidly absorbed and has a high bioavailability
► Fluoxetine	1–6 days	The active metabolite of fluoxetine is lipophilic and migrates slowly from the brain to the blood. The metabolite has a biological half-life of 4–16 days.
► Methadone	24–36 h	Orally effective. Exhibits auto induction: it induces the expression of the hepatic microsomal enzyme system CYP3A4, which metabolizes methadone itself
Water	7–10 days	Drinking large amounts of alcohol will reduce the biological half-life of water in the body.
► Alcohol	No half-life	Percentage of alcohol in your blood goes down by 0.015/h at a constant rate. Metabolism is zero-order kinetics (enzymes are saturated, and the rate of disappearance of ethanol in the body is INDEPENDENT of concentration. Thus, concentration falls off linearly, not exponentially. No half-life



Pharmacokinetics. Fig. 5. Schematic representation of where metabolism occurs during the absorption process. The fraction of the initial dose appearing in the portal vein is the fraction absorbed, and the fraction reaching the blood circulation after the first-pass through the liver defines the bioavailability of the drug administered orally (www.nature.com/.../v2/n3/images/nrd1032-i2.gif, Image at: www.nature.com/.../v2/n3/box/nrd1032_BX3.html).

As the drug becomes progressively less fat soluble it simultaneously loses the ability to cross the blood-brain barrier and to produce a pharmacological effect. However, some drug metabolites are pharmacologically active, producing the same effects as the parent drug. For example, heroin is metabolized to a number of metabolites, including ▶ morphine, N-morphine, ▶ codeine, and 6-monoacetylmorphine, all of which have pharmacological properties characteristic of the original drug.

Other drug metabolites can produce a completely different activity from the parent drug. Certain drug metabolites may be even more toxic than the parent drug: Methanol (methyl alcohol) is an example of a drug metabolized to produce two very toxic metabolites, formaldehyde and formic acid. It is these metabolites which are considered responsible for disruption of the acid-base balance in the body and for damage to the optic nerve, both of which pose serious problems in methanol poisoning.

Both types of liver enzymes, microsomal and cytoplasmic, are inducible – therefore, repeated drug exposure causes the enzymes to increase in number; the result is a faster metabolic rate – that is, a more rapid conversion of the ingested drug into its metabolites. This increased metabolic rate (speeding up of the process) can result in increased intensity and speed of onset of drug effects if the original drug was inactive and the metabolites active. This process can result in decreased intensity and duration of effect, if the original drug was active and the metabolites was inactive. Many enzymes are genetically polymorphic, and their presence and number in the body is under genetic control. Three main phenotypes occur in these cases with individuals categorized as extensive, intermediate, or poor metabolizers accordingly. For instance, this applies to ▶ MDMA (ecstasy) metabolism and nicotine metabolism as a result of the genetic polymorphism of CYP2D6 and CYP2A6, respectively.

▶ Zero-order elimination is described when a constant amount of drug is eliminated per unit time, independent of the concentration of the compound. Zero-order reactions are typically found when the enzyme required for elimination to proceed is saturated by the drug. Zero-order kinetics explains when an individual, who drinks 20 units of beer before midnight will fail a breathalyzer test at 8 am the following morning. In this instance, the pathways responsible for alcohol metabolism are rapidly saturated and work to their limit. The removal of alcohol through oxidation by ▶ alcohol dehydrogenase in the liver is thus limited. Hence the removal of a large concentration of alcohol from blood may follow zero-order kinetics.

Excretion: The kidney acts as a pressure filter through which the blood passes. Most of the water and some of the dissolved substances contained in the blood are reabsorbed during its passage through the kidney. Substances that are fat soluble tend to diffuse back into the bloodstream, whereas residual water and unreabsorbed substances are eliminated during urination. The process of reabsorption and active excretion in the tubules of the kidneys and the time lapse between urine formation and urination, make it is difficult to use urine concentrations of drugs and drug metabolites as a base for accurate estimates of blood concentration of these substances. The drug concentrations determined in urine drug screening are therefore, only a rough indication of blood

concentrations (Jenkins 2008). Salivary drug concentrations on the other hand have a much better correlation with blood (Wollff et al. 1999).

The intestines are a site of drug excretion as well as a site of drug absorption. Some drugs and drug metabolites have chemical characteristics which cause them to be actively secreted (or "pushed out") into bile as they pass through liver cells, and the drug-containing bile then empties into the intestines. Thus, these drugs and metabolites may be excreted in the faeces. As is the case with the kidney, however, the net excretion by this route may be greatly reduced by subsequent reabsorption into the bloodstream of the fat-soluble compounds (including psychoactive drugs) further along in the intestines. In this instance, the drugs will go through the process of excretion all over again (► enterohepatic cycling), and the drug effect may be prolonged.

Volatile drugs such as solvents are commonly excreted in the breath and for general anesthetics; breath may be the major route of elimination. For substances such as alcohol however, it is a minor route. Nevertheless, it is possible through stimulation of breathing to increase the loss of drug from the body. Since the amount excreted in the breath can be reliably related to the blood level, the concentration of alcohol in the breath, as measured by the Breathalyzer test, serves to estimate the degree of intoxication. There are many routes of elimination, including sweat and saliva (and in lactating women, milk) and these all play a role in drug elimination. Though the latter are minor routes, they can be important in forensic analysis.

Just as the parameter, V_D is required to relate blood concentration to the total amount of drug in the body, so there is a need to have a parameter to relate drug concentration to the rate of elimination. ► Clearance, denoted by CL, is that factor. The CL of a drug is the volume of plasma from which the drug is completely removed per unit time. The elimination half-life is related to CL and V_D by the following equation:

$$t_{1/2} = \frac{\ln 2 \cdot V_D}{CL}$$

In clinical practice, this means that it takes just over 4.7 times the $t_{1/2}$ for a drug's concentration in plasma to reach steady state after regular dosing is started, stopped, or the dose changed (Table 2). For example, methadone has a half-life of 24–36 h; this means that a change in the dose will take the best part of a week to have full effect. For this reason, drugs with a very long half-life (e.g., amiodarone, elimination $t_{1/2}$ of about 58 days) are usually started with a loading dose to achieve their desired clinical effect more quickly (Hallworth and Watson 2008).

Pharmacokinetics. Table 2. The elimination of a compound from the systemic circulation expressed as a function of its half-life.

Number of half-lives elapsed	Fraction remaining	Percentage remaining	
0	1/1	100	
1	1/2	50	
2	1/4	25	
3	1/8	12	0.5
4	1/16	6	0.25
5	1/32	3	0.125
6	1/64	1	0.563
7	1/128	0	0.781
...	...	...	
N	$1/2^n$	$100(1/2^n)$	

The CL of a drug: The amount eliminated, is proportional to the concentration of the drug in the blood. The fraction of the drug in the body eliminated per unit time is determined by the elimination constant (kel). This is represented by the slope of the line of the log plasma concentration versus time.

$$CL = kel \times V_D$$

Rate of elimination equals clearance times the concentration in the blood. It can be shown that the kel equals the log of 2 divided by the $t_{1/2} = 0.693/t_{1/2}$ and likewise, $CL = kel \times V_D$, so, $CL = 0.693 V_D/t_{1/2}$, which shows $t_{1/2} = 0.693 \times V_D/CL$.

The rate of elimination (R_{oe}) is thus the clearance (CL) times the concentration in the plasma (Cp).

$$R_{oe} = CL \times Cp$$

While the fraction of the total drug removed per unit time is CL/V_D

If the volume of distribution is increased, then the kel will decrease, the $t_{1/2}$ will increase, but the CL would not change.

Physiological Tolerance or Drug Tolerance

► Drug Tolerance is encountered when an individual's reaction to a drug decreases so that larger doses are required to achieve the same effect. It can involve both psychological and physiological factors. The main characteristic of drug tolerance is that the process if reversible. That is, cessation of use of the drug will diminish the degree of tolerance. The rate at which tolerance develops and is lost depends on the particular drug, the dosage, and the frequency of use. Another feature

of tolerance is that differential development occurs for different drug effects.

When considered in the context of pharmacokinetics, tolerance can be conveniently divided into a number of forms that relate to the mechanisms involved (Pratt 1991).

- *Dispositional (pharmacokinetic) tolerance*: results from a change in absorption, distribution, metabolism or excretion of a drug which leads to a decreased quantity of the substance reaching the site it affects.
- ▶ *Pharmacodynamic tolerance*: arises from adaptational changes occurring in the brain. These include cellular adaptive processes like *down regulation* (reduced number) and/or *desensitization* (reduced sensitivity) of drug receptors at the primary site of drug action as well as changes in neurotransmitter function in neuronal pathways downstream from the initial interaction. In opioid tolerance, several mechanisms contribute to opioid receptor desensitization, but the N-methyl-D-aspartate (NMDA) receptor cascade seems to be a common and important link.
- ▶ *Cross tolerance*: results when tolerance to one drug is extended to another of a different chemical class.

Cross-References

▶ Absorption
▶ Area Under the Curve
▶ Bioavailability
▶ Clearance
▶ Distribution
▶ Drug Tolerance
▶ Elimination Half-Life
▶ Enterohepatic Cycling
▶ Excretion
▶ First-Order Elimination Kinetics
▶ Liberation
▶ Metabolism
▶ Volume of Distribution
▶ Zero-Order Elimination Kinetics

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Pharmacokinetics Study

▶ Phase I Clinical Trial
▶ Pharmacokinetics

Pharmacological fMRI

Synonyms

phMRI

Definition

Pharmacological MRI (phMRI) refers to the assessment of the functional response to ligand-induced receptor stimulation or inhibition after drug administration. For this purpose, different functional MRI methods including CBF-, CBV- or BOLD-fMRI can be applied to measure changes in cerebral perfusion. Image recording before, during, and after drug administration allows for drawing conclusions on the effect of pharmacological compounds on brain activity. With such an experimental design, one tests acute effects of the drug itself in the brain ("challenge

phMRI"). With "modulation phMRI" on the other hand, one investigates how neurotransmitter systems are involved in neuronal systems engaged by other processes, such as cognitive challenge.

Cross-References
► BOLD Contrast
► Cerebral Perfusion
► Functional MRI

Pharmacotherapy

Definition
Use of a chemical substance (medication) in the treatment of a medical condition or illness.

Cross-References
► Drug Interactions

Phase I Clinical Trial

Definition
Phase I clinical trials are often the first time a potential new medication is given to humans. It follows extensive animal testing for both efficacy and safety. Typically, healthy paid volunteers are administered progressively higher doses in the same session or, more commonly, over several sessions that are conducted in specialized laboratories equipped and staffed to monitor carefully the subject's physiological and behavioral response. In most phase I trials, plasma samples are taken to measure levels of the drug and its metabolites to determine rates of metabolism and elimination and develop a pharmacokinetic model of the drug's biodisposition.

Cross-References
► Abuse Liability Evaluation
► Phase II Clinical Trial
► Phase III Clinical Trial
► Randomized Controlled Trials

Phase II Clinical Trial

Synonyms
Controlled clinical trial

Definition
Phase II clinical trials are designed to assess both safety and efficacy of new medications or new uses of existing medications. Subjects are patients with the disorder that the medication is intended to treat. There are usually rigorous inclusion and exclusion criteria for selecting subjects for study. Typically, Phase II trials are preceded by a Phase I trial. Early Phase II trials may be used to select doses for more extensive later Phase II trials. Phase II trials include at least one dose of the proposed new treatment and at least one comparison group. The comparison may be a ► placebo; it may be an existing approved medication or both. Thus, Phase II trials are often called controlled clinical trials.

Cross-References
► Abuse Liability Evaluation
► Phase I Clinical Trial
► Phase III Clinical Trial
► Randomized Controlled Trials

Phase III Clinical Trial

Synonyms
Controlled clinical trial

Definition
Phase III clinical trials are designed to assess both safety and efficacy of new medications or new uses of existing medications under conditions similar to those where it would be used clinically. Subjects are patients with the disorder that the medication is targeted to treat. Phase II trials include the study medication and one or more comparison groups. The comparison may be a ► placebo, an existing approved medication, or both. Typically, Phase III trials are preceded by one or more Phase II trials; however, Phase III studies enroll a greater number of subjects. Many Phase III trials utilize several clinical sites and are referred to as multisite or multicenter trials. In one variation of a randomized controlled trial, patients are switched from one medication to another using a crossover design. In another variation, patients receive sequenced treatment utilizing a specific protocol for moving them from one treatment to another. A well-known sequenced clinical trial in psychopharmacology is known as the STAR*D trial of treatment alternatives for depression (http://www.nimh.nih.gov/health/trials/practical/stard/backgroundstudy.shtml). Phase III trials are

often referred to as pivotal clinical trials with positive results and a reasonable balance of benefits and risk needed for regulatory approval of the new medication. After approval, a medication enters Phase IV testing which is comprised primarily of post-marketing surveillance (or pharmacovigalence) of adverse side effects.

Cross-References

► Abuse Liability Evaluation
► Phase I Clinical Trial
► Phase II Clinical Trial
► Randomized Controlled Trials

Phasic Neuronal Firing

► Phasic Neurotransmission

Phasic Neurotransmission

Synonyms

Phasic neuronal firing; Phasic neurotransmitter release

Definition

Phasic neurotransmission is characterized by a bursting mode of neuronal firing that quickly releases high quantity of neurotransmitter in the synapse. This form of neural transmission is usually triggered by behaviorally relevant signals and is opposed to "tonic" neurotransmission, which instead is the maintenance of low steady levels of extracellular neurotransmitter.

Cross-References

► Synaptic Plasticity

Phasic Neurotransmitter Release

► Phasic Neurotransmission

Phasic Signal Transmission

Definition

Signal transmission that is triggered by neuronal activity.

Phencyclidine

Synonyms

Angel dust; PCP

Definition

Phencyclidine (PCP) was originally developed as a general anesthetic agent by Park-Davis & Co. in the late 1950s, but during the initial clinical trials it was discovered that approximately 30% of the patients, as they emerged from anesthesia, developed psychotic reactions that had a close resemblance to ► schizophrenia. Subsequent studies found that after intravenous administration PCP induced a dysphoric, confusional state characterized by feelings of unreality, changes in body image, profound sense of aloneness or isolation, and disorganization of thoughts and amnesia; in many subjects negativism and hostility also occurred together with ► hallucinations and repetitive motor behavior. PCP could in healthy volunteers produce schizophrenia-like impairment of primary attention, motor function, proprioception, and symbolic and sequential thinking. Despite its ► dysphoric profile in patients, PCP was subject to abuse under the street name "Angel dust." Its primary mechanism of actions is noncompetitive inhibition of the ion channel of the ► NMDA receptor, by binding inside the channel. However, PCP is also a muscarinic antagonist, a dopamine, 5-HT and noradrenaline reuptake inhibitor, a sigma 1 and 2 ligand, a cholinesterase inhibitor, and can block voltage-gated potassium channels.

Cross-References

► Animal Models of Psychiatric States
► Excitatory Amino Acids and Their Antagonists

Phenelzine

Synonyms

Nardil

Definition

Phenelzine (2-phenylethylhydrazine) is an antidepressant that inhibits irreversibly and nonselectively monoamine oxidase (MAOI), still in widespread clinical use, that is claimed to be effective against major depressive disorders, particularly in treatment-resistant patients. It is also used in the treatment of dysthymia, bipolar depression,

panic disorders, social anxiety disorder, bulimia, and post-traumatic stress disorder. As is the case for many other antidepressants, phenelzine requires ca. 2–6 weeks of daily treatment to become therapeutically effective.

Due to its prominent side effects, phenelzine is considered only as a treatment of last resort. Among the adverse side effects are dizziness, disturbances in vision, appetite and food, sleep, blood pressure, thermoregulation, and sexual functions. Like other MAOIs, phenelzine interacts with tyramine-containing foods (the so-called cheese effect), overindulgence of which can result in a hypertensive crisis.

Cross-References
- ▶ Antidepressants
- ▶ Monoamine Oxidase Inhibitors

Phenobarbital

Synonyms
Phenobarbitone

Definition
Phenobarbital is a barbiturate drug used widely as an anticonvulsant agent. It has a very long duration of action after a relatively slow onset of effects. It was synthesized at the Bayer pharmaceutical firm by 1904 and first marketed in 1912. It has been superseded with respect to its original use as an anxiolytic, sedative, and hypnotic agent, partly because of the dangers of overdose leading to coma and death. It shares many other properties with its shorter-acting relative pentobarbital.

Cross-References
- ▶ Abuse Liability Evaluation
- ▶ Anxiolytics
- ▶ Barbiturates
- ▶ Driving Under Influence of Drugs
- ▶ Hypnotics
- ▶ Insomnia
- ▶ Sedative, Hypnotic, and Anxiolytic Dependence

Phenobarbitone

- ▶ Phenobarbital

Phenothiazines

Definition
A group of drugs that includes key members of the first generation of antipsychotic substances that brought about major changes in treatment of schizophrenia. Among the widely used drugs in this category are chlorpromazine, trifluoperazine, and fluphenazine.

Cross-References
- ▶ Antipsychotic Drugs
- ▶ First-Generation Antipsychotics

Phenotype/Genotype

Definition
Genotype is the specific genetic constitution of an organism including the gene allelic makeup. Phenotype is the physical trait or characteristic arising from the genotype.

Cross-References
- ▶ Genetically Modified Animals
- ▶ Phenotyping of Behavioral Characteristics

Phenotyping of Behavioral Characteristics

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Synonyms
Behavioral characterization; Behavioral phenotyping

Definition
Animal behavior can be viewed as the outward manifestation of an orchestrated and complex functioning of the central nervous system (CNS) and how it interacts with the internal and external environment. Phenotyping of behavioral characteristics in its widest sense refers to behavioral paradigms in which aspects of the behavioral

repertoire of a subject are analyzed, either under baseline conditions or after an experimental challenge, with the aim to assess CNS function. Most frequently sensory, locomotor, motivational, emotional, social, cognitive, consumptive, reproductive or reward-related behaviors are assayed. The subjects participating in a study may be either animal or human.

Principles and Role in Psychopharmacology

The goal of phenotyping of behavioral characteristics is usually either (1) the assessment of the neurobiology of certain behaviors by the use of lesions, systemic or local drug applications, or other experimental manipulations or (2) the examination of the effects of drugs in a drug-discovery screening or profiling context, or (3) the analysis of CNS-specific gene function by the use of genetically altered animals, for example, knockout mice, or in the case of human subjects, by relating human genetic haplotypes to disease-relevant behavioral characteristics assessed with neurophysiological or neuropsychological methods. Moreover, all three aspects are important for the development and assessment of animal models of neurological and psychiatric disorders. These are generated by combining manipulations (e.g., stress, chemical, lesion, surgical, genetic, environmental) with a test which has a robust behavioral readout.

Most behavioral phenotyping methods carried out in animals were initially developed either for studying the neuronal circuits involved in normal and pathological behaviors, or for the preclinical analysis of compounds in pharmaceutical industry – whereby rats, birds, or monkeys were primarily used as subjects (Sahgal 1993). With the completion of the genome sequences of human and several other species, the determination of gene and protein function, and understanding their role in disease mechanisms, became one of the major challenges in biomedical science. Due to its amenability to transgenic techniques, the mouse became the most used model organism in the endeavor to develop a complete functional annotation of the human genome and to employ the same information to better understand human disease and its underlying physiological and pathological basis. In this context, the experimental designs for characterizing rat behavior were transformed to successfully work in mice, and the term "Behavioral Phenotyping" is most frequently used in the context of behavioral characterization of mouse mutants. The development of this field owed much to the publication of reviews suggesting "test batteries" and to the publication of comprehensive guidebooks on mouse-behavioral phenotyping methodology (e.g., Crawley 2000; Crusio and Gerlai 1999), which encouraged many molecular geneticists and neuroscientists to use these techniques for their research. While, behavioral phenotyping is also growing among other model organisms including the fruitfly (*Drosophila melanagoster*), the worm (*C. elegans*), the sea slug (Aplysia), and the Zebrafish (*Danio rerio*) we will focus this article on rodents.

Examples of Frequently Used Behavioral Phenotyping Tests in Lab Rodents

Behavioral phenotyping procedures were developed to analyze animal models for human neuropsychiatric dysfunctions like ▶ posttraumatic stress disorder, other ▶ anxiety disorders, ▶ depression, ▶ schizophrenia, ▶ autism, attention-deficit hyperactivity disorder (▶ ADHD), ▶ addiction, mental retardation, or motor, sensory, or cognitive deficits related to neurodegenerative diseases like ▶ Parkinson's Disease, ▶ Alzheimer's Disease, ▶ Huntingtin's Disease, Stroke, or Prion Diseases.

For the analysis of emotionality, most frequently tests for unconditioned anxiety-related behavior are applied, in which the animals are usually exposed to novel environments, which puts them in the conflict between the urges to explore and to avoid possible dangers. Most frequently, the ▶ open-field test and the ▶ elevated plus-maze test are used to this end, and an elevated zero-maze is sometimes used as an alternative to the plus-maze. Additionally, light–dark avoidance tests are used to assess anxiety, and the ▶ social interaction test is applied to assess social anxiety.

Rodent tasks relevant to human depression are primarily stress-induced reductions in avoidance or escape, termed behavioral despair. The most widely used rodent models of symptoms of depression are the ▶ forced swim test and the ▶ tail suspension test. The ▶ learned helplessness paradigm may also be used.

▶ Prepulse Inhibition is a frequently used task that assesses sensorimotor-gating phenotypes, and is considered to have face, construct, and a high-predictive validity for schizophrenia and other neuropsychiatric diseases involving dysfunctions of sensorimotor integration in man.

To assess motor functions, frequently the open-field test and voluntary wheel-running are used to assess locomotor activity levels. The accelerating rotarod, balance-beam tests, and the vertical pole test are often used to assess motor coordination and balance. In addition, grip strength is measured using a specialized grip strength meter, and gait abnormalities can be analyzed by manual or automated analysis of the footprint pattern. Assessment of swimming ability can reveal motor or vestibular deficits not detected by other motor coordination and balance tests.

For behavioral assessment of sensory abilities, reflex responses are used whenever possible to reduce possible confounding factors, for example, the motivation of the animal to participate in the test. Elicitation of the optokinetic nystagmus is a reflex response that is used to assess functionally intact vision. Hearing deficits can be revealed by measuring the acoustic startle reflex, either by the use of a clickbox or, more precisely, by specialized acoustic startle chambers. Pain sensitivity is frequently assessed using the hot-plate test (requiring circuitry in the brain and the spinal cord) or the tail-flick test (spinal reflex). Taste and olfactory abilities are often assessed in choice tests.

Aversively and appetitively motivated tasks are used to assess cognitive function. For the analysis of conditioned anxiety or fear learning, most frequently, procedures like, for example, ▶ active avoidance, ▶ contextual-fear and ▶ cued-fear conditioning, or fear-potentiated startle are applied, in which the animals have to learn the association between a conditioned stimulus and a mild footshock. The ▶ Morris water-maze or the ▶ radial arm-maze are most frequently used to assess ▶ spatial learning, reference memory, and ▶ working memory, and appropriate versions of the T-maze and the Y-maze task are also used to assess working memory. ▶ Social recognition tasks are applied to analyze social memory and olfactory function, and object recognition tasks are applied to assess object memory. Schedule-controlled operant tasks can also be used to assess different aspects of learning and motivational behavior; and one such task, the ▶ five-choice serial reaction-time task has been developed to assess sustained and divided ▶ attention.

Repeated testing on the accelerated rotarod is applied to assess motor learning. Rodent tasks relevant to human addiction are primarily procedures that assess the rewarding properties of substances like ▶ self-administration of drugs, ▶ conditioned place preference paradigms, or generalization to drugs of abuse in ▶ drug discrimination procedures.

Applications

Behavioral phenotyping methodology has been used in the search for new and improved pharmaceuticals. It may be used not only to identify compounds with specific actions, but also to exclude unwanted side effects of a new compound, for example, motor effects or abuse potential.

Since the advent of functional genomics, behavioral phenotyping is frequently applied in the analysis of genetic and molecular functions, with the aim to identify new targets for therapeutic development. Genetic studies in the mouse are important for the elucidation of molecular pathways underlying behavior. The goal of this endeavor is not only the identification of genes that control brain function and influence behavior, but also the understanding of genetic factors involved in human psychiatric disorders (Tarantino and Bucan 2000). These disorders are associated with quantitative phenotypes called "intermediate traits" or "▶ endophenotypes," some of which, in contrast to the full-complex disorder, can readily be modeled in mice. These traits are risk factors which are considered to be closer to the genetic etiology than the full syndrome. Examples of such endophenotypes are anxiety in depression, prepulse inhibition and working memory deficits in schizophrenia, and social interaction deficits in autism and schizophrenia (Gottesman and Gould 2003). Since the rather recent emergence of the endophenotype concept in neuropsychiatric research, some work has been devoted to appropriately modeling human endophenotypes in mice and inspecting the function of candidate genes for human endophenotypes identified, for example, by human association or linkage studies in adequate genetic mouse models.

Since 1997, behavioral phenotyping methodology has been used in many large-scale mouse projects (see Gondo 2008 for overview). In several European, North American, and Asian large-scale phenotype-driven random-mouse mutagenesis screens aiming for the discovery of novel genes, among other techniques also behavioral phenotyping methodology was applied to detect so far unknown genes involved in defined behaviors. The development of large-scale mouse mutagenesis projects increased the demand for comprehensive robust and reliable phenotyping platforms for all body systems, including CNS function. In this context, the German National Genome Research Network established in collaboration with the pan-European consortium EUMORPHIA, a mouse phenotyping center with open access to the scientific community, called "German Mouse Clinic" (http://www.mouseclinic.de/, Gailus-Durner et al. 2005).

To overcome the bottleneck of comprehensive phenotypic characterization of the large number of mutants generated by the large-scale mutagenesis projects, several mouse phenotype assessment centers were built in Europe that work together under the roof of EUMODIC (European Mouse Disease Clinic, http://www.eumodic.org/). These mouse clinics use the standardized tests contained in EMPReSS (the European Mouse Phenotyping Resource of Standardized Screens, empress.har.mrc.ac.uk), and make their phenome data publicly available in the EuroPhenome database (http://www.europhenome.org/).

Pitfalls

Several factors can influence behavioral phenotyping results, and therefore need to be considered in the context of data reproducibility (Wahlsten 2001). Due to developmental and degenerative processes, the age of the subject can play a role, as well as the time point of testing due to circadian rhythms of many biological processes. Therefore, experimental subjects and controls of the same age should be tested concurrently; in the case of mutants, ideally littermates are used as controls. Caution should be made in extrapolating data between species as the effects of manipulations may vary. Moreover, within a given species there are marked differences between strains, and this should also be taken into account when phenotyping or analyzing behavioral data.

Because the previous experience of handling experimental manipulations or drug injections can influence the performance of a subject in a particular test, it might be desirable to use experimentally naive subjects for each kind of experiment. Practically, this approach increases the number of animals needed and is simply not feasible when mouse mutants are used, due to the comparatively long time needed to breed a sufficient amount of animals for concurrent testing of mutants and littermate controls in a statistically meaningful number. As a solution to this problem, frequently a series of tests is applied, in which the tests are usually ordered from those that are considered the least stressful for the subject to those considered the most stressful. Likewise, in comprehensive phenotyping platforms like mouse clinics behavioral phenotyping is done first, before more invasive experimental manipulations are performed on the animals, and the experimental history is documented. In case of a positive phenotyping result using such "test batteries," the putative phenotype should be confirmed in a new batch of subjects.

The more comprehensive the phenotyping, the less likely are mis- or overinterpretations of individual data sets. This is particularly important when screening for phenotypes in mutants of genes with unknown functions. For example, locomotor, exploratory, or emotional phenotypes may be confounded or even caused by sensory deficits, skeletal malformations, or metabolic alterations, and may thus not inevitably reflect the effects on brain function. Likewise, apparent cognitive phenotypes may not be centrally mediated but may be caused by alterations in sensory perception. Because one of the goals of behavioral phenotyping is the analysis of endophenotypes related to human neuropsychiatric disorders, it seems important to exclude alternative, not CNS-specific explanations for putative phenotypes.

Experimenter and the kind of equipment used are also known to influence phenotyping results. Therefore, careful descriptions of experimental procedures and thorough training of an experimenter are essential, as well as precise (technical) specifications of the (automated) equipment. For example, consortia like EUMORPHIA and EUMODIC (see above) that share the phenotyping effort and put particular emphasis on data reproducibility, undergo considerable efforts to ensure their procedures yield comparable results and validate them in cross-laboratory comparisons (Mandillo et al. 2008). However, since also environmental factors like diet, animal husbandry, housing conditions, cage structure, and so on, can have an impact, there may be practical limitations to standardization.

Advantages and Limitations of Behavioral Phenotyping Procedures

The advantages of behavioral phenotyping procedures reside in (1) their applicability to a wide range of scientific questions, from drug profiling to functional genomics; (2) their utility in the analysis of functions at the molecular level, as shown in many pharmacological studies as well as in studies with mouse mutants, for example, mutants of the dopaminergic and serotonergic neurotransmitter systems; and (3) relative ease of collecting high-quality quantitative data. On the other hand, the more comprehensive the analysis is supposed to be, the more time and the more animals are needed. If mouse mutants are used, the time and costs required for breeding have to be taken into account, which can be particularly high in the case of conditional mutants. However, mutant mice are extremely valuable when dissection of the functional role of a molecule cannot be approached using other techniques – for example, when pharmacological compounds are unavailable or have poor selectivity for a particular receptor subtype (Cryan and Holmes 2005).

If mutants of genes of completely or mainly unknown function are analyzed, behavioral phenotyping results should be interpreted in the context of analyzes of other body systems, particularly neuropathological and pathological analyzes. Especially, locomotor and motor-related emotional phenotypes should be comprehensively investigated, to check for possible dysmorphological, sensory, or metabolic contributions to the phenotype.

We suggest that it is prudent and most appropriate to use convergent tests that draw on different aspects of the behavioral system under investigation. In general, behavioral techniques are most effective when used in conjunction with other techniques to generate converging lines of evidence regarding the role of a molecule in a neural pathway.

Cross-References

- ▶ Active Avoidance
- ▶ Addiction
- ▶ ADHD: Animal Models
- ▶ Anxiety
- ▶ Attention
- ▶ Autism Spectrum Disorders and Mental Retardation
- ▶ Conditioned Place Preference
- ▶ Depression
- ▶ Drug Discrimination
- ▶ Elevated Plus-Maze
- ▶ Learned Helplessness
- ▶ Open Field Test
- ▶ Posttraumatic Stress Disorder
- ▶ Prepulse Inhibition
- ▶ Schizophrenia
- ▶ Self-Administration of Drugs
- ▶ Social Recognition
- ▶ Spatial Learning
- ▶ Working Memory

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Phentermine

Definition

Phentermine is an ▶ amphetamine derivative that is used as an antiobesity agent. It was present in the fenfluramine–phentermine association known as Fen–Phen, which has been withdrawn from the market because of the risk of heart valve disease. In contrast to ▶ fenfluramine, it is still available in many countries. In addition to its appetite-suppressant effects, it induces most of the sympathetic effects of amphetamine derivatives, with increased blood pressure, heart rate, agitation, and insomnia, and carries the risk of abuse and dependence.

Cross-References

- ▶ Appetite Suppressants

Phenylalanine and Tyrosine Depletion

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Synonyms

Acute tyrosine depletion; Acute tyrosine/phenylalanine depletion

Definition

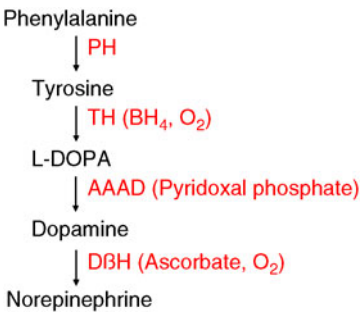
The acute phenylalanine/tyrosine depletion (APTD) method was developed as a safe and rapid way to transiently decrease ▶ dopamine (DA) neurotransmission in humans. The method entails the administration of a protein mixture that is selectively deficient in amino acids (AA) that are used to make DA. Since ingestion of this mixture decreases the availability of the necessary raw material, the neurotransmitter's synthesis and availability for release decrease as well. A manipulation based on the same principles – ▶ acute tryptophan depletion (ATD) – is widely used to transiently decrease serotonin transmission.

Current Concepts and State of Knowledge

The Catecholamine Metabolic Pathway

DA is a monoamine. As the name suggests it is made from a single amine, in this case the essential AA, phenylalanine. Essential AAs are those that we need to obtain from our diet. When we ingest protein, phenylalanine is cleaved and the liver enzyme, phenylalanine hydroxylase (PH), adds a hydroxyl group (oxygen+hydrogen, OH) to yield tyrosine. Tyrosine, in turn, can also be obtained from our diet. Irrespective of how we obtain it, tyrosine can then be carried across the ▶ blood brain barrier by a two-tiered transport system (one active and saturable, the other

diffusional) that acts on various large neutral AAs (LNAA: phenylalanine, tyrosine, tryptophan, valine, leucine, isoleucine, histidine, and methionine). Tyrosine can then enter DA neurons via a similar transport system on the cell's membrane. Inside the DA cell, tyrosine is a substrate for tyrosine hydroxylase (TH). TH adds a second OH group to yield 3,4-dihydroxy-L-phenylalanine, more commonly known as L-DOPA. L-DOPA is then a substrate for L-aromatic amino acid decarboxylase (AAAD or AADC) producing DA. Finally, vesicular monoamine transporters remove DA molecules from the cytosol and place them in storage vesicles. Within noradrenergic neurons, these vesicles contain dopamine-β-hydroxylase (DβH), an enzyme that hydroxylates the DA to ► norepinephrine (NE). DβH and AADC are 100–1,000 times more active than TH, and the hydroxylation of tyrosine to L-DOPA is considered the rate-limiting step (Fig. 1).



Phenylalanine and Tyrosine Depletion. Fig. 1. The catecholamine metabolic pathway. The essential amino acid, phenylalanine, is hydroxylated to tyrosine in the liver. Tyrosine from this dietary sources is then carried into the brain. Within catecholamine neurons, tyrosine is then hydroxylated by tyrosine hydroxylase into 3,4-dihydroxy-L-phenylalanine, and this constitutes the rate-limiting step in catecholamine synthesis. Decreases in tyrosine availability within a cell act like a drain, drawing in more of the amino acid. If tyrosine levels are insufficient, dopamine synthesis decreases. Tyrosine hydroxylase activity is also influenced by the availability of three other substrates, molecular oxygen, tetrahydrobiopterin, and dopamine itself. The first two increase tyrosine hydroxylase activity, while the latter is inhibitory. Similarly, the decarboxylation of L-DOPA to dopamine is affected by concentrations of pyridoxal phosphate (vitamin B_6), while the hydroxylation of dopamine to norepinephrine is affected by oxygen and ascorbate acid (vitamin C). *PH* phenylalanine hydroxylase; *TH* tyrosine hydroxylase; l-*DOPA* 3,4-dihydroxy-L-phenylalanine; *AAAD* aromatic amino acid decarboxylase; *DβH* dopamine beta hydroxylase; BH_4 tetrahydrobiopterin; O_2 molecular oxygen.

Acute Phenylalanine/Tyrosine Depletion (APTD)

Under normal physiological conditions, TH is only 75% saturated. Since TH is also the rate-limiting enzyme in DA synthesis, manipulations of tyrosine availability affect DA production. These effects might be particularly pronounced when the cell firing rate and precursor use is high. A method that exploits these features is called APTD.

In APTD studies, participants ingest an AA mixture that either does or does not contain phenylalanine and tyrosine (Table 1). Ingestion of the mixture induces protein synthesis in the liver. If the mixture lacks phenylalanine and tyrosine, the liver uses what it can extract from plasma. Since these plasma quantities are modest, levels decrease substantially. At the same time, plasma levels of AAs that were in the ingested mixture increase. This combination of effects markedly decreases the ratio of tyrosine to other LNAAs. Since this increases competition for access to the LNAA transporter, the amount of tyrosine that is able to enter the brain plummets (Wurtman et al. 1974; Fernstrom and Fernstrom 1995).

Studies conducted in rats, nonhuman primates, and humans indicate that the achieved tyrosine depletion significantly decreases DA synthesis and release. This includes evidence from postmortem tissue and in vivo microdialysis studies in rodents, cerebrospinal fluid (CSF) studies in monkeys, and both neuroendocrine and functional neuroimaging studies in humans. Although APTD might also affect NE metabolism, most evidence suggests an absence of significant effects on NE release. This preferential effect on DA was not predicted a priori, but the feature has been exploited to use APTD as a more selective probe than originally envisaged. Although effects of APTD on the trace amines are theoretically possible also, this has not been reported.

AA Mixture Composition: Rats, Vervet Monkeys, and Humans

Multiple APTD mixture recipes have been developed (Table 1). The two most common versions for the use in humans were developed by research groups at McGill University and Oxford University. The McGill recipe contains 16 AAs given in the proportion that is found in human milk. The Oxford recipe has similarities, but it is without histidine and six nonessential AAs: alanine, arginine, cysteine, glycine, proline, and serine. Compared with the McGill mixture, the Oxford control mixture contains proportionally more phenylalanine and tyrosine, exactly 10.8% for both, as compared to 5.4% and 6.6%, respectively in the McGill recipe. Both APTD mixtures yield decreases in plasma phenylalanine and tyrosine levels within the range of 50–70%, and decreases in their

Phenylalanine and Tyrosine Depletion. Table 1. Balanced mixtures.

Balanced Mixtures					Rats (mg)
Amino Acids	Men (g)	Men (g)	Vervet Monkeys (g)	Rats (mg)	
	(Leyton et al. 2000)	(McTavish et al. 1999a)	(Palmour et al. 1998)	(McTavish et al. 1999b)	(Jaskiw and Bongiovanni 2004)
L-Alanine	5.5		0.55		
L-Arginine	4.9		0.49		
L-Cysteine	2.7		0.27		
Glycine	3.2		0.32		
L-Histidine	3.2		0.32		
L-Isoleucine	8	15	0.80	300	415.5
L-Leucine	13.5	22.5	1.35	450	623.2
L-Lysine monohydrochloride	11	17.5	1.10	350	350
L-Methionine	3	5	0.30	100	100
L-Phenylalanine	5.7	12.5	0.57	250	
L-Proline	12.2		1.22		
L-Serine	6.9		0.69		
L-Threonine	6.5	10	0.65	200	200
L-Tryptophan	2.3	2.5	0.23	50	50
L-Tyrosine	6.9	12.5	0.69	250	
L-Valine	8.9	17.5	0.89	350	350

ratio to LNAAs in the range of 80–90%. Unequivocal differences in the elicited behavioral effects have not been identified. Direct comparisons between the two mixtures, though, have not been conducted.

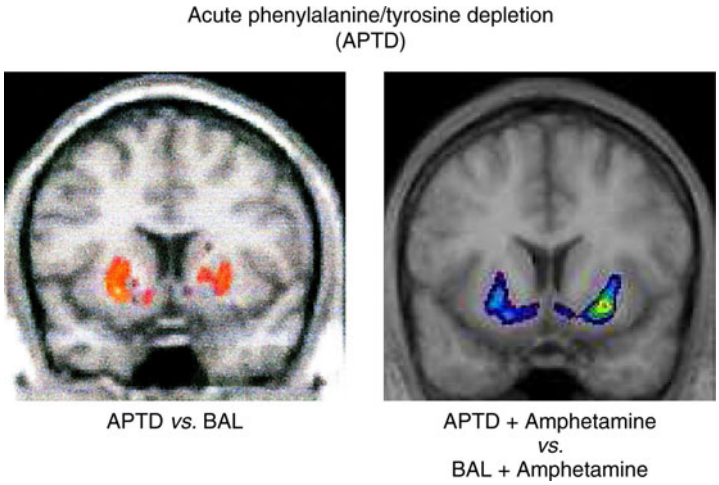
The McGill group has also developed a version of the APTD mixture for use in vervet monkeys. The formula is identical to that used in humans, though adjusted accordingly for the monkey's lower body weight. At least two versions for use in rodents have also been described, and they can be administered by gavage or intraperitoneal injection. Again, direct comparisons of their effects have not been reported but unequivocal differences are not evident in the literature.

Advantages and Disadvantages of APTD

Compared with the other methods for decreasing DA transmission, APTD has both advantages and disadvantages. On the plus side, the effects develop and dissipate rapidly, beginning as soon as 3 h after ingestion and disappearing three to four hours later. Transient nausea is sometimes reported, and 5–10% of subjects will regurgitate the mixture, but these sensations subside. Experience suggests that subjects who retain the mixtures for a minimum of 45–60 min achieve a decrease in plasma phenylalanine and tyrosine levels within the usual range. These mild adverse effects compare well to those associated with other methods for decreasing DA transmission. For example, administration of the competitive TH inhibitor, α-methyl-*para*-tyrosine (AMPT) typically requires 48–72 h inpatient observation, and can lead to motor dyskinesias and crystalluria. The former effect likely reflects large DA depletions within the nigrostriatal pathway, and this can be either an advantage or a confound depending on the outcome of interest. DA receptor antagonists can also be used. Positron emission tomography ► PET imaging studies suggest that receptor blockade up to 70% or 80% can be achieved without eliciting extrapyramidal side effects or hyper-prolactinemia, but available compounds either do not bind to all DA receptor subtypes or are nonspecific, binding also to multiple non-DA receptors.

Neurophysiological Effects of APTD

► Microdialysis studies conducted in rats suggest that APTD does not affect extracellular DA levels when animals are tested at rest, but potent effects are seen during



Phenylalanine and Tyrosine Depletion. Fig. 2. The figure depicts functional neuroimaging evidence that acute phenylalanine/tyrosine depletion (APTD) decreases extracellular dopamine levels in human striatum. At left, the colored t-map superimposed on the anatomical magnetic resonance image delineates regions where binding of the D2/D3 receptor ligand [^{11}C]raclopride was significantly higher following APTD versus ingestion of a nutritionally balanced control mixture (BAL), indicative of decreased extracellular dopamine levels (Montgomery et al. 2003). The image at right shows regions where [^{11}C]raclopride binding was higher on a test day with amphetamine plus APTD, as compared to amphetamine plus BAL, indicative of decreased drug-induced dopamine release (Leyton et al. 2004). Both effects occurred primarily within more ventral than dorsal regions of the striatum. The right side of each image represents the right side of the brain.

periods of increased DA cell firing (Jaskiw and Bongiovanni 2004) or release (McTavish et al. 1999b). These effects are dose-dependent, and APTD can diminish stimulated DA release by up to 70% (McTavish et al. 1999b). In humans, APTD increases circulating levels of prolactin, a neuroendocrine index of decreased DA transmission within the tuberoinfundibular pathway. In functional neuroimaging studies, APTD also decreases striatal DA release (Fig. 2), and this has been seen in the absence of an experimental challenge (Montgomery et al. 2003); however, whether this reflects a decrease in resting DA release or a diminished response to the mild stress of having an hour-long brain scan is difficult to disentangle. Irrespective, larger changes are reported to occur when participants are given a pharmacological challenge; that is, APTD decreases amphetamine-induced DA release, and the magnitude of this effect is twice of what is seen in subjects tested at "rest" (Leyton et al. 2004). One consequence of the APTD-induced decrease in DA transmission appears to be a disruption in the ability of different components of cortical–subcortical neurocircuits to work in coordination; that is, whereas cortical and basal ganglia structures exhibit high intercorrelations in activity levels when participants are engaging in a familiar neurocognitive task, these correlations are significantly reduced following APTD (Nagano-Saito et al. 2008). Based on these observations, it was proposed that normal DA tone is required to permit the efficient transfer of information throughout cortico-striatal circuitry.

Neurocognitive Effects of APTD

The APTD literature remains relatively small, but a number of behavioral effects have been reported. These include changes in the ability of subjects to preferentially respond to reward-related cues, to adjust responding appropriately when reward parameters change, and to sustain selective, focused interest in affectively relevant events. Some studies have also identified effects on spatial working memory, but an equal number of published studies yielded negative results; functional neuroimaging studies suggest that the variable results might reflect individual differences in the magnitude of DA depletion achieved.

Effects of APTD on Mood and Motivational States

APTD alone does not appear to lower mood in healthy individuals. In comparison, a now replicated finding is that APTD potentiates the mood-lowering effect of a psychological challenge. In people with mood disorders, a dissociation is seen also; tyrosine depletion reduces manic symptoms in bipolar patients but does not

reinstate depressive symptoms in recovered patients with a history of major depression.

Effects of APTD on Substance Use

A frequent application of the APTD method has been in addiction research. APTD is reported to decrease psychostimulant effects of amphetamines, the ability of ► cocaine and cocaine-paired cues to elicit ► craving, alcohol self-administration in a free-choice task when the participants are light social drinkers, and the tendency to sustain responding on a ► progressive ratio breakpoint task for successive units of an alcoholic beverage when the participants are heavy social drinkers. In comparison, in nicotine-dependent smokers the results have been quite variable.

Conclusions

Overall, the APTD method has proven to be an effective method to decrease DA transmission in human brain. Although, the effects might be smaller than those produced by other methods, the rapid, transient, and selective effects as well as more modest side effect profile are compelling for ethical reasons and simplify the interpretation of results.

Cross-References

► Addiction
► Amine Depletors
► Aminergic Hypotheses for Depression
► Impulsivity
► Mania
► Mood Disorders
► Tryptophan Depletion
► Working Memory

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Phenylketonuria

Synonyms

PKU

Definition

Phenylketonuria is a genetic disorder (autosomal recessive) in which the body lacks the enzyme required to break down the amino acid phenylalanine. Failure to break down phenylalanine leads to its, and related compounds, buildup, causing damage to the central nervous system. A strict diet begun at birth can help mitigate the negative consequences, namely mental retardation, hyperactivity, and motor control problems. Screening newborn infants for phenylketonuria is a standard medical practice.

Modified from the Diagnostic and Statistical Manual of the American Psychiatric Association, Fourth edition (► DSM-IV) and the NIH-NLM MedlinePlus Encyclopedia (online)

Phenylpropanolamine

Synonyms

Norephedrine

Definition

Phenylpropanolamine is an amphetamine derivative that has been used as a stimulant, decongestant, and anorectic agent. Its psychomotor stimulant effects are much weaker than those of ► amphetamine in humans. It has been widely used in cough and cold preparations. It has been withdrawn from several countries because of the risk of

stroke. It has been subject to abuse in mixtures with other mild stimulants such as ► caffeine and ephedrine, with which it interacts to produce more powerful psychomotor activation.

Cross-References
► Appetite Suppressants
► Psychostimulants

Phenytoin

Definition
Phenytoin is an antiepileptic drug that controls seizure activity in epilepsy patients in much the same way as drugs such as ► carbamazepine, namely, by controlling the over activity of nerve cells during an epileptic attack by acting at a protein called sodium channels. In addition to its antiepileptic effects, phenytoin like a number of other antiepileptic drugs has been used clinically to treat various ► mood disorders, although it is not registered for these uses.

Cross-References
► Anticonvulsants
► Bipolar Disorder
► Mood Stabilizers

Pheromones

Definition
Pheromones are chemicals transported outside of the body to send messages to individuals of the same species. There are many different pheromones, for example, alarm, food trail, or sex pheromones, that affect both behavior and physiology. Pheromones are detected by the olfactory epithelium and also in most mammals (but not humans) by the vomeronasal organ, a patch of G-protein-coupled receptor tissue in the nasal cavity.

Cross-References
► Autism: Animal Models

Philosophical Basis

► Ethical Issues in Animal Psychopharmacology

phMRI

► Pharmacological fMRI

Phobic Anxiety

► Agoraphobia

Phosphodiesterase Inhibitors

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Synonyms
PDE inhibitors

Definition
There are 11 families of ► phosphodiesterases (PDEs; PDE1–PDE11), which degrade the second messengers cAMP and/or cGMP. The activity of PDEs can be selectively inhibited with drugs. The most widely known PDE inhibitor is sildenafil, which is one of the three ► PDE5 inhibitors approved for the treatment of ► erectile dysfunction and more recently arterial ► pulmonary hypertension. In addition, two ► PDE3 inhibitors are approved for treating ► congestive heart failure or ► intermittent claudication, respectively. At the moment, PDE inhibitors are explored as possible therapeutic CNS targets for pain (PDE4, PDE5), memory loss (PDE2, PDE4, PDE5, PDE9), Alzheimer's disease (PDE4, PDE5), depression (PDE4), ► schizophrenia (PDE10), or stroke (PDE3, PDE5).

Pharmacological Properties

History
In 1886 the activity of PDEs was actually first described as it was noted that ► caffeine had bronchodilator properties. Later on, this effect was attributed to cyclic nucleotide cAMP and that caffeine-inhibited cAMP-specific PDEs. In 1970 PDEs were identified in rat and bovine tissue and it was demonstrated that PDEs hydrolyze the phosphodiesteric bond of cAMP and cGMP (Bender and Beavo 2006). From then on more PDEs were identified

and characterized. Until now 21 classes of genes for PDEs in humans, rats, and mice have been identified.

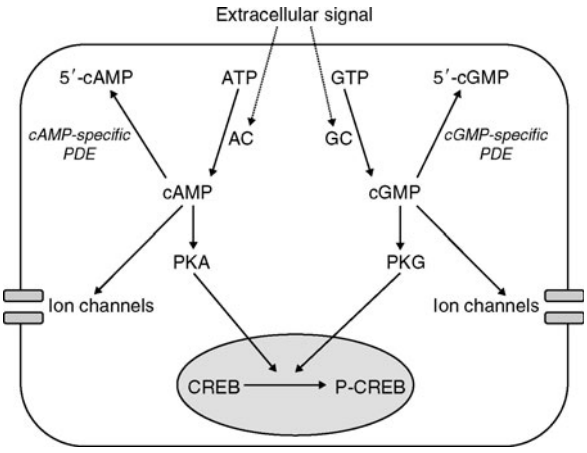
PDEs have been classified into 11 families (PDE1–PDE11) based on several criteria such as subcellular distributions, mechanisms of regulation, and enzymatic and kinetic properties. Most of these families have more than one gene product (e.g., PDE4A, PDE4B, PDE4C, PDE4D). In addition, each gene product may have multiple splice variants (e.g., PDE4D1–PDE4D9). In total, there are more than 100 specific PDEs (Bender and Beavo 2006).

Caffeine is a nonselective PDE inhibitor and it also inhibits cGMP-specific PDEs such as PDE5. cGMP causes vasodilatation in blood vessels by regulating their smooth muscle physiology. In addition, PDE5 also has an action on smooth muscles of contractile organs such as the penis. The most widely known PDE5 inhibitor is ▶ sildenafil. It was initially developed for the treatment of arterial hypertension and angina pectoris (Puzzo et al. 2008). In 1998 sildenafil was approved by the US Food and Drug Administration (FDA) for the treatment of erectile dysfunction and marketed under the name Viagra. Under the name of Revatio it was also approved for the therapy of pulmonary artery hypertension in 2005.

The discovery of sildenafil started the research and development of numerous inhibitors of PDE5. At the same time, it stimulated researchers to explore other classes of PDEs for their therapeutic potential in different disorders. In addition, the previously explored PDEs, such as PDE4 were reevaluated after first being dismissed as a fruitful target due to side effects and a lack of specificity or efficacy of the developed PDE inhibitors (Esposito et al. 2009). For instance, in 1984 the PDE4 inhibitor ▶ rolipram was developed as a putative antidepressant, but it never made it to the market due to severe emetic side effects (e.g., nausea, vomiting).

Mechanisms of Action

PDEs hydrolyze the second messengers cAMP and/or cGMP, which are synthesized by adenylate and guanylate cyclase, respectively. However, the intracellular concentrations of both cyclic nucleotides are especially regulated by the PDE activity as its hydrolysis capacity far exceeds the capacity for synthesis. Besides this absolute and temporal regulation of cyclic nucleotides, PDEs contribute to their compartmentalized signaling as different PDEs are localized at some specific sites in the cell such as the plasma or nuclear membrane, or cytosol. Thus, PDEs play a key role in the intracellular, signal transduction pathways in various biological systems as is illustrated in Fig. 1. cAMP and cGMP transfer an extracellular signal (e.g., neurotransmitter or hormone) to their effector proteins, protein kinase A and protein kinase G, respectively. Both kinases phosphorylate other enzymes or transcription factors, thus influencing the signal transduction. In addition, both cyclic nucleotides regulate their corresponding cyclic nucleotide-gated ion channels, which depolarizes synaptic terminals and thus influences signaling pathways. For instance, cGMP regulates cGMP-gated ion channels and thus directly regulates the ion flux, which depolarizes the presynaptic terminal and influences glutamate release. Eventually, changes in signal transduction are translated into a biological system-dependent physiological and cellular response (Halene and Siegel 2007; Menniti et al. 2006; Puzzo et al. 2008; Reneerkens et al. 2009).



Phosphodiesterase Inhibitors. Fig. 1. Intracellular, signal transduction pathways. An extracellular signal (e.g., neurotransmitter or hormone) activates adenylate cyclase (AC) and guanylate cyclase (GC), which produce their corresponding cyclic nucleotides out of ATP and GTP, respectively. cAMP activates protein kinase A (PKA) and cGMP activates protein kinase G (PKG). Both PKA and PKG can phosphorylate other enzymes or transcription factors such as CREB in the nucleus. Besides gene expression, cAMP and cGMP also regulate cAMP- and cGMP-gated ion channels, respectively, which depolarizes the synaptic terminals. Eventually, these processes will result in a cellular response. Phosphodiesterases (PDEs) hydrolyse cAMP and/or cGMP leading to the formation of the inactive 5′-cAMP and 5′-cGMP, respectively. PDE inhibitors are selective for cAMP and/or cGMP degrading PDEs. In this way, a selective PDE inhibitor can specifically influence the cellular response of a biological system. (Adapted from Puzzo et al. 2008.)

PDEs itself are regulated by intracellular cyclic nucleotide concentrations, phosphorylation (e.g., protein kinase G), interaction with regulatory proteins, subcellular compartmentalization, and binding of Ca^{2+}/calmodulin (Cheng and Grande 2007).

The specific localization of the different PDEs in the brain and the body will predict which certain physiological function may be influenced by some PDE inhibitors, but not by others. Table 1 gives an overview of the distribution of the different PDEs. Obviously, the PDE5-inhibitor sildenafil can be used for the treatment of erectile dysfunction since PDE5 is expressed in human cavernosal smooth muscle. Since PDE10A is highly expressed in the striatum where it regulates signal transduction in the corticostriatothalamic circuit, it is, therefore, an interesting target for schizophrenia and related disorders of basal ganglia function. In contrast, PDE4 is highly expressed in the ► hippocampus, which is a key structure in the limbic system, and is, therefore, considered as a useful target for treatment of mood disorders or cognitive deficits.

Pharmacokinetics

Only the ► pharmacokinetics of compounds that have been approved by the FDA and are also being evaluated for CNS applications are described.

The PDE3-inhibitor cilostazol is given orally and has a half-life of about 11–13 h. Cilostazol is metabolized and eliminated by CYP3A4 and CYP2C19, two isoenzymes of the cytochrome P450 system in the liver, after which it is predominantly excreted via the kidneys (Chapman and Goa 2003).

Sildenafil, vardenafil, and tadalafil are rapidly absorbed in the gastrointestinal tract at the level of the small intestine. The ► half-life of sildenafil and vardenafil is about 3–4 h. In contrast, tadalafil has a long half-life of about 18 h. All three compounds are metabolized and eliminated in the liver by CYP3A4. For sildenafil CYP2C9 is also partly involved. All three metabolized PDE5 inhibitors are excreted predominantly via the liver into the feces but also via the kidneys into the urine (Puzzo et al. 2008).

If a compound can be used to target central nervous system-related disorders it is vital that it crosses the

Phosphodiesterase Inhibitors. Table 1. Localization of different phosphodiesterases (PDEs) and PDE isoforms in the body and brain of rodents and humans in adulthood.

PDE	Localization in body	Localization in the brain (per isoform)
PDE1	Heart, smooth muscles, lungs	Hippocampus – 1A, 1B, 1C; cortex – 1A, 1B, 1C; olfactory bulb – 1A, 1B; striatum – 1A, 1B; thalamus – 1A; amygdala – 1C; cerebellum – 1A, 1C
PDE2A	Heart, adrenal cortex, platelets	Hippocampus, cortex, striatum, amygdala, hypothalamus, midbrain
PDE3	Heart, smooth muscles, kidneys, platelets	Throughout brain
PDE4	Wide variety of tissues: e.g., smooth muscles, lungs, kidneys, testes	Hippocampus – 4A, 4B, 4D; cortex – 4A, 4B, 4D; olfactory bulb – 4A; striatum – 4A, 4B, 4D; thalamus – 4A; hypothalamus – 4A, 4B, 4D; amygdala – 4A; midbrain – 4A, 4B, 4D; cerebellum – 4A, 4B, 4D
PDE5	Smooth muscles, skeletal muscles, lungs, kidneys, platelets	Hippocampus, cortex, cerebellum
PDE6	Rod and cone cells in retina	Pineal gland
PDE7	Heart, skeletal muscles, liver, kidneys, testes, pancreas	Hippocampus – 7A, 7B; cortex – 7A, 7B; olfactory bulb – 7A; striatum – 7A, 7B; midbrain – 7B
PDE8	Heart, liver, kidneys, lungs, testes, thyroid	Hippocampus – 8A; cortex B – 8A; olfactory bulb – 8A; striatum – 8A; thalamus – 8A; midbrain – 8A
PDE9A	Kidneys, spleen, prostate, various gastrointestinal tissues	Hippocampus, cortex, olfactory bulb, striatum, thalamus, hypothalamus, amygdala, midbrain, cerebellum
PDE10A	Heart, skeletal muscles, lungs, liver, kidneys, testes, pancreas, thyroid	Hippocampus, cortex, striatum, midbrain, cerebellum
PDE11A	Skeletal muscles, liver, kidneys, testes, prostate, thyroid	Pituitary

Only clear expression levels are taken into consideration with an overlap between species if possible. Note that this table does not provide information with respect to the level of expression (protein or mRNA) of the different PDEs

► blood–brain barrier. Especially when the compound itself is required centrally to be effective, as otherwise alternatives have to be developed such as a central administration application for the drug. Sildenafil has been demonstrated in preclinical animal studies to penetrate the brain. For vardenafil this still needs to be established. Tadalafil has been shown preclinically to not cross the blood–brain barrier; while in contrast to sildenafil, it did not attenuate the memory performance deficit in a mouse model of ► Alzheimer's disease (Puzzo et al. 2009).

Efficacy

Table 2 summarizes the PDE inhibitors currently on the market or in development. For CNS applications also preclinical evidence is mentioned. More detailed information about the status of clinical development of a particular compound can be found at http://clinicaltrials.gov/. To check whether a drug is approved by the FDA, see http://www.accessdata.fda.gov/scripts/cder/drugsatfda/.

The PDE1-inhibitor vinpocetine (Cavinton, Intelectol) is not approved by FDA as a drug, but it is widely used as a supplement for vasodilation and as a nootropic for the improvement of memory. The latter effect is likely to be related to vasodilatation. However, the relevance of the possible therapeutic effect of vinpocetine can be questioned as it has not been shown to be of real benefit in the clinic.

Currently, the most selective PDE2 inhibitor available is BAY 60-7550 and it has been shown to improve memory in rodents (Boess et al. 2004). Exisulind (Aptosyn) is another developed PDE2 inhibitor, which also has the PDE5-inhibiting activity. This drug induces apoptosis in a broad range of cancer cell lines and inhibits the formation and growth of cancer in several animal models. Presently, this compound has been tested in clinical Phase-III trials for breast, lung, prostate, and colon tumors.

Cilostazol (Pletal) is a PDE3 inhibitor and has been approved by the FDA for the treatment of intermittent claudication. It is also being investigated in a Phase-IV study as a prevention of stroke recurrence and safety for bleeding complications in acute stroke. Enoximone (Perfan) and milrinone (Primacor) are also PDE3 inhibitors, which have been developed for the treatment of congestive heart failure. While Milrinone has been approved by the FDA for this indication, enoximone is in the Phase III of development. Their mode of action is via cAMP/PKA-mediated facilitation of intracellular Ca^{2+} mobilization. In addition, vasodilatory action plays a key role in improving hemodynamic parameters in certain patients.

► PDE4 inhibitors were initially considered as a possible target for the development of drugs for the treatment of depressive disorders (Esposito et al. 2009). In this respect the PDE4-inhibitor ► rolipram has been widely investigated. First clinical studies showed a good antidepressant response to rolipram treatment. However, rolipram produces severe dose-limiting emetic side effects including headache, gastric hypersecretion, nausea, and vomiting in humans. This has put a serious hold on the further development of rolipram and other related PDE inhibitors. It also prevented rolipram from reaching the market. But since the approval of PDE5 inhibitors for the treatment of erectile dysfunction, PDE inhibitors in general have received renewed interest as a possible therapeutic target for the treatment of diseases. Along similar lines, a clinical ► Phase-II trial has recently started to reevaluate the antidepressant properties of rolipram.

At the moment, "second generation" PDE4 inhibitors are being developed, which are supposed to have less-emetic side effects, and are being studied for other disorders besides that of depression. Recently, a clinical Phase-II trial has been completed investigating whether the PDE4-inhibitor MK0952 improves cognition in patients with mild-to-moderate Alzheimer's disease. Furthermore, the PDE4 inhibitors cilomilast (Ariflo) and rofluminast have been clinically tested up to ► Phase III as anti-inflammatory drugs for the treatment of asthma and chronic obstructive pulmonary disease (COPD). However, they have not been approved by the FDA yet. Ibudilast (or AV-411) is another PDE4 inhibitor in development as an anti-inflammatory drug. However, this compound not only inhibits PDE4 but also serves as a glial activator, and other clinical CNS applications are being explored in Phase-II studies, i.e., pain and drug abuse.

The PDE5-inhibitor sildenafil was the first FDA-approved treatment of erectile dysfunction. Although PDE5 inhibition causes relaxation of smooth muscles in blood vessels, it is also of particular importance for the treatment of erectile dysfunction in that it causes relaxation of smooth muscles in organs such as the penis (Puzzo et al. 2008). In women, sildenafil has an effect on the contractile state of the uterus and blood flow in the clitoris. Therefore, sildenafil is also considered as a possible treatment for female sexual arousal disorder (FSAD) (completed Phase-II trial). Sidenafil is on the market as Viagra. Two more PDE5 inhibitors also reached the market for the treatment of erectile dysfunction as well, vardenafil (Levitra) and tadalafil (Cialis), respectively. Vardenafil is the more-potent PDE5 inhibitor when compared with sildenafil and tadalafil. The latter is considered

Phosphodiesterase Inhibitors. Table 2. Overview of the PDEs and their possible clinical applications.

Type	Number of genes	Property	Substrate	Selective inhibitors	FDA-approved and possible therapeutic applications. CNS applications in Bold
PDE1	3	Ca^{2+}-CaM stimulated	cAMP/cGMP	vinpocetine, calimidazolium, CH51866	**Memory loss–vinpocetine (Cavinton, Intelectol)**
PDE2	1	cGMP stimulated	cAMP/cGMP	bay 60-7550, EHNA, exisulind	**Memory loss–Bay 60-7550 (preclinical).** Cancer–exisulind (Aptosyn)
PDE3	2	cGMP inhibited	cAMP	cilostazol, cilostamide, enoximone, milrinone, lixazinone, OPC-33540, SK&F 95654	**Stroke – cilostazol.** Intermittent claudication–cilostazol (Pletal). Congestive heart failure – Milrinone (Primacor). Congestive heart failure–enoximone (Perfan)
PDE4	4	cAMP specific	cAMP	rolipram, Ro 20-1724, cilominast, rofluminast, ibudilast, MK0952, V11294A, L-826,141, AWD 12-281, HT0712, SCH 351591	**Cognitive impairment in mild to moderate Alzheimer's disease – MK0952. Depression–rolipram**. **Pain – ibudilast**. Astma, Chronic obstructive pulmonary disease (COPD) – cilominast (Ariflo), rofluminast
PDE5	1	cGMP specific	cGMP	sildenafil, vardenafil, tadalafil, SK&F 96231, DMPPO, udenafil, avanafil, DA-8159, cilominast	**Memory loss – sildenafil, vardenafil (preclinical). Stroke–sildenafil. Pain – sildenafil (preclinical)**. Erectile dysfunction – sildenafil (Viagra), vardenafil (Levitra), tadalafil (Cialis). Female sexual arousal disorder (FSAD) – sildenafil. Pulmonary hypertension – sildenafil (Revatio)
PDE6	4	Photoreceptor	cGMP	sildenafil, vardenafil, tadalafil, DMPPO	–
PDE7	2	cAMP high affinity	cAMP	BRL 50481, IC242, BMS-586353	–
PDE8	2	cAMP high affinity	cAMP	–	–
PDE9	1	cGMP high affinity	cGMP	BAY 73-6691	**Memory loss – BAY 73-6691 (preclinical)**
PDE10	1	cAMP-inhibited	cGMP	papaverine, PF-2545920, PQ-10, TP-10	**Schizophrenia – PF-2545920**
PDE11	1	Dual substrate	cAMP/cGMP	tadalafil	–

The properties and substrate specificity are depicted. In addition, the commonly used selective and nonselective PDE inhibitors are mentioned. FDA-approved compounds as well as compounds in clinical phases of development are given. For possible CNS applications also preclinical evidence is given. All CNS applications are in bold

Nonselective inhibitors: caffeine, theophylline, 3-isobutyl-1-methylxanthine (IBMX; all but PDE8), dipyidamole (PDE5, 6, 7, 9, 10, 11), zaprinast (PDE5, 6, 9, 10, 11), SCH 51866 (PDE5, 7, 9, 10, 11), E4021 (PDE5, 6, 10, 11)

as second-generation oral drug and it has the longest half-life while its effects last the longest as well.

Because of its vasodilatatory properties, sildenafil is also FDA approved under the name of Revatio for the treatment of hypertension of the pulmonary artery. For the same application, a clinical Phase-III trial with tadalafil has just been completed, while a Phase-II trial of vardenafil is ongoing.

Sildenafil has been successfully used to treat serotonin reuptake inhibitor (► SSRI)-associated erectile dysfunction. In women, recently a Phase-IV study has been completed which assessed the efficacy of sildenafil in women with SSRI-associated sexual dysfunction. In addition, a Phase-IV study has just been completed that measured the impact of treatment with sildenafil on the depressive symptoms and quality of life in male patients with erectile

dysfunction who have untreated depressive symptoms. However, it will be difficult to disentangle whether a possible beneficial effect on mood is due to the treatment of the sexual dysfunction or whether PDE5 inhibition directly leads to an improvement in depressive symptoms and thus, an attenuation of the erectile/sexual dysfunction. Of note, no direct antidepressant potential of sildenafil has been found in preclinical rodent studies (Brink et al. 2008).

At the moment, a Phase-I study is evaluating whether sildenafil has ► neuroprotective properties in the treatment for stroke. Another interesting CNS application could be neuropathic pain as sildenafil was effective in the treatment of pain in animal models (Ambriz-Tututi et al. 2005).

There is substantial evidence that PDE5 inhibition has cognition-enhancing effects in several animal species including rodents and monkeys (Reneerkens et al. 2009). However, until now convincing evidence in humans is still lacking. Three studies have explored the effects of sildenafil on human cognition. However, in two studies with healthy human volunteers no effect or only an indirect enhancing, i.e., electrophysiological, effect on cognition was found. It is to be noted that in both studies the number of participants could have been too low to detect any subtle effect. Hemodynamic studies in humans indicate that possible effects on cognition after sildenafil administration are not likely to be related to cerebrovascular mechanisms. Preclinical animal studies indicate that an improved second-messenger signaling in synaptic transmission between neurons might be a more plausible mechanism. A third study tested the cognition in patients with schizophrenia, who received sildenafil added to antipsychotic treatments (Goff et al. 2009). However, sildenafil was not effective. Probably, its dose was not high enough to overcome the antipsychotic medication. A very important recent finding is that the expression of PDE5 is strongly reduced in brains of Alzheimer's disease patients (Reyes-Irisarri et al. 2007). Along similar lines, PDE5 inhibition did not improve memory in aged rats. Thus, when developing a PDE inhibitor for the treatment of cognitive decline in ► dementias including Alzheimer's disease, other PDEs might provide better targets than PDE5.

PDE9 does not show an Alzheimer-related reduction in expression patterns (just like PDE2). The only available PDE9 inhibitor is BAY 73-6691 and, interestingly, it improved memory performance in rodents (Van der Staay et al. 2008). This suggests that it might have therapeutic potential for the treatment of memory dysfunction.

Until very recently, the PDE10A-inhibitor PF-2545920 (or MP-10) was in a Phase-II clinical study for the treatment of schizophrenia. However, this study has just been terminated for a reason unknown. The action mechanism of PDE10A inhibition was attributed to be modulation/normalization of dopaminergic cortico-striatothalamic function. In this respect, increased cAMP levels are assumed to be of more importance than cGMP, although PDE10A itself predominantly hydrolyses cGMP.

Safety/Tolerability

Only safety and tolerability of compounds which have been approved by the FDA and are also being evaluated for CNS applications are discussed.

Possible side effects of the PDE3-inhibitor cilostazol include, most commonly, not only headache, but also diarrhea, abnormal stools, irregular heart rate, and palpitations. Since cilostazol is a quinolinone derivative, it is therefore dangerous for people with severe heart problems and hence, can only be given to people without this indication.

Sildenafil, vardenafil, as well as tadalafil have side affects such as headaches, facial flushing, nasal congestion, and dyspepsia (indigestion). However, these effects are transient. All three PDE inhibitors can act on PDE6, which is present in the retina; and high doses have been reported to cause adverse visual events, including nonarteritic anterior ischemic optic neuropathy; and thus, can cause vision problems (e.g., blurred vision). Moreover, tadalafil also potently inhibits PDE11, an enzyme with an unknown physiological function. Because of the possible vasodilatatory effects, these compounds are not suited for patients with cardiovascular indications or hypotensives.

An approach to circumvent the side effects of PDE inhibitors is to develop very selective inhibitors at the level of the isoform or splice variant. At the same time, the function of interest may be more specifically targeted. For example, there are three splice variants of PDE5, PDE5A1–PDE5A3 (Puzzo et al. 2008). While the first two are found nearly in all tissues, the third one is specific to smooth muscles.

The emetic side effects of the available PDE4 inhibitors, which inhibit more or less all four isoforms – PDE4A, PDE4B, PDE4C, and PDE4D, prevented until now that they have reached the market (Esposito et al. 2009). Preclinical animal research already indicated that the antidepressant potential of PDE4A in the hippocampus was related to specific splice variants of PDE4A. Moreover, in a patient with Alzheimer's disease it was found that the expression of most splice variants of PDE4D were decreased in the hippocampus, whereas two variants were increased. These findings underscore the need to develop specific inhibitors of PDE4-splice variants as cognition enhancers or antidepressants (Reneerkens et al. 2009).

Conclusions

Besides the already approved clinical application of erectile dysfunction, pulmonary hypertension, congestive heart failure, and intermittent claudication, PDE inhibitors offer a promising target for a wide array of diseases including CNS-related disorders such as Alzheimer's disease, depression, schizophrenia, or stroke. Yet, the future in disease-specific PDE inhibitors lies in the development of splice variant-specific inhibitors that have limited aversive side-effect profiles within the effective dose range for its clinical application. Whether this will be achieved remains a challenge thus far.

Cross-References

- ▶ Congestive Heart Failure
- ▶ Erectile Dysfunction
- ▶ Intermittent Claudication
- ▶ PDE3 Inhibitors
- ▶ PDE4 Inhibitors
- ▶ PDE5 Inhibitors
- ▶ Phosphodiesterases
- ▶ Pulmonary Hypertension
- ▶ Rolipram
- ▶ Sildenafil

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Phosphodiesterases

Definition

Phosphodiesterases are enzymes that hydrolyze the second messenger cyclic nucleotides cAMP and/or cGMP. Thus, phosphodiesterases influence intracellular signal transduction pathways in various biological systems. There are 11 families of phosphodiesterases, PDE1–PDE11. This classification is based on their subcellular localizations, mechanisms of regulation, and enzymatic properties. Each family consists of multiple splice variants. In total, there are more than 100 specific PDEs. They are specifically distributed over the body and the brain.

Cross-References

- ▶ PDE3 Inhibitors
- ▶ PDE4 Inhibitors
- ▶ PDE5 Inhibitors
- ▶ Phosphodiesterase Inhibitors

Physical Dependence

Synonyms

Abstinence syndrome; Physiological dependence; Withdrawal syndrome

Definition

Physical dependence results when certain drugs are administered or self-administered regularly for extended periods of time and is revealed when drug administration is discontinued and a typical withdrawal syndrome appears. The time to onset for the withdrawal effects depends upon how rapidly the drug is eliminated from the body. For example, in ▶ alcohol physical dependence, the withdrawal signs and symptoms emerge within 12–24 h of discontinued use whereas for ▶ benzodiazepine physical dependence, the withdrawal syndrome may not emerge for several days corresponding to the slow elimination of active metabolites from the body. The extent or magnitude of the withdrawal signs and symptoms is related to the amount and duration of drug exposure preceding withdrawal. Each class of drugs has a typical withdrawal syndrome. Laboratory studies of physical dependence often employ antagonist drugs, which will precipitate a withdrawal syndrome. For example, ▶ naloxone or ▶ naltrexone will produce precipitated withdrawal in a person or animal made opioid-dependent, producing a constellation of signs and symptoms similar to those seen after spontaneous withdrawal. It should be noted that despite the name "physical dependence," signs and symptoms of withdrawal syndromes are often psychological and behavioral in nature, for example, an increase in anxiety in humans or impaired performance of a previously learned task in animals. Withdrawal syndromes are self-limiting in duration, subsiding after a period of time that depends upon the drug class and severity of dependence, among other factors.

Cross-References

▶ Abuse Liability Evaluation
▶ Alcohol
▶ Benzodiazepines
▶ Cross-Dependence
▶ Nicotine
▶ Opioid Dependence and Treatment
▶ Sedative, Hypnotic, and Anxiolytic Dependence

Physiological Cell Death

▶ Apoptosis

Physiological Dependence

▶ Physical Dependence

Physostigmine

Definition

Physostigmine is an anticholinesterase that crosses the ▶ blood–brain barrier. It is reported to improve performance in short-term and ▶ working memory in animals and humans by stimulating nicotinic and muscarinic receptors and used as a cholinergic replacement therapy for conditions such as ▶ dementia. In humans however, the side effects of lethargy, nausea, and general misery are produced by physostigmine.

Phytotherapy

▶ Herbal Remedies

Pimozide

Definition

Pimozide is a first-generation antipsychotic that acts as a dopamine D2 receptor antagonist. It is a diphenylbutylpiperidine derivative with high potency, a ▶ receptor binding profile comparable to that for ▶ haloperidol but more selective for the D2 receptor, and it has a long ▶ half-life. Following reports of sudden unexplained deaths the Committee on the Safety of Medicines recommended ECG before treatment. A history of arrhythmias or congenital QT prolongation is a contraindication for its use. Pimozide should not be combined with other potentially arrhythmogenic drugs. It has been regarded as a less-sedating compound but the frequency of extrapyramidal symptoms is relatively high.

Cross-References

▶ Antipsychotic Drugs
▶ First-Generation Antipsychotics
▶ Movement Disorders Induced by Medications
▶ Schizophrenia

Pinazepam

▶ Benzodiazepines

Pipotiazine

Definition

Pipotiazine is a first-generation antipsychotic of the phenothiazine class. It is one of the less widely used drugs of this type but pipotiazine palmitate has been used in a depot (long-acting) formulation; a Cochrane review concluded that "it is a viable choice for both clinician and recipient of care." Side effects typical of first-generation antipsychotics have been reported, including rare instances of neuroleptic malignant syndrome.

Cross-References

- ▶ First-Generation Antipsychotics
- ▶ Neuroleptic Malignant Syndrome
- ▶ Phenothiazines

Piracetam

Synonyms

2-oxopyrrolidin-1-acetamide

Definition

Piracetam is putative cognitive enhancer (nootropic) with an unknown mechanism of action, although it is believed to facilitate ▶ cholinergic transmission and to positively modulate ▶ glutamate receptors: these putative mechanisms and a wealth of preclinical data explain its use in a number of dementias, including in Parkinson's disease-associated dementias, Alzheimer's and Down's syndrome, vascular dementias, dyslexia, etc. The clinical data supporting its effects are controversial. Piracetam is not registered in the USA, where it has as an orphan drug status for the treatment of myoclonus.

Cross-References

- ▶ Cognitive Enhancers
- ▶ Dementias and Other Amnestic Disorders
- ▶ Nootropics

Pitocin

- ▶ Oxytocin

PK

- ▶ Pharmacokinetics

PKU

- ▶ Phenylketonuria

Place Cells

Synonyms

Place fields

Definition

Place cells are neurons that exhibit a high rate of firing whenever an animal is in a specific location in an environment corresponding to the cell's "place field." Place cells were first identified in the ▶ hippocampus of rats by O'Keefe and Dostrovsky, although cells with similar properties have been found in the hippocampus of primates and humans. Furthermore, neurons that display place-selective changes in activity have been identified in a number of other brain regions, including regions of the temporal cortex, the ▶ amygdala, and the striatum. Based on this discovery, it has been proposed that a primary function of the rat hippocampus is to form a cognitive map of the rat's environment. On initial exposure to a new environment, place fields become established within minutes. The place fields of cells tend to be stable over repeated exposures to the same environment. In a different environment, however, a cell may have a completely different place field or no place field at all, a phenomenon referred to as "remapping."

Place Conditioning

- ▶ Conditioned Place Preference and Aversion

Place Fields

- ▶ Place Cells

Place Learning

► Spatial Learning in Animals

Placebo-Controlled

Definition

Term used to describe a method of clinical research in which an inactive substance is given to one group of participants (i.e., the control group), while the treatment (e.g., drug, therapy, vaccine) is given to another group of participants (i.e., the treatment group).

Placebo Effect

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Synonyms

Placebo response

Definition

The placebo effect is the reduction of a symptom, or a change in a physiological parameter, when an inert treatment (the placebo) is administered to a subject who is told that it is an active therapy with specific properties. The placebo effect, so far considered a nuisance in clinical research, has now become a target of scientific investigation to better understand the physiological and neurobiological mechanisms that link a complex mental activity to different functions of the body. Usually, in clinical research the term placebo effect refers to any improvement in the condition of a group of subjects that has received a placebo treatment, thus it represents a group effect. The term placebo response refers to the change in an individual caused by a placebo manipulation. However, these two terms are often used interchangeably. It is important to realize that there is not a single placebo effect but many, which occur through different mechanisms in different conditions, systems, and diseases.

Current Concepts and State of Knowledge

Methodological Aspects

The identification of a placebo effect is not easy from a methodological point of view and its study is full of drawbacks and pitfalls. In fact, the positive effects following the administration of a placebo can be due to many factors, such as spontaneous remission, regression to the mean, symptom detection ambiguity and biases (Benedetti 2008a). All these phenomena must be ruled out through adequate control groups. For example, spontaneous remission can be discarded by means of a no-treatment group, which gives us information about the natural course of a symptom. Regression to the mean, a statistical phenomenon due to selection biases at the enrolment in a clinical trial, can be controlled by using appropriate selection criteria. Symptom detection ambiguity and biases can be avoided by using objective physiological measurements. It is also important to rule out the possible effects of co-interventions. For example, the mechanical insertion of a needle for the injection of an inert substance may per se induce analgesia, thus leading to erroneous interpretations.

When all these phenomena are ruled out and the correct methodological approach is used, substantial placebo effects can be detected, which are mediated by psychophysiological mechanisms worthy of scientific inquiry. Therefore, this psychological component represents the real placebo effect.

Mechanisms

The placebo effect is basically a context effect, whereby the psychosocial context (e.g., the therapist's words, the sight of medical personnel and apparatuses, and other sensory inputs) around the medical intervention and the patient plays a crucial role. Today, we know that the context may produce a therapeutic effect through at least two mechanisms: conscious anticipatory processes and unconscious conditioning mechanisms (Benedetti 2008b; Enck et al. 2008; Price et al. 2008). In the first case, the expectation and anticipation of clinical benefit may affect the response to a therapy. In the second case, contextual cues (e.g., color and shape of a pill) may act as ► conditioned stimuli that, after repeated associations with an ► unconditioned stimulus (the pharmacological agent inside the pill), are capable alone of inducing a clinical improvement. In the case of ► pain and ► Parkinson's disease, it has been shown that conscious ► expectancies play a crucial role, even though a conditioning procedure is performed, whereas placebo responses in the immune and endocrine systems are mediated by unconscious ► classical conditioning.

The neural mechanisms underlying the placebo effect are only partially understood and most of our knowledge comes from the field of pain and analgesia, although Parkinson's disease, immune and endocrine responses, and ► depression have more recently emerged as interesting models. In each of these conditions, different mechanisms seem to take place, so that we cannot talk of a single placebo effect but many (Benedetti 2008a).

As far as pain is concerned, there is now compelling experimental evidence that the ► endogenous opioid systems play an important role in some circumstances. There are several lines of evidence indicating that placebo analgesia is mediated by a descending pain modulating circuit, which uses endogenous opioids as neuromodulators. This evidence comes from a combination of imaging and pharmacological studies. By using positron emission tomography (► PET imaging), it was found that some cortical and subcortical regions are affected by both a placebo and the opioid agonist remifentanil, thus indicating a related mechanism in placebo-induced and opioid-induced analgesia (Petrovic et al. 2002). In particular, the administration of a placebo affects the rostral anterior cingulate cortex (rACC), the orbitofrontal cortex (OrbC) and the brainstem. Moreover, there is a significant covariation in activity between the rACC and the lower pons/medulla at the level of the rostral ventromedial medulla (RVM), and a subsignificant covariation between the rACC and the periacqueductal gray (PAG), thus suggesting that the descending rACC/PAG/RVM pain-modulating circuit is involved in placebo analgesia. In a different study with functional ► magnetic resonance imaging (fMRI), it was shown that placebo administration produces a decrease of activity in many regions involved in pain transmission, such as the thalamus and the insula (Wager et al. 2004; Price et al. 2008).

A clearcut involvement of endogenous opioids is shown by several pharmacological studies in which placebo analgesia is antagonized by the opioid antagonist naloxone. In addition, it has been shown that the endogenous opioid systems have a somatotopic organization, since local placebo analgesic responses in different parts of the body can be blocked selectively by ► naloxone (Benedetti 2008a). By using in vivo receptor binding techniques, placebos have been found to induce the activation of *mu* opioid receptors in different brain areas, such as the dorsolateral ► prefrontal cortex, ► nucleus accumbens, insula and rACC. It is also worth noting that opioids are activated together with dopamine, e.g., in the nucleus accumbens, thus indicating a complex interaction between different neurotransmitters (Scott et al. 2008).

The placebo-activated endogenous opioids do not act only on pain transmission, but on the respiratory centers as well, since a naloxone-reversible placebo respiratory depressant effect has been described. Likewise, a reduction of beta-adrenergic sympathetic system activity, which is blocked by naloxone, has been found during placebo analgesia. These findings indicate that the placebo-activated opioid systems have a broad range of action, influencing pain, respiration, and the autonomic nervous system (Colloca and Benedetti 2005). The placebo-activated endogenous opioids have also been shown to interact with endogenous substances that are involved in pain transmission. In fact, on the basis of the anti-opioid action of ► cholecystokinin (CCK), CCK-antagonists have been shown to enhance placebo analgesia, thus suggesting that the placebo-activated opioid systems are counteracted by CCK during a placebo procedure (Colloca and Benedetti 2005).

It is important to point out that some types of placebo analgesia appear to be insensitive to naloxone. For example, if a placebo is given after repeated administrations (pre-conditioning) of the non-opioid painkiller ketorolac, the placebo analgesic response is not blocked by naloxone.

The release of endogenous substances following a placebo procedure is a phenomenon that is not confined to the field of pain, but it is also present in other conditions, such as Parkinson's disease. As occurs with pain, in this case patients are given an inert substance and are told that it is an ► anti-Parkinson drugs that produces an improvement in their motor performance. A study used PET imaging in order to assess the competition between endogenous dopamine and ^{11}C-raclopride for D_2/D_3 receptors, a method that allows the identification of endogenous dopamine release (de la Fuente-Fernandez et al. 2001). This study found that the placebo-induced expectation of motor improvement activates endogenous dopamine in both the dorsal and ventral striatum, a region involved in reward mechanisms, which suggests that the placebo effect may be conceptualized as a form of reward.

Placebo administration in Parkinson patients also affects the activity of neurons in the subthalamic nucleus, a brain region belonging to the basal ganglia circuitry and whose activity is increased in Parkinson's disease (Benedetti 2008a). Verbal suggestions of motor improvement during a placebo procedure are capable of reducing the firing rate and abolishing the bursting activity of subthalamic nucleus neurons, and these effects are related to clinical improvement.

Depressed patients who receive a placebo treatment were shown to present metabolic changes in the regions

involved in reward mechanisms, such as the ventral striatum. In addition, in patients with unipolar depression, placebo treatments were also found to be associated with metabolic increases in the prefrontal, anterior cingulate, premotor, parietal, posterior insula, and posterior cingulate cortex, and metabolic decreases in the subgenual cingulate cortex, para-hippocampus, and thalamus. Interestingly, these regions are also affected by ► antidepressants, such as the selective serotonin reuptake inhibitor, ► fluoxetine, a result that suggests a possible role for serotonin in placebo-induced antidepressant effects (Benedetti 2008b).

Anxiety has also been found to be affected by placebos, with the involvement of those brain regions that also take part in placebo analgesia, e.g., the rACC and OrbC. In addition, placebo responsiveness in social anxiety has been found to be linked with genetic variants of serotonin neurotransmission, which suggests that part of the variability in placebo responsiveness may be attributable, at least in some conditions, to genetic factors (Benedetti 2008a).

Placebo responses in both the immune and endocrine systems can be evoked through classical conditioning. After repeated administrations of drugs, if the drug is replaced with a placebo, immune or hormonal responses can be evoked that are similar to those obtained by the previously administered drug, thus resembling the typical ► conditioned drug effects (Benedetti 2008b). For example, immunosuppressive placebo responses can be induced in humans by repeated administration of cyclosporine A (unconditioned stimulus) associated to a flavored drink (conditioned stimulus), as assessed by interleukin-2 (IL-2) and interferon-γ (IFNγ) mRNA expression, in vitro release of IL-2 and IFNγ, and lymphocyte proliferation. Likewise, if a placebo is given after repeated administrations of sumatriptan, a serotonin agonist of the $5\text{-HT}_{1B/1D}$ receptors that stimulates growth hormone (GH) and inhibits cortisol secretion, a placebo GH increase and a placebo cortisol decrease can be found.

The Nocebo Effect

The nocebo effect, or response, is a placebo effect in the opposite direction. Mainly due to ethical constraints, the nocebo effect has not been investigated in detail, as has been done for the placebo effect. In fact, a nocebo procedure is per se stressful and ► anxiogenic, as it induces negative expectations of clinical worsening. For example, the administration of an inert substance along with verbal suggestions of pain increase may induce a hyperalgesic effect. In this case, anticipatory anxiety plays a fundamental role. Nocebo hyperalgesia has been found to be blocked by proglumide, a nonspecific CCK-A/CCK-B receptor antagonist. This suggests that expectation-induced hyperalgesia is mediated, at least in part, by CCK (Enck et al. 2008). These effects of proglumide are not antagonized by naloxone, thus endogenous opioids are not involved.

Dopamine also plays a role in the nocebo hyperalgesic effect. In fact, whereas placebo administration induces the activation of dopamine in the nucleus accumbens, the administration of a nocebo is associated with a deactivation of dopamine (Scott et al. 2008).

Implications

According to the classical methodology of ► randomized controlled trials, any drug must be compared with a placebo in order to assess its effectiveness. If the patients who take the drug show a considerable clinical improvement than the patients who take the placebo, the drug is considered to be effective. However, in light of the recent advances in placebo research, some caution is necessary in the interpretation of some clinical trials. In fact, by considering the complex cascade of biochemical events that take place after placebo administration, any drug that is tested in a clinical trial may interfere with these placebo/expectation-activated mechanisms, thus confounding the interpretation of the outcomes (Colloca and Benedetti 2005). As we have no a priori knowledge of which substances act on placebo-activated endogenous opioids, or dopamine, or serotonin – and indeed almost all drugs, e.g., ► analgesics and ► opioids, might interfere with these neurotransmitters – one way to eliminate this possible pharmacological interference is to make the placebo-activated biochemical pathways, so to speak, "silent." This can be achieved by the hidden administration of drugs (Colloca et al. 2004).

In fact, it is possible to eliminate the placebo (psychological) component and analyze the pharmacodynamic effects of a treatment, free of any psychological contamination, by administering drugs covertly. In this way, the biochemical events that are triggered by a placebo procedure can be eliminated. To do this, drugs are administered through hidden infusions by machines, so that the patient is not made aware that a medical therapy is being carried out. A hidden drug infusion can be performed through a computer-controlled infusion pump that is preprogrammed to deliver the drug at the desired time. It is crucial that the patient does not know that any drug is being injected, so that he or she does not expect anything. The computer-controlled infusion pump can deliver a drug automatically, without a doctor or nurse in the room, and without the patient being aware that a treatment has been started. Ethical issues need to be considered.

The analysis of different treatments, either pharmacological or not, in different conditions has shown that an

open (expected) therapy, that is carried out in full view of the patient, is more effective than a hidden one (unexpected). Whereas the hidden injection represents the real pharmacodynamic effect of the drug, free of any psychological contamination, the open injection represents the sum of the pharmacodynamic effect and the psychological component of the treatment. The latter can be considered to represent the placebo component of the therapy, even though it cannot be called placebo effect, as no placebo has been given. Therefore, by using hidden administration of drugs, it is possible to study the placebo effect without the administration of any placebo.

The influence of psychological factors on drug action is also shown by the balanced-placebo design (Benedetti 2008a). In this design, four groups of patients (1) receive the drug and are told it is a drug, (2) get the drug and are told it is a placebo, (3) get a placebo and are told it is a placebo, and (4) get a placebo and are told it is a drug. This design is particularly interesting because it indicates that verbally induced expectations can modulate the therapeutic outcome, both in the placebo group and in the active treatment group. It has been used in many conditions, such as alcohol research, smoking, and amphetamine effects (Benedetti 2008a).

Cross-References

- ▶ Analgesics
- ▶ Antidepressants
- ▶ Anti-Parkinson Drugs
- ▶ Cholecystokinins
- ▶ Classical Conditioning
- ▶ Conditioned Drug Effects
- ▶ Ethical Issues in Human Psychopharmacology
- ▶ Expectancies
- ▶ Magnetic Resonance Imaging (Functional)
- ▶ Opioids
- ▶ Positron Emission Tomography (PET) Imaging
- ▶ Randomized Controlled Trials

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Placebo Response

▶ Placebo Effect

Plant Toxins

▶ Neurotoxins

Plaques

Definition

The major component is β-amyloid, which is not further degraded or removed by crossing the blood–brain barrier; accumulation of β-amyloid causes oligomerization and polymerization to build up insoluble plaques mainly in extraneuronal tissue.

Plasticity

▶ Elasticity
▶ Synaptic Plasticity

Platelet Activation

Definition

Platelet activation represents a central moment in the process that leads to thrombus formation. When endothelial damage occurs, platelets come into contact with exposed collagen and von Willebrand factor, becoming

activated. They are also activated by thrombin or by a negatively charged surface, such as glass. Platelet activation further results in the scramblase-mediated transport of negatively charged phospholipids to the platelet surface, providing a catalytic surface for the tenase and prothrombinase complexes. Activated platelets change in shape and pseudopods form on their surface, determining a star-like appearance.

Platelet Storage Granules

Definition

Platelets contain numerous storage granules. Activated platelets excrete the contents of these granules into their canalicular systems and, then, into surrounding blood. There are two types of granules: dense granules (containing ADP or ATP, calcium, serotonin, and other monoamines) and alpha-granules (containing platelet factor 4, PDGF, fibronectin, B-thromboglobulin, vWF, fibrinogen, and coagulation factors V and XIII).

Platelets

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Synonyms

Thrombocytes

Definition

Platelets are small cytoplasmic bodies derived from ▶ megakaryocytes. They circulate in the blood and are mainly involved in ▶ hemostasis. Platelets have no nucleus and display a lifespan of 7–10 days. When damage to the endothelium of blood vessels occurs, platelets go through ▶ activation, change shape, release granule contents and, finally, aggregate and adhere to the endothelial surface in order to form the blood clot.

Besides their chief role in the process of hemostasis, platelets express several signaling molecules, including various ▶ neurotransmitters. Therefore, considering the accessibility of platelets by a simple blood withdrawal, it is not surprising that several researchers tried to take advantage of this opportunity to get a glimpse on a variety of molecules involved in neural transmission.

Current Concepts and State of Knowledge

Platelets as Peripheral Markers of Neurotransmitter Dysfunction

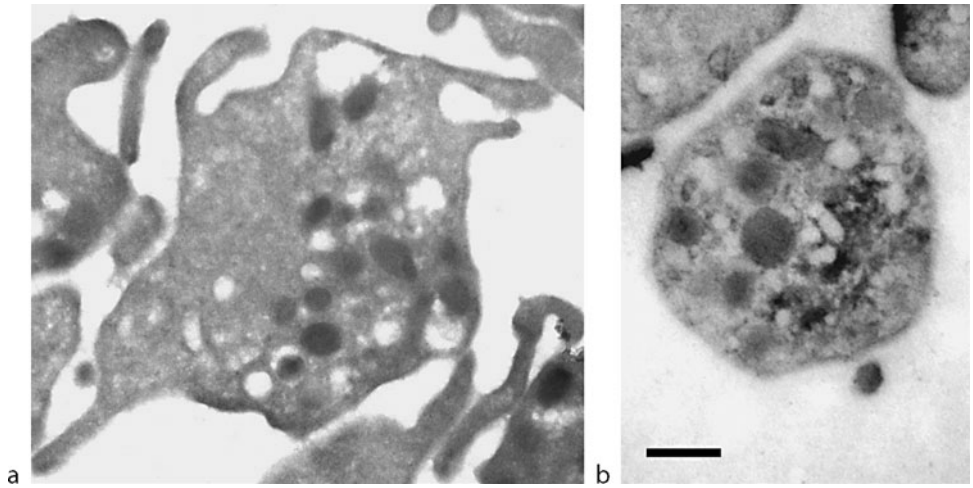
Human platelets have been repeatedly considered as potentially useful tools for modeling neurochemical dysfunctions in neurological and psychiatric patients. In fact, although the main function of the platelet is related to hemostasis, they are implicated with various signaling molecules that operate into the CNS as well. More specifically, platelets store, release, and ▶ uptake several neurotransmitters, such as serotonin, dopamine, glutamate, and GABA, frequently expressing cognate functional receptor molecules.

Considering that most of the neuropsychiatric disorders do not allow to study in details the involved pathomechanisms directly into the nervous system, platelets offer the advantage of being readily accessible upon a simple blood withdrawal. Hence, in this chapter we will consider them as ▶ peripheral markers of neurotransmitter dysfunction in neuropsychiatry.

However, as a final caveat we should remember that technical factors and reproducibility obviously play an extremely important role and influence the characterization of any suitable peripheral neurochemical marker. Platelets unfortunately display quite a strong tendency to activation, changing shape, and releasing granule contents, if careful procedures are not used when performing blood sampling and platelet separation. As an example, a generous needle gage and avoiding the tourniquet use might be critical issues for circumventing these phenomena, especially when measuring granule contents or performing electron microscopy procedures (see Fig. 1A, with respect to a less activated platelet shown in B).

Serotonin Uptake and Release

Human platelets are capable of producing very little amounts of ▶ serotonin (5-hydoxytryptamine, 5-HT) but represent the major storage site for this neurotransmitter outside the central nervous system. Platelets actively uptake serotonin, store it in electron-dense granules and release it, together with other platelet factors, in response to a number of signals (Paasonen 1965). Specific transporter molecules (SERT) located on platelet membranes are responsible for the highly selective uptake of serotonin, although there is some affinity for the other ▶ monoamines (e.g., norepinephrine, dopamine) (Omenn and Smith 1978). Molecular cloning has revealed



Platelets. Fig. 1. Bar = 500 nm. Electron microscopy photographs courtesy of Virginia Rodriguez-Menendez.

that the amino acid sequence of the human platelet SERT protein is identical to the neuronal SERT, and platelet high-affinity uptake system for serotonin displays kinetic and pharmacological characteristics similar to those reported in brain synaptosomes. All this makes platelets good model systems for investigating alterations of monoamine neurotransmission occurring in neuropsychiatric diseases.

Platelet SERTs have been studied in psychiatric and neurological patients, both as ► binding of radioligands on platelet plasma membranes, and as activity in intact platelets (Mellerup and Plenge 1986). Platelet serotonin uptake was demonstrated to be decreased in depressed patients, both adult and children, with respect to controls, before and during antidepressant treatment, although not all the studies agree (Fisar and Raboch 2008). No significant correlations were found between serotonin uptake kinetics and the severity of the depressive disorder. Abnormalities of platelet serotonin uptake have been reported also in patients with Down's syndrome and ► Huntington's disease, and a reduced platelet content of this neurotransmitter has also been demonstrated, again, in Down's syndrome.

The use of specific serotonin receptor antagonists has shown the presence on platelet surface of the 5-HT_{2A} receptor subtype involved in the amplification of platelet aggregation by recruiting additional platelets once the process has been initiated. Using [^{3}H]-ketanserin as a radioligand, a significant decrease in the affinity of platelet 5-HT_{2A} receptors was observed in patients affected by migraine, and a significant reduction in the number of binding sites was found in tension-type headache as well. Interestingly, a role for platelet-released serotonin in the pathogenesis of migraine has also been hypothesized, and differences between serotonin and other monoamines levels claimed to explain the diversity between migraine with and without aura (Joseph et al. 1992).

Platelets. Table 1. Monoamine functions in human platelets in neuropsychiatric diseases. ADHD, attention deficit/hyperactivity disorder; BPD, borderline personality disorder; DP, depression; DS, Down syndrome; HD, Huntington's disease; M, migraine; N/A, not investigated; PD, Parkinson's disease; PSG, platelet storage granules; SZ, schizophrenia; TH, tension-type headache.

	Serotonin	Dopamine
Uptake	DP: ↓; DS: ↓; HD: ↓	HD: ↑; Parkinsonisms: ↓; Acute SZ: ↑ in PSG; Gilles de la Tourette: ↓ in PSG; Naïve PD: ↓ in PSG
Binding	M: ↓ affinity 5-HT 2A; TH: ↓ density; BPD: ↓	DP: ↑; SZ: ↑; ADHD: ↓
Level	DS: ↓	N/A

Major findings related to monoamine functions in human platelets in neuropsychiatric diseases are summarized in Table 1.

Dopamine

Besides serotonin, other monoamines, such as ► dopamine, are actively concentrated by platelets within dense bodies. Although the significance of the uptake of dopamine in platelets is uncertain and the concentration gradient is very much lower with respect to serotonin, a number of clinical investigations have been performed

in samples obtained from patients affected by various neuropsychiatric disorders in order to study possible dopaminergic pathomechanisms.

The results of the studies focusing on platelet dopamine levels are quite variable. A recent study reported increased platelet dopamine levels in patients with migraine both, with, and without aura, although in an earlier study interictal platelet dopamine levels were found unchanged in women affected by migraine.

Although platelets are not generally regarded as useful models for exploring dopamine transporters (DAT), given the prevalence therein of SERTs, an increase of dopamine uptake has been described in platelets from patients with Huntington's disease, while a reduction was found in parkinsonisms.

To avoid the controversial issues deriving from assessing dopamine uptake in intact platelets (presence of a specific dopamine uptake mechanism versus dopamine entry via the serotonin uptake system) the uptake of [^{3}H]-dopamine has been measured in previously separated ▶ platelet storage granules (PSG). These granules possess the vesicular monoamine transporter 2 (VMAT2) responsible for monoamine storage into secretory vesicles (Zucker et al. 2001). An increase in dopamine accumulation has been described in platelets of acute schizophrenic patients, while a decrease was observed in Gilles de la Tourette and naïve ▶ Parkinson's disease patients. Furthermore, using high affinity [^{3}H]-dihydrotetrabenazine binding to platelets, an elevated VMAT2 density was found in untreated major depression, ▶ schizophrenia, and former heroin addict patients treated with ▶ methadone, while a decreased density was observed in children and adolescents with attention deficit/hyperactivity disorder and in both healthy and schizophrenic habitual smokers.

The Glutamatergic System

Human platelets store, release, and uptake ▶ glutamate, at the same time expressing fully functional cognate receptors. Notably, the available data indicate that platelets might represent an extremely suitable model for specifically studying the dysfunction of the glutamatergic system in neuropsychiatric disorders, since display very similar properties with respect to the CNS (Tremolizzo et al. 2004). However, although platelets do express all the components of a functional glutamatergic system, its specific role is far from being fully understood. Even so, NMDA and AMPA receptors have been repeatedly shown in both platelets and ▶ megakaryocytes, and a role for glutamate in ▶ platelet activation and/or aggregation has already been proposed. Moreover, platelets express the three major glutamate transporters, EAAT1, EAAT2, and EAAT3 (Zoia et al. 2004), and a functional high affinity sodium-dependent glutamate reuptake system has been successfully described more than 20 years ago. Apparently this reuptake system might represent a major source of the amino acid removal from blood, and also displays very similar regulatory mechanisms and susceptibility to toxins with respect to the CNS homologue. The two major vesicular glutamate transporters (VGLUT-1, VGLUT-2) are expressed as well, packing glutamate (probably in dense bodies), and releasing it following aggregation together with several other mediators (as a counterproof aspirin treatment reduces glutamate release). Although the possible significance of these findings still need to be definitively addressed in relation to platelets and hemostasis physiology, current data indicate that those functions involved in glutamate homeostasis in platelets may represent suitable windows for studying CNS alterations.

As a matter of fact, glutamate receptor sensitivity, for example assessed by flow cytometry, has been studied in platelets obtained from patients affected by schizophrenia, psychotic depression, and major depression, suggesting the possibility of mirroring an hypofunction of glutamate receptors that may be implicated in the pathogenesis of these psychiatric disorders (see Table 1). Moreover, glutamate/aspartate uptake, assessed as [^{3}H] glutamate influx (Mangano and Schwarcz 1981), has been investigated in platelets obtained from patients affected by various neuropsychiatric conditions, such as bipolar disorder, ▶ Alzheimer's disease, ▶ Parkinson's disease, amyotrophic lateral sclerosis, ▶ Huntington's disease, migraine, acute ischemic stroke, and Down syndrome, in the attempt of mirroring an excitotoxic dysfunction previously demonstrated in the CNS of these patients. Also glutamate release following aggregation, assessed by ▶ HPLC as the difference between pre and post plasma levels, has been investigated in disease, mainly in a setting of migraine and stroke, since the release of this amino acid might mediate, at least in part, the experienced symptoms, activating both central and peripheral (i.e., endothelial, leukocytic) receptors (keeping in mind that the release function might be especially prone to the already discussed methodological issue of preparation-induced activation). Interestingly, ▶ lamotrigine, a drug able to interfere with the symptoms of migraine aura, works by blocking glutamate release, possibly, at least in part, directly from platelets.

Major findings related to the glutamatergic system in human platelets in neuropsychiatric diseases are summarized in Table 2.

Platelets. Table 2. Glutamatergic and GABAergic functions in human platelets in neuropsychiatric diseases. AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; BD, bipolar disease; DP, depression; DS, Down syndrome; GABA-T, GABA transaminase; HD, Huntington's disease; MA, migraine with aura; MoA, migraine without aura; N/A, not investigated; PBR, peripheral benzodiazepine receptors; PD, Parkinson's disease; SZ, schizophrenia; TH, tension-type headache.

	Neuropsychiatric disorders	Neurodegenerative diseases	Cerebrovascular disease	Headache
Glutamate	SZ, DP: ↑ receptor sensitivity; BD, DS: ↓ uptake	AD, ALS, PD: ↓ uptake; HD: = uptake	Acute ischemic stroke: ↓ uptake and release	MA: ↑ uptake; MoA: ↓ uptake; MA and MoA: ↑ release
GABA	Absence epilepsy: ↓ uptake; epilepsy, epileptic syndromes, and alcoholism: GABA-T modifications; DP + anxiety and panic disorders/SZ: ↓ PBR; DP: = PBR	AD, PD: ↓ PBR	N/A	MoA: ↑ PBR; TH: ↑ levels

GABA and Peripheral Benzodiazepine Receptors

Platelets express ► GABA transporters and the uptake of this amino acid has been reported disrupted in patients affected by absence epilepsy, although the functional impact of the antiepileptic drugs taken by the patients has not been completely clarified. Also GABA transaminase (GABA-T) has been studied, mainly in a setting of various epileptic syndromes, such as juvenile myoclonic, refractory localization-related, and childhood absence epilepsy, showing different modifications. GABA-T represents the main enzyme responsible for GABA catabolism and the inhibition of this enzyme produces a considerable elevation of GABA concentrations: often the modulation of such elevation has been correlated with many pharmacological effects, mainly in the field of antiepileptic drugs. GABA-T activity in blood platelets might be altered also in some neuropsychiatric disorders, such as alcoholism, epilepsy, and Alzheimer's disease.

A related GABAergic marker, the 18 kDa Translocator Protein (TSPO) (the new nomenclature for the peripheral-type benzodiazepine receptor, PBR) has also been studied in human platelets, evaluating the binding of the radioactive antagonist [^{3}H]PK11195; a decrease of this parameter was shown in platelets obtained from patients affected by ► depression with associated adult separation anxiety disorder, ► panic disorder, and ► schizophrenia with aggressive behavior, among other psychiatric diseases. On the other hand, no changes were shown in a population of untreated depressed patients, while an upregulation was present, for example, in primary fibromyalgia patients. Interestingly, ► Bmax values of PBR binding have been shown to be positively correlated with scores for trait anxiety, suggesting that it might be associated with the personality trait for anxiety tolerance (Nakamura et al. 2002).

Major findings related to the GABA and PBR in human platelets in neuropsychiatric diseases are summarized in Table 2.

Cross-References

► Excitatory Amino Acids and Their Antagonists
► Receptor Binding
► Translational Research

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Pleomorphism

► Genetic Polymorphism

Pliancy

► Elasticity

Plus Maze Test

► Elevated Plus Maze

Point of Subjective Equality

► Indifference Point

Poisons

► Neurotoxins

Polymorphism

Definition

In biology, polymorphism is the presence of distinct subtypes of gene products within a single family. Genetic polymorphisms are the result of evolution and are hereditable. Of great interest for psychopharmacology are polymorphisms characterized by variations in the genetic sequence coding for specific receptor subtypes, which often confer higher or lower ► affinity for the ligand, or influence functionality of the receptor (or plasma membrane transporter) itself. These differences in affinity/functionality are hypothesized to be important for the manifestation of certain psychiatric disorders, personality traits, and different responses to medications between individuals. Polymorphisms are variations in DNA that are too common to be attributable to new mutations; the frequency of a polymorphism has been defined as at least 1% in a given population.

Cross-References

► Genetic Polymorphism
► Single-Nucleotide Polymorphism

Polyphagia

► Hyperphagia

Polypharmacy

Definition

The use of multiple drugs to treat a single or a number of conditions.

Polysomnography

Definition

Polysomnography is a diagnostic tool that outlines sleep architecture by monitoring multiple physiological parameters that may include EEG (electroencephalogram) activity, leg movements, eye movements (electrooculogram), muscle activity (electromyogram), body temperature, heart and respiration rate.

Cross-References

► Insomnia
► Parasomnias
► Sleep Disturbances

Porsolt Test

► Behavioral Despair

Positive and Negative Scale for Schizophrenia

► PANSS

Positive Symptoms

Definition

Positive symptoms are manifestations of psychoses such as fixed, false beliefs (delusions) or perceptions without cause that are present in mentally ill, but not in healthy individuals. They contrast with negative symptoms of ► schizophrenia such as apathy and lack of drive.

Positron Emission Tomography (PET) Imaging

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Synonyms

PET imaging; Positron emission tomography; Radiotracer imaging

Definition

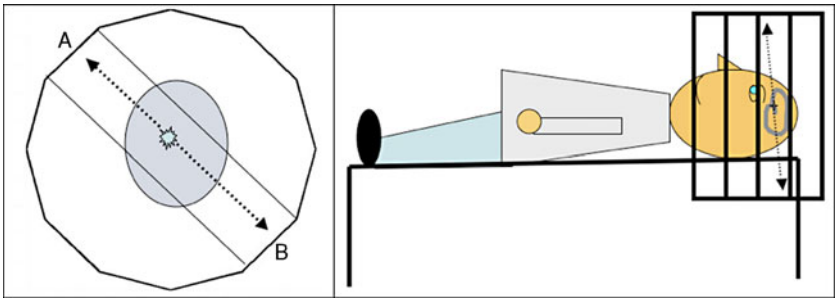
PET is a noninvasive technique that allows quantitative imaging data to be obtained from internal organs (including brain) in vivo, in humans as well as in animal models. Molecules that interact with biologic systems of interest are tagged with positron-emitting isotopes and injected into subjects, usually in very small quantities (► tracer dose). The decay process of the isotope results in the emission of photons that are detectable by the imaging system. These data can be used to infer the concentrations of the radiolabeled molecule (► radiotracer) in the tissues being imaged. Depending on the nature of the radiotracer, the technique can be used to estimate parameters related to receptor density and availability, drug occupancy, fluctuations in endogenous transmitter levels at neurotransmitter receptors/transporters, and rates of various metabolic processes.

Principles and Role in Psychopharmacology

PET imaging has been used as a noninvasive tool to probe many questions with implications for the field of psychopharmacology. Some of these are examination of receptor/transporter availability at many different neuroreceptor targets in patient populations relative to healthy control subjects, measurement of drug receptor occupancy through competition models, detection of fluctuations in endogenous neurotransmitter levels following pharmacologic or task-based stimulation, and examination of various metabolic processes. This essay is organized in three sections, followed by brief concluding remarks: (1) a brief description of the physical principles underlying the imaging system, (2) a description of the pharmacokinetic methodology common to most PET studies, and (3) a survey of the currently available probes and targets studied with PET.

Physical Principles of PET

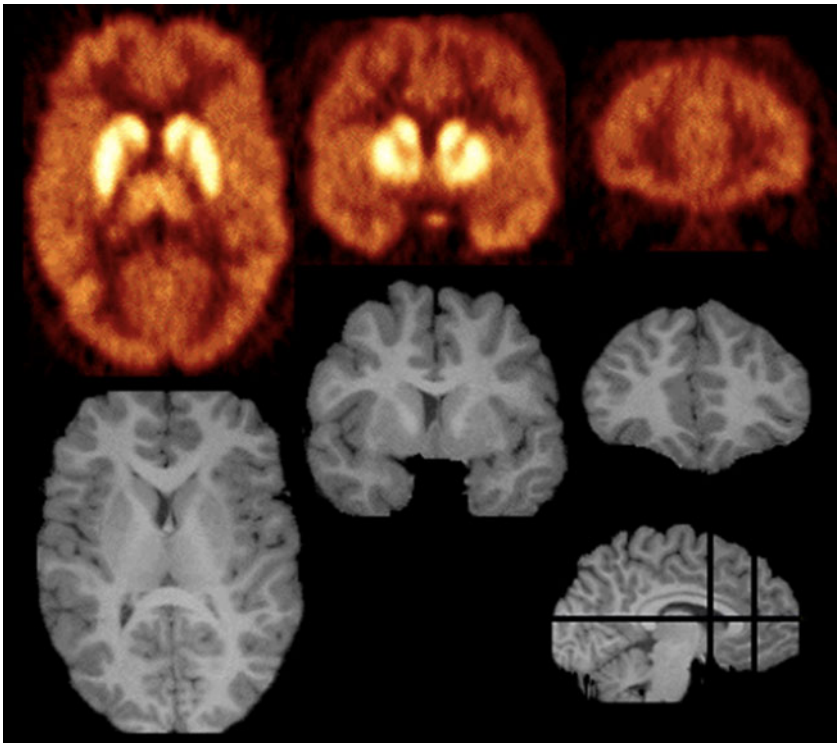
Positrons are the antiparticles of electrons. They have the same mass as electrons but positive, rather than negative electric charge. Unstable isotopes that emit positrons when they decay can be produced in a cyclotron; many academic medical centers currently have onsite cyclotrons that can produce isotopes for PET imaging. Several of these isotopes can be readily incorporated into small molecules suitable as biologic tracers. Among these are carbon (^{11}C, half-life = 20.4 min), fluorine (^{18}F, half-life = 109.8 min), and oxygen (^{15}O, half-life = 122 s). When a positron is emitted, it briefly interacts with local atoms, losing kinetic energy during the resulting collisions. When its energy is low enough, the positron will be attracted to and captured by an electron; the pair will mutually annihilate and emit a pair of 511 keV photons. Conservation of momentum dictates that the total momentum of the 2 photons is equal to that of the positron–electron pair at the time of their annihilation. As this momentum is small, the photons travel in nearly opposite directions (their momenta cancel each other), approximately along a line from the location of the annihilation event (Fig. 1, left panel). The imaging system contains



Positron Emission Tomography (PET) Imaging. Fig. 1. *Left:* A schematic detector ring. An annihilation event occurs in an imaged object as seen along the long axis of the subject (from head to toe). If the emitted photons (paths represented by dashed arrows) strike detectors A and B within a coincidence timing window (several nanoseconds for most scanners), a coincidence event is recorded along the line between A and B. Right: A schematic stack of rings, viewed from the side. A tomographic image is formed by combining data from all the rings.

rings of detectors composed of scintillating materials that surround the imaged object. Combined with electronic components that are attached to these detectors, the arrival of photons at the detector arrays can be counted with very high temporal resolution (on the order of nanoseconds). If a pair of photons are detected in two different detectors within a specified time interval (a "coincidence timing window," typically 4–12 ns), the scanner treats these as having originated from a single annihilation event occurring somewhere along the line between the two detectors (a "line of response"). Computer-intensive mathematical methods can then be applied to this collection of coincidence event data to infer the original distribution of the annihilation events. Typical modern systems contain from 20 to 40 of these detector rings stacked in parallel to form a cylindrical field of view (Fig. 1, right panel); the data from these can then be recombined to form a three dimensional image of the original distribution of the radiotracer, composed of a series of slices through the object (a "tomogram," literally a "slice picture," see Fig. 2).

The preceding description of the data acquisition and reconstruction is greatly simplified – there are many confounds and sources of noise and image degradation that must be accounted for. For example, many of the photons produced by annihilation events interact with the tissues intervening between the locus of the annihilation and the detector; some of these are scattered in different directions and others absorbed completely ("attenuated"). A description of the methods for correcting these confounds is beyond the scope of this chapter (see Cherry et al. 2003; Valk et al. 2003 for detailed expositions) but a key point is that PET utilizes coincidence detection, in contrast to the related technologies such as single photon computed tomography (SPECT). This results in an accurate estimate of the fraction of photons that are attenuated in any line of response through an imaged object, and this, in turn, leads to a level of quantitative accuracy that is not practically attainable with other technologies. Because of this level of quantitative accuracy, the concentration of radiotracer in tissues can be accurately inferred, during a single contiguous interval of time, or dynamically over a sequence of sampling times after injection of the tracer. The implications for psychopharmacology are that detailed mathematical models can be formed of the tracer pharmacokinetics, the interaction between tracer pharmacokinetics and endogenous transmitters or



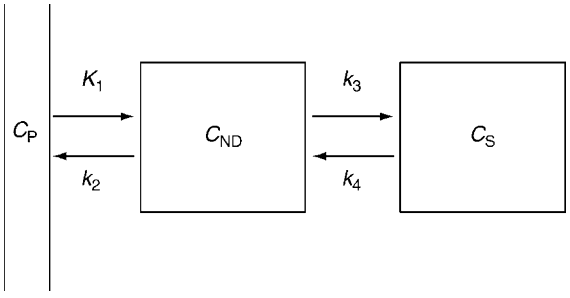
Positron Emission Tomography (PET) Imaging. Fig. 2. A PET image and coregistered high resolution MRI from the same subject. The data, acquired using the dopamine D_2 antagonist radioligand [^{11}C]FLB457, are summed over the entire 90 min of the scan. The saggital MRI slice (bottom right) shows the slice levels for the transverse and coronal views.

exogenously administered drugs, or, of rates of metabolic processes. Physiologic parameters can be estimated by fitting data to these models.

Pharmacokinetic Models and Methods

General principles: The ▶ pharmacokinetic schemes used to estimate parameters both for ▶ reversible binding receptor radioligands and for many metabolic processes are called compartment models. Compartments can be spatially distinct, but they can also be different states of the radiolabel occupying the same spatial domain, such as bound versus unbound, or parent radiotracer versus metabolic product. Figure 3 is a schematic representation of a standard compartment model used with reversibly binding radioligands.

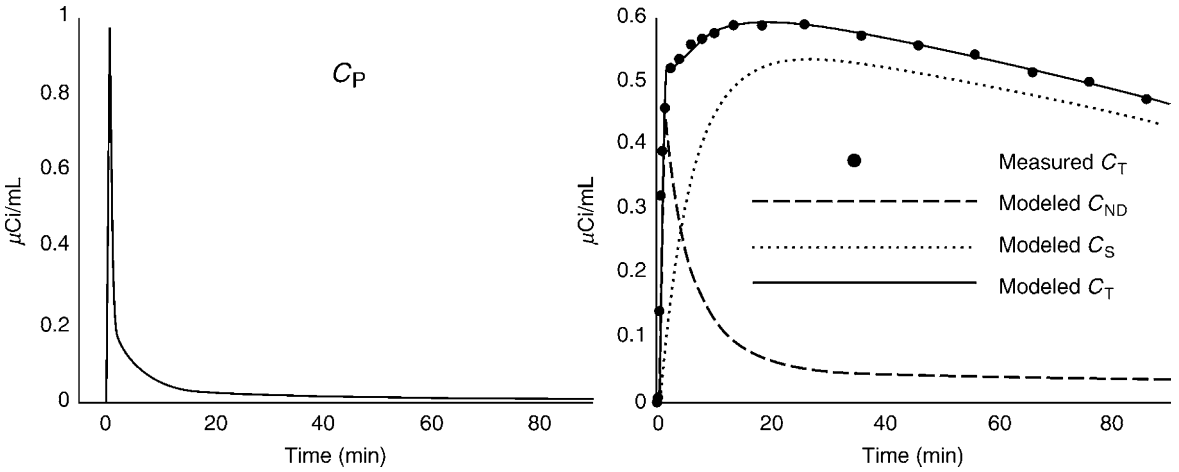
Corresponding to the compartment model, are systems of linear first-order, ordinary differential equations (ODEs). The ODEs express the temporally dynamic relationship between the input source of radioligand to the tissue (either the concentration in arterial plasma, or the concentration in a tissue devoid of the biologic process of interest, but similar to the tissue of interest in other respects, a "reference tissue") and the resulting concentration in the tissue of interest (usually brain or specific brain regions for targets of interest in psychopharmacology). "First-order" implies that the models operate according to the convention that movement from a source compartment to a target compartment is proportional to the concentration in the source compartment; the validity of this assumption in the case of reversibly binding receptor ligands is predicated on the use of tracer dose so that the associated mass action law, which is second-order when higher concentrations are used, can be treated as pseudo



Positron Emission Tomography (PET) Imaging. Fig. 3. A 2-tissue compartment model (2TC). C_P radioligand concentration in arterial plasma; C_{ND} nondisplaceable compartment, the sum of free and nonspecifically bound tracer in tissue; C_S specifically bound ligand, i.e., ligand-receptor complex; K_1 through k_4 are rate constants governing the fractional transfer between compartments per unit time.

first-order. By using some data-fitting method such as least squares minimization to regress observed data onto the model, the rate constants can be estimated. In turn, various mathematical combinations of the rate constants represent physiological parameters of interest. There is an extensive literature on methods for data fitting and parameter estimation in PET (see Slifstein and Laruelle 2001; Slifstein et al. 2004; Valk et al. 2003 for overviews).

Receptor imaging: The form of PET imaging most frequently used in applications relevant to psychopharmacology involves the use of radioligands that bind selectively and reversibly to target neurotransmitter receptors and transporters. These are usually administered as a single ▶ bolus injection, though there are some tracers amenable to a ▶ bolus plus constant infusion administration that induces steady-state conditions in ligand concentrations. The compartment configuration shown in Fig. 3 presents a model frequently used with reversible tracers. In the figure, C_P represents the concentration of radioligand in the arterial plasma, the input to brain tissue. C_{ND} ("nondisplaceable") is the sum of freely dissolved tracer in the brain and tracer that is nonspecifically bound to membranes. These quantities are combined to a single compartment based on the assumption that equilibration between free and nonspecifically bound ligand occurs on a much more rapid time scale than the specific binding process does, and can therefore be treated as if constantly in equilibrium. Models in PET frequently involve simplifying assumptions of this type in order to insure that they are not over-parameterized for statistical fitting. C_S represents specifically bound ligand–receptor complex. The movement of tracer between C_P and C_{ND} is governed by a transport law, whereas exchange between the states C_{ND} and C_S is governed by a mass action law. These various states of the radioligand cannot be distinguished in the PET signal; it is comprised of the sum of all sources of radioactive decay in the spatial locus being imaged, and is sometimes referred to as C_T (total concentration, Fig. 4). The parameters of greatest interest in receptor imaging are the density of receptors available for binding to the radioligand (▶ B_{max} or B_{avail}, nM) and the ▶ affinity of the radioligand for receptor (K_D^{-1} where K_D (nM) is the ▶ equilibrium dissociation constant). These quantities cannot be estimated separately from single tracer dose scans – multiple scanning sessions with increased radiotracer concentrations that bind to a significant fraction of receptors would be required for this purpose. The quantity that is readily estimated is the ▶ binding potential, a parameter that is proportional to the product of B_{max} and affinity, or B_{max}/K_D. There are several possible constants of proportionality, according to which



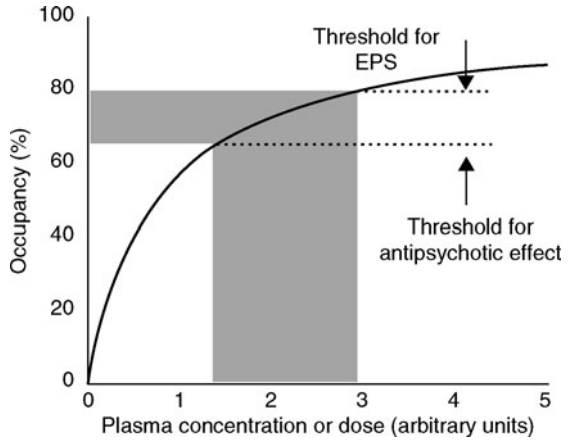
Positron Emission Tomography (PET) Imaging. Fig. 4. Arterial plasma input and resulting PET data and model fit. These data show the time course of the dopamine D_1 receptor tracer [^{11}C]NNC112 in the striatum of an anesthetized baboon. Plasma input to brain (C_P) on left, and the compartments represented in Fig. 3 on the right. The discrete dots represent the measured C_T, the three continuous curves are the fit to the model.

of several approaches to experimental design and derivation of the binding potential estimate is used. The version appearing most frequently in the literature, however, is called BP_{ND} (Innis et al. 2007), equal to $f_{ND}\ B_{max}/K_D$ where f_{ND} is the fraction of C_{ND} that is freely dissolved, f_{ND} = free ligand/(free + nonspecifically bound ligand). The rate constants can be shown to have the following physiological interpretations: $K_1 = FE$, where F is flow (actually, perfusion, mL cm^{-3} min^{-1}) and E is the first-pass extraction fraction (unitless), $k_2 = K_1/V_{ND}$ where V_{ND} is the nondisplaceable equilibrium distribution volume, C_{ND}/C_P at equilibrium, (mL cm^{-3}), $k_3 = k_{on} f_{ND} B_{max}\ (\text{min}^{-1})$, where k_{on} is the association rate of the receptor-ligand complex and k_4 (min^{-1}), is k_{off}, the dissociation rate of the receptor ligand complex. As K_D is equal to k_{off}/k_{on}, it is apparent that k_3/k_4 is equivalent to BP_{ND}. However, BP_{ND} is rarely estimated directly from the fitted values of k_3 and k_4. Rather, more involved methods utilizing various constraints to make the estimated BP_{ND} more statistically robust are employed (see Slifstein and Laruelle 2001; Slifstein et al. 2004; Valk et al. 2003 for further details).

Applications of receptor imaging to psychopharmacology: If another ligand – an endogenous transmitter or an exogenously administered drug – competes with the radioligand at the binding site on the receptor, then it can be shown, again invoking tracer dose conditions for the radioligand, that the binding potential is reduced by the factor $1/(1+L/K_i)$, where L is the concentration of the ligand and K_i is its affinity for the binding site. This in turn implies that the relative difference between the binding potential with and without the competing ligand on board, [BP_{ND}(competitor on board) − BP_{ND}(baseline)]/BP_{ND}(baseline), is equal to $L/K_i/(1+L/K_i)$, the fraction of receptors occupied by the competitor. This technique can be used to infer the occupancy of a receptor by a drug, or to demonstrate that a stimulus induces transmitter release.

In a seminal study, Farde et al. (1988) used the dopamine D_2 receptor radioligand [^{11}C] raclopride to measure the occupancy of D_2 receptors by the antipsychotic drug ▶ haloperidol in patients with schizophrenia, and presented the concept of a therapeutic window – the idea that there is a minimal receptor occupancy necessary to achieve antipsychotic efficacy, but a maximum tolerable occupancy above which extrapyramidal symptoms would appear (Fig. 5). The in vivo competitive binding technique has subsequently been used in many published studies examining drug receptor occupancy. While a large number of these have continued to examine D_2 occupancy by antipsychotics, the method has been used to look at other receptor systems as well, including various 5-HT receptors, nicotinic and muscarinic ACh receptors, NK1, adenosine 2, histamine, CB1, mu-opioid receptors, 5-HT and DA transporters, and other targets. The approach has been widely used by pharmaceutical companies in both drug development and in postmarketing studies characterizing efficacious occupancies.

A similar imaging technique can be used to infer fluctuations in endogenous neurotransmitters as a result

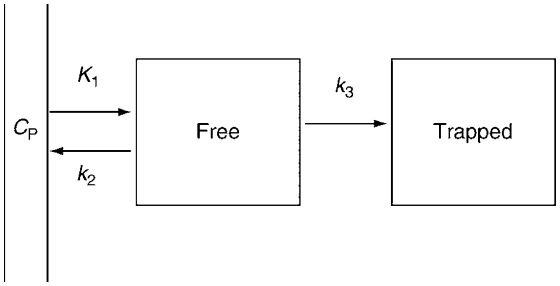


Positron Emission Tomography (PET) Imaging. Fig. 5. The concept of a therapeutic window, showing a range over which an antipsychotic drug is efficacious, but below the threshold for extrapyramidal symptoms. (After Farde et al. 1988.)

of either pharmacological or task-based stimuli. Again, the system that has been the most amenable to this type of study has been dopamine release at the D_2 receptor. Many studies have been performed in which dopamine release and/or inhibition of reuptake has been induced by ► amphetamine, ► methylphenidate, or other compounds, or by tasks hypothesized to induce dopamine release, for example, by incorporating a monetary reward for accurate task execution. There has been considerable evidence that the simple competitive interaction model described earlier is not adequate to explain the decrease in binding potential following amphetamine. In particular, the decrease lasts much longer than the apparent increased dopamine release as measured with ► microdialysis in animal models. On the other hand, the binding decrease is highly correlated with amphetamine dose and with the microdialysis measurements, and does not occur if dopamine stores have been pharmacologically depleted prior to the scan, suggesting that the competitive binding plays at least some role in the observed effect. Also, while an effect consistent with the occupancy model has been detected with several radioligands in the benzamide ([^{123}I]IBZM, [^{11}C]raclopride, [^{18}F]fallypride) and catecholamine ([^{11}C]NPA) classes, paradoxical *increases* in radioligand binding following amphetamine have been observed using the ► butyrophenone radioligand *N*-[^{18}F]methylspiperone. A number of mechanisms have been proposed to explain both the extended duration of the amphetamine effect and the different results observed with different radioligands, including receptor trafficking and differential responses to internalized receptors, differences in binding sites, and differences in ► pharmacokinetic properties with concomitant differences in robustness of quantification of the various radioligands. At this time, these issues remain unresolved. Recently, there has been some investigation of the use of agonist, rather than antagonist radioligands, based on the premise that they may be more sensitive to the affinity state of the receptor for endogenous neurotransmitters, and, therefore, endogenous dopamine might compete more successfully with these, leading to greater sensitivity to the differences across conditions or populations in stimulated dopamine release. Studies using anesthetized animals have demonstrated increased sensitivity of [^{11}C]NPA and [^{11}C]PHNO, both $D_{2/3}$ agonists, to amphetamine stimulation relative to [^{11}C]raclopride, and early studies with [^{11}C]PHNO in healthy human volunteers have also shown increased amphetamine effect in the dorsal striatum compared to previously published reports utilizing [^{11}C]raclopride. The competitive binding method has proved to be much more difficult to use with receptors other than the dopamine D_2 receptor. Several investigators have been unable to detect the amphetamine effect on binding of dopamine D_1 radioligands. Researchers have had mixed results detecting pharmacologically-induced increases in serotonin levels as well, with some investigators reporting decreases in [^{18}F]MPPF or [^{18}F]MEFWAY binding to 5-HT_{1A} receptors in animal models following stimulated increases in serotonin levels either by ► fenfluramine or ► SSRIs, while others have been unable to detect changes with [^{18}F]MPPF or [^{11}C]WAY100,635. See Laruelle (2000) for a comprehensive examination of competitive binding techniques in PET and SPECT, especially as pertains to dopamine $D_{2/3}$ receptor imaging.

Finally, it is worth noting that receptor imaging has been used to infer some more subtle pharmacological effects, such as the "GABA-shift" observed at the ► benzodiazepine binding site on the $GABA_A$ receptor with the PET radioligand [^{11}C]► flumazenil, in which radioligand binding increased when GABA levels were increased by reuptake inhibition (Frankle et al. 2009), presumably due to increased affinity through allosteric interaction between the GABA and benzodiazepine binding sites.

Metabolism imaging: The models used for metabolism imaging can vary potentially according to the mechanism being studied. In this section, two widely used metabolism tracers are described: [^{18}F]DOPA and [^{18}F]FDG. Both of these ligands are substrates for some, but not all enzymes that act on an endogenous compound, and thus partially follow the same metabolic pathway. Both of these reach a stage in the metabolic process in which they are



Positron Emission Tomography (PET) Imaging. Fig. 6. An irreversible trapping model.

assumed to be irreversibly trapped, and thus the model is based on the assumption of irreversible accumulation. In each case, there has been a considerable body of literature demonstrating that this assumption is oversimplified and that more accurate estimates of the measured process can be obtained using more complex models that account for the further progress of the radiolabeled metabolites after the putative trapping stage. Nonetheless, the trapping models are still widely used due to their simplicity and ease of implementation, and so are described here. A basic compartment model for ► irreversible trapping is shown in Fig. 6. Unlike the receptor models in the previous section, there is no notion of equilibrium. As long as free radioligand is in the tissue, the concentration in the trapped compartment continues to increase as k_3 times the free concentration. However, one can envisage a hypothetical steady state in which influx to the tissue from plasma just balances the sum of efflux back to the plasma plus the conversion into the trapped form, so that the free concentration is constant. Under these conditions, the free concentration equals $K_1/(k_2+k_3)$ times the plasma concentration C_P, and the steady state rate of conversion into the trapped form, therefore, equals $K_1k_3/(k_2+k_3)$ times the plasma concentration. This parameter is often referred to as K_{in}, the steady state uptake rate for an irreversible compartment model.

[^{18}F]DOPA is a substrate for amino acid decarboxylase (AADC), the enzyme that catalyzes L-dihydroxyphenylalanine (DOPA) into ► dopamine within the dopaminergic terminals. [^{18}F]DOPA readily passes the ► blood–brain barrier and cell membranes, and is metabolized by AADC into 6-fluorodopamine (6-FDA), effectively ^{18}F labeled dopamine, in dopaminergic terminals. 6-FDA, like endogenous dopamine, does not cross the blood–brain barrier and so is "trapped" in the proximity of the terminals at the stages of loading into vesicles, release through exocytosis and reuptake into the terminal, the main path followed by endogenous dopamine in the striatum, where reuptake through dopamine transporters is the dominant mode of clearance from the synapse. Thus K_{in}, estimated with the irreversible trapping model, represents a lumped marker of presynaptic dopaminergic condition. 6-FDA is, however, a substrate for monoamine oxidase (MAO) and for catechol-*O*-methyltransferase (COMT). Both of these enzymes are present in the extracellular environment, and the radiolabeled metabolic by-products from 6-FDA metabolism can readily diffuse across the blood–brain barrier. Numerous studies have demonstrated that failure to account for this loss of radiolabel from the brain results in underestimation of the true uptake rate, and several approaches have been proposed for its incorporation into the modeling and design of [^{18}F]DOPA experiments. See Cumming and Gjedde (1998) for a detailed discussion of the metabolism of [^{18}F]DOPA.

^{18}F labeled 2-fluoro-2-deoxy-*D*-glucose (FDG) is arguably the most extensively used PET radioligand. The development of FDG for use with PET followed the groundbreaking work of Sokoloff et al. (1977) with [^{14}C]DG, a ^{14}C labeled tracer which is an analog of glucose and partially follows its metabolic pathway. Thus, FDG is a useful probe for measuring the cerebral glucose metabolism rate (CMR_{glu}). In more recent times, techniques such as fMRI have become more prevalent for studies measuring brain metabolic activity, owing to their better temporal and spatial resolution and the less invasive nature of the procedure. FDG has gone on to be used extensively as a clinical tool in radiological diagnostic procedures in other fields such as oncology. But given the historic nature of the role of FDG in the use of PET to study the brain, a brief description of the model is included here. FDG is a substrate for the same carrier protein that transports glucose into brain tissue. It is also a substrate for hexokinase, the enzyme that metabolizes glucose, and is phosphorylated into FDG-6-PO4. FDG-6-PO4 does not follow further steps of glucose metabolism. It does dephosphorylate, but because dephosphorylation of FDG-6-PO4 is slow compared to the forward process, FDG-6-PO4 is treated as a trapped state. Here, K_{in} represents the steady state phosphorylation rate of FDG. This is proportional, not identical, to CMR_{glu}, owing to the fact that the transport and phosphorylation rates are different for the two compounds. When multiplied by a conversion factor accounting for this difference (1/LC, the "lumped constant," because it lumps two conversion factors together) then K_{in}/LC times the plasma glucose concentration is taken as an estimate of brain glucose metabolism. In analogy with observations made about metabolism of [^{18}F]DOPA, the dephosphorylation step, while small, still contributes to

Positron Emission Tomography (PET) Imaging. Table 1. A sample of PET probes currently used in research with human subjects.

System	Ligand	Target	Description
Dopamine	[^{11}C]raclopride	$D_{2/3}$ receptors	$D_{2/3}$ antagonist; useful in striatum only
	[^{18}F]fallypride	$D_{2/3}$ receptors	$D_{2/3}$ antagonist; useful in striatum, thalamus and limbic regions
	[^{11}C]fallypride	$D_{2/3}$ receptors	Similar to the [^{18}F] version; [^{11}C] label allows multiple scans on 1 day for quantitative analysis in extrastriatal regions
	[^{11}C]FLB457	$D_{2/3}$ receptors	$D_{2/3}$ antagonist; useful in cortical regions
	[^{11}C]PHNO	$D_{2/3}$ receptors	$D_{2/3}$ agonist; D_3 preferring (strong signal in globus pallidus)
	[^{11}C]NPA	$D_{2/3}$ receptors	$D_{2/3}$ agonist
	[^{11}C]MNPA	$D_{2/3}$ receptors	$D_{2/3}$ agonist
	[^{11}C]NNC112	D_1 receptors	D_1 antagonist; useful in cortex and striatum
	[^{11}C]SCH23390	D_1 receptors	D_1 antagonist; useful in cortex and striatum
	[^{11}C]PE2I	DA transporters	Striatal and extrastriatal DAT ligand
	[^{11}C]altropane	DA transporters	
	[^{18}F]CFT	DA transporters	
	[^{11}C]CFT	DA transporters	
	[^{18}F]DOPA	DA terminals	Substrate for amino acid decarboxylase (AADC); indicator of DA synthesis and turnover; presynaptic DA function
	FMT		Substrate for AADC
	[^{11}C]DTBZ	VMAT2	
Serotonin	[^{11}C]MCN	5-HT transporter	The first PET tracer for SERT
	[^{11}C]DASB	5-HT transporter	Improved signal to noise ratio compared to [^{11}C]MCN; allows more accurate quantitation
	[^{11}C]AFM	5-HT transporter	Recently developed tracer; shows promise for imaging in moderate density cortical regions
	[^{11}C]HOMADAM	5-HT transporter	Recently developed tracer; shows promise for imaging in moderate density cortical regions
	[^{11}C]WAY 100635	5-HT_{1A} receptors	5-HT_{1A} antagonist
	[^{18}F]MPPF	5-HT_{1A} receptors	5-HT_{1A} antagonist
	[^{18}F]FCWAY	5-HT_{1A} receptors	Requires coadministration of other compounds to reduce defluorination
	[^{11}C]CUMI101	5-HT_{1A} receptors	Recently developed 5-HT_{1A} agonist
	[^{11}C] MDL100,907	5-HT_{2A} receptors	Selective 5-HT_{2A} antagonist
	[^{18}F]Altanserin	5-HT_{2A} receptors	^{18}F label makes altanserin conducive to bolus + infusion design; there may be a confound associated with bbb penetrant radiolabeled metabolites
	[^{11}C]P943	5-HT_{1B}	Recently developed 5-HT_{1B} ligand
	[^{11}C] AZ10419369	5-HT_{1B}	Recently developed 5-HT_{1B} ligand
Norepinepherine	[^{18}F]MeNER	Norepinepherine Transporter	
	[^{11}C]MRB	Noreprinepherine Transporter	

Positron Emission Tomography (PET) Imaging. Table 1. (continued)

System	Ligand	Target	Description
Opioid	[^{11}C]carfentanil	Mu-opioid receptors	Potent mu-agonist
	[^{11}C] dipernorphine	Opioid receptors	Non selective
Acetylcholine	2-F-18-FA-85380	Nicotinic receptors	Specific to alpha 4 beta 2* subtype; requires very long (8 h) scans
	[^{18}F]FP-TZTP	Muscarinic M2	Selective M2 agonist
Glycine transporter	[^{11}C]GSK931145	Glycine transporter 1	Recently developed glyt 1 ligand
	[^{18}F]FCPyPB	Glycine transporter 1	Recently developed glyt 1 ligand
GABA	[^{11}C]flumazenil	Benzodiazapine site on $GABA_A$ receptors	
Substance P	[^{18}F]SPA-RQ	NK1 receptors	
Enzymes	[^{11}C]deprenyl	Monoamine oxidase (MAO)-B	
	[^{11}C]clorgyline	MAO-A	

underestimation of K_{in} if it is not accounted for. In further analogy with [^{18}F]DOPA, the irreversible model, and further simplifications of it, are still the most widely used, due to convenience of implementation.

Survey of Probes and Targets

Table 1 in this section is intended to give a general sense of the targets relevant to psychopharmacology that are currently accessible by PET imaging. It is extensive, but not necessarily exhaustive. Criteria for inclusion are that radioligands have been used with human subjects in at least one published study (there are many, many more that never progress that far, for one reason or another) and that use is ongoing – ligands that appear to be obsolete due to absence from publications for many years are not included. The table demonstrates that by far the most explored system in PET is the dopaminergic, followed by the serotonergic, but many other systems have or are beginning to be imaged as well.

Conclusions and Future Directions

PET imaging is unique among methods in pharmacology, for it provides highly quantitative measurements of relevant properties noninvasively in vivo. The studies described in this chapter have provided important data about neurochemical processes in living human brains that are not attainable through any other currently available technology. The field is limited by the availability of probes; any system can be studied provided a suitable radiotracer can be developed. The dopaminergic and serotonergic receptor systems have proved particularly amenable to probing with PET, and this has been fortuitous for the field of psychopharmacology due to the prominent role these systems play in psychiatric and neurologic conditions. Less progress has been made in the study of other systems, especially amino acid transmitters, but these systems are also of great interest to psychopharmacology – for example, many studies have implicated dysfunction in the glutamate and GABA systems in schizophrenia. The challenge of the future for PET is to continue to expand into these and other neurochemical systems.

Cross-References

- ▶ Antipsychotic Drugs
- ▶ Magnetic Resonance Imaging (Functional)
- ▶ Magnetic Resonance Imaging (Structural)
- ▶ Pharmacokinetics
- ▶ Receptor Binding
- ▶ SPECT Imaging

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Postnatal Neurogenesis

► Neurogenesis

Postnatal Period

Definition

An interval of time following birth, typically subsuming the neonatal and infant stages of development.

Postpsychotic Depression

► Postpsychotic Depressive Disorder of Schizophrenia

Postpsychotic Depressive Disorder of Schizophrenia

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Synonyms

Associated depression in schizophrenia; Depression superimposed on residual schizophrenia; Depression NOS; Postpsychotic depression; Secondary depression in schizophrenia

Definition

Postpsychotic depressive disorder of schizophrenia (PPDDS) is a clinical condition that occurs when an individual with the pre-existing diagnosis of ► schizophrenia manifests the syndrome of ► depression subsequent to the remission, or partial remission, of a florid psychotic episode of schizophrenia. PPDDS is diagnosed only during the residual phase of schizophrenia that follows the active psychotic phase (the active phase representing the presence of symptoms meeting Criterion A of schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition – DSM-IV) (American Psychiatric Association 2000) (► DSM-IV). Negative symptoms or attenuated manifestations of active phase symptoms (e.g., odd beliefs or unusual perceptual experiences) may, however, persist at the time of diagnosis of PPDDS. The diagnosis of PPDDS requires the presence of features sufficient to meet the DSM-IV criteria for the diagnosis of a major depressive episode and must also, specifically, include the presence of depressed mood (► Emotion and Mood). Symptoms that are due to the direct physiological effects of medication, a substance of abuse, or general medical condition are not counted toward the diagnosis of PPDDS.

Context of the Definition of "Depression"

"Depression" is a term that can be used in a variety of contexts. It can refer to an affect, a symptom, a syndrome, or a disease. As an affect, the term "depression" refers to the experience of sad mood, which is an appropriate response to a stimulus such as a sad event or sad story. This is part of a full range of appropriate affect and is not pathological.

As a symptom, the term "depression" refers to a mental state involving an experience of sadness, joylessness, and/or emptiness, which is exaggerated in comparison to the circumstances and is associated with psychic pain or distress. The degree to which this type of "depression" is pathological depends on the degree of exaggeration and the amount of suffering that is involved.

The syndrome of "depression" occurs when a defined group of signs and symptoms is present simultaneously with adequate severity and duration. The DSM-IV definition of "depression" is the most common contemporary definition of "depression" and this definition is at the level of a syndrome. It includes features such as sad mood or tearfulness, sleep disturbance, appetite disturbance or fluctuations in weight, reduced energy level or excessive

fatigue, psychomotor agitation or retardation, anhedonia, reduced interest level, impaired concentration or ability to think or make decisions, feelings of excessive or inappropriate guilt and/or worthlessness, pessimism, feelings of helplessness and/or hopelessness, recurrent thoughts of death, and suicidal ideation, intent, or behavior. Interestingly, many of these features were initially incorporated into the DSM-III diagnosis of "depression" (the predecessor of DSM-IIIR and, more recently DSM-IV) on the basis of their being associated with a favorable response to an antidepressant (at that time meaning a tricyclic or MAO-inhibitor) medication. Other widely recognized features of depression at the syndrome level that were not quite as predictive of response to early antidepressant medications (e.g., diurnal variation) did not become part of the DSM-III diagnostic definition.

The definition of "depression" as a disease state would require an in-depth understanding of the causation and pathophysiology of depression as a distinct biomedical condition – which is arguably still beyond our grasp. To wit, we as yet have no "tissue level" diagnostic criteria (such as a blood test, electrophysiological or imaging test, biopsy, or even autopsy finding), which confirms the diagnosis of "depression." Indeed, we cannot even be certain that the diagnosis of "depression" really belongs at the disease level, or whether "depression" is better characterized (like fever, seizures, or congestive heart failure) as being a clinical syndrome (syndrome-level diagnosis), which can occur in a variety of different "disease" states.

The definition of PPDDS given earlier is at the level of a syndrome.

Epidemiology

"Depression" has long been described as a feature in many patients diagnosed as having schizophrenia (McGlashan and Carpenter 1976), and many studies have been undertaken to explore and/or document the frequency of occurrence of depressive symptoms and/or depressive syndromes in people with schizophrenia (Siris and Bench 2003). These studies have varied considerably in terms of the populations that were assessed, the definitions of schizophrenia and depression, which were employed, the interval of observation which was involved, and the setting and treatment situation of the patients. The results for the observation of depression occurring in schizophrenia have ranged from a rate of 6% to 75%, but both the modal and the median frequency of occurrence was 25%. "Depression" has been associated with higher rates of adverse outcomes in schizophrenia, such as poor social adjustment, reduced quality of life, undesirable life events, relapse into psychosis, and rehospitalization. Additionally, it is of importance that the symptom or syndrome of depression, along with the symptom of hopelessness and the occurrence of events involving loss, have been identified as the most frequent correlates of suicidal ideation and behavior in schizophrenia, a tragic outcome that has been estimated to occur at a frequency of 4–12% in schizophrenia (Siris 2001) (► Suicide).

Differential Diagnosis

There are a variety of conditions that can present with the clinical features representative of PPDDS (Siris 2000; Siris and Bench 2003). These include medical disorders, effects of treatments used for medical disorders, effects of other substances, ► neuroleptic side effects (including ► akinesia, ► akathisia, and neuroleptic-induced dysphoria), negative symptoms of schizophrenia, acute and chronic disappointment reactions, the prodrome of psychotic relapse, ► schizoaffective disorder, and the expression of an independent primary diathesis for depression in an individual who also has schizophrenia.

Sad mood and/or a syndrome that can mimic depression can be a feature of a variety of medical conditions including anemias, endocrinopathies, metabolic abnormalities, infectious diseases, cancer, cardiovascular, autoimmune, or neurological disorders. Many commonly prescribed medications can also have depression occurrence as a side effect. These include beta-blockers, various other antihypertensive medications, sedative hypnotics, antineoplastic agents, nonsteroidal anti-inflammatory agents, sulfonamides, and indomethacin. Other medications can be associated with depression at the time of their discontinuation (► Withdrawal Syndromes). Examples of these include corticosteroids and ► psychostimulants. Various substances of use and/or abuse (e.g., alcohol, cannabis, or cocaine) can also be associated with depression-like presentations, either at the time of their acute use, chronic use, or discontinuation. Additionally, the withdrawal state from two commonly used legal substances, ► nicotine and ► caffeine, can also involve dysphoria and other features that can easily be interpreted as the syndrome of depression.

Antipsychotic medications, perhaps more frequently, first-generation antipsychotics, have been associated with side effects that can also be phenocopies of depression (Awad 1993) (► First-Generation Antipsychotics). It may be relevant to this observation that ► dopamine is an important neurotransmitter in the "pleasure" pathways of the brain. Thus, blocking dopamine receptors, as antipsychotic medications do, could lead to an experience that is the opposite of pleasure. This effect has been described either as a primary impact of neuroleptic agents on mood or as a component of one of the two classical

► extrapyramidal neuroleptic side effects of akinesia or akathisia (► Medication-induced movement disorder). Akinesia is marked by a general diminution of motor behavior, causing patients to appear to be non-spontaneous, i.e., "as if their starter-motor is broken." Akathisia reflects the opposite of this: patients' appearance (frequent fidgeting and/or restless movements) and subjective experience is "as if their starter-motor won't turn off." Both akinesia and akathisia can be associated with substantial dysphoria, and akathisia has been associated with suicide risk. Both akinesia and akathisia can also be present in subtle rather than blatant forms. Subtle akinesia can occur in the absence of large muscle stiffness or cogwheel rigidity. Subtle akathisia may be reflected in a generalized tendency toward behavioral excesses, such as over-talkativeness or wandering into other people's territory.

"Negative" symptoms of schizophrenia can also present as a phenocopy of depression. Loss of pleasure, loss of interest, and decreased activity and/or initiative are features of the negative symptoms syndrome, which have their counterparts in depression, and this is a central reason why affective features (manifest sad mood) and cognitive features (guilt, hopelessness) are so important in distinguishing depression from negative symptoms in schizophrenia. The phenotypic similarities between "negative" symptoms, "parkinsonian" symptoms, and "retarded depression" have given rise to speculation that each of these expressions may represent the common syndrome of "akinesia" being manifest in each of these situations (Bermanzohn and Siris 1992).

In addition to the aforementioned biological and pharmacological issues, persons with schizophrenia often have much to be disappointed about in terms of how their lives are progressing in comparison to their hopes and original expectations. Consequently, both acute and chronic disappointment reactions are common. Acute disappointment reactions are generally relatively brief and can be linked to some recent event that was damaging to the patient's wishes, prospects, self-concept, or self-esteem (taking into account, of course, that such an insult is not always obvious in the face of potential idiosyncrasies of the patient's thinking or communication). Chronic disappointment reactions (also sometimes referred to as the demoralization syndrome) of longer, even open-ended, duration are based on a history of repeated failures or losses, and consequently can be more difficult to disentangle from other types of depression occurring in the course of schizophrenia (Frank 1973).

Another important condition that can mimic depression in schizophrenia is the prodrome of psychotic relapse (► Prepsychotic States and Prodromal Symptoms). When decompensating into a new psychotic episode, a patient may become dysphoric, anhedonic, restless and/or withdrawn, pessimistic, or apprehensive. Such an individual may also experience sleep or appetite disturbances, unstable energy levels and/or difficulty concentrating. The feature that distinguishes this state from depression is the eventual emergence of frank psychotic symptomatology, but this feature may not make its appearance for a week or more. In the interim, the patient's condition may strongly mimic that of depression.

Schizoaffective disorder also enters into the differential diagnosis of PPDDS (► Schizoaffective Disorder). To be diagnosed with schizoaffective disorder, a patient must have a period of overlap between florid psychotic symptoms and either a major depressive episode, a manic episode, or a mixed episode, as well as a period of at least 2 weeks of florid psychotic symptoms (including ► hallucinations or ► delusions) in the absence of prominent mood symptoms during the same episode of illness. Additionally, for the diagnosis of schizoaffective disorder, the symptoms that meet the criteria for the mood episode must be present for a "substantial portion" of the total duration of the active and residual phases of the illness (American Psychiatric Association 2000). Some authors also consider it to be a case of PPDDS when a patient with schizoaffective disorder (rather than the diagnosis of schizophrenia) manifests the syndrome of depression subsequent to the resolution of florid psychotic symptomatology (Siris and Bench 2003).

Finally, there is the case where PPDDS may be manifest in a patient who has co-existing independent diatheses for the psychosis of schizophrenia and for the syndrome of depression. The argument that this, logically, would be a statistical rarity is countered by the argument that the respective diatheses may well be continuous variables rather than categorical ones – and that each diathesis may promote or aggravate the expression of the other (Siris 2000).

Role of Pharmacotherapy

Initial Approaches

When a patient presents with a new episode of PPDDS, the first response should not necessarily be to change medications. Rather, a careful study of history needs to be done, which would include an assessment of any recent changes in medications (psychiatric or otherwise and including attention to adherence issues), a consideration of possible medical conditions, an exploration of potential psychosocial stressors, and an investigation of the possible use (or discontinuation) of substances. An exploration of risk factors for suicide is also indicated, and protective steps to safeguard the patient should be taken if necessary (Siris 2001). The

initial intervention would be to raise the level of monitoring and provide supports. If the "depression" is an acute disappointment reaction, it will resolve itself. If it is a component of the prodrome of a new psychotic episode, that also will soon declare itself, and the increased monitoring will maximize the opportunity to attenuate the episode with appropriate treatment, thereby limiting psychiatric and social/vocational morbidity. Medical conditions, the role of medications employed to treat medical conditions, and the possible role of substance use or abuse can also be addressed in this initial phase.

Treatment of the Persisting Syndrome of PPDDS

When it is apparent that the syndrome of PPDDS is stably present, and in particular it is clear that the patient is not in the process of deteriorating into a new psychotic episode, it is appropriate to consider whether the dosage of antipsychotic medication is excessive (► Antipsychotic Drugs). Unnecessary high doses of antipsychotic medication may contribute to neuroleptic-induced ► dysphoria or the neuroleptic side effects of akinesia or akathisia. Once antipsychotic medications have been established at the lowest doses, which are consistent with adequate antipsychotic activity in a given patient, the treatment of akinesia can be undertaken with adjunctive antiparkinsonian medication (► Anti-Parkinson Drugs). For example, benztropine may be tried in doses up to a full dose of 2 mg po TID, ► anticholinergic side effects permitting. Occasionally, even higher doses of antiparkinsonian medications may be tried if anticholinergic side effects such as constipation, difficulty in urinating, or dry mouth (a crude but meaningful test for the bioavailability of the anticholinergic effect) are not present and the akinesia persists. Alternatively, a non-anticholinergic antiparkinsonian agent such as amantidine may be tried as an adjunct to the antipsychotic medication. In the case of akathisia, anticholinergic antiparkinsonian medications are unlikely to be helpful, but benzodiazepines are often useful (► Benzodiazepines), and beta-blockers often work as well (► Beta-Adrenoceptor Antagonists).

Switching from a "typical" (first-generation) antipsychotic agent to an "atypical" (second-generation) antipsychotic agent is another adjustment of the medication regimen to consider in cases of PPDDS (Siris 2000) (► Second and Third Generation Antipsychotics). The literature is inconsistent, but suggests that, in some cases, negative symptoms are reduced with second-generation antipsychotics (SGAs), and/or extrapyramidal side effects are lessened (Möller 2008). There is also a literature suggesting, subject to a variety of methodological limitations, that rating scores for depression may be improved by the use of SGAs in schizophrenia (Möller 2008). Indeed, SGAs have sometimes been touted as possessing augmenting antidepressant effects when used as adjunctive agents in patients with major depression.

There is also a role for adjunctive antidepressant medications in the treatment of PPDDS, particularly when extrapyramidal side effects have been ruled out (Siris and Bench 2003) (► Antidepressants). Patients must be maintained on adequate doses of antipsychotic medications when antidepressants are used, but the antidepressant drugs can gradually be raised to full therapeutic dosages. Vigilance should be maintained, however, for the possibility that the antipsychotic and the antidepressant might each interfere with the metabolism of the other, resulting in the possibility of adverse pharmacokinetic interactions (► Drug Interactions), perhaps particularly when specific serotonin reuptake inhibitors (SSRIs) are involved (Möller 2008). Although most of the controlled studies of adjunctive antidepressant use in PPDDS come from the era of first-generation antipsychotics (FGAs) and ► tricyclic antidepressants, the subsequent wide use of combinations including both FGAs and SGAs and a wide variety of more novel antidepressants nevertheless suggests both safety and utility for a variety of regimens (Siris et al. 2001).

Although proper studies have not been done to support the use of lithium (► lithium) or anticonvulsants (► Mood Stabilizers) (► Anticonvulsants) in PPDDS, it is rational to consider a trial of these agents, perhaps particularly in patients who manifest features of schizoaffective disorder, have a history of excitement or an episodic course as a component of their illness, or have family histories of affective disorders. Similarly, although there are not specific data to support it, ECT can be on the list of other treatments that might be useful in cases of PPDDS.

It is additionally important to provide adequate psychosocial support, increasing structure, reducing stress, and building skills, confidence, and self-esteem for patients during their treatment for PPDDS. This is particularly the case when the patient is suffering from a chronic disappointment reaction (demoralization syndrome) and needs to learn new strategies of thinking to foster success and happiness. However, proper psychosocial supports may be pivotal as well during pharmacological interventions because, from the patients' point of view, these interventions can literally change their world and they may need help in moving ahead from long-held, but now suboptimal, old ways of adapting to their old worlds toward new ways of productively adapting to their new worlds.

Conclusion

A syndrome of post-psychotic depressive disorder of schizophrenia (PPDDS) is commonly noted to occur in the residual phase of schizophrenia, after the resolution of florid psychotic symptoms. PPDDS can be a source of considerable morbidity, and even mortality, and consequently merits clinical attention.

The phenomenology of PPDDS may represent any one of a number of conceptually distinct states, including organic or medical factors, acute or chronic use, discontinuation of a variety of medications or substances, mood or parkinsonian side effects to antipsychotic medications, an expression of the "negative" symptoms of schizophrenia, an acute or chronic disappointment reaction, the prodrome of relapse into a new psychotic episode, an expression of schizoaffective disorder, or the expression of a diathesis of affective disorder distinct from the schizophrenia diathesis. In each case, appropriate psychopharmacologic and psychosocial management of the condition is crucial for preventing suffering and promoting functioning.

Cross-References

- ▶ Anti-Parkinson Drugs
- ▶ Anticonvulsants
- ▶ Antidepressants
- ▶ Antipsychotic Drugs
- ▶ Benzodiazepines
- ▶ Beta-Adrenoceptor Antagonists
- ▶ Drug Interactions
- ▶ Emotion and Mood
- ▶ First-Generation Antipsychotics
- ▶ Lithium
- ▶ Mood Stabilizers
- ▶ Prepsychotic States and Prodromal Symptoms
- ▶ Schizoaffective Disorder
- ▶ Schizophrenia
- ▶ Second and Third Generation Antipsychotics
- ▶ Suicide
- ▶ Withdrawal Syndromes

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Postsynaptic Proteins

Definition

Proteins present at the dense postsynaptic membrane complex characteristic of excitatory glutamatergic synapses in the brain. Including postsynaptic density 95 (a marker of excitatory postsynaptic sites in hippocampal pyramidal cell dendritic spines); protein phosphatases (enzymes that remove a phosphate group from their substrate by hydrolyzing phosphoric acid monoesters into a phosphate ion and a molecule with a free hydroxyl group).

Post-Translational Amino Acid Modification

- ▶ Post-Translational Modification

Post-Translational Modification

Synonyms

Post-translational amino acid modification; Post-translational protein modification; PTM

Definition

Post-translational modifications (PTMs) are chemical alterations to a primary protein structure, often crucial for rendering a protein its biological activity. PTMs are usually catalyzed by substrate-specific enzymes (which themselves are under strict control by PTMs). The covalent alteration of one or more amino acids occurring in a protein after the protein has been completely translated and released from the ribosome.

Cross-References
► Electrospray Ionization (ESI)
► Imaging Mass Spectrometry (IMS)
► Mass Spectrometry (MS)
► Matrix-Assisted Laser Desorption Ionization (MALDI)
► Metabolomics
► Neuropeptidomics
► Proteomics
► Two-Dimensional Gel Electrophoresis

Post-Translational Protein Modification

► Post-Translational Modification

Post-Traumatic Stress Disorder

Synonyms
PTSD

Definition
This is an emotional condition or illness resulting from quite frightening or life-threatening experiences. Those who suffer from the disorder continually reexperience the precipitating traumatic events in some way and tend to avoid all places and people that are associated with those events. They are usually quite sensitive to normal life experiences (hyperarousal). Although the symptoms of PTSD were described during the American Civil War and World War I, only since 1980 has PTSD been recognized as a formal diagnosis. Approximately 7 to 8% of people in the USA develop PTSD in their lifetime, while the prevalence of the disorder among combat veterans and rape victims ranges from 10 to as high as 30%.

Cross-References
► Traumatic Stress (Anxiety) Disorder

Post-Trial Surprise

► Unblocking

Potency

Synonyms
Measure of drug activity

Definition
A measure of the concentration of a drug at which it is effective. Commonly expressed as the ED_{50} or EC_{50}, the concentration of an agonist or PAM that produces 50% of its maximal possible effect, or IC_{50}, the concentration of a compound that produces 50% of its maximal possible inhibition. A highly potent drug evokes a larger response at low concentrations. A compound's potency is proportional to its affinity and efficacy.

Cross-References
► Agonist
► Allosteric Modulator
► Antagonist
► ED_{50}
► Inverse Agonists
► Partial Agonist

Potentiation

► Drug Interactions

Power Spectral Analysis

Synonyms
Fourier analysis of time series; Fourier transform; Frequency estimation

Definition
Power spectral analysis refers to a collection of methods used to decompose a time series of data into its elementary frequency (i.e., defined physically in cycles/s or Hertz) components. A power spectrum is a function that describes the frequencies of oscillation present in the original time series and the power or variance that each frequency contributes to the amplitude changes recorded in the original time series. The method allows one to discover in the power spectrum the presence of repeatable rhythms in what may appear to be a largely random process when seen in the original time series.

Cross-References
► Electroencephalography

Power Spectrum

► Spectrograms

Pragmatic Outcome

► Effectiveness

Pramipexole

Definition

Pramipexole is a non-ergot dopamine D2, D3, D4 agonist with strong preference for the D3 receptor. It is approved for the treatment of ► Parkinson's disease (PD) and restless leg syndrome (RLS). The mechanism of action of pramipexole in the treatment of PD is believed to be related to its ability to stimulate dopamine receptors in the striatum. Side effects in patients treated for PD include ► hallucinations and somnolence, including falling asleep during activities of daily living. There have also been occasional reports of ► gambling, compulsive shopping, and other excessive behaviors. The mechanism of action for RLS is not clear, as the neurobiology of RLS is still largely unknown. Pramipexole is currently being investigated for usage in severe fibromyalgia and depression.

Cross-References

► Dopamine Receptor Agonists

Prazepam

Definition

Prazepam is a benzodiazepine with anxiolytic, anticonvulsant, sedative, and muscle-relaxant properties. Prazepam's therapeutic properties are largely attributed to its active metabolite desmethyldiazepam that displays a very long ► half-life. The clinical indication for prazepam is the short-term treatment of ► anxiety. Like most similar compounds, its long-term use is subject to tolerance, abuse, dependence, and withdrawal.

Cross-References

► Benzodiazepines
► Sedative, Hypnotic, and Anxiolytic Dependence

Prazosin

Synonyms

Hypovase®; Minipress®; Vasoflex®

Definition

Prazosin hydrochloride is an antagonist at α-1 noradrenaline receptors. Its clinical use is in the treatment of hypertension, but in behavioral pharmacology experiments it is used to block brain α-1 noradrenaline receptors.

Cross-References

► Motor Activity and Stereotypy

Prediction Error

Definition

The mismatch between the unconditioned stimulus (UCS) expected and the UCS that in fact occurs, which generates new learning. The concept of prediction error arises directly from discrepancy theories of associative learning, for example, Rescorla–Wagner (1972). This is a terminology applied in classical (Pavlovian) conditioning and the importance of prediction error for new learning provides a constraint on the general importance of temporal coincidence as the sole determinant of new learning.

Cross-References

► Classical (Pavlovian) Conditioning

Predictive Validity

Definition

The term refers to one of the criteria used to assess the validity of animals models for psychiatric states. A similarity in response to a manipulation in the model and in the human syndrome is indicative of predictive validity. Most commonly, this refers to the actions of drugs that alleviate or worsen the condition; predictive validity is high if drugs known to alleviate the disease in humans also attenuate the measures taken in the model, and if drugs that do not work in the human are also ineffective in the model. Such a model may have the ability to predict the effectiveness of a drug in humans.

Cross-References

► Animal Models of Psychiatric States
► Construct Validity
► Face Validity

Preference Reversal

Synonyms
Switch in preference

Definition
A *preference reversal* is a change in a subject's preferred choice.

Cross-References
► Behavioral Economics

Prefrontal Cortex

Synonyms
Prefrontal lobe

Definition
The prefrontal cortex is the entire part of the cerebral cortex that is located in front of the premotor areas. It plays an important role in ► executive function, complex cognitive behaviors, ► working memory, ► attention, expression of personality, and appropriate social behavior. It has been subdivided into the medial prefrontal cortex, involved in behavioral error monitoring; ventral/orbital prefrontal cortex, related to emotional control; and dorsolateral prefrontal cortex, related to spatial working memory and executive functions. Recent evidence suggests that additionally, the frontal pole (the anterior tip of the brain) is an important component involved in executive functions. The prefrontal cortex is needed for behavioral planning, categorizing and sequencing complex actions. It is supplied by inputs from association cortices and receives strong dopaminergic, noradrenergic, serotonergic and cholinergic inputs that modulate its activity. Its outputs are directed to the corpus striatum, ► amygdala, and other subcortical centers. The prefrontal cortical projections to the ► nucleus accumbens mediate the compulsivity and impulsivity associated with drug taking.

Cross-References
► Cognitive Enhancers
► Short-Term and Working Memory in Animals
► Short-Term and Working Memory in Humans

Prefrontal Lobe

► Prefrontal Cortex

Pregabalin

Definition
An antagonist of alpha-2 delta calcium channels, with anticonvulsant and analgesic properties, and efficacy in acute treatment and relapse prevention in ► Generalized anxiety disorder (GAD). It diminishes both physical or somatic symptoms (such as tachycardia and tremor) and psychological or psychic symptoms such as worrying and irritability. Drowsiness can sometimes be troublesome, but can also be useful in GAD patients with marked sleep disturbance.

Premenstrual Dysphoric Mood Disorder

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Synonyms
Late luteal phase dysphoric disorder; Premenstrual syndrome; Premenstrual tension

Definition
Premenstrual dysphoric disorder (PMDD) affects 3–5% of premenopausal women and is characterized by moderate to severe mood symptoms, with or without physical symptoms. Symptoms are present during the week prior to menstrual flow and absent in the postmenstrual week. Women must experience at least one of four key mood symptoms (irritability, mood lability, anxiety/tension, or depressed mood) and have at least five symptoms in total in order to meet the research diagnostic criteria included in the Diagnostic and Statistics Manual for Mental Disorders, Fourth Edition [DSM-IV] (American Psychiatric Association 2000). Physical symptoms frequently include breast tenderness, bloating, fatigue, and cramping, while irritability, anxiety/tension and depressed mood are the three most common mood symptoms, in that order). Women with

PMDD are symptomatic during the majority of menstrual cycles and note a significant impairment in important areas of daily functioning during the ► premenstruum. PMDD is not merely the worsening of an on-going psychiatric disorder or a state that is secondary to a general medical condition. Importantly, two months of ► prospective daily ratings are required to confirm the diagnosis of PMDD.

Relationship of PMDD to Other Premenstrual Syndromes

After some debate, late luteal phase dysphoric disorder was renamed PMDD and included in Appendix B of the ► DSM-IV, which provides research criteria for disorders requiring further study. PMDD and PMS are often used interchangeably; however, there are diagnostic differences that warrant consideration (Table 1). Much of the world refers to premenstrual mood and physical distress as premenstrual tension syndrome (PMTS), a diagnosis found in the World Health Organization (WHO)'s International Classification of Diseases, tenth edition (► ICD-10). PMDD has several features that distinguish it from PMS (American College of Obstetrics and Gynecology [ACOG] criteria) and PMTS (ICD-10 criteria), as outlined in the following text. The timing of symptoms with respect to the menstrual cycle is consistent among the two diagnoses. However, the number, type, and severity of symptoms are highly divergent, with the diagnosis of PMDD being far more stringent, emphasizing the affective symptoms that are not merely the worsening of an ongoing psychiatric disorder (Freeman 2003; Halbriech 2007).

PMDD is also associated with significant impairment in at least one domain of daily functioning. Women typically report that impairment is greatest in the interpersonal realm, at home with family and friends.

Role of Pharmacotherapy

The symptoms of PMDD occurring during the luteal phase suggest that ovulation and its associated fluctuations in ovarian steroids are important for the manifestation of symptoms. A seminal study found that women with PMDD experienced symptom improvement with ► gonadotropin releasing hormone (GnRH) agonist treatment, only to experience a return of mood symptoms when estradiol or progesterone was added back. These data support the theory that women with PMDD, but not healthy controls, are "sensitive" to ovarian hormone exposure. While the suppression of ovulation with GnRH agonist treatment is effective in the majority of women with PMDD, it is not a long-term treatment option secondary to the negative health effects of extended hypoestrogenism in young premenopausal women. Interestingly, ovulation suppression with oral contraceptives is not effective and can worsen mood symptoms in women with PMDD. An exception to this is contraceptive treatment with agents containing the progestin drosperinone, which have shown greater efficacy than placebo in controlled trials (Pearlstein et al. 2005; Yonkers et al. 2005).

The mainstay of treatment for PMDD includes daily or luteal phase administration of a selective serotonin reuptake inhibitor (SSRI). SSRIs are well tolerated and a majority of women respond within the first few days of medication use. That PMDD is preferentially responsive to treatment with SSRIs versus antidepressants with alternative mechanisms of action is one factor that implicates

Premenstrual Dysphoric Mood Disorder. Table 1. Diagnostic criteria for PMS/PMTS and PMDD.

	PMS/PMTS	PMDD
Number of symptoms	1	5
Type of symptoms	Physical or psychological	At least one symptom has to be irritability, mood lability, anxiety/tension, depression
Symptom pattern	Symptoms present in the premenstruum and remit within a few days of menstrual flow	Symptoms present in the premenstruum and remit within a few days of menstrual flow
Functional impairment	Required for ACOG criteria (PMS) but not for ICD-10 (PMTS)	Required
Daily symptom ratings	Required for ACOG criteria (PMS) but not for ICD-10 (PMTS)	Required
Comorbidity	Not discussed in the ACOG or ICD-10 criteria for either PMS or PMTS, respectively	Must not be merely the exacerbation of an ongoing disorder

ACOG American College of Obstetrics and Gynecology; *ICD-10* International Statistical Classification of Diseases and Related Health Problems 10th Revision; *PMS* premenstrual syndrome; *PMTS* premenstrual tension syndrome

► serotonin in the pathogenesis of PMDD. However, the rapid onset of symptom relief with SSRI administration suggests that the pathogenesis of PMDD is distinct from other disorders (e.g., ► major depression, ► panic disorder, ► obsessive–compulsive disorder) for which SSRIs are effective therapies. Moreover, the rapid onset of effectiveness also appears to implicate other neurotransmitter systems, such as gamma aminobutyric acid (► GABA), in symptom expression and response to treatment (Amin et al. 2006; Epperson et al. 2002). ► SSRIs increase allopregnanolone, a potent $GABA_A$ receptor agonist. Table 2 provides doses of each of the SSRIs that have been shown to be effective in the treatment of PMDD.

Daily Administration

A recent meta-analysis of 12 randomized, placebo-controlled studies confirmed that the daily administration of an SSRI is effective in the treatment of PMDD (Brown et al. 2009). Several, but not all, of these studies found clinically meaningful improvement in physical symptoms such as breast tenderness, cramping and bloating, in addition to improvements in irritability and other behavioral symptoms. Daily administration is ideal for women with shorter cycles who have severe symptoms starting at the time of ovulation that extend into the first week of menstrual flow. Such women are symptomatic much of the month and could benefit from continued treatment. Certainly, if there is any question that a woman may have mild depression, recurrent brief depression, dysthymia, or generalized anxiety disorder, it would be preferable to use daily administration until one of these other disorders that frequently masquerade as PMDD could be ruled out. In a study of women claiming to have PMDD who presented to a premenstrual dysphoric disorder specialty program, over 30% were diagnosed with a mood and/or anxiety disorder (Bailey and Cohen 1999). As the overlap in the type of symptoms seen in PMDD and a number of other psychiatric disorders is considerable, the importance of using daily ratings to examine the pattern of symptom onset and offset cannot be underestimated.

Premenstrual Dysphoric Mood Disorder. Table 2. Selective serotonin reuptake inhibitors.

Drug	Usual therapeutic dose (mg/day)	
	Daily administration	Luteal phase administration
Fluoxetine	10, 20[a]	10, 20
Sertraline	25, 50[b]	25, 50[b]
Paroxetine	10, 30	not studied
Paroxetine CR	12.5, 25	25
Citalopram	10–30[c]	10–30

[a]One study found 60 mg/d to be more effective than placebo but not more effective than 20 mg/d
[b]Some studies used graded dosing between 50–100 mg/d
[C]Dosing was titrated from 10–30 mg/d

Luteal-Phase Administration

A review of 12 randomized, placebo-controlled clinical trials provides strong evidence that intermittent or luteal phase treatment with an SSRI is effective in the treatment of PMDD (Brown et al. 2009). Luteal phase administration is best reserved for women whose daily ratings and clinical evaluation clearly confirm the diagnosis of PMDD. The benefit of luteal phase administration is considerable. Drug costs are lower and many women prefer to use a medication on an as-needed basis. Luteal phase administration with a shorter half-life SSRI (e.g., sertraline, paroxetine CR) is preferable for women who experience significant changes in sexual function/interest when using an SSRI. Interestingly, the tolerability of going on and off an SSRI seems to be more than adequate. However, women who discontinue SSRI treatment for PMDD are at high risk for having a return of symptoms in the subsequent luteal phase (Pearlstein et al. 2003).

Conclusions

PMDD is a relatively common clinical phenomenon with the onset during the teen years and the early 20s. That PMDD is preferentially responsive to SSRI treatment and returns upon medication discontinuation provides support for serotonin and menstrual cycle related fluctuation in ovarian hormones in the pathogenesis of PMDD. The completion of 2 months of prospective daily ratings is not only required for the diagnosis, but it is also crucial for women who wish to use the luteal phase administration of an SSRI.

Cross-References

► Gonadotropin Releasing Hormone Agonist
► Luteal Phase
► Premenstruum
► Prospective Daily Ratings

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Premenstrual Syndrome

► Premenstrual Dysphoric Mood Disorder

Premenstrual Tension

► Premenstrual Dysphoric Mood Disorder

Premenstruum

Definition

The premenstruum is a term used by clinicians and researchers for the portion of the menstrual cycle that occurs immediately prior to the onset of menstrual flow. While there is no specified number of days referred to as the premenstruum, it typically includes the few days to a week prior to the onset of menses.

Premonitory Urge

Definition

By age 10 years, many patients with ► tic disorders will describe a feeling or urge prior to the execution of their tics. This sensation or warning may be located at the anatomical site of the tic or may be described as a more general feeling of unease or discomfort. Patients who describe the premonitory urge often report that there is momentary relief from this sensation following the performance of the tic.

Prenatal Exposure to Alcohol

Definition

Exposure to alcohol in utero by maternal abuse or use of alcohol.

Prenatal MAM Model

Definition

An animal model in which pregnant female rats are treated with the drug methylazoxymethanol (MAM). MAM blocks mitosis for a period of about 24 h and thus interfere with normal (brain) development. Depending on the timing of the MAM treatment, different brain regions will be more or less affected, leading to different behavioral alterations in adulthood. Although different protocols exist, the model most often used as a simulation model for ► schizophrenia involves treatment on gestational day 17. In adulthood, these animals develop a large number of schizophrenia-like phenomena.

Cross-References

► Schizophrenia: Animal Models
► Simulation Model

Prenatal Period

Definition

An interval of time from conception to birth.

Preparatory Behavior

► Appetitive Responses

Pre-Psychotic Prodrome

► Pre-psychotic States and Prodromal Symptoms

Pre-psychotic States and Prodromal Symptoms

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Synonyms

At-risk mental state; Pre-psychotic prodrome; Schizophrenia prodrome

Definition

The "prodromal phase" that precedes a first psychotic episode is a period characterized by increasing levels of nonspecific subthreshold symptoms associated with significant distress and growing functional impairment. This phase often continues for several years prior to the emergence of diagnostically-specific psychotic symptoms, with significant social disability becoming apparent well before the first psychotic episode. Because the psychotic disorders usually manifest during adolescence, a period of major developmental change, they may have particularly devastating consequences on lifetime functioning, highlighting the need for early intervention in order to minimize ongoing disability.

Role of Pharmacotherapy

The psychotic disorders occur at a frequency of around 2% in the general population and thus are relatively rare. However, their onset is most common during late adolescence and early adulthood, a period of life where critical developmental tasks are being accomplished in the psychological, social, educational, and vocational domains. Because serious mental illness substantially disrupts these processes and often leads to ongoing long-term disability, the early detection and treatment of people at risk of psychosis, before the onset of frank psychotic disorder, has long been a major goal in psychiatric practice.

The existence of a prodromal phase prior to a first episode of psychosis or a relapse of ► schizophrenia was noted over a century ago, prompting the first calls for early treatment as a means of preventing serious illness and ongoing disability. However, until relatively recently, research into the possibilities for early intervention has been limited by the lack of effective treatments, as well as the widespread perception that the ongoing disability associated with the psychotic disorders was inevitable. Over the last decade the advent of more effective drugs, particularly the atypical antipsychotics, and the development of better psychosocial treatments has led to the realization that good long-term outcomes are possible for patients and rekindled interest in the area of early intervention. An important result of this renewed research effort is a series of careful epidemiological studies that have enabled the characterization of the "psychosis prodrome," a significant advance which has finally allowed early therapeutic intervention in the psychotic disorders to become a real possibility. These research findings have now been translated into evidence-based clinical practice in a growing number of specialized early intervention services worldwide and have made a major contribution to the improved outcomes that are now expected for young people who are experiencing the onset of a psychotic illness (Yung et al. 2004).

Retrospective studies of first-episode psychosis patients, examining the course of illness from the premorbid period through to the emergence of frank psychosis, have shown that the first episode is almost always preceded by a prodromal period of several years that are characterized by increasing levels of psychological symptoms, significant distress, and a marked decline in social and vocational functioning compared to pre-morbid levels. In general, negative symptoms such as decreased concentration, reduced drive, and lack of energy predominate early in the prodromal phase, accompanied by nonspecific symptoms including sleep disturbance, anxiety, and irritability. Affective symptoms, primarily depression, are also common. These symptoms tend to accumulate exponentially until relatively late in the prodrome, when subthreshold positive symptoms (psychotic symptoms) emerge. Ultimately, these positive symptoms intensify and culminate in the transition to frank ► psychosis. Typically, increasing levels of social and vocational disability accompany the increase in symptomatology, with significant disability becoming apparent well before the first psychotic episode. The degree of disability that develops during the prodromal period appears to set a ceiling for the extent of the eventual recovery, highlighting the need for early intervention (Yung et al. 2004).

Because these prodromal symptoms, including subthreshold psychotic-like experiences, are nonspecific and occur frequently in the general population, especially among adolescents and young adults, they cannot be considered as diagnostic of a pre-psychotic state in their own right. Additional risk factors and specific criteria are necessary to exclude false positive cases in order to avoid unnecessary treatment and the stigma often associated with the diagnosis of a mental illness. In order to increase the prognostic specificity of these prodromal symptoms, two additional risk factors have been developed based on

our clinical experience and the available epidemiological evidence, to add to the screening criteria. The first of these is being aged between 14 and 30, since young people in this age range are at greatest risk of developing a psychotic disorder. The second is a need for clinical care, since young people who are not distressed by their symptoms and who have not experienced a decline in their functioning are less likely to become seriously unwell in the near future. A careful prospective study of a young, help-seeking population identified a subset of young people who appear to be at incipient risk of frank psychosis. The specific criteria defining this ultra-high risk (UHR) group fall into three groups (1) having experienced attenuated psychotic symptoms during the previous year; (2) having brief episodes of frank psychotic symptoms that resolve spontaneously over the previous year; and (3) having a schizotypal personality disorder, or a first degree relative with a psychotic disorder, and recently experiencing a significant decline in functioning (Table 1) (McGorry and Singh 1995; Yung and McGorry 1996). Up to 40% of the young people who met these UHR criteria made a transition to psychosis within the following year, a rate several hundred-fold greater than the expected incidence rate for first-episode psychosis in the general population. These criteria have since been validated in a series of international studies. However, it should be borne in mind that while they do identify a group of young people who are at incipient risk of psychosis, the identification itself is by no means a diagnosis per se; the majority of young people who fulfill the UHR criteria do not develop a full-threshold psychotic disorder.

The elaboration of operationalized criteria that significantly reduce the risk of inappropriate treatment has not only proven to be clinically useful, but has also catalyzed renewed efforts into developing effective early intervention strategies designed to prevent, or at least delay the onset of psychosis and other serious mental illness. Clearly, the young people who fulfill these UHR criteria have demonstrable clinical needs, and thus effective treatment is called for not only on human, but also on medical and ethical grounds. Current early intervention strategies range from the psychologically-based, including psychoeducation, supportive psychotherapy, cognitive behavioral therapy (CBT), and family work; to the biologically-based, including symptomatic treatment for depression, anxiety and any sub-threshold psychotic symptoms, through to experimental neuroprotective approaches. The global aim of treatment in the prodromal phase is to provide comprehensive clinical care designed to reduce presenting symptoms, and if possible, to prevent these symptoms from worsening and developing into an acute psychosis.

Currently Accepted Strategies for Treatment of Prodromal Symptoms

Studies have shown that around 25% of these at-risk young people have a concomitant diagnosis of depression, and that over 60% of UHR patients will experience a depressive disorder during their lifetime. Thus, treatment

Pre-psychotic States and Prodromal Symptoms. Table 1. Ultra High Risk criteria: (1) must be aged between 14 and 29 years, (2) have been referred to a specialized service for help, and (3) meet the criteria for one or more of the following three groups.

Group 1: Attenuated positive psychotic symptoms	• Presence of at least one of the following symptoms: ideas of reference, odd beliefs or magical thinking, perceptual disturbance, paranoid ideation, odd thinking and speech, odd behavior and appearance • Frequency of symptoms: at least several times a week • Recency of symptoms: present within the last year • Duration of symptoms: present for at least 1 week and no longer than 5 years
Group 2: Brief limited intermittent psychotic symptoms	• Transient psychotic symptoms. Presence of at least one of the following: ideas of reference, magical thinking, perceptual disturbance, paranoid ideation, odd thinking or speech • Duration of episode: less than 1 week • Frequency of symptoms: at least several times per week • Symptoms resolve spontaneously • Recency of symptoms: must have occurred within the last year
Group 3: Trait and state risk factors	• Schizotypal personality disorder in the identified individual, or a first-degree relative with a psychotic disorder • Significant decline in mental state or functioning, maintained for at least 1 month and not longer than 5 years • This decline in functioning must have occurred within the past year

with cognitive behavior therapy and/or antidepressants, most commonly the ► SSRIs, may be indicated. These therapies are generally well-accepted and well-tolerated by this patient group, and lead to significant clinical improvement. Some preliminary evidence suggests that antidepressants may have a protective effect if initiated early enough in the illness process; effective treatment of depression may help to limit the development of negative symptoms and social withdrawal. ► Anxiety is also extremely common in this patient group, with around 25% of these young people having a current diagnosis of an anxiety disorder, while around 30% experiences an anxiety disorder in their lifetime. ► Benzodiazepines may be prescribed to relieve short-term anxiety and sleep disturbance and to reduce agitation. Because anxiety tends to increase as positive symptoms develop, effective treatment of anxiety may help to relieve the stress associated with any subthreshold psychotic symptoms that may be present, and allow the patient to better cope with social and vocational difficulties as they arise, limiting the functional decline that occurs during the prodromal period (Yung et al. 2004).

Subthreshold psychotic symptoms are almost inevitably present in UHR patients. However, in general, antipsychotic treatment should be avoided if at all possible. Indications for antipsychotic treatment include rapid deterioration, hostility, and aggression that poses a risk to the patient or others, severe suicidality, or depression that does not respond to other treatments. Antipsychotics may also be trialed for patients who have not responded to psychosocial interventions and who are still unwell and functioning poorly. If medication is warranted, the ► atypical antipsychotics should be used on a trial basis for a limited time only, and at the lowest dose possible, to minimize the risk of extrapyramidal side effects (see below). If there is clinical benefit and resolution of symptoms after 6 weeks, the medication may be continued for a further 6 months to 2 years, with the consent of the patient (Yung et al. 2004).

The atypical antipsychotics are the agents of first choice for young patients since they have been shown to be associated with fewer extrapyramidal side effects than the potent first-generation agents. Apart from the movement disorders, the major side effects reported for the atypical agents include significant weight gain and an increased risk of diabetes and metabolic disturbance. Other common side effects include sedation, fatigue, and decreased libido, and less commonly, prolactinemia and cardiac arrhythmias. In the few studies involving first-episode and prodromal patients that have been published so far, apart from weight gain, the other side effects reported have been relatively mild and/or transient, and thus the atypical antipsychotics appear to be well tolerated in this vulnerable patient group (International Early Psychosis Association Writing Group 2005).

Experimental Strategies for Short-Term Symptomatic Treatment of Prodromal Patients

The safety and efficacy of two atypical antipsychotics, ► amisulpride and ► aripiprazole, for the relief of symptoms in young people at incipient risk of psychosis has been tested in two recent clinical trials. One of these involved a group of 124 young people, where participants received amisulpride (flexibly dosed at 50–800 mg/day) plus needs-based psychosocial support, or psychosocial support alone for a period of 12 weeks (Rurhmann et al. 2007). Regardless of their treatment group, participants were permitted to take ► citalopram for moderate to severe depression, and ► lorazepam, ► temazepam, or ► chloral hydrate for agitation or sleep disturbances, and if necessary, biperiden was prescribed for extrapyramidal symptoms. While both groups improved over the course of this study, the amisulpride group showed a reduction in symptoms that was at least double that of the control group across a range of measures designed to assess the levels of positive and negative symptoms, as well as general psychopathology. Both groups also showed an improvement in their levels of functioning, and again, this was significantly greater in the amisulpride group than in the control group.

The final mean daily dose of amisulpride was 118.7 ± 10.7 mg, which was well within the lower end of the dose range. Four of 61 participants in the amisulpride group developed ► akathisia, compared to 1 of 43 in the control group, with biperidin being prescribed for 3 of the 4 participants from the amisulpride group. The most frequent side-effects associated with amisulpride were related to a marked increase in prolactin levels, commonly seen in response to the benzamides, particularly when associated with an SSRI. As a consequence, transient menstrual disturbances emerged in 4 females, 1 developed a prolonged cycle, and 1 dropped out due to amenorrhoea. Two males developed erectile and ejaculatory dysfunction, and 1 other decreased desire and ► erectile dysfunction (Rurhmann et al. 2007).

In the second study, the safety and efficacy of 5–30 mg/day aripiprazole for symptomatic relief was been tested in an 8-week pilot trial of 15 young people experiencing attenuated positive symptoms (Woods et al. 2007). All participants were permitted to continue any antidepressant, mood stabilizing, or stimulant medication that they had been prescribed, but not to begin new

medications or change existing doses during the study period. However, lorazepam was allowed for anxiety or agitation, and benztropine was prescribed for extra-pyramidal symptoms, if necessary. Individual and family-centered psychosocial support was available for all participants.

At the end of the study, the mean daily dose of aripiprazole was 15.67 mg, and adherence to medication was over 90% for the entire study period. Eleven of the 15 participants were no longer experiencing positive symptoms, and all participants showed a significant improvement in their levels of positive, negative and general symptoms and in their overall functioning. Notably, while the 2 participants who completed the study without responding to aripirazole chose not to continue treatment, the remaining 11 participants elected to remain on medication. The most common adverse effect reported was emergent akathisia, which occurred in 8 participants, though this usually remitted after management, with 4 participants requiring benztropine at the end of the trial. Weight gain was minimal, with a mean of 1.2 kg gained over the trial period (Woods et al. 2007).

Experimental Strategies Designed to Prevent the Onset of Psychosis

To date, only three clinical trials of pharmacological treatments specifically designed to prevent the onset of psychosis have been published. Our group ran the first of these trials, which aimed to test the efficacy of 6 months of low dose ▶ risperidone treatment plus CBT in preventing the onset of psychosis in a group of 59 UHR young people recruited from within our clinical service (McGorry et al. 2002). Participants were randomized to either the control group or the intervention group, with the control group receiving supportive psychotherapy and general case management. As well as these elements, the intervention group undertook a CBT program designed to develop an understanding of their symptoms, to learn strategies to enhance their control of these symptoms and to reduce associated distress. In addition, this group received 1–2 mg of risperidone daily for the 6 months of the treatment phase. Risperidone therapy was commenced at 1 mg/day then increased to 2 mg/day provided no adverse effects were experienced, and if necessary, the dosage was reduced to 1 mg/day. All participants were permitted to take sertraline for moderate to severe depression, and temazepam for insomnia.

At the end of the 6-month treatment phase, 3 of the 31 young people in the intervention group had developed frank psychosis, compared to 10 of the 28 in the control group. However, by the 12-month assessment another 3 patients in the intervention group had made a transition to psychosis, while no more transitions had occurred in the control group. Adherence to the CBT component was high, while adherence to risperidone therapy was variable; 13 patients were classed as non-adherent (<50% of doses taken), 4 as partially adherent (>50% of doses taken), while 14 were considered fully adherent (almost 100% of doses taken). Interestingly, only 1 of the patients considered fully adherent developed frank psychosis. Adverse effects were noted in only 4 patients; 1 developed minor rigidity and 3 experienced mild sedation, and all were relieved by lowering the dose of risperidone. The mean final dose was 1.3 ± 0.901 mg/day. Not surprisingly, the use of ▶ sertraline was lower in the intervention group (41.9%) than in the control group (60.7%). Sertraline treatment did not affect the rate of transition to psychosis in the control group, since this was not significantly different in those who had been prescribed sertraline and those who had not (McGorry et al. 2002).

Medium-term follow-up of our study cohort 3–4 years after initial assessment showed that a further 4 patients from the intervention group and 2 from the control group had become psychotic since their 12-month assessments, which indicates that the "window of vulnerability" in these UHR young people continues well beyond the first year after their presentation to a clinical service and initial treatment. Over 80% of all participants reported that they had sought professional help for psychological concerns since their 12-month assessment, and among those who had not developed frank psychosis, 70% of those in the control group and 54% of the intervention group had been prescribed either antidepressants or anxiolytics over this period, emphasizing the need for care in these young people who although not psychotic, are significantly compromised by their illness (Phillips et al. 2007).

The second trial was designed to test the safety and efficacy of ▶ olanzapine at doses of 5–15 mg/day in preventing the onset of psychosis in a group of 60 UHR young people (McGlashan et al. 2006). Participants were recruited after referral by clinicians or in response to advertisements, and randomly assigned to either the olanzapine or the placebo groups. In this study, concomitant psychoactive medications were not allowed, and all participants had access to supportive psychosocial interventions as needed. The treatment phase ran for 12 months, and was followed by a 12-month follow-up period and a 6-month period of open-label olanzapine treatment for all patients who experienced a conversion to psychosis.

At the end of the 12-month treatment phase, 5 of the 31 participants who had received olanzapine treatment had become psychotic, compared to 11 of the 29 participants in the placebo group. All 5 patients from the olanzapine group who converted to psychosis did so within the first 4 weeks of the treatment phase, while the 11 patients from the placebo group who made this transition did so throughout the entire 12 months of the treatment phase. Those in the olanzapine group showed an improvement in their levels of positive symptoms that was not seen in the placebo group, while both groups showed an improvement in their overall levels of functioning. Notably, during the 12-month follow-up after all medication was ceased, positive symptoms worsened in both groups, with the participants from the former olanzapine group showing a statistically significant increase in the levels of positive symptoms experienced. During this period, 3 of the 9 patients remaining in the study from the former olanzapine group converted to psychosis, while 2 of the 8 remaining placebo group patients developed psychosis. The only significant adverse effects associated with olanzapine treatment were fatigue and weight gain, with 29% of the participants in the olanzapine group reporting fatigue compared to 3% in the placebo group, and 61% of the olanzapine group showing weight gain compared to 17% in the placebo group. The mean weight gain in the olanzapine group was 8.79 ± 9.05 kg, or 12.7% of the mean body weight, while that in the placebo group was 0.3 ± 4.24 kg, in line with other studies in patients suffering from schizophrenia. However, this weight gain was not accompanied by changes in blood laboratory values suggesting an increased risk of cardiovascular disease or diabetes (McGlashan et al. 2006).

A very recent study involved the use of omega-3 essential fatty acids (EFA) for indicated prevention of psychosis in a group of 81 UHR young people (Amminger et al. 2009). Participants were randomized to either the placebo group or the EFA group, and underwent a 12-week trial of treatment with 1.2 g/day EFA (a balanced mix of 700 mg EPA+480 mg DHA) and a 12-month follow-up period. All participants were offered the same psychosocial support package, and antidepressants and benzodiazepines were allowed for the treatment of depression and anxiety, if necessary. Significantly, at the end of the 12-month follow-up period, 2 of the 41 (4.9%) participants in the EFA group had made the transition to frank psychosis, compared to 11 of the 40 (27.5%) participants in the placebo group. Significant reductions in the levels of positive, negative, and general symptoms were seen in the EFA group, along with an increase in overall functioning, and most interestingly, these benefits were continued after the cessation of the 12-week intervention phase. Furthermore, the number needed to treat (NNT) of 4 calculated in this study compared favorably to the NNTs of 4 and 4.5 that were reported in the trials of the antipsychotics described earlier (McGlashan et al. 2006; McGorry et al. 2002). No adverse effects were reported in either group, while the high level of compliance (over 80%) and low withdrawal rate (6% overall) indicate that this intervention was very well accepted by the participants.

This extremely promising study is the first trial of a natural substance for the indicated prevention of psychosis and the alleviation of prodromal symptoms. The evident clinical benefits and the absence of side effects suggest that the omega-3 fatty acids may indeed be a viable alternative to antipsychotic medication, offering a similar degree of overall therapeutic gain without the potentially serious and often distressing side effects associated with these agents.

Given the marked symptomatic improvements seen in response to low doses of antipsychotic medication, these preliminary studies suggest that the atypical antipsychotics may provide significant therapeutic benefits to prodromal patients, particularly those with subthreshold psychotic symptoms. Furthermore, these agents, either alone or in combination with CBT, may at least delay progression to full-blown psychosis in UHR patients. Their relatively favorable side-effect profiles means that at low doses the atypical antipsychotics were generally safe and well tolerated in this patient group; however, further large scale placebo-controlled trials are necessary to establish the risk/benefit ratio of these interventions before evidence-based treatment recommendations can be made for either the antipsychotic medications or more experimental neuroprotective agents such as the omega-3 fatty acids.

Conclusions

Current clinical experience indicates that young people experiencing prodromal symptoms, and in particular those at UHR of developing a psychotic disorder, should be treated with the aim of ameliorating their symptoms and preventing further deterioration in the course of their illness. The results of the few experimental trials that are currently available indicate that these young people may benefit from various therapeutic intervention strategies including cognitively-oriented psychotherapy and/or specific indicated prevention with low-dose atypical antipsychotic medication or neuroprotective agents such as the omega-3 fatty acids, and that treatment should be continued for longer than 6 months, given that these patients remain symptomatic and vulnerable to the onset of psychosis well after their initial detection and

treatment. However, since the evidence for the use of antipsychotics in prodromal patients is still preliminary, their use has not yet been endorsed in routine clinical practice. At this stage, indicated prevention for the psychotic disorders remains a major goal for researchers in this area.

Apart from relieving the increasing distress and disability associated with prodromal symptoms, early intervention provides numerous other advantages to these vulnerable young people. Effective treatment allows them to remain in education, training, or employment, with minimal disruption due to illness and thus they maintain better levels of social functioning and a higher quality of life than might otherwise be expected. Early engagement in therapy means that even those who do become psychotic can be treated promptly without needing emergency or inpatient care, thereby avoiding the distress and trauma associated with psychiatric hospitalization. Finally, early intervention and effective treatment allows the best chance of a full social and functional recovery, the best possible outcome in both economic and human terms.

Cross-References

- ► Antipsychotic Drugs
- ► Antipsychotic Medication: Future Prospects
- ► Benzodiazepines
- ► Neuroprotection
- ► Schizophrenia
- ► Second and Third Generation Antipsychotics
- ► SSRIs and Related Compounds

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Prepulse Inhibition

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Synonyms

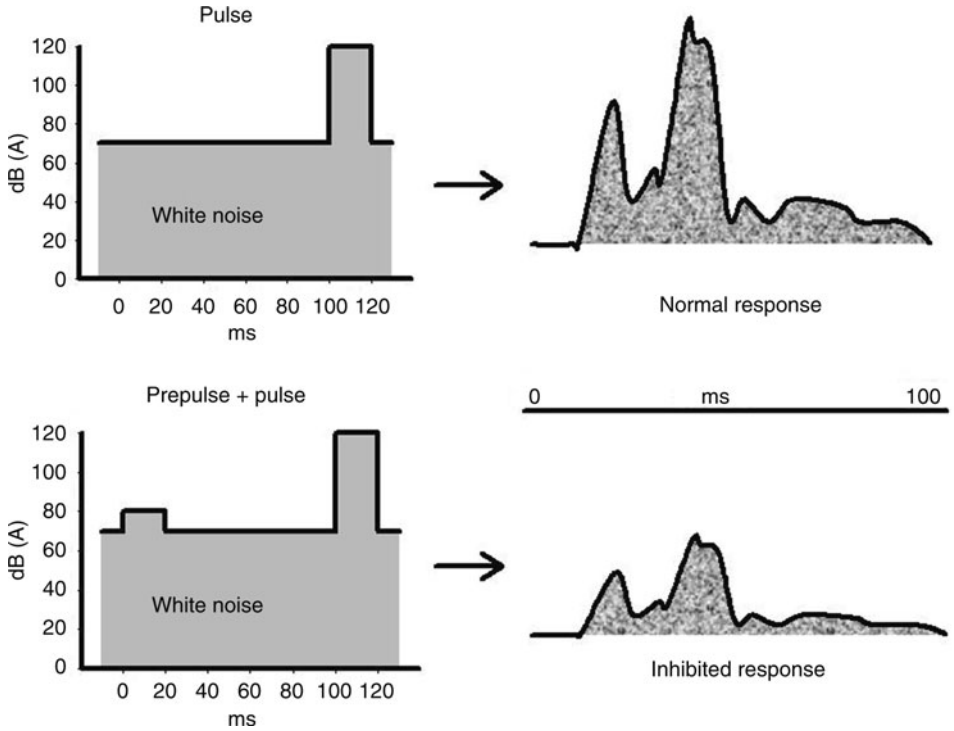
Sensorimotor gating; Sensory gating; Startle modulation

Definition

When mammals are exposed to a sudden stimulus, typically a loud acoustic noise, a startle response is elicited. Prepulse inhibition of the startle response, an operational measure of sensorimotor gating, is a cross-species measure of the normal decrement in startle when a barely detectable prestimulus immediately precedes (30–500 ms) a startling stimulus (see Fig. 1) (Graham 1975; Ison and Hoffman 1983). While the startling event is typically an acoustic or tactile (e.g., airpuff or shock) stimulus having a rapid onset, the prepulse or prestimulus can be in the same or different modality, including light, electrical shock, airpuff, sound, or brief gap in the background noise.

Impact of Psychoactive Drugs

Attentional and information processing dysfunctions have long been considered important in understanding schizophrenia and other psychiatric disorders. Prepulse inhibition is disrupted in certain neuropsychiatric disorders that are characterized by an inability to filter or "gate" sensory (and, theoretically, cognitive) information. Theoretically, impairments in basic information processing functions such as sensorimotor gating contribute to disordered thought and cognitive fragmentation observed in psychotic disorders such as ► schizophrenia (Braff and Geyer 1990). Prepulse inhibition is used commonly as an operational measure of sensorimotor gating in studies in rodents, infrahuman primates, and humans. Patients with schizophrenia exhibit reduced sensorimotor gating as indexed by prepulse inhibition when compared to healthy control subjects and several categories of nonpsychotic



Prepulse Inhibition. Fig. 1. Diagrammatic representation of prepulse inhibition of startle. The top panel illustrates a pulse-alone trial in which startle is elicited by a 120 dB(A) noise burst above a 70 dB(A) background. The startling stimulus is presented for 20 msec in this example. The startle response is typically measured for 100 (rodents) or 250 (humans) msec after the on set of the pulse. The lower panel illustrates the prepulse-plus-pulse trail, in which startle inhibited by a weak (e.g. 80 dB(A) prepulse given 30-1000 msec (in this example 100 msec onset-to-onset) before the same startle-eliciting noise used in the pulse-alone trial. In experiments examining tactile rather than acoustic startle, the pulse is an air-puff or mild electric shock to the neck (humans) or back (rodents). The right side of each panel illustrates the measured response, typically assessed using the electromyographic signal from orbicularis occuli muscle as a measure of the eyeblink response in humans or using an accelerometer-based signal as a measure of the whole-body flinch response in rodents. A typical test session includes presentations of serveral pulse-alone trials and several occasions of prepulse trials that may vary in the intensity of the prepulse stimulus or the interval between the prepulse and pulse onsets.

psychiatric disorders (Braff et al. 2001). Strikingly, similar prepulse inhibition abnormalities have also been observed in unmedicated and non-psychotic schizotypal patients and asymptomatic first-degree relatives of schizophrenia patients, supporting a strong role for genetic influences on sensorimotor gating. The reproducibility of the finding in schizophrenia, the fact that abnormal prepulse inhibition parallels a putative central abnormality in the disease, and the fact that prepulse inhibition is a conserved phenomenon among vertebrates make prepulse inhibition a promising candidate ► endophenotype to use in genetic association studies and animal models of schizophrenia (Swerdlow et al. 2009). The identification of genetic contributions to startle and prepulse inhibition in humans can be readily confirmed and extended in parallel studies using genetically engineered mice or other relevant strains of rats or mice (Geyer et al. 2002).

Using startle plasticity measures such as prepulse inhibition is advantageous in neuroscientific research for a number of reasons. First, startle plasticity in rodents has proven face, predictive, and construct validity for startle plasticity in humans. Second, startle behavior remains relatively stable across repeated testing sessions in mice, rats, healthy humans, and clinically stable psychiatric patients. This stability enables one to use longitudinal designs to explore developmental and environmental perturbations on prepulse inhibition over time and across experience. Third, startle and prepulse inhibition involve fairly rapid tests that do not involve complex stimuli, increasing their ease of use and their reliability. Since

startle relies on a simple reflex measure, its reliability and reproducibility is greater than more complex behavioral measures that are modulated by competing behaviors or motivations (e.g., approach/avoidance behavior), and increases the chances of translation of these effects to humans. Fourth, the neuroanatomical and neurochemical substrates mediating and modulating startle plasticity are well defined, allowing greater hypothesis generation and interpretability before and after obtaining results.

The neuroanatomical substrates that contribute to the modulation of prepulse inhibition in rats have been studied extensively, providing an excellent example of the regulation of behavior by integrated neuronal circuits (Swerdlow et al. 2001). The deficits in prepulse inhibition observed in psychiatric patient populations appear to reflect abnormal information processing and may result from pathology within forebrain cortico-striato-pallidopontine circuitry that modulates this form of startle plasticity (Koch 1999; Swerdlow et al. 2001). Furthermore, a wide range of developmental and pharmacological manipulations have been found to alter prepulse inhibition in rats, leading to multiple rat models having utility in the identification of antipsychotic medications (Geyer et al. 2001). Prepulse inhibition has shown good predictive validity as a screen for ▶ antipsychotic drugs. In keeping with the ▶ dopamine hypotheses of psychotic disorders such as schizophrenia and mania, dopamine agonists such as ▶ apomorphine and ▶ amphetamine disrupt prepulse inhibition in rodents. These effects can be reversed by antipsychotics having selective antagonist effects at dopamine D2, but not dopamine D1 receptors. One important aspect of animal models of schizophrenia is their ability to distinguish between typical and atypical antipsychotic drugs. Prepulse inhibition deficits induced by apomorphine are reversed by both typical and ▶ atypical antipsychotics. Thus, although the ability of antipsychotics to restore prepulse inhibition in apomorphine-treated rats strongly correlates with their clinical potency, when used with the dopamine agonist apomorphine, this paradigm fails to make the important distinction between these two classes of antipsychotic drugs. In contrast, the prepulse inhibition disruptions produced by glutamate antagonists (e.g., ▶ phencyclidine, dizocilpine, and ▶ ketamine) differentiate between typical and atypical antipsychotics to some degree (Geyer et al. 2001). Specifically, typical antipsychotics such as ▶ haloperidol do not attenuate the prepulse inhibition-disruptive effects of glutamate antagonists in rats, while ▶ clozapine and some other atypical antipsychotics reduce the disruption in prepulse inhibition produced by these psychotomimetics in both rats and mice. Thus, prepulse inhibition already serves an important role in the identification of novel treatments for schizophrenia (Braff and Light 2004) and may ultimately contribute to our understanding of other psychiatric disorders such a ▶ bipolar disorder, ▶ panic disorder, and ▶ post-traumatic stress disorder.

Cross-References

▶ Habituation
▶ Schizophrenia
▶ Sensorimotor Gating
▶ Sensory Gating
▶ Startle

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Presynaptic Bouton

Definition

A widening of an axon that contains the components to form the presynaptic part of a synapse.

Price

▶ Behavioral Economics
▶ Intracranial Self-Stimulation

Primary Insomnia

Definition

Primary insomnia is a complaint of difficulty in initializing or maintaining sleep or of non-restorative sleep that lasts for at least 1 month and causes clinically significant distress or impairment in social, occupational, or other important areas of functioning. The disturbance in sleep does not occur exclusively during the course of another sleep disorder or mental disorder and is not due to the direct physiological effects of a substance or a general medical condition.

Cross-References

► Insomnias
► Sleep

Primate Models of Cognition

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Definition

Cognition is an array of higher-order processes that occur between sensory processing and motor output and that are inferred from animals' behavior. It includes constructs such as attention, memory, and executive control, and the behavioral tests used to study such constructs need to provide specificity, selectivity, and reproducibility. All behavioral tests have in common the need for perception, action, and attention to varying degrees, and so it is important for any drug study that the test employed should differentiate effects caused by the modulation of one or the other of these processes, as well as the particular cognition under investigation. This is especially true when studying the actions of drugs given peripherally, which can have widespread influences in all regions of the brain including regions primarily involved in sensory processing or motor output.

Principles and Role in Psychopharmacology

Behavioral tests of cognition have had a long tradition in the field of primate neuropsychology. Originally, testing took place in the Wisconsin General Test Apparatus (WGTA) with the experimenter sitting in front of the monkey, behind a one-way mirror. Given that vision is an extremely important sense for monkeys, tests tended to be designed around objects or spatial locations. This contrasted with that of human neuropsychology in which the tests so often involved language and pen and paper. Consequently, the extrapolation of results from primate studies into the clinic was fraught with difficulty, as the tests used to measure a particular cognitive process differed considerably between humans and monkeys. After a seminal paper by L Weiskrantz, in 1977, the recognition of the advantages of testing humans and monkeys on the same tests led to much closer integration of human and monkey neuropsychological studies. In addition, the important advantages of automated and computer controlled testing devices over manually operated ones (e.g., WGTA) were recognized, eliminating experimenter–subject interactions and increasing the degree of experimental control and efficiency (Bartus and Dean 2009). However, the ease of presenting tests in the WGTA or other manually operated environments should not be underestimated, not least due to the comparative ease at which monkeys can learn a range of different cognitive tests when the response and the reward are spatially contiguous. The spatial (and thus also temporal) separation of a response and the associated reward recruits additional cognitive processes, probably dependent on the frontal lobes, which may not be the focus of interest, but may need to be taken into account when interpreting the results.

Currently, there are an array of cognitive tests designed to measure specific aspects of primate cognition, which are available for the psychopharmacologist. In many cases, it is possible to test monkeys on a battery of such tests allowing the effects of drugs to be compared across a range of different cognitive functions within the same animal.

Attention

Attention can be selective or ► divided, ► sustained or not. If selective, the attention may be directed at a specific spatial location or a particular sensory cue e.g., red circle. Alternatively, ► attention may transcend specific sensory cues and occur instead at the level of higher-order perceptual dimensions e.g., color or shape, in which case, it is said that an animal has developed an ► attentional set (see the section on Cognitive Flexibility). A variety of tests have been developed to study attentional abilities in monkeys and the majority of them are dependent on an intact frontal and parietal cortex. The serial reaction time task, first developed in humans and later used to study attention in rats, investigates the ability of monkeys to locate a briefly presented target in one of a number of

spatial locations (Spinelli et al. 2004; Weed et al. 1999). It tests aspects of both divided and selective attention. In a version for monkeys (Cambridge Neuropsychological Test Battery, ► CANTAB: Lafayette Instrument company), five circles are presented on a touch sensitive computer screen, and a small colored stimulus is briefly presented in one of those locations (Fig. 1a). To start each trial, the monkey must perform an orienting response to ensure readiness to perform the trial, i.e., press down a lever, and after a variable delay, respond to where they saw the colored stimulus. The demands on divided attention can be increased or decreased by altering the number of spatial locations in which the target stimulus may appear. In contrast, the level of selective attention can be modulated by varying the duration of the target presentation. Other manipulations involve altering the lengths of the inter-trial interval and the length of time the animal waits at the start of a trial for the onset of the target stimulus, both of which increase overall difficulty and reduce successful performance. Such manipulations are especially useful if the cognitive enhancing effects of a drug are under investigation. Another test of attention that assesses the monkey's ability to focus attention using advanced information is a cued reaction time test. Here, four outlines of circles are presented on a touch sensitive computer screen and similar to that described earlier, the monkey must depress a lever to start the trial and respond to the circle that turns white as quickly as possible. In a cued version, a cue light appears above the circle that will become the next target thereby improving the speed of reaction time to that target. By comparing reaction and movement times in the cued and uncued conditions, a specific measure of selective attention can be obtained (Decamp and Schneider 2004). A variation of this task, first developed by MI Posner and colleagues, tests the abilities of monkeys to shift visuospatial attention and includes trials in which the cue is invalid and the target appears on the side opposite to that of the cue. The difference in the speed of responding to a target at expected (valid) and unexpected (invalid) locations is taken as a measure of ability to shift attention.

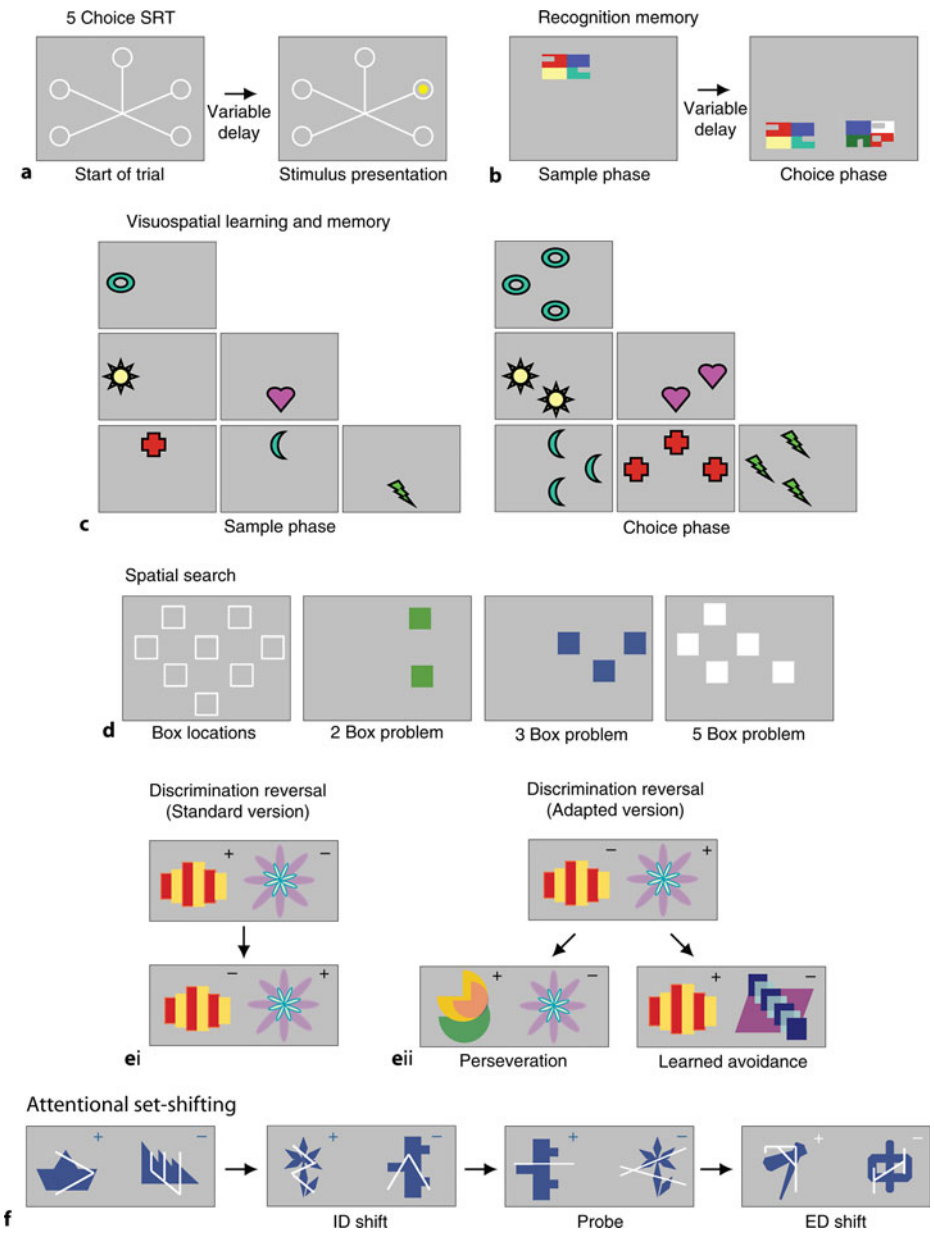
Memory

Recognition Memory

The classic test of recognition memory or the judgment of the prior occurrence of an object involves monkeys being presented with a novel object and then, after a variable delay (e.g., 5 s to 24 h) being presented with two objects, the previously seen object and a novel object. In the ► delayed "match to sample" (DMS) version, monkeys have to select the previously seen object while in the ► delayed "non-match to sample" (DNMS) version monkeys have to choose the novel object. It was first described by M Mishkin and J Delacour in 1975. This test differs from the working memory tasks described in the following text in that each pair of objects is only seen once, or at least only once within a session and therefore tests the ability of monkeys to recognize objects as familiar or not. The presence of delay-dependent deficits is taken to indicate a mnemonic impairment while poor performance at very short delays might indicate, instead, a perceptual deficit. However, to avoid artifacts attributable to the provision of extensive experience at short delays, followed by testing with less familiar long delays, it is important to intermix different delay lengths. For psychopharmacological studies, it is often beneficial to titrate the duration of the delay interval of each monkey to obtain matched levels of performance accuracy. This helps to equate levels of difficulty across monkeys and to avoid ceiling effects in the highest performing monkeys (Buccafusco 2008). More recently, D(N)MS has been run with computer graphic stimuli presented on touch screen monitors (e.g., Fig. 1b) by a number of different research laboratories including those of D Gaffan and EA Murray. In the DMS version, the number of stimuli at the time of choice can be varied, along with the degree to which the different choices differ from one another perceptually. Drug manipulations during sample presentation, choice phase and during the retention interval can target ► encoding, ► retrieval and ► consolidation, respectively. Two distinct processes may underlie recognition memory, recollection, and familiarity judgment. Performance on this test is dependent upon an intact perirhinal cortex.

Visuospatial Memory

A variety of tests have been used to study visuospatial memory, which is the ability to integrate visual and spatial information and to recall that information subsequently. It is dependent on the ► hippocampus and related circuitry. One such test is a scene discriminations task in which, on each trial, an artificially constructed unique "scene" is presented consisting of randomly selected attributes including a colored background containing ellipse segments of different colors, sizes, and orientations and typographical characters (Gaffan and Parker 1996). In the foreground, one of two objects is rewarded. Monkeys learn these discriminations over a series of sessions in which each unique scene is presented once each session. Subsequently it is possible to investigate the ability of monkeys to recall these discriminations, to relearn them as well as to acquire new discriminations and thus, as for recognition memory,



Primate Models of Cognition. Fig. 1. Examples of some of the cognitive tasks used successfully in studies of primate psychopharmacology. **a**. The five choice serial reaction time (SRT) test used in monkey CANTAB. in which on each trial, after a variable delay, monkeys have to detect the brief presentation of a stimulus in one of five spatial locations. **b**. An example of a recognition memory test depicting stimuli similar to those used in monkey CANTAB. See text for details. **c**. A visuospatial learning and memory test also from monkey CANTAB. The stimuli used here are for illustrative purposes and are not the actual stimuli used in monkeys CANTAB. Examples of one, two or three stimulus trial types are illustrated. **d**. A spatial search task in which monkeys have to respond once, and once only to each of a number of spatial locations on the screen (out of a possible eight locations) in order to get reward. An example of 2, 3 and 5 box problems are shown. The different colors help to differentiate the different box problems from one another. **e**i. Example of a discrimination reversal task, as described in the text. Which stimulus is rewarded and which is not is shown by the "+" and "−" signs, respectively. An example of a test to separate out whether a reversal deficit is due to perseveration or learned avoidance is shown in **e**ii. **f**. Examples of a series of discriminations involving an ID shift, probe test, and ED shift, as described in the text.

to investigate encoding and retrieval. An alternative test, known as the paired associate learning test (vsPAL, CANTAB) involves learning to associate different patterns in distinct spatial locations (Fig. 1c). On any one trial (sample phase), one or more patterns may be presented, one at a time, in distinct spatial locations and the monkey must learn which pattern(s) is(are) associated with which spatial location(s). The monkeys are subsequently tested on this knowledge (choice phase) by presenting the pattern in two or more spatial locations and requiring them to respond to the pattern in the correct spatial location (Taffe et al. 2004). Performance on the first attempt of the choice phase is a test of how well monkeys recall the information. However, subsequently monkeys are presented the sample and choice phases, an additional number of times to determine how rapidly they can learn this information. Because on the first attempt, monkeys have to remember multiple information across a short delay, this test loads quite heavily on working memory and is sensitive to frontal lobe dysfunction. This particular test is able to differentiate probands who will subsequently be diagnosed with Alzheimer dementia as opposed to other forms of mnemonic deficit related to normal aging and depression.

Executive Functions

Executive functions can be thought of as general-purpose control mechanisms that coordinate specific cognitive processes in order to optimize performance. They include holding information on-line and updating information in working memory, marshaling attentional resources, monitoring behavior and its outcomes, and inhibiting inappropriate strategies and responses.

Working Memory

► Working memory is a short-term memory system that allows for the active maintenance and manipulation of information that is not present in the outside world. This concept of working memory involves temporary buffers of information and an attentionally constrained central executive. Tests of working memory measure a monkey's ability to remember information for a short period of time when that information is no longer present in the environment. Whether the information is remembered or not is determined by how well their response is guided by this information after a variable delay. The information to be remembered is usually visual, i.e., remembering the spatial location of a stimulus or the form/color of a stimulus, but other sensory modalities can be used. It involves presenting a stimulus to the monkey for a brief period of time (seconds) and then after a variable delay requiring the subject to use that information to guide their subsequent responding. One of the most well-known versions of this test is the spatial working memory test, whereby a monkey either watches food reward being hidden in one of two food wells to the left and right of the animal or alternatively fixates a central cross while a spot of light is briefly flashed (e.g., 100 ms) in one of eight spatial locations in the surround. In both cases, the animal must remember the location of the stimulus for a brief delay, e.g., 1–30 s, and then make a response (arm reach/saccade) to the remembered location at the end of the delay period. In object working memory tests, an object is presented centrally in a WGTA or a visual pattern is presented on a computer screen (sample phase) for a short period of time during which the monkey may have to respond to the stimulus to demonstrate that the stimulus has been seen (Weed et al. 1999). Following a variable delay the same visual stimulus, along with another one is presented to the left and right of the center, and the animal has to choose the object/pattern that matches the sample object/pattern. The smaller the stimulus set used and thus, how frequently the same stimulus is seen across trials, increases the level of interference between trials and increases the load on working memory. By comparing responding following a delay with that at zero delay it is possible to look at the effects of a drug on those processes specifically involved in short term/working memory as compared to other more general perceptual and rule learning processes. In the spatial versions of the test it is important to ensure that the monkey does not use a mediating response to bridge the delay between the stimulus disappearing and the response being made and thus reducing the load on working memory. The addition of distraction during the delay period allows for attentional mechanisms and working memory processes to be assessed within the same session. The distractor can take the form of additional, related stimuli presented during the delay that are irrelevant to the task or alternatively, a burst of loud noise may be presented.

Monitoring Behavior

Self-ordered search tasks. Self-ordered search tasks were originally used in studies of human frontal lobe and were later adapted for studies in monkeys by M Petrides. In these original versions, monkeys were presented with variable numbers of objects (usually three) and across a series of three trials they were presented with the same three objects. Food could be retrieved each trial as long as they selected a different object on each occasion. Thus, the monkey must monitor within working memory its earlier choices in order to avoid returning to objects that have already been selected. Spatial versions require animals to

search through a series of spatial locations in order to find food reward. In those versions of self-ordered tasks in which food is obtained by selecting an object or spatial location for the first time, but not on repeated selections, the task is very similar to a foraging test. Alternative, computerized versions in which stimuli are presented on a touch sensitive computer screen (Fig. 1d) tend not to reward monkeys until they have responded once and once only to a series of spatial locations (Collins et al. 1998). In the latter, monkeys are having to perform sequences of actions in order to gain reward, which may depend upon distinct prefrontal circuitry to those tasks in which the stimuli themselves are associated with reward. Besides monitoring of actions, the spatial search tasks can also be used to assess simple planning ability, especially if the number of boxes/locations is increased, as implementation of a strategy, such as following a clockwise or anticlockwise strategy reduces demands upon working memory.

Cognitive Flexibility

Cognitive flexibility is the ability of animals to adapt their responding to changes in the environment. In the tasks described in the following text, previously rewarded responses or strategies have to be inhibited in favor of the development of new responses and strategies. Different aspects of cognitive flexibility are associated with different regions of ▶ prefrontal cortex, with many neuropsychiatric disorders being associated with cognitive inflexibility.

Discrimination reversal tasks. These typically involve presenting two stimuli to a monkey, usually two visual objects, and the animal learns, through trial and error, that a response to one of the objects leads to food reward while a response to the other does not. Having learnt this discrimination to a particular level of performance, usually around 90% correct over a series of trials, the reward contingencies reverse such that the previously rewarded stimulus is no longer associated with reward but the previously unrewarded stimulus is now associated with reward. How rapidly an animal learns to reverse their responding to match the change in reward contingencies is a measure of how flexible their behavior is. The stimuli can be from any sensory dimension, smell, audition, somatosensation, and vision. Visual discriminations are used most commonly in primate studies as visual cues are particularly salient for primates. The stimuli are either spatial in nature, i.e., left is rewarded, but right is not, or they involve visual features such as shapes or color. A typical discrimination reversal task is shown in Fig. 1ei where an animal may receive a series of reward contingency reversals.

A selective deficit in cognitive flexibility is shown by intact performance on the original discrimination, ruling out perceptual deficits, and an impairment on the subsequent reversal or series of reversals; a deficit seen following damage to the orbitofrontal cortex and ventromedial striatum. A more fine-grained analysis is then required to determine the nature of the underlying reversal deficit. Some useful information can be gleaned from a careful analysis of the errors that are made while performing the reversal. The pattern of errors on a reversal task is very distinctive. First monkeys tend to respond to the previously rewarded stimulus, almost exclusively, known as the perseverative stage. Then, they respond randomly to both stimuli (chance stage) and finally begin to respond more to the previously unrewarded, but now rewarded stimulus (learning stage). By analyzing the numbers and proportions of errors made at these three stages some insight can be gained as to whether animals have problems (1) disengaging their attention and inhibiting their responding to the previously rewarded stimulus (▶ perseveration) or alternatively (2) learning to respond to a stimulus that they had previously learnt was not associated with reward (learned avoidance). If it is the former, animals would make more errors in the perseverative stage, but if it is the latter, then they may make more errors in the chance and/or learning stages. It has been highlighted that in the classic discrimination reversal task, there are only two stimuli to choose from, and thus the only error is a response to the previously rewarded stimulus. A better measure of whether the deficit is truly perseverative in nature may be gained by requiring the animal to perform a three-stimulus visual discrimination reversal task as highlighted by JD Jentsch and JR Taylor. In which case, an error would include, not only a response to the previously rewarded stimulus but also a response to the other, previously unrewarded stimulus. Thus, a more generalized impairment in reversal learning may manifest itself as errors made equally to both of the currently, unrewarded stimuli while a perseverative deficit would still be characterized by errors made primarily to the stimulus that had been previously rewarded. This version can rule out perseverative responding as an underlying cause of a reversal deficit.

However, if perseverative responding is seen, the underlying cause of the perseverative deficit is still unclear. It may still be a consequence of the subject avoiding the two, previously unrewarded stimuli, rather than due to a failure to inhibit responding to the previously rewarded stimulus. To differentiate these two possibilities, the following design can be used. At the reversal stage of the discrimination task, one of two different versions of the discrimination is given. One version includes the previously rewarded stimulus and a novel stimulus and the monkey has to choose the novel stimulus. The other version includes the

previously unrewarded stimulus and a novel stimulus and the monkey has to select the previously unrewarded stimulus (Fig. 1eii). If the perseverative deficit seen in the original, discrimination reversal task is truly perseverative then the monkey should be impaired on the former but not the latter. In contrast, if the deficit is due to the animal actively avoiding the previously unrewarded stimulus, then they should be impaired on the latter and not the former (Clarke et al. 2006).

Object Retrieval test. Another commonly used test of cognitive flexibility that has proven useful in psychopharmacological studies is a test of object retrieval in which monkeys have to make a detour reach around the sides of a clear Perspex box in order to retrieve the food reward inside. Performance on this test is dependent upon the orbitofrontal cortex and the caudate nucleus (and also large lesions of dorsolateral prefrontal cortex including Walker's areas 9,46 and 8). It not only investigates the ability of monkeys to inhibit a prepotent response tendency to reach directly for the food reward but also their ability to switch their responding between the left and right sides of the box, as on some trials the opening is on the left and other trials, on the right (Jentsch et al. 1999).

Attentional set (rule) -shifting tasks. The psychological and neural mechanisms underlying flexible responding to changes in stimulus-reward contingencies are not the same as those required for the flexible use of rules to guide responding. One of the most commonly used tests to study rule switching in humans is the Wisconsin Card Sorting Test (WCST), which requires subjects to sort a pack of cards according to one particular perceptual dimension, e.g., shape, and then to switch to sorting them according to another dimension, e.g., number. A number of different versions of this test have been adapted for use in nonhuman primates, the different versions focussing on different aspects of the original task. In one such version (Roberts et al. 1988), monkeys are presented with a series of visual discriminations composed of bidimensional stimuli using abstract dimensions of "shape" and "line" (Fig. 1f). The monkey has to learn that one particular perceptual dimension is relevant to the task and that an exemplar from that dimension is associated with food reward, i.e., the blue boat, regardless of the white line superimposed over it. Animals then perform a series of such discriminations in which the same dimension remains relevant throughout but each discrimination is composed of novel bidimensional stimuli in which one exemplar from the relevant dimension is associated with food each time (► intradimensional shift, IDS). In the critical set-shifting test (or ► extradimensional shift, EDS) a discrimination is presented in which the previously relevant dimension is no longer relevant and the subject has to learn, through trial and error, that an exemplar from the previously irrelevant dimension is now rewarded. This requires monkeys to shift their ► attentional set from one dimension to another and is similar to the shift of category in the WCST. Impairment at the EDS stage is dependent upon the lateral PFC. The advantage of this test is that it separates out some of the component parts of the WCST, including the ability to develop an attentional set, to apply the rule across different discriminations and then to switch from using one rule to using another. A distractor probe test, in which the exemplars from the irrelevant dimension of a well-learned discrimination are replaced for one session only with novel irrelevant exemplars, can be used to investigate how much an animal is distracted by the irrelevant dimension. This particular task has a major emphasis on learning. In contrast, other primate rule switching tests are more akin to the WCST and require monkeys to learn to select, from a set of three stimuli, the stimulus that matches the sample stimulus according to a particular perceptual dimension (Mansouri et al. 2006). In these tasks, the monkeys receive extensive training on the matching to sample rules before they are able to perform the task successfully. Both these and the previously described discrimination tests require subjects to use feedback in the form of reward to guide their responding at the time of the shift. In contrast, another set of task-switching paradigms focus on the mechanisms underlying task switching per se, and in these cases, cues signal which particular rule is in operation at any one time (Stoet and Synder 2008).

Cross-References

► Behavioral Flexibility
► Rodent Models of Cognition
► Short-Term and Working Memory in Animals
► Spatial Learning in Animals

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Priming

Definition
The facilitation of performance following prior exposure to a stimulus.

Problem Gambling

Definition
Gambling behavior that persists despite negative consequences or a desire to stop gambling. Problem gambling has been used at times inclusive and at other times exclusive of pathological gambling.

Cross-References
► Pathological Gambling

Procedural Memory

Definition
Long-term memory of skills and procedures.

Prochlorperazine

Definition
Prochlorperazine is an antipsychotic that acts as a dopamine D2 receptor antagonist. It is a piperazine-phenothiazine derivative. It has prominent antiemetic and anti-vertigo activity. It is used infrequently as an antipsychotic, but lower doses are used to treat severe nausea, vomiting, vertigo, and labyrinthine disorders.

Cross-References
► Antipsychotic Drugs
► First-Generation Antipsychotics

Procyclidine

Definition
Procyclidine is an anticholinergic drug that blocks M1, M2, and M4 muscarinic receptors. It is used to treat symptoms of ► Parkinson's disease and drug-induced extrapyramidal symptoms such as acute ► dystonia. Signs of toxicity are similar to those of other anticholinergic drugs, including confusion, agitation, hallucination, pupil dilatation, fever, and tachycardia. It is no longer available in the USA.

Cross-References
► Antimuscarinic/Anticholinergic Agent

Product Information

► Summary of Product Characteristics

Progestins

Definition
Progestins are also a class of hormones with progesterone being the primary progestin produced by the ovary. When progesterone is metabolized via the 5a-reductase enzyme, many of the metabolites have anxiolytic actions through their effects at the ► $GABA_A$ receptor.

Programmed Cell Death

► Apoptosis

Progressive-Ratio Schedule

Definition

A ► schedule of reinforcement used in operant conditioning. Laboratory animals or humans are trained to emit an operant response to obtain a reinforcer such as food or drug. Following each reinforcer delivery, the number of responses required to earn the next reinforcer is increased until the animal stops responding for a prolonged period of time. The ratio requirement for the delivery of successive reinforcers increases through a predetermined series. The progression is usually either arithmetic or exponential. The point at which responding ceases is called the "► breakpoint" and commonly serves as the main dependent variable in studies that utilize progressive-ratio schedules. The evaluation of the reinforcing efficacy of abused drugs is one application of these schedules.

Cross-References

► Drug Self-Administration

Prolift

► Reboxetine

Promazine

Definition

Promazine is a first-generation antipsychotic that acts as a dopamine D2 receptor antagonist. It is an aliphatic ► phenothiazine with very low antipsychotic potency. Its primary use is for the treatment of agitation and restlessness in the elderly. Promazine is usually well tolerated, with a low incidence of extrapyramidal symptoms.

Cross-References

► Antipsychotic Drugs
► First-Generation Antipsychotics
► Schizophrenia

Promethazine

Definition

Promethazine is a first-generation antihistamine and antiemetic medication, acting as a histamine H_1 receptor antagonist. It can also have strong sedative effects and in some countries, it is prescribed for insomnia when benzodiazepines are contraindicated. It is a main ingredient of "Purple drank" (a slang term for a recreational drug popular in the hip-hop community of the southern United States), being part of a prescription-strength cough syrup also containing ► codeine.

Cross-References

► Abuse Liability Evaluation
► Driving Under Influence of Drugs
► Insomnia
► Sedative, Hypnotic, and Anxiolytic Dependence

Propofol

Definition

Propofol is a short-acting ► hypnotic used for sedation and general anesthesia. It has also been found useful for terminal sedation in palliative care. It has potential for abuse and dependence.

Propranolol

Definition

Propranolol is an ► anxiolytic acting as a nonselective ► β-adrenergic receptor antagonist. Originally prescribed to treat hypertension and, subsequently, for the prevention and treatment of migraine, the use of propranolol has expanded due to its anxiolytic properties, so as to include treatment of specific forms of acute stress reactions such as performance anxiety. As an anxiolytic, propranolol is usually not administered chronically but only acutely, prior to specific ► panic and anxiety-inducing events. Furthermore, this drug is often prescribed in treating alcohol withdrawal-induced tremors and tachycardia and also in the treatment of antipsychotic-induced movement disorders. In addition to this, recent preclinical studies suggest that it may also hold promise for the treatment of some drug dependencies. The side effects of propranolol are usually mild and transient and include

light-headedness, depression, insomnia, nightmares, disorientation, nausea, decreased heart rate (bradycardia), and hypotension. Withdrawal symptoms after abrupt termination of chronic therapy are usually mild but may include chest pain, increased heart rate (tachycardia), headache and trembling.

Prosaccade Task

Definition

A simple ► eye movement task in which participants make a saccade (typically from a central location) toward a sudden onset target. Important measurements include the saccade latency, peak velocity, amplitude, and duration.

Prospective Daily Ratings

Definition

Prospective daily ratings can consist of a daily diary in which one volunteers symptoms experienced over the course of the day. However, most daily ratings require that the individual rate themselves with respect to the presence and/or severity of specific symptoms each day. That ratings are done each day over a period of time makes them prospective in nature. Completing daily diaries in this manner helps to decrease the bias that can occur with retrospective recall of symptoms. One of the most commonly used prospective daily ratings in PMDD research is the Daily Record of Severity of Problems.

Prospective Memory

Definition

Remembering to do something in the future.

Prostanoids

Definition

A class of endogenous chemicals that includes prostaglandins, which mediate inflammation, the thromboxanes, which mediate vasoconstriction, and the prostacyclins, which are involved in the resolution of inflammation. Cyclooxygenase catalyzes the synthesis of prostaniods.

Protein Array

► Protein Microarray

Protein-Binding Microarray

► Protein Microarray

Protein Kinase Inhibitors

► Kinase Inhibitors

Protein Microarray

Synonyms

Protein array; Protein-binding microarray

Definition

Protein microarray is a multiplex approach to identify protein–protein interactions, to identify the substrates of protein kinases, to identify transcription factor protein-activation, or to identify the targets of biologically active small molecules. The most common protein microarray is the antibody microarray, where antibodies are spotted onto the protein chip and are used as capture molecules to detect proteins from cell lysate solutions.

Cross-References

► Post-Translational Modification

Protein Synthesis and Memory

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Definition

Numerous studies support the prevalent hypothesis that the lasting storage of new information requires a

sequence of tightly intertwined and precisely regulated molecular steps necessary for the initiation of protein synthesis in certain areas of the brain. Thus, the induction of protein synthesis is understood as a key molecular element not only for the ▶ consolidation but also for ▶ extinction, ▶ reconsolidation and persistence of ▶ long-term memory.

Impact of Psychoactive Drugs

Protein Synthesis as a Mechanism of Memory

Protein synthesis is necessary for a variety of functions in diverse systems, including ▶ long-term potentiation and the consolidation, extinction, reconsolidation, and persistence of long-term memory (Abraham and Williams 2008; Alberini 2008; Quirk and Mueller 2008; Tronson and Taylor 2007), (▶ Inhibition of memory), (▶ Declarative and Non-Declarative Memory), (▶ Reference Memory and Consolidation). This assertion relies mainly on findings showing the amnesic effect of protein synthesis inhibitors, including ▶ anisomycin, ▶ cycloheximide, ▶ puromycin and ▶ emetine. The use of most of these antibiotics has been criticized since the finding that some of them produce brain lesions and therefore their amnesic effects can be explained by these rather than by a time-dependent, specific influence on protein synthesis. However, at the doses regularly used in memory experiments, anisomycin appears to be devoid of such effects, and thus has been for the past 30 years the most widely used protein synthesis inhibitor (but see Canal et al. 2007).

By far, the brain structure best studied in terms of the involvement of protein synthesis both in long-term potentiation and in long-term memory consolidation is the ▶ hippocampus, particularly the CA1 area (▶ Long-Term Potentiation and Memory), (▶ Molecular Mechanisms of Learning and Memory). Many studies have been carried out observing similar effects in mammalian septum, ▶ amygdala, and thalamus, as well as in the auditory, ▶ prefrontal, and entorhinal cortices. It is indeed likely that the changes in the expression of proteins related to memory consolidation are, similar to many other neuronal molecular changes, very specific as to brain regions as they are to behavioral tasks. And of course in many tasks more than one brain area is involved in consolidation, and protein synthesis may be required in all of them. This appears to be the case in auditory fear conditioning and in conditioned taste aversion, in which the insular cortex and the central amygdaloid nucleus are involved, and also in one-trial inhibitory avoidance (▶ Classical (Pavlovian) conditioning), (▶ Conditioned place preference and aversion), (▶ Conditioned Taste Aversions), (▶ Passive avoidance), and (▶ Pavlovian fear conditioning). Studies with anisomycin on reconsolidation show that, depending on the task, protein synthesis in the hippocampus or the amygdala is also involved. However, for other learning tasks, such as conditioned taste aversion for example, protein synthesis in the central amygdala is important for consolidation, but not reconsolidation of the task.

The findings on the influence of anisomycin and other protein synthesis inhibitors on hippocampal long-term potentiation and long-term memory consolidation correlate quite well, particularly when examined together with the large number of timed biochemical events and effects that have been measured in the CA1 region in both physiological processes, (▶ Synaptic Plasticity). Indeed, except perhaps by the finding that in the chick brain and in mammalian CA1 there are two peaks of sensitivity to mRNA and protein synthesis inhibitors in memory formation – one shortly after learning and another one about 3 h later – in most types of learning so far analyzed, only the second peak has been unequivocally detected. Importantly, not only the consolidation of brief forms of learning is followed by a series of clear-cut biochemical events in CA1 identical both in nature and in timing to those of long-term potentiation (Izquierdo et al. 2006), but potentiation of the CA3–CA1 synapses has been in fact observed during long-term memory consolidation of both one-trial avoidance and trace eye-blink conditioning, which strongly suggests that consolidation relies on long-term potentiation at least in these tasks.

The effects of protein synthesis inhibitors, particularly anisomycin, on memory are well established. The amount of inhibition needed in order to observe amnesia or lack of memory formation has been determined to be around 85%. The duration of the inhibition needed to cause amnesia has been determined in various tasks and structures, and ranges between 1 and 2–3 h. For a variety of reasons, anisomycin effects on acetylcholinesterase, tyrosine hydroxylase, corticosteroidogenesis, or MAPK activation are unrelated to its amnesic effects.

Some recent findings indicate proteins synthesized via intervention of the mTOR pathway in the consolidation of long-term memory and long-term potentiation. Also, a role in the maintenance of long-term facilitation in the mollusk *Aplysia* has been described for proteins synthesized locally in dendrites (Hawkins et al. 2006). Facilitation in *Aplysia* is quite used as a model of memory formation, and there is evidence that protein synthesis in dendrites may be important for memory formation but not reconsolidation.

Several of the proteins synthesized in the hippocampus 3 h or less after behavioral training have been

identified, and many of them are known to play a major role in memory formation. In fact, at least 33 different genes have been shown to be modulated by one-trial avoidance training; most of them were upregulated.

Traditionally, new memories are associated with the need for ► gene expression and protein synthesis in areas of the brain relevant to each learning. Curiously, from time to time there have been proposals that protein synthesis may not be necessary for memory formation, and that protein synthesis inhibitors cause amnesia for some other reason. Certainly, ► short-term memory (► Short-Term and Working Memory in Animals), (► Short-Term and Working Memory in Humans) lasting a few minutes or hours is not dependent on gene expression or protein synthesis, but no doubt long-term memory certainly is fully dependent on both. Among the recent alternative proposals, there is one suggesting that long-term memory may rely on post-transcriptional changes only, such as indeed short-term memory has been shown to be, or alternatively, that it might depend on an indirect modulatory effect of peripheral or central catecholamines. For a careful analysis and strong refutations of these proposals, see Alberini (2008) and Hernandez and Abel (2008).

Cross-References

► Behavioral Flexibility: Attentional Shifting, Rule Switching, and Response
► Classical (Pavlovian) Conditioning
► Conditioned Place Preference and Aversion
► Conditioned Taste Aversions
► Declarative and Non-Declarative Memory
► Gene Expression and Transcription
► Inhibition of Memory
► Instrumental Conditioning
► Long-Term Potentiation and Memory
► Molecular Mechanisms of Learning and Memory
► Passive Avoidance
► Pavlovian Fear Conditioning
► Reference Memory and Consolidation
► Short-Term and Working Memory in Animals
► Short-Term and Working Memory in Humans
► Synaptic Plasticity

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Protein Tau

Definition

A normally soluble microtubule-binding protein that when hyperphosphorylated loses solubility altering the neuronal cytoskeletal through the formation abnormal intracellular filamentous inclusions, main component of neurofibrillary tangles which is one of the histopathological findings associated with ► Alzheimer's disease.

Proteomics

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Synonyms

Studies on proteins expressed by the genetic material of an organism

Definition

The proteome is the genome complement of proteins, and proteomics is the study of proteomes in a cell at any given time. Neuroproteomics defines the entire protein complement of the nervous system. It represents a higher complexity than the transcriptome, and it displays a higher degree of dynamics due to ► posttranslational

modifications (► PTMs). Two main approaches of this field are profiling and functional proteomics. Profiling proteomics includes the description of the whole proteome of a cell, tissue, organ or organism and comprises organelle mapping and differential measurement of expression levels between cells or conditions. Functional proteomics aims to characterize protein activity, by determining protein interactions and the presence of PTMs.

Current Concepts and State of Knowledge

The analysis of proteomes is significantly more challenging than that of genomes. Measuring ► gene expression at the protein level is potentially more informative than the corresponding measurement at the mRNA level. Though certain RNAs are known to function as effector molecules, proteins are the major actors and catalysts of biological function. Proteins contain several dimensions of information, which represent the actual rather than the potential functional state as indicated by mRNA analysis. These dimensions include the abundance, state of PTM, (sub) cellular localization and association and interaction with each other. PTMs of a protein can determine its activity state, localization, turnover, and interactions with other proteins. More than 300 different types of PTMs are currently known. Changes in gene expression at the level of the message, mRNA expression, may not directly correlate with protein expression since mRNA is not the functional endpoint of gene expression. Recent investigations show that differences in protein concentrations are only 20–40% assigned to variable mRNA levels, emphasizing the importance of posttranscriptional regulation. In general, protein concentrations depend on the translation rate and the degradation rate, i.e., the protein turnover. In addition to the complexity at the transcriptional level, proteome approaches have to deal with the considerable increase in isoforms due to multiple PTMs (Tyers and Mann 2003).

Proteomics Methodologies

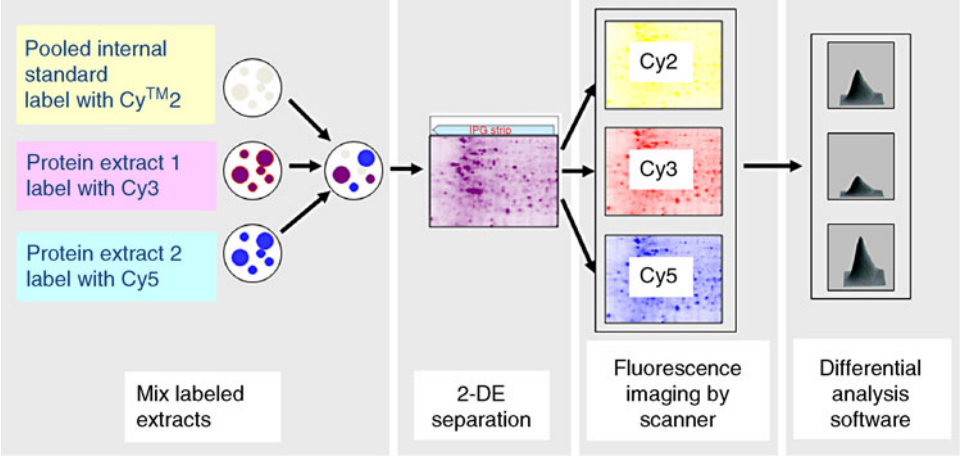
Proteomics technologies (both expression profiling and functional approaches) have widely expanded in recent years. Because of protein diversity, a range of techniques have emerged, which depend on integration of biological, chemical and analytical methods. The main proteomic technologies of today utilize ► mass spectrometry (MS) coupled with global protein separations (Aebersold and Mann 2003) and methods based on protein arrays (Phizicky et al. 2003). The global protein separation methods are conventionally divided into gel-based and gel-free, where the gel-free are all MS based. The protein arrays are not global in the sense that they typically depend on the availability of antibodies. The methodologies are complementary and are increasingly used in combination with each other. Even though their analytical windows overlap, each of them covers selected sets of proteins that are not identified by the other techniques (Choudhary and Grant 2004).

► Two-dimensional gel electrophoresis. The global protein separation method two-dimensional gel electrophoresis (2-DE) enables the possibility to resolve several thousand proteins in a single sample. 2-DE mainly produces data which allow the investigator to determine whether a particular protein shows an increase or decrease when comparing two different conditions. The limited dynamic range and poor reproducibility between gels have been of major concern with traditional 2-DE experiments (Westermeier et al. 2008).

In a typical gel-based proteomics experiment the proteins in a sample are separated by 2-DE, stained, and each observed protein spot is quantified by its staining intensity. Selected spots are excised, and analyzed by MS after "digestion" (see below). Pattern-matching algorithms as well as interpretation by skilled researchers are required to relate the 2-DE patterns to each other in order to detect characteristic patterns and differences among samples. The major limitation of 2-DE techniques is a relatively low throughput particularly in cases where many proteins have to be identified with subsequent MS analysis which is very time-consuming (Westermeier et al. 2008).

Detecting changes in protein expression is improved by the introduction of fluorescence difference gel electrophoresis (DIGE). 2-D-DIGE enables the pre-labeling and separation of up to three samples on a single 2-D gel providing quantitation of proteins. Up to three protein samples are labeled with size- and charge-matched CyDye DIGE fluorochromes and co-separated on the same 2-D electrophoresis gel. Gels using the 2-D-DIGE method usually contain three samples labeled with three distinct fluorescent dyes, Cy2, Cy3 and Cy5. The Cy2 dye is typically used to label an internal standard, which is a mix of all samples in the experiment, and the other two dyes are then employed to label two biological samples of interest. The strength of the internal standard is to help the mapping of spots/proteins between gels and thus make the different gels more comparable. The internal standard is also used in some methods for normalization within and between gels (Westermeier et al. 2008) (Fig. 1).

Mass spectrometry-based proteomics. The coupling of chromatographic separation methods with MS is commonly utilized for qualitative and quantitative characterization of highly complex protein mixtures. The advances in chemical tagging and isotope labeling techniques have



Proteomics. Fig. 1. Workflow for a standard 2-D difference gel electrophoresis (DIGE) experiment. Samples are labeled with molecular weight and charge matched CyDye DIGE Fluors, minimal dyes. This permits multiplexing of up to two samples and a pooled internal standard on the same first and second dimension gel. Gels are scanned on an imager and processed using analysis software.

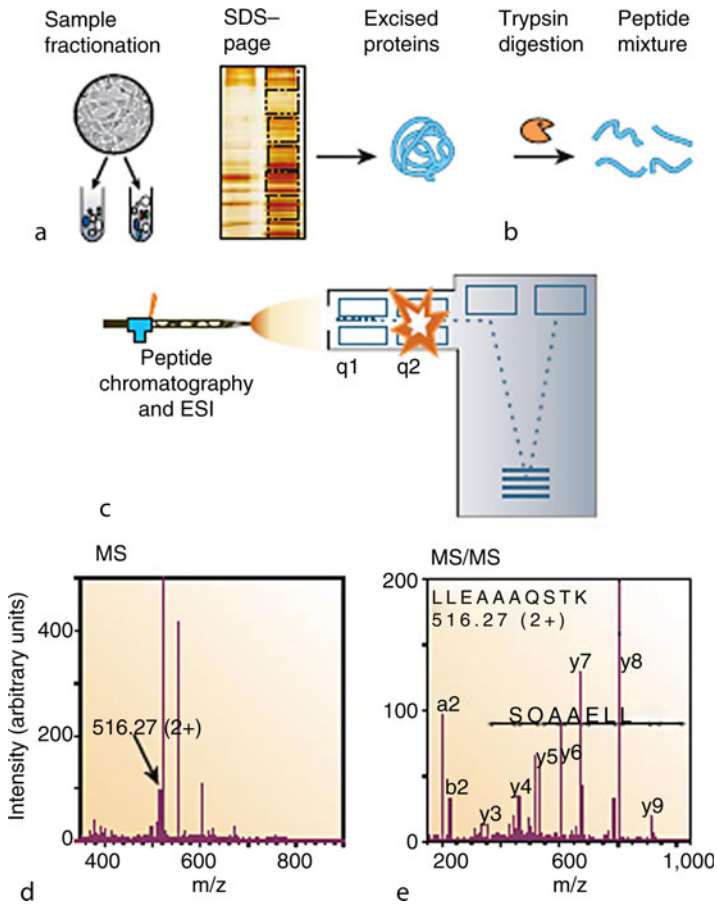
improved the quantitative analysis of proteomes. ► High performance liquid chromatography (► HPLC) methods provide powerful tools of protein and peptide separation of protein mixtures. Primary advantages of liquid chromatographic (LC) separation are the flexibility of the methods and the possibility to link LC directly to MS. Proteins and peptides can be separated based on their physical properties, including affinity, charge (ion exchange), hydrophobicity (reversed phase), and size (size exclusion) (Aebersold and Mann 2003).

Presently two ionization techniques, ► electrospray ionization (► ESI) and ► matrix-assisted laser desorption ionization (► MALDI) are playing a significant role in the field of MS-based proteome analysis. ESI ionizes the analytes out of a solution and is therefore readily coupled to chromatographic and electrophoretic separation tools. MALDI sublimates and ionizes the samples out of a dry, crystalline matrix via laser pulses. There are four basic types of mass analyzers currently used in proteomics research. These are the ion-trap, time-of-flight (TOF), quadrupole, and Fourier transform ion cyclotron (FT-MS) analyzers. These analyzers can be stand alone or, in some cases, put together in tandem to take advantage of the strengths of each (Aebersold and Mann 2003).

There are two complementary approaches for the MS analysis of proteins (Aebersold and Mann 2003). The bottom-up method is generally used for identifying proteins and determining details of their sequence and PTMs. Proteins of interest are digested with a sequence specific enzyme such as trypsin, and the resulting tryptic peptides are analyzed by ESI or MALDI, which allow intact peptide molecular ions to be put into the gas phase. The MS analysis takes place in two steps. The masses of the tryptic peptides are determined; next, these peptide ions are fragmented in the gas phase. The masses of the peptide fragments yield information on their sequence and modifications. Prior to being introduced to the MS the tryptic peptides usually are separated on reversed phase LC directly coupled to the ESI source (Fig. 2). For quantitative analysis of proteins by MS stable-isotope labeling of proteins can be used. These methods utilize either metabolic labeling, tagging by chemical reaction, or stable-isotope incorporation via enzyme reaction of proteins or peptides (Aebersold and Mann 2003). Labeled proteins or peptides are combined, separated and analyzed by MS and/or tandem MS for identifying the proteins and determining their relative abundance.

In the top-down approach, intact protein ions are introduced into the gas phase and are then fragmented in the mass spectrometer. If enough numbers of informative fragment ions are observed, the analysis can provide a complete description of the primary structure of the protein and reveal all of its modifications. Until recently, it has proved difficult to produce extensive gas-phase fragmentation of intact large protein ions, but novel techniques such as electron transfer dissociation promise to drastically improve this situation.

► Neuropeptidomics. The core proteomics tools, including 2-DE in combination with MS, are limited to the analysis of proteins >10 kDa. Other technologies are



Proteomics. Fig. 2. Typical MS-based proteomics experiment. The general proteomics experiment consists of five stages. (**a**) the proteins to be analyzed are isolated from cell lysate or tissues by biochemical fractionation (such as SDS polyacrylamide gel electrophoresis (PAGE) or multidimensional LC) for reduction of the sample complexity or affinity selection (for enrichment of a sub-proteome), (**b**) the proteins are degraded enzymatically to peptides, usually by trypsin, (**c**) the peptides are separated by one or more steps of high performance liquid chromatography (HPLC) in very fine capillaries and eluted into an electrospray ionization (ESI) ion source, (**d**) after evaporation, multiply protonated peptides enter the mass spectrometer and a mass spectrum of the peptides eluting at this time point is taken, (**e**) the computer generates a prioritized list of these peptides for fragmentation and a series of tandem mass spectrometric (MS/MS) experiments follows. The outcome of the experiment is the identity of the peptides and therefore the proteins making up the purified protein population (modified from Aebersold and Mann 2003).

therefore necessary to identify small endogenous proteins and peptides such as present in brain samples. Neuropeptidomics is the technological approach for detailed analyses of endogenous peptides from the nervous system/brain. It is a relatively new direction in proteomics research that covers the gap between proteomics and ► metabolomics and overlaps with both areas. Peptidomics methodologies are generally based on separating complex endogenous peptide mixtures by multistep LC approaches, usually nL/min flow capillary reversed-phase LC (nanoLC), or gel- or liquid-based isoelectric focusing combined with MS for sequence analysis. The levels of peptides in the brain reflect certain information about physiological status; this information can be revealed when MS is used to generate broad profiles of the dynamic neuropeptide patterns (Svensson et al. 2007).

MALDI ► imaging mass spectrometry. MALDI mass spectrometric tissue imaging (► MALDI-IMS) of peptides and proteins in the brain is performed in thin (10–20 µm) tissue sections *in situ* (Stoeckli et al. 2001). The sections are typically coated with a raster of matrix droplets before an ordered array of mass spectra is

acquired from each matrix spot. This way each spectrum reflects the local molecular composition at known *x*, *y* coordinates. Image profiles of selected peptides and proteins in the section are generated by extracting their corresponding mass-to-charge (m/z) ranges from the spatially acquired MS data files. The approach yields information on the spatial localization of the peptides and proteins in the tissue analyzed, without the requirement of extensive sample manipulation. Applications of MALDI-IMS range from low-resolution peptide and protein profile images of selected areas in e.g., mouse brain to single neural cell peptide profiling analyzes and high-resolution imaging of proteins and drugs.

► Protein microarrays. Protein and peptide microarrays involve the spotting of proteins (including antibodies or other affinity reagents directed against defined proteins) and peptides at high density on surfaces such as glass slides and can be used for both profiling and functional proteomics. Antibody microarrays hold potential for high-throughput protein profiling. A complex mixture, such as a brain cell lysate, is passed over the microarray surface to allow the antigens present to bind to their cognate antibodies or targeted reagents. The bound antigen is detected either by using lysates containing fluorescently tagged or radioactively labeled proteins, or by using a secondary antibody against each antigen of interest. Functional protein arrays allows for testing of activities and interactions with lipids, nucleic acids and small molecules as well as other proteins (Phizicky et al. 2003).

Understanding the Brain Molecular Organization and Complexity

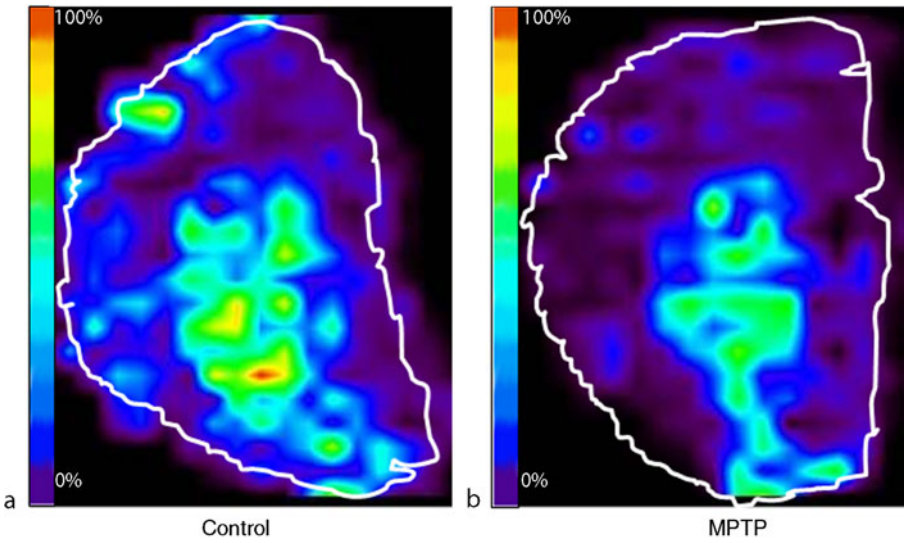
There are a variety of applications for proteomic technology in psychopharmacology and neuroscience. These range from defining the proteome of a particular cell type, identifying changes in brain protein expression under different experimental (including pathological) conditions, profiling protein modifications and mapping protein-protein interactions. All of them have their strengths and limitations and a major challenge is to determine the most appropriate proteomic technology to the system studied. Large-scale proteomic analysis can help unravel the complexities of brain function as many of the activities of the brain involve intricate signaling networks and changes in PTMs (Choudhary and Grant 2004). Clinical research aims to benefit from proteomics by both the identification of new drug targets and the development of new diagnostic markers.

Proteome global mapping. Detailed analysis of the mouse brain proteome has established 2-DE protein indices of thousands of proteins, with MS annotations of ~500. Proteins from all functional classes have been identified by such analyses. However, membrane proteins are typically underrepresented in 2-DE due to poor solubility in the initial isoelectric focusing step of the method, which requires relatively large amounts of starting material. Another approach using multidimensional LC coupled to ESI MS/MS does not have this bias against membrane proteins and identified close to 5,000 proteins from 1.8 mg of rat brain homogenate with an average of 25% protein sequence coverage. The proteins identified included membrane proteins, such as neurotransmitter receptors and ion channels implicated in important physiological functions and disease.

Neuropeptidomics has been used to profile a large number of neuropeptides from the brain and the central nervous system. Strategies that reduce complexity and increase the dynamic range of endogenous peptide detection, particularly fractionation methods and separations based on the peptides' chemical and physical properties and bioinformatics approaches, have resulted in the discovery and chemical characterization of novel endogenous peptides. Some of these, such as peptides originated from the secretogranin-1, ► somatostatin, prodynorphin (► endogenous opioids), and ► cholecystokinin precursors appear differentially expressed in the ► striatum with and without 3,4-dihydroxy-L-phenylalanine (► l-Dopa) administration in 6-hydroxydopamine (► 6-OHDA) ► animal models for ► Parkinson's disease (Nilsson et al. 2009).

The MALDI IMS technique has been applied to animal models of ► neurodegenerative (► neurodegeneration) disorders to investigate peptide and protein expression, particularly to compare patterns in pre- and post-lesions using 6-OHDA and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (Fig. 3). In these affected brains, the IMS molecular tool identified changes in complex protein patterns and identified specific proteins involved in specific brain regions (Svensson et al. 2007). IMS has also been utilized to reveal the regional distribution of psychopharmacology agents in the brain such as ► clozapine (► atypical antipsychotic drugs). IMS images revealing the spatial localization in rat brain tissue sections following administration of ► clozapine were found to be in good correlation with those using an autoradiographic approach. The results are encouraging for the potential applicability of this technique for the direct analysis of drug candidates in intact tissue slices (Cornett et al. 2007).

The utility of *functional proteomics* has been recently exploited to elucidate cellular mechanisms in the brain, of particular importance in the area of signal transduction. Reversible phosphorylation of proteins is the most widely



Proteomics. Fig. 3. IMS analysis of brain tissue sections after 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) treatment. The relative ion density of PEP-19 from one control (**a**) and one MPTP-treated animal (**b**) shows that there is a reduction of PEP-19 expression in the striatum. Typically, in this experiment, about 400 distinct mass signals were detected in the mass range of 2–30 kDa (modified from Svensson et al. 2007).

studied type of signal transduction. Recent synapse phosphoproteomics studies analyzing phosphorylation sites of proteins identified 974 sites in mouse synaptosomes and 1,563 in postsynaptic densities isolated from mouse cortex, midbrain, cerebellum and hippocampus. Phosphoproteomics has identified phosphorylation sites that are altered in Alzheimer's disease, particularly in the microtubule-associated ▶ protein Tau (Bayes and Grant 2009).

Characterization of protein complexes provided information about molecular organization as well as cellular pathways. A multi-bait yeast two hybrid screen of proteins relevant to ▶ Huntington's disease, found 186 protein-protein interactions, of which 165 had not been previously described and which might be relevant to the pathology of Huntington's disease (Bayes and Grant 2009).

Advantages and Limitations in Neuroproteomics

While many of the proteomics approaches have focused on determining the proteins or peptides present in the cell and their relative expression levels, the specific aim of proteomics would be to simultaneously identify, quantify and analyze a large number of proteins within their functional context. The shift in focus from a proteomics discovery mode to a functional approach creates challenges that are at present unmet in all aspects of the proteomic experiment, including the experimental design, data analysis, storage, and publication of data. (Choudhary and Grant 2004).

Sample preparation is a major source of variation in the outcome of proteomic experiments. After tissue or body fluid sampling, proteases and other protein-modifying enzymes can rapidly change composition of the proteome. As a direct consequence, analytical results will reflect a mix of *in vivo* proteome and *ex vivo* degradation products. Vital information about the pre-sampling state may be destroyed or distorted, leading to variation between samples and incorrect conclusions. Sample stabilization and standardization of sample handling are imperative to reduce or eliminate this problem. A recently introduced tissue stabilization system which utilizes a combination of heat and pressure under vacuum has been used to stop degradation in brain and loss of PTMs (e.g., phosphorylations) tissue immediately after sampling (Soloview et al. 2008; Svensson et al. 2007). This methodology provides an improvement to proteomics by greatly reducing the complexity and dynamic range of the proteome in tissue samples and enables enhanced possibilities for discovery and analysis of clinically relevant protein and peptide biomarkers. Rapid removal of neuronal tissue, dissection, and freezing are obvious important procedures for the maintenance of the proteome state in the animal. Human *post mortem* studies present problematical challenges in neuroproteomics, where careful documentation of *post mortem* time interval, brain pH, and agonal state is of greatest importance (Soloview et al. 2008).

Proteomic studies by definition result in large amounts of data. The analysis as well as interpretation of the enormous volumes of proteomic data to effectively use their content remains an unsolved challenge, particularly for

MS-based proteomics. The development of tools for the integration of different experimental approaches enabling analyses of such proteomic data sets using statistical principles is an important task for the future (Aebersold and Mann 2003).

MS-based peptidomics technologies in combination with sophisticated bioinformatics tools have great potential for the discovery of novel biologically relevant neuropeptides. It is likely that a considerable number of ▶ neuropeptides are still to be discovered. The human genome contains ~550 genes belonging to the G protein-coupled receptor class of proteins. For 25% of these the natural endogenous ligands remain elusive until today, and novel neuropeptides are very plausible candidates. Improved peptidomics approaches and technologies may therefore identify novel biologically important neuropeptides (Svensson et al. 2007).

MALDI-IMS has become an important tool for assessing the spatial distribution of molecular species in brain tissue sections and for the elucidation of molecular signatures indicative of disease progression and drug treatment. The technique allows simultaneous measurements of hundreds of different molecules in tissue specimens without disrupting the integrity of samples. It can trace the distribution of pharmaceuticals and their various metabolites in the brains of dosed animals and can be successfully applied to monitor the changes in the proteome organization upon drug application. Functional information obtained in MALDI-IMS studies can be correlated with proteomic profiles and routine immunohistochemical staining, thereby providing an in-depth comprehension of molecular mechanisms underlying health and disease (Cornett et al. 2007; Stoeckli et al. 2001).

A catalog of the complete neuroproteome will propose new directions to understand brain function. Differential proteomics permits correlations to be drawn between the range of proteins produced by a cell or tissue and the initiation or progression of a disease state. It permits the discovery of new protein markers for diagnostic purposes and the study of novel molecular targets for brain drug discovery. The markers identified may have a wide range of potential applications, such as clinical diagnostic and prognostic tools. Proteomic information has superior functional value and can generate knowledge of cellular protein networks. Proteomics technologies are progressing fast and their increasing usage as a functional high-throughput approach is adding to vital biological findings in areas not accessible to genomics studies.

Cross-References

▶ Electrospray Ionization (ESI)
▶ Imaging Mass Spectrometry (IMS)
▶ Mass Spectrometry (MS)
▶ Matrix-assisted Laser Desorption Ionization (MALDI)
▶ Metabolomics
▶ Neuropeptidomics
▶ Posttranslational Modification
▶ Protein Microarrays
▶ Two-dimensional Gel Electrophoresis

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Prozac

▶ Fluoxetine

Pseudo-Hallucination

Definition

A subject experiencing "pseudo-hallucinations" retains the capacity to recognize that these "novel" experiences are transient and drug induced, as opposed to true hallucinations in which no such discernment is possible.

Pseudo-Parkinsonism

► Akinesia

Pseudopregnant

Definition

A hormonal state similar to pregnancy that is induced in mice by mating a female with a vasectomized male. In this state, the uterus is receptive to an implanted embryo.

Cross-References

► Genetically Modified Animals

Psychedelics

► Hallucinogens
► Hallucinogen Abuse and Dependence
► Ritual Uses of Psychoactive Drugs

Psychiatric Disorder

► Neuropsychiatric Disorders

Psychoactive Drug

Definition

A chemical substance that acts primarily upon the central nervous system where it alters brain function, resulting in temporary changes in perception, mood, consciousness, or behavior.

Cross-References

► Sex Differences in Drug Effects

Psychometric Function

Definition

The mapping between an independent variable under experimental control, such as stimulation strength or cost, and a measure of behavioral output, such as response rate or time allocation.

Psychometric Tests

Definition

Tests or apparatus that measure and quantify physical dimensions (e.g., time taken, number, rate, accuracy, speed) of information processing by sensory, cognitive, and motor systems.

Psychomotor Function

► Psychomotor Performance in Humans

Psychomotor Performance in Humans

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Synonyms

Psychomotor function; Skilled performance

Definition

Humans have an innate capacity to react to environmental stimulation which, by way of learning and experience, develops into a range of coordinated motor behaviors that are appropriate responses to the sensory information perceived by an individual. These motor behaviors range in complexity from the instantaneous reflex reactions that follow the accidental grasping of a hot poker, through simple ► sensori-motor behaviors such as poking a fire, climbing stairs, steering a car, to the skilled psychomotor functions necessary to climb a rickety staircase at night or drive a car in heavy motorway traffic during a rainstorm. Such highly complex motor behaviors, i.e., psychomotor performance, result from the ► cognitive processing of sensory and perceptual information.

The sense organs receive and convey information to the brain but rarely, except in the case of reflex reactions and simple sensori-motor behaviors, are such data transmitted without interpretation by the cognitive system. The perception, i.e., interpretation, of environmental events and circumstances allows sensory information to be

manipulated within the cognitive system and decisions made regarding the appropriate motor response(s) necessary for an immediate adaptive motor reaction. An individual will select from the array of stimuli available and choose to place more reliance on some cues and ignore others in accordance with prior learning, previous experiences, prejudices, and established habits. Such over/under-emphasis of some stimuli augments inter-individual differences in overall psychomotor performance due to the individual's concurrent needs, motivations, and expectations. Perception is dependent on maintaining an appropriate level of ► attention and remaining vigilant. The extent to which an individual is able to divide or shift attention between two or more relevant stimuli is an important variable in determining the overall capacity for psychomotor performance.

The motor component of psychomotor performance becomes more coordinated with sensory input because of learning and practice. Basic sensori-motor skills (e.g., steering a car) are quite robust and resistant to environmental influences but any faulty cognitive judgment or decision can cause a major impairment of psychomotor performance (e.g., car driving) if "unrealistic" demands are made on motor reactions.

It is the speed, reliability and validity of the processing of environmental information, particularly where the circumstances are complex or rapidly changing, which determine the appropriateness and precision of psychomotor performance. Any alteration in the reliability or validity of perceptual input will increase the possibility of errors in cognitive processing which, in turn, will be reflected as an impairment of overall psychomotor performance. However, if the cognitive system itself is directly affected by trauma, disease or the administration of a psychoactive drug, then the processing of perceptions will be similarly influenced and the associated motor reactions will necessarily change. Such changes in the integrity of the coordination between sensory and motor functions will lead to an impairment of psychomotor performance together with a subsequent loss of competence and increased risk of accident when undertaking the activities of everyday living in the home, at work, and on the road ► driving and flying under influence of drugs

It is virtually impossible, within the context of everyday scenarios, to measure psychomotor performance reliably: there are too many uncontrolled influences and variables and inter- and intra-individual differences are too great. The measurement of psychomotor performance requires an instrument where the relevant stimulus is readily perceived and its inherent information processed in a straightforward manner, without the necessity of having to rely on learning, previous experience, or the adoption of particular viewing strategies. The cognitive processing requirements have to be easy to understand and the motor responses undemanding and uncomplicated. Overall, psychomotor performance is dependent on vigilance, attention and the speed, accuracy and coordination of sensori-motor behavior, and, most importantly, the speed, capacity, and flexibility of the cognitive system. The basic elements (sensory, cognitive, and motor) can be measured using the standardized application of ► psychometric tests within a controlled environment to minimize the effects of the numerous extraneous influences both on the individual and on the test performance.

Psychopharmacologists are primarily interested in the behavioral effects of drugs but it is a basic assumption of human psychopharmacology that the effects of a particular psychoactive drug will be manifest by the changes it produces in psychomotor performance, as measured by psychometric tests. The major task of a human psychopharmacologist is not only to devise valid and reliable psychometrics by which such characteristic drug-induced changes can be measured but also to develop appropriate methodologies to control the studies by which the effects of drugs are to be assessed.

The successful assessment of the effects of drugs by way of the changes produced in psychomotor performance can only by done with studies in which the intrinsic and extrinsic sources of variability in psychomotor performance are controlled.

Inter-Individual Variability

A major variable in determining the effect of a drug on psychomotor performance is the psychological state of the individual at the time of testing. Most pharmacodynamic studies of drugs are performed in healthy, psychologically "normal" volunteers. This certainly does not preclude the use of psychometric tests in patient populations but study design issues will be different. As it is not possible to obtain psychologically identical individuals with comparable levels of psychomotor ability, the underlying inter-subject variability must be reduced by controlling it via the use of a crossover-design where each subject acts as their own control and receives each and every treatment in a random order. A parallel group design, where individuals are randomly allocated to receive only one of the treatment conditions, is much less suitable to control individual differences, even when large group numbers are used and subjects are screened and pre-assigned to treatments to ensure similar mean psychometric test scores across treatment groups. Pre-assignment does nothing to reduce the magnitude or speed of individual

reactions to a particular drug. Individual differences can also be reduced by using a neuropsychological test to screen out potential subjects with a pre-existing abnormal or reduced cognitive function (e.g., Mini-Mental State Examination, ►Wisconsin Card Sorting Test; Wechsler Adult Intelligence Test, especially the sub-scales for block design and picture completion). Neuropsychological test results indicate an individual's degree of abnormality in comparison with normative values from large-scale databases. They are not, in themselves, reliable in the test–retest protocols necessary for studying the pharmacodynamic effects of a drug on psychomotor performance. However, a similar pre-screening of experimental subjects' levels of neuroticism and extraversion/introversion (e.g., Eysenck Personality Inventory) can help reduce the influence inter-subject personality differences have on psychometric test performance. The established effects of age and sex, etc., on psychomotor performance can be simply controlled by pre-selecting and stratifying groups of subjects.

Treatment Variables

All treatments must be identical and matching with no discernible difference in color, size, shape or taste and they must be administered ►double-blind where neither the subject nor the person collecting the psychometric test scores are aware of the order in which the treatments are given. The subjective experiences of taking a substance believed to be a "drug" – even when it is actually pharmacologically inert – change psychometric test scores in susceptible subjects. These effects are controlled by the use of a ►placebo effect condition, which is regarded as another drug and included in the randomization and allocation of treatments. The psychometric test scores following active drug treatments can then be compared to those obtained following treatment with the placebo condition to indicate the psychoactive effects of the drug itself. A placebo control is an essential feature of all psychometric assessment of drug effects. Changes in psychomotor performance observed with active drugs are valid only if seen to be significantly (from the application of appropriate statistical analysis, probability levels, confidence intervals, etc.) different with respect to the results obtained with a matching placebo.

Testing Variables

Not all psychometric tests have an established sensitivity for the detection of changes produced by psychoactive drugs and an individual test will not always detect the particular effects of a specific drug. As well as reinforcing the need to use a psychometric test battery assessing a range of psychomotor activities, such considerations clearly show the need to demonstrate the sensitivity of a particular test battery to drug induced change for a specific, especially unknown, drug. This is done by the use of a ►verum (positive internal control), a drug with well-understood and robust effects on the psychometric tests to be used. It is usual for the positive controls to belong to the same pharmacological or therapeutic class as the drug under investigation although they are often used at supra-therapeutic doses to ensure that performance is reliably changed. The verum is used only to demonstrate the sensitivity of the psychometric battery and the results obtained with it must not be included in comparisons with active treatments to demonstrate the latter's improved side-effect profiles, etc. Most positive internal controls (e.g., lorazepam, alprazolam, zolpidem, amitriptyline, promethazine, mirtazepine, etc.) are used because they are known to lengthen reaction time, impair working memory and thinking, disrupt sensori-motor coordination and cause an overall impairment of psychomotor performance. However, the use of ►psychostimulants (e.g., amphetamine, methylphenidate) as positive internal controls will indicate the extent to which a test battery is able to detect changes in psychomotor performance due to CNS activation. Unpredictable variation in psychometric test scores can occur with repeated testing if there are auditory/visual distractions present during testing or if noticeable changes in ambient temperature or lighting occur. Psychometric testing must be conducted in a stable environment that remains constant both during each test period and between each occasion testing is conducted. As some external events are unpredictable, e.g., power failures, thunderstorms, etc., the sequence of administration of treatments should be balanced across the various days when testing takes place in accordance with a ►Latin Square design to ensure that any random effects of extraneous variables on psychometric test scores will be spread equally across all treatment conditions.

Psychometric Tests

Below is a list of some of the psychometric tests that have been used in published studies of the effects of psychoactive drugs: there are many more (Baselt 2001; Hindmarch 2004). The three part division of the tests does not imply a rigid classification, but shows that although some psychometric tests might emphasize individual sensory, cognitive, or motor functions, it is overall psychomotor performance – the integration of sensory and motor systems via the cognitive processing of information – which is measured (Table 1).

Psychomotor Performance in Humans. Table 1. Psychometric Tests Used to Measure the Effects of Drugs.

Psychometric Tests Used to Measure the Effects of Drugs		
Sensory Ability	**Attention and Cognition**	**Motor Ability**
pursuit rotor; Gibson Spiral Maze; dynamic visual acuity; angle perception; Maddox-Wing test; auditory discrimination; letter cancelation; simple reaction speed (visual, auditory).	critical flicker fusion frequency; two-flash threshold; rapid visual information processing; memory tests with immediate and/or delayed recall for short-term (Sternberg test), executive, recognition (pictures, words, faces, numbers, prose, semantic categories, nonsense syllables, music) and spatial (Corsi blocks) abilities; syntactic/logical reasoning (Tower of London); learning (Rey's test, paired associates); CDR test systems; vigilance (continuous performance, Pauli test, auditory vigilance, divided attention tasks, Dinges' psychomotor vigilance test, Erikson and Erikson's response competition test); mental arithmetic; time estimation; Stroop test; verbal fluency; free word association; on-the-road car driving (brake reaction time); digit-symbol-letter-manipulation (copying, substitution, matching, differentiation); mental arithmetic (serial subtraction of numbers, simple mathematics with or without auditory interference).	peg board; card dealing; trail making; on-the-road car steering (standard deviation of lateral position); body balance; finger tapping; compensatory, continuous or adaptive tracking; wrist actigraphy.

Although the effects of a particular drug on psychomotor performance can be assessed by an individual psychometric test, it is usual to employ a test battery (group of tests each reflecting a different aspect of psychomotor performance) particularly when a new substance with unknown or supposed psychoactive effects is to be investigated.

There is no consensus as to which tests are the most suitable for combination and inclusion in a psychomotor performance test battery. Some researchers place emphasis on the sensitivities and robustness of a particular test that other authors may find less reliable. The choice of tests may be influenced by the level of existing information regarding the known, or expected, effects of the drug(s) to be assessed.

It is most usual to regard impaired psychomotor performance as a necessary consequence of the administration of a sedative drug but psychostimulants, by causing over-activation of the sensory input of information, can also impair psychomotor performance.

Typically, a psychomotor test battery will involve assessments of sensori-motor coordination, vigilance, and/or ► divided attention, complex reaction time, executive or short-term memory and mental ability (arithmetic, logical reasoning). The exact composition of any test battery is not crucial but the proven sensitivity of the component tests to the psychoactive effects of drugs is a prerequisite for the inclusion of a particular individual test.

Psychophysiological measures, e.g., saccadic eye movements, sleep ► polysomnography (including the multiple sleep-wakefulness test and the maintained- wakefulness test) and continuous 24-h ► electroencephalography; can provide objective measures of the effects of drugs on sleep and daytime arousal. There is no doubt that lowering of arousal , as revealed by these psychophysiological assessments, will directly impair psychomotor performance. However, psychophysiological assessments are not, in themselves, tests of psychomotor performance. Similarly, subjective ratings of sleepiness e.g., Stanford Sleepiness Scale, visual analog rating scales, Epworth Sleepiness Scale and especially the Leeds Sleep Evaluation Questionnaire (Parrott and Hindmarch 2008), which was specifically developed to measure the changes in the subjective ratings of sleep and early morning performance following the administration of psychoactive drugs, will not automatically indicate the psychomotor effects of a drug but such subjective data can provide valuable information regarding the total impact of a psychoactive drug in clinical use.

Current Concepts and State of Knowledge

Psychometric tests have to be parsimonious in the demands they make on sensory, cognitive and motor systems if they are to be reliable measures of psychomotor performance suitable for use in a wide population of individuals of different ages, personality traits, skill levels and intellectual abilities. The increased availability of computer programs to present, control and collect results from psychometric tests has led to the automation of many psychometric test batteries. Such accurate and consistent presentation of the stimulus component of a psychometric test and the error free recording of results are efficient ways of ensuring the reliability of a test battery. However, the programming of computerised test batteries must take into

account important inter-subject differences in speed of reaction, comprehension of test instructions, etc. particularly when several tests are presented one after the other. The pace at which the individual tests are presented may give rise to pressures on performance and cause unpredictable effects which are not due to the effects of study medications. If psychometric tests are developed in a straightforward manner with realistic stimulus recognition, information processing and motor response requirements (especially the demands made on ► short-term and working memory in humans) then the effects of learning on psychomotor performance can be minimized although pre-study practice on even the simplest of psychometric tests is always required.

Computerised tests are able to present information at a rate and magnitude which can exceed the information processing capacity of some subjects, especially the elderly and those under the influence of drugs. When faced with too much information, individuals will adopt various strategies-some of which will require extensive learning-as in the playing of a computer game. Strategic perceptual and/or complex information processing requirements and/or the need for a finely controlled or coordinated motor response will increase the effects of inter- and intra-individual variability and effect the validity and reliability of the results obtained.

In short, psychometric tests for the measurement of psychomotor performance must be straightforward in their stimulus perception, information processing and motor response requirements. Furthermore, their sensitivity to drug activity has to be demonstrated by way of the use of verum controls. It is also necessary to evaluate a range of doses of a particular drug, not only because in clinical use patients often take 'supra-dose' regimens but also because psychomotor impairment effects might be dose related (Holgate et al. 2003).

Although measuring different aspects of psychomotor performance, many individual psychometric tests utilize speed of reaction as one of the motor response measures. Research on age-related changes in mental capacity suggests that a fundamental part of the cognitive system governs the speed of processing information (Kail and Salthouse 1994). Use can be made of this concept when assessing the effects of drugs on psychomotor performance by combining the reaction time components from each of the response-based tests in a particular test battery.

Tests of psychomotor performance are primarily used to assess the effects of CNS active drugs. A major step forward in validating this use of psychometrics has been the advent of human positron emission tomography (► PET) studies of the effects of psychoactive drugs, e.g., antihistamines (Yanai and Tashiro 2007). PET studies have differentiated between antihistamines in their capacity to penetrate the brain and occupy, ranging from virtually 0 to 90%, histamine -1 receptors ► histaminic agonists and antagonists.

The extent a particular antihistamine occupies H1-receptors in the brain is generally correlated with the degree of psychomotor impairment found from placebo and verum controlled studies of the same drug, (Shamsi and Hindmarch 2000). This not only helps elucidate the mechanisms by which drugs, in this instance antihistamines, act but also validates the use of psychometric tests to measure drug induced changes in human psychomotor performance.

Cross-References

► Attention
► Driving and Flying Under the Influence of Drugs
► Histaminic Agonists and Antagonists
► Pharmacodynamic Tolerance
► Placebo Effect
► Short-term and Working Memory in Humans
► Spatial Memory in Humans
► Verbal and Non-Verbal Learning in Humans

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Psychomotor Stimulants

► Indirect-Acting Dopamine Agonists
► Psychostimulants

Psychopharmacology

Synonyms

Neuropsychopharmacology

Definition

Psychopharmacology is the scientific field that utilizes drugs or other chemical agents to understand neural function, to prevent and treat mental illness and drug abuse, and to understand how nontherapeutic psychoactive drugs and natural substances alter human mood, memory, motor activity, endocrine, and other centrally mediated functions.

Cross-References

► Classification of Psychoactive Drugs
► History of Psychopharmacology

Psychophysics

► Psychophysiological Methods

Psychophysiological Methods

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Definition

Stern (1964), in the first edition of the journal *Psychophysiology* established by the Society for Psychophysiological Research, defined the field as where behavioral variables are manipulated and the effects of these independent variables are observed on physiological measures as dependent variables. This definition has been expanded by Furedy (1983) in the first edition of the International Organization of Psychophysiology's *International Journal of Psychophysiology* to "the study of physiological processes in the intact organism as a whole by means of unobtrusively measured physiological processes." Clearly, the nature of what constitutes "unobtrusive" in this context is subjective, but is an acknowledgment that the process of measurement can influence the measure itself. At least in some senses, the relationship between physiology and psychology implied by the term "psychophysiology" is the converse of that described by "physiological psychology" or "biological psychology" which relate to the study of the biological and physiological underpinnings of psychological processes. Psychophysiological methods are utilized in both human and animal studies. Furedy (1983) argues that this is only the case when the interest of the experimenter is focused on psychological processes of the whole intact organism.

Principles and Role in Psychopharmacology

The Role of Psychophysiology and Breadth of Techniques

As suggested earlier, the very definition of psychophysiology is a subject of some debate. Nathan Kline (1961) took an existential approach in his paper "On the relationship between neurophysiology, psychophysiology, psychopharmacology, and other disciplines." He argued that ambiguities in bioscience arise from asking a question in one "universe of discourse" (e.g., psychology) and seeking the answer in quite a different one (e.g., physiology). This is a potential issue with respect to the term psychophysiology and, indeed, psychopharmacology. Kline developed a number of laws regarding the relationship between disciplines including the "Law of Technique." This law states that the technique used to obtain information does not necessarily determine the "universe of discourse" in which it is used. This remains relevant, especially to the use of psychophysiological methods within psychopharmacology, as this spans three or more disciplines. To illustrate this, consider an example based on one given in Furedy's (1983) discussion of the definition of psychophysiology. ► Anxiety, via effects on the autonomic nervous system (ANS), causes changes in heart rate and other cardiac parameters such as the electrocardiograph (ECG) T-wave amplitude. If during a stress-exercise test in a patient with suspected cardiac pathology, a decrease in T-wave amplitude is seen, a physiological explanation will relate to cardiac pathology. However, from a psychophysiological perspective, the effects of the ANS on the myocardium need to be considered. For example, if the patient has great anxiety regarding his or her heart, the test may constitute a psychological as well as a physical ► stressor. Further, the psychopharmacologist would also take into account the antidepressant or anxiolytic medication that the patient may be taking which may be modifying the psychophysiological response. The technique or measurement (T-wave amplitude) is common to these three "universes of discourse," but each views or uses it in different ways.

It can therefore be seen that within the research area of psychopharmacology, psychophysiology is a tool to assist in the measurement of drug-induced changes in psychological

processes. When studying the effects of potentially psychoactive drugs, one of the greatest challenges is having objective "outcome measures" that demonstrate the effect of the drug. It is essential to measure the effect of a drug on mood, for example, when developing an antidepressant. Such an outcome has fundamental importance regarding the therapeutic use of the drug. However, the psychological process involved can only be measured in a subjective way in humans and only very indirectly in animals. Alternative and additional outcome measures, which can be assessed more objectively and in a range of situations, are essential to facilitate a number of investigations including the study of the ▶ pharmacokinetics of a drug, understanding dose–response relationships and the mechanism of action of the drug itself, drug safety, and investigating ▶ drug interactions.

There is almost an infinite number of psychophysiological (as defined earlier) outcome measures used in psychopharmacology, limited only by the ingenuity of the scientists involved. These include, for example, direct methods of investigating the effects of a drug on the physiological function of the central nervous system such as measuring changes in the brain electrical activity using ▶ electroencephalography (EEG) and magnetoencephalography (MEG). These techniques can be utilized in a myriad of ways. A common method of using the EEG to acquire information is to record ▶ event-related potentials (ERPs), that is, EEG activity recorded time locked to some event such as the presentation of a stimulus to a subject, or a subject's response. Examples of ERPs include the "▶ P300" (referring to a positive voltage deflection occurring around 300 ms after the presentation of rare or task relevant stimuli) and "▶ mismatch negativity" (a negative voltage deflection occurring after presentation of a stimulus that is deviant, for example, in terms of loudness, duration, or frequency), both of which have been widely used as outcome measures in psychopharmacological research. In recent years, there has been an explosion of novel analysis techniques of EEG data, much of which is focused around exploration of the frequencies of the signals contained within the EEG, which further enhances its potential utility as an outcome measure. At their heart, EEG and MEG techniques offer the opportunity for investigating the effects of psychopharmacological agents with high temporal resolution.

Recent decades have seen an explosion of neuroimaging techniques including their application in psychopharmacology. In the simplest types of paradigms, the notion is that a psychoactive substance leads to changes in psychological processes that are reflected by changes in the cerebral blood flow which can be measured using positron emission tomography (▶ PET) or functional ▶ magnetic resonance imaging (fMRI). Such techniques offer the opportunity of providing high-resolution spatial information regarding the site of action of the drugs. PET and other imaging methodologies can also be utilized with radio-labeled ligands to investigate a whole range of pharmacological processes including transmitter release and receptor binding.

Perhaps the most direct method of exploring the effects of a psychopharmacological agent on psychological processes is the use of neuropsychological tests to examine changes in cognition. ▶ Cognitive enhancement is a particular goal of a branch of psychopharmacology, for example, in the treatment of ▶ dementias. However, in addition, cognition can be utilized as an objective outcome measure in treatment studies using reliable neuropsychological tests of proven validity. Such tests can be combined with, for example, EEG or fMRI to provide additional information regarding which temporal and spatial component of a cognitive task is being influenced by the psychopharmacological agent.

Historically, some of the most widely used psychophysiological techniques have utilized the close interaction between the central nervous system and the ▶ neuroendocrine system. Such neuroendocrinological techniques offer the advantage of the simplicity of sample collection by measuring hormonal levels most commonly in plasma. The technique can be used in a number of different ways. For example, ▶ stress in a number of forms leads to the activation of the ▶ hypothalamic–pituitary–adrenal (HPA) axis with a consequent release of corticosteroids. The effect of a psychopharmacological agent on stress can be assessed by examining changes in peripheral corticosteroids. This is a classic example of where Furedy's (1983) point about the measures being "unobtrusive" is a key issue. If the method by which samples are collected is stressful, this may lead to an alteration in the measured levels of corticosteroids. An alternative neuroendocrinological strategy is to assume that changes in transmitter systems in higher centers are reflected in similar changes in these transmitter systems that control neuroendocrine function. An example of this approach, much in evidence in the 1980s and 1990s, is the use of growth hormone and prolactin responses to serotonergic probes such as ▶ tryptophan or ▶ buspirone, to assess the presumed functional status of hypothalamic 5-HT_{1A} receptors in mood disorders and following administration of ▶ antidepressants.

All of the above-mentioned methods can be considered as within Furedy's (1983) definition of "psychophysiological." However, within the specialty of psychopharmacology, the term in common usage usually refers to the more peripheral physiological effects of changes in the central

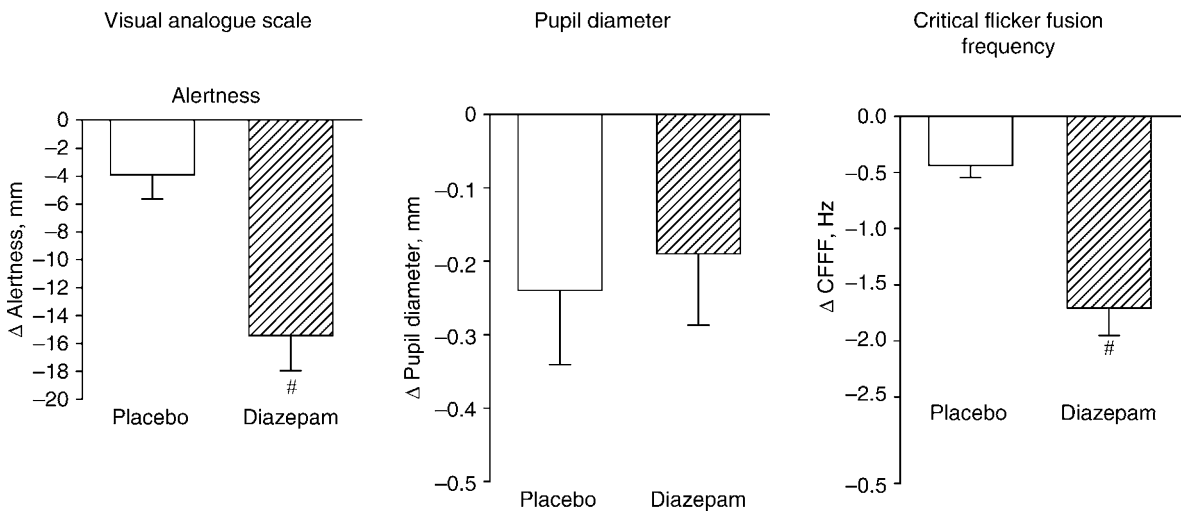
(psychological) function. Many, but certainly not all, of these effects relate to changes in the autonomic nervous system function as indexed by, for example, changes in pupil diameter, heart rate variability, and electrodermal responses.

Principles of Psychophysiological Methods as Applied in Psychopharmacology

Furedy (1983) argued that psychophysiology is different from physiological psychology in that the latter is related to the study of the physiological underpinnings of psychological processes. However, this is a "legitimate" area of study for the psychophysiologist, as perhaps the most important principle of psychophysiology is that the mechanism connecting the psychological process with the physiological response is known. Essentially, the issue here is the same as in any area of research when two measures are correlated; correlation does not imply causation. Heart rate may well be observed to increase when a person is anxious. However, it is necessary to be convinced that it is anxiety (a psychological process) in any particular circumstance that is leading to an increase in heart rate, to make it a viable psychophysiological measure. In psychopharmacology, the situation is even more complex when using psychophysiological outcome measures, because it is also important to know if the drug could be directly influencing the physiological response. A good example of this is the use of PET and fMRI imaging exploring blood flow changes in response to administration of a pharmacological agent. Before concluding that changes in the image signal relate to the effects of the drug on a particular psychological process, it is essential to know if the drug has direct effects on cerebral blood flow.

To illustrate the issues around the importance of understanding the mechanisms underlying psychophysiological effects and other principles of these methods, work in the area of arousal will be described.

A potential psychophysiological outcome measure to assess arousal is the diameter of a subject's pupil. Pupil diameter has a close relationship with arousal, with decreased arousal being accompanied by constriction of the pupil (miosis). This is believed to reflect decreased sympathetic activity as levels of arousal drop. The ▶ benzodiazepines, (e.g., ▶ diazepam), as anxiolytic and sedative drugs, cause a decrease in arousal. This can be assessed subjectively, for example, using visual analog scales (Fig. 1). Psychophysiology offers a more objective outcome measure. However, diazepam does not lead to any change in papillary diameter (Hou et al. 2007, Fig. 1). Does this paradox suggest that either diazepam is not sedating or pupillary diameter is a poor psychophysiological outcome measure? The former option seems an unlikely explanation. In the study by Hou et al. (2007), additional psychophysiological measures of alertness were also conducted. These included the ▶ critical flicker fusion frequency (▶ CFFF) test. This involves determining the frequency at which a flickering light gives rise to the sensation of a steady light. This is measured by



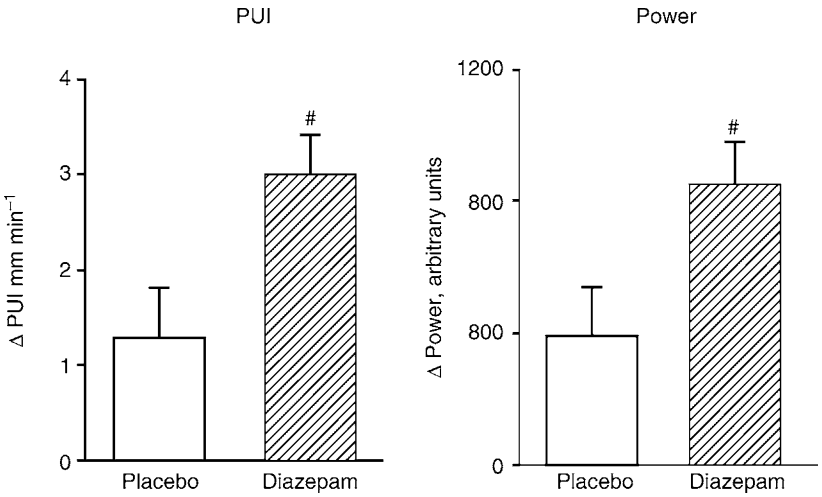
Psychophysiological Methods. Fig. 1. Level of alertness following a single oral dose of diazepam 10 mg given to 16 healthy male volunteers. Alertness assessed using a visual analogue scale, pupil diameter and critical flicker fusion frequency. # $p < 0.05$ versus placebo. Full details of the study and the methods used can be found in Hou et al. 2007 from where the figures have been obtained.

exposing the subjects both to a low-frequency flicker and increasing the frequency to the point at which the subject has the sensation that the flickering stops, and a high-frequency flicker that decreases to the point at which the flicker is detected. The CFFF is the mean of the two. As in all areas of science, having well-designed methodology that is objective, valid, and replicable is essential. The CFFF is a test that has been in usage since the 1950s and it is well accepted as a psychophysiological measure of arousal (Tomkiewicz and Cohen 1970). Hou et al. (2007) showed a significant effect of diazepam on the CFFF (Fig. 1), suggesting that diazepam does indeed have an effect on arousal and this can be measured both subjectively and objectively. They provided data that suggest that the paradox of the lack of effect of diazepam on pupil diameter relates to a lack of effect on either the sympathetic or parasympathetic influence on the iris. This highlights the importance of being aware of both the pharmacology of the drug being studied and the mechanism of the psychophysiological tests being used.

However, it is incorrect to think that diazepam has no effect on the pupil. In addition to simply measuring the pupil diameter, Hou et al. (2007) also measured spontaneous pupillary fluctuations, by analyzing these data in two ways: first, by performing an analysis of the frequency of fluctuations using a ► Fast Fourier Transformation to obtain an assessment of power, and second, by a "pupillary unrest index," (PUI) which is the distance travelled by the margin of the pupil in 1 min. These two measures reflect "pupillary fatigue waves" (Ludtke et al. 1998) that are believed to closely parallel fluctuations in the activity of the noradrenergic neurons of the locus coeruleus (Aston-Jones and Cohen 2005), influenced by arousal. While diazepam has no effect on static pupil diameter (Fig 1), it significantly increases the pupillary fluctuation power and PUI (Hou et al. 2007, Fig. 2), in line with its proposed sedating effects and the results from the CFFF test. The study illustrates the importance of utilizing a range of methodologies relating to different mechanisms and pathways whenever possible to be able to draw legitimate conclusions regarding the effect of the drug. Further, the study illustrates the complexity and ingenuity of many modern psychophysiological tests.

Advantages and Limitations of Psychophysiological Methods

As described earlier, the most obvious advantage of psychophysiological methods is their use in providing objective outcome measures of the effects of psychopharmacological agents, and as such, they relate to the very essence of the discipline. There is an enormous range of such techniques and it is impossible to delineate all their advantages and limitations here. The various methods span a range of ease of use, cost, and utility. Their main limitations are when there is a lack of a clear understanding of the mechanism underlying the response being measured, and the direct and indirect effects that a drug may be having on it.



Psychophysiological Methods. Fig. 2. Pupillary spontaneous fluctuations following a single oral dose of diazepam 10 mg given to 16 healthy male volunteers. Data show the effect of diazepam on both the power of the fluctuations and the pupillary unrest index (PUI). # $p < 0.05$ vs. placebo. Full details of the study and the methods used can be found in Hou et al. 2007 from where the figures have been obtained.

Cross-References
- ▶ Benzodiazepines
- ▶ Cognitive Enhancement
- ▶ Drug Interactions
- ▶ Electroencephalography
- ▶ Event-related Potentials
- ▶ Magnetic Resonance Imaging
- ▶ Neuroendocrine Markers of Drug Action
- ▶ PET Imaging
- ▶ Pharmacokinetics

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Psychose Passionelle

- ▶ Delusional Disorder

Psychosis

Definition
The word "psychosis" is used to describe conditions that affect the mind, in which there has been some loss of contact with reality. A psychotic episode can be caused by several psychiatric disorders. Somatic disorders can also cause psychotic symptoms, as well as prescribed and non-described drugs.

Psychosocial Interventions

Definition
Psychosocial interventions are measures usually provided in addition to medical treatment for psychiatric patients. They can consist of counseling through social workers, different psychotherapeutic methods such as cognitive behavioral therapy (CBT), interpersonal therapy, subliminal stimulation, supportive-expressive therapy, and contingency management approaches such as voucher incentives.

Psychostimulant Addiction

Synonyms
Psychostimulant dependence

Definition
Psychostimulant addiction (dependence) is a chronic, relapsing disorder diagnosed by the hallmark of compulsive drug-taking and drug-seeking to the exclusion of other important life activities. The feeling states of craving (an intense desire for the drug) and euphoria are primary correlates of the addiction. Brain areas important for decision making, learning, memory, and behavioral control are altered in individuals addicted to psychostimulants and other abused drugs.

Cross-References
- ▶ Cocaine Dependence
- ▶ Craving
- ▶ Decision Making

Psychostimulant Dependence

- ▶ Psychostimulant Addiction

Psychostimulants

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Synonyms
Psychomotor stimulants; Stimulants

Definition
Psychostimulants are drugs that diminish fatigue and elevate mood and alertness.

Pharmacological Properties

History

Psychostimulants are a broad family of drugs that include compounds from naturally occurring plant alkaloids (e.g., ▶ caffeine, ▶ cocaine, ephedrine, ▶ nicotine) to synthetic ▶ amphetamine derivatives such as D-amphetamine, ▶ methamphetamine, and 3,4-methylenedioxymethamphetamine (▶ MDMA; ecstasy) as well as ▶ methylphenidate. Some of these psychostimulants are available over-the-counter (e.g., caffeine) or under prescription for a given medical indication (e.g., ▶ methylphenidate), while others are illicit and available only on the black market (e.g., MDMA). The use of psychostimulants has been recorded throughout history, dating back to Paleolithic times when Ethiopian nomads brewed *Coffea arabica* (coffee) into a stimulating beverage, North American Indians smoked wild tobacco *Nicotiana* variants, and Peruvian Indians chewed the leaves of *Erythroxylum coca* (cocaine) to enhance endurance and energy, while Chinese physicians utilized *Ephedra vulgaris* (ephedrine) to treat fever, nasal congestion, and asthma. The scientific literature has focused on several members of the broad family of psychostimulants, including caffeine, cocaine, amphetamine derivatives, and nicotine.

Caffeine has been consumed in concoctions derived from plant sources since prehistoric times. This mild stimulant and diuretic found naturally in coffee, tea, and cocoa is currently the most widely used psychoactive substance in the world. Employed to enhance alertness and reduce fatigue, caffeine is now an additive to many other food substances, including beverages which boast names such as *Jolt*, *Surge*, and *Full Throttle*. Caffeine is used medically to enhance the ▶ efficacy of medications used in the treatment of migraine and pain, and is occasionally used to stimulate respiration, or to overcome the sedative effects of antihistamines.

Cocaine is one of about a dozen alkaloids of the Coca plant and was first isolated in 1855. By the late 1800s, cocaine was widely used for its analgesic properties and was sold over-the-counter until 1916. By the early twentieth century, the addictive properties of cocaine were well known, and, in 1970, cocaine was officially made illegal and classified as a ▶ Schedule-II drug (limited medical uses) in the United States under the ▶ Comprehensive Drug Abuse Prevention and Control Act of 1970 (Controlled Substances Act). Cocaine is used in various forms including powder, freebase, and crack, and is currently one of the most-popular, abused street drugs in Western society. The powder form of cocaine is snorted or injected while freebase or crack cocaine is smoked. The therapeutic uses of cocaine are limited to its application as a topical analgesic in ear, nose, and throat surgeries. Street names abound for the various abused forms of cocaine, including coke, snow, flake, blow, candy, rock, and toot, for example.

The use of amphetamine derivatives dates back to Neolithic times in China and Africa where herbs in the genus *Ephedra* (Ma huang) and *Catha edulis* (khat or qat) were employed for their stimulant properties. Ephedrine was isolated from the *Ephedra* plant in the late 1800s, and was soon utilized widely to treat asthma. In the 1920s, interest in finding a synthetic substitute for ephedrine brought about the extensive characterization of the structurally similar compound amphetamine which had first been synthesized in 1887. Soon thereafter, amphetamine was marketed to treat nasal congestion, ▶ narcolepsy, and ▶ attention deficit hyperactivity disorder (ADHD) and subsequently, a number of amphetamine analogs were developed and characterized, including the now-popular street drugs, methamphetamine and MDMA (ecstasy).

Amphetamine use was common during World War II when soldiers were issued the stimulant to decrease fatigue and increase alertness. In the 1950s, legally manufactured tablets of amphetamine and methamphetamine were utilized by college students, truck drivers, and athletes across the United States to stay awake and get more energised. Amphetamines were widely prescribed through the 1960s to suppress appetite and enhance weight loss. While effective for this purpose, the high abuse liability of amphetamine outweighed their utility for this indication. Due to the epidemic of amphetamine use, the US Bureau of Narcotics and Dangerous Drugs [BNDD; later named the Drug Enforcement Administration (DEA)] shifted all amphetamine products to Schedule II in 1971 under the Controlled Substances Act. A prescription then became required for possession of an amphetamine. In 1988, the growth in abuse of MDMA and evidence to suggest its systemic toxicity prompted the classification of this amphetamine derivative as ▶ Schedule I-controlled substance (due to its high abuse potential and no currently accepted medical use). Street names for amphetamines include speed, uppers, crosses, and black beauties.

Nicotine is the active psychostimulant alkaloid of the tobacco plant. Introduced to Western society in the 1500s, tobacco had been used by Native Americans and Asians for centuries before. By 1964, scientists had concluded that tobacco smoking was causally linked to lung cancer and heart disease, and health warnings were deemed mandatory for tobacco products. The principal therapeutic use of nicotine and ▶ nicotine agonists (e.g., the partial ▶ agonist varenicline) is in the treatment of ▶ nicotine dependence.

Effects in Humans

The constellation of subjective effects that characterize the "intoxication" induced by psychostimulants and that capture the attention of users as "pleasant", includes euphoria, mood elevation, enhanced feelings of well-being, and motor and mental stimulation, although each psychostimulant provokes a unique subjective profile. For example, caffeine is generally not euphorigenic, while MDMA users also report feelings of closeness with other people, increased empathy, and perceptual alterations when under the influence of this drug. Despite their subjective effects that are perceived as positive, psychostimulants also have many negative consequences. Some stimulant users report anxiety, decreased appetite and weight loss, feelings of restlessness, irritability, and sleep disturbances. Other negative consequences include cardiac arrhythmia, seizures, and myocardial infarction. Higher doses, which are often used to intensify the high, may also induce aggressiveness, disorientation, hallucinations, paranoia, muscle twitches, tremors, and vertigo. Additionally, high doses of MDMA evoke hyperthermia, which can lead to life-threatening conditions such as multiple organ failure; cocaine can also elicit hyperthermia, but this effect is less reported than that evoked by MDMA.

When taken chronically, psychostimulants (especially, cocaine and amphetamine derivatives) may lead to ▶ stereotypical and repetitive behavios. Compulsive drug-taking and drug-seeking can develop while the emergence of additional psychiatric disorders can be observed, including ▶ anxiety, ▶ depression, and a paranoid psychosis that shares some features of ▶ schizophrenia. Toxic physiological reactions are also observed. Individuals addicted to psychostimulants are remarkably willing to risk death, incarceration, medical and psychiatric complications, job loss, and family turmoil in pursuit of the drug.

Mechanisms of Action

▶ Dopamine is the most-prominent, well-studied neurotransmitter involved in the effects of psychostimulants. The dopamine mesoaccumbens pathway, originating in dopamine somata of the ▶ ventral tegmental area and terminating in the ▶ nucleus accumbens, mediates the reinforcing effects of natural rewards (i.e., food and sex) and also serves as a common substrate for the acute rewarding effects of all drugs of abuse, regardless of their individual mechanisms of action (for review, see Kelley 2004). In addition, dopaminergic influence, in conjunction with glutamatergic neurotransmission, within nodes of the extended, limbic corticostriatal circuitry (▶ prefrontal cortex, ▶ amygdala, ▶ hippocampus) is integral in coordinating reward-related associative learning and motivated behaviors that contribute to aspects of addiction such as ▶ craving, ▶ withdrawal, and relapse (Kelley 2004). While dopamine is integral to the normal function of this brain circuitry, regulatory oversight of the signaling involved in reward circuits is provided by multiple ▶ neurotransmitters.

Each psychostimulant presents a distinct profile of actions that mediates its psychostimulant effects. The caffeine molecule bears structural resemblance to the endogenous neurotransmitter adenosine and appears to evoke its psychostimulant effects due to its action as an adenosine receptor ▶ antagonist in the brain (Ferre 2008). This action of caffeine occurs at the adenosine A_{2A} receptor which plays a critical role in the control of dopamine function in reward and arousal. Additional actions of caffeine in the body abound while metabolites of caffeine also contribute to its biological profile. There is also emerging evidence that selective A_{2A} adenosine receptor antagonists may prove useful in the pharmacotherapy of stimulant addiction (Ferre 2008), although this hypothesis remains to be fully explored (see Psychostimulant Addiction below).

Amphetamines and cocaine present a multifaceted regulatory impact over ▶ monoamine function, and the chemical structure of the amphetamine molecule is a determinant of its exact pattern of influence over neuronal function (Sulzer et al. 2005). The effects of cocaine and amphetamine derivatives in humans are thought to be mediated by their ability to enhance synaptic concentrations of monoamines via actions at neurotransmitter ▶ transporters for dopamine, ▶ serotonin (5-HT), and ▶ norepinephrine. These transporters are found in the outer membranes of monoamine neurons and act to reuptake neurotransmitters released by the nerve terminal. In fact, reuptake serves as the primary mechanism of inactivation for released monoamine neurotransmitters. Amphetamine derivatives display different profiles of ▶ affinity for and efficacy at the three monoamine transporters. In general, amphetamine derivatives increase synaptic monoamine levels through both the blockade of reuptake and reversal of the membrane-localized transporter for these monoamines. The reversal of the transporter results in release of monoamines from the nerve terminal, providing an additional mechanism for elevation of synaptic neurotransmitters. The parent molecule, amphetamine, has greatest affinity for the ▶ dopamine transporter, while methamphetamine and MDMA have greater affinity for the ▶ serotonin transporter when compared to the dopamine or ▶ norepinephrine transporter. Amphetamines can interfere with the storage of monoamines in compartments (vesicles) inside neurons,

and can retard degradation of monoamines. Both of these actions further result in increased accumulation of free neurotransmitter in the nerve terminal (Sulzer et al. 2005).

Cocaine binds to the monoamine transporters and inhibits reuptake of dopamine, serotonin, and norepinephrine. Thus, by blocking reuptake, cocaine increases the length of time that the monoamines remain in the synapse available to activate their receptors. Cocaine is also reported to have affinity for the serotonin 5-HT_3 receptor, M_1 and M_2 ▶ muscarinic receptor, and σ-receptors, although their roles in mediating the stimulant effects of cocaine are not clear.

Nicotine acts as a psychostimulant at very low doses through activation of endogenous nicotine receptors, proteins that are normally activated by the endogenous neurotransmitter ▶ acetylcholine. Its actions result in increased levels of DA in reward circuits of the brain, providing a neuroanatomical basis for its stimulant effects.

Psychostimulant Addiction

The new millennium dawned on a continuing societal struggle with the consequences of use and abuse of psychostimulants. Stimulant abuse remains an alarming concern and the issues are complex. On the one hand, stimulants have diverse therapeutic utility in a large population for which they are essential (e.g., attention deficit disorders). On the other hand, the abuse of illicit stimulants such as cocaine, methamphetamine, and other substituted amphetamines does not show signs of abatement. For example, the United Nations Drug Control Program (UNDCP) estimates that cocaine use affects about 13 million people (0.3% of the global population above age 15 years), making cocaine the second, most-common illegal drug of abuse (United Nations Office on Drugs and Crime 2007). Despite the general decline in illicit drug use among US teens, little systematic change for 8th–12th graders has been noted in use, perceived risk of use, or disapproval of use of crack cocaine or powder cocaine in the past 4 years (Johnson et al. 2006). In addition, a growing number of individuals now seek treatment for cocaine addiction in the United States; epidemiological studies suggest that approximately 16% of the people who use cocaine become dependent on the drug (Substance Abuse and Mental Health Services Administration 2007). The "cocaine problem," combined with the escalating abuse of methamphetamine and prescription amphetamines, is a colossal challenge which must be tackled with all available resources. The recidivism rate of stimulant users is very high, and access to effective treatment modalities are so rare, that new, easily available and effective treatments are needed. To achieve this goal, an essential understanding of the neurobiological mechanisms underlying stimulant-abuse disorders and their persistence is required. The long history and cyclical nature of stimulant abuse, the emergence and subsidence of a given psychostimulant as an abused favorite, concurrent with the emergence of yet others, suggest that there is a need to take a long and realistic view. There will be a continuing need to deal with the problems of stimulant-use disorders, either with those known or those that will emerge in the future.

The transition from psychostimulant use to addiction occurs most evidently for cocaine and amphetamines, particularly methamphetamine. Addiction in vulnerable individuals can be viewed in stages from initial use to active abuse with escalating and sustained dependence on the drug. Psychostimulant dependence (addiction) is diagnosed as the hallmark of compulsive drug-taking and drug-seeking to the exclusion of other important life activities. Although patients cite many behavioral reasons for why they use a psychostimulant, the feeling states of craving (an intense desire for the drug) and euphoria are primary reinforcers of the addiction. Drug-induced euphoria and craving alternate over time, exerting positive and negative reinforcement to form a cycle of addiction that becomes increasingly entrenched and uncontrollable. The severity of stimulant addiction can progress very rapidly in vulnerable individuals. While it may take years or decades for alcoholics to develop end-stage alcoholism, progression to severe dependence among stimulant abusers typically occurs more rapidly. Rapid progression is particularly common with the smoked, freebase form of cocaine known as crack, probably because the intrapulmonary route is the quickest means of delivering a ▶ bolus of cocaine to the brain. Because cocaine and amphetamine addiction involves brain reward centers, the strength and characteristics of stimulant use take on an almost primary survival drive. The inability of patients to control stimulant use illustrates the power of reward centers over behavior, and partially explains the relapsing nature of cocaine and amphetamine dependence (Volkow and Li 2004).

The etiology of stimulant-use disorders includes genetic, psychological, pharmacological, neural, and environmental determinants. Major advances in understanding the neurobiology of addiction have been generated over the last 25 years revealing the complex biological processes that trigger and sustain addictive behavior and the physiological ramifications of chronic exposure to abused drugs (Everitt and Wolf 2002; Kalivas and Volkow 2005; Kelley 2004). The escalation from drug use to drug addiction is linked inextricably to brain pathophysiology, composed of a myriad of neuroadaptive responses (termed ▶ Neuroplasticity), that develops during chronic drug exposure

and alters normal homeostasis. Some of these neuroadaptations underlie the evolution of strong mnemonic associations between environmental cues and the drug-taking experience as well as emerging psychiatric complications. Cessation of drug use during ▶ abstinence represents another phase of addiction during which drug withdrawal, "craving," poor impulse control, and reactivity to drug-associated environmental cues challenge the best intentions of the addict to remain abstinent. Each of these hallmark phases (predrug exposure, early drug exposure, chronic abuse, dependence, withdrawal, abstinence) are stages during which brain circuits that normally control the intertwined processes of reward, motivation, memory, stress responsivity, and emotional processing accumulate adaptations that contribute significantly to the behavioral sequelae of addiction. The normality of these circuits are dependent upon the function of overlapping neurotransmitters in the brain, and the impact of a given psychostimulant on these neurotransmitters set in motion the turmoil of addiction. Drug-induced neuroadaptations of genes and proteins in these circuits have been described and include neurotransmitter transporters and receptors, synthetic enzymes, and numerous transcription factors. However, the specific protein changes that contribute to neural plasticity associated with drug exposure, the reversibility of such modifications, how it all fits together remains to be determined.

The complex neuronal interconnectivity is genetically determined, but environmentally tweaked, to provide infinitely unique individuals. This ▶ epigenetic background provides the fertile soil into which the use of a drug of abuse is introduced; if the individual is vulnerable to the rewarding and reinforcing effects of the drug, then the transition from use to abuse and then to dependence can be set in motion. Time-locked modifications in neurotransmitter functionality culminate in neuronal plasticity in these circuits, a devolutionary process that presumably results in the patterns of drug-taking and drug-seeking behavior which characterize addiction.

Modeling Psychostimulant Addiction in Animals

The development of effective approaches to treatment of stimulant addiction relies on well-designed clinical research in drug-using subjects, as well as preclinical research in which rigorous experimental control and specific behavioral and pharmacological manipulations can be undertaken to model and control the progression of drug-taking and drug-seeking across time. These models have greatly enhanced our understanding of the roles of dopamine, serotonin, and other neurotransmitters in the rewarding, reinforcing, and conditioned effects of stimulants (Bubar and Cunningham 2008; Kalivas and Volkow 2005). These preclinical advances originally focused the field on the dopamine neurotransmitter system as a relevant target for medications development for psychostimulant abuse. However, clinical trials have not yet identified dopamine-based pharmacotherapies which lack abuse liability, yet exhibit efficacy to enhance abstinence, reduce craving, and prevent relapse. Alternative investigations now suggest that in addition to dopamine, other neural systems play equally important roles in addictive processes, including ▶ serotonin, ▶ glutamate, ▶ adenosine, ▶ GABA, and ▶ neuropeptides; and these results have generated interesting new prospects for pharmacotherapy. These systems may function to modulate the neural output of the anatomically defined reward circuit and in the wider circuit of reciprocal interactions termed the limbic cortical–ventral striatopallidal circuit (Everitt and Wolf 2002).

The animal model with the greatest face validity to model the reinforcing and rewarding effects of drugs of abuse is the intravenous ▶ drug self-administration paradigm, which has been well characterized in rodents and nonhuman primates (Mello and Negus 1996). Drugs of abuse are readily self-administered by animals and in general, drugs that are self-administered correspond to those that have a high-abuse potential in humans. The advantage of this model is that it most closely resembles the different stages of human drug dependence – acquisition, maintenance, and relapse – which have led to a greater understanding of the neurobiological underpinnings of addictive behavior. Drug self-administration is solidly based upon the ▶ operant conditioning principle of "reinforcement." In drug self-administration, the presentation of a stimulus (e.g., cocaine as an appetitive "reward") contingent upon a behavioral response increases the probability that that behavior will reoccur. Based upon the ability of an animal to make an operant response (e.g., nose poke or lever press) which is reinforced by the presentation of a psychostimulant reward, this assay is widely used to study environmental and pharmacological variables important in the initiation, maintenance, and escalation of drug-taking behavior. For intravenous self-administration studies, the subject acquires a drug infusion by performing a discrete response. The number and pattern of responding required for each infusion is determined by the ▶ schedule of reinforcement imposed by the experimenter. Drug availability typically is signaled by an environmental stimulus, and the dependent variables are the number of infusions obtained or the rate of responding (i.e., lever presses or nose pokes) during a session (Mello and Negus 1996).

Modeling Drug-Seeking and Relapse

A basic definition of relapse in the context of drug abuse and addiction is the return to drug-seeking and drug-taking behavior following a period of abstinence. Often the role of craving – defined as an intense desire for a specific object or experience – is invoked as a primary motivating force behind relapse, and pharmacological means to reduce this behavior are being sought as potential "abstinence enhancers." It is widely known that conditioned cues associated with psychostimulant use are a major factor in relapse to continued use, and it is clear that associations between environmental cues and the drug-taking experience become well consolidated into memory. In fact, the molecular pathways of drug addiction overlap prominently with those involved in learning and memory processes, as elegantly reviewed by Kelley 2004. The ▶ reinstatement of drug self-administration paradigm possesses good predictive and face validity for modeling the activation of craving states by conditioned environmental stimuli (e.g., places in which a drug was consumed or drug-associated paraphernalia) in drug-dependent individuals. In these models, conditioned cues previously associated with psychostimulant reward (e.g., lights, tones) are presented in the absence of the drug either to trigger the operant responses engendered in the drug-taking situation of self-administration or reinforce the continued drug-seeking by presentation of the cues upon the behavioral response. The use of noncontingent ("priming") injections of drugs to induce reinstatement of drug self-administration has equally been found to produce a robust degree of reinstatement and is a good model for pharmacologically induced relapse in addiction (Mello and Negus 1996). The preclinical models described have been developed and shaped to further the understanding of processes involved in the transition of psychostimulant use to addiction. In addition, the imperative to discover the means to reverse neuroplastic events resultant from psychostimulant exposure and to therapeutically improve function in the addicted brain requires refined preclinical models.

The Future

We have entered the world of personalized medicine in which a patient's unique genetic and phenotypic profile will ultimately provide the signposts to tailor diagnosis and treatment for diseases, with reduced side-effect profiles. The science in chronic diseases such as cancer and diabetes is rapidly advancing in these goals to provide new targeted diagnostics and medications for treatment tailored to provide the best clinical response in an individual. The vision to improve our diagnostic and prognostic capabilities with identified disease biomarkers for psychostimulant abuse and addiction, to understand vulnerability to addiction and relapse, and to treat this complex disorder with maximal efficacy is now within reach of addiction scientists.

One important research imperative has been the development of effective, accessible treatment medications for stimulant addiction (Mello and Negus 1996). Effective medications for alcohol, opioid, and nicotine addiction are available. For example, nicotine gum, patches, and lozenges are therapeutically useful in smoking cessation programs, and the recent launch of the nicotine receptor partial agonist, ▶ varenicline, provides an additional option. However, there are currently no approved medications for treatment of dependence on cocaine or amphetamine derivatives such as methamphetamine, although over 60 medications have been tested in clinical trials (Vocci and Ling 2005). The initial focus of medications development for cocaine addiction was to utilize compounds that act at dopamine receptors or the reuptake transporter. However, agents that act as dopamine D_1 or D_2 receptor antagonists were either ineffective or resulted in unwanted side effects. Another strategy studied was the use of the selective dopamine transporter inhibitor GBR12909; however, the ▶ Phase I trials were halted early because of potential cardiovascular toxicity. ▶ Antidepressants have also been employed in ▶ open-label and ▶ placebo-controlled clinical trials; however, both ▶ tricyclic antidepressants such as desipramine and selective serotonin reuptake inhibitors (▶ SSRIs), such as ▶ fluoxetine, were found to be ineffective in several studies.

Several drugs with various mechanisms of action are currently under study in cocaine- and/or methamphetamine-dependent subjects in outpatient clinical trials (www.clinicaltrials.gov) in which efficacy to decrease drug-positive urines and/or reduce craving are measured:

- D-*Amphetamine*: Oral administration of D-amphetamine or methamphetamine appears to be effective at reducing cocaine use and craving. Under evaluation in Phase I and ▶ Phase II trials for cocaine dependence, amphetamine pharmacotherapy is an example of an agonist-replacement therapy similar to the use of methadone for ▶ opioid dependence.
- *Aripiprazole*: An ▶ atypical antipsychotic - that acts as an antagonist at dopamine D_2 receptors and serotonin 5-HT_{2A} receptors, ▶ aripiprazole may be useful for treatment of cocaine dependence in individuals with comorbid schizophrenia. This drug is also under evaluation for treatment of cocaine-dependent polydrug users being maintained on methadone as well as in

methamphetamine-dependent patients to reduce craving and relapse.

- *Caffeine*: Preclinical studies demonstrating the involvement of adenosine receptors in the reinforcing effects of cocaine and methamphetamine prompted initiation of Phase I and Phase II clinical trials evaluating utility of the nonselective adenosine receptor antagonist caffeine to reduce cocaine use and modulate related behaviors (impulse control and cue reactivity). Basic research studies with *SYN115*, a more selective antagonist at the adenosine A_{2A} receptor, are also being initiated in cocaine-dependent subjects to determine its effects on behavior and brain function in these individuals.
- *Citalopram/escitalopram*: Unlike other SSRIs, ▶ citalopram was shown to reduce cocaine use and craving, possibly due to its additional actions as a serotonin 5-HT_{2C} receptor agonist. Phase-II and ▶ Phase III clinical trials are being conducted to evaluate citalopram and its S-enantiomer ▶ escitalopram for cocaine dependence.
- ▶ Disulfiram: An inhibitor of dopamine β hydroxylase (DβH), the enzyme that converts dopamine into norepinephrine, disulfiram has been shown to reduce craving and withdrawal associated with cocaine administration, particularly in subjects that naturally have low levels of DβH activity. Disulfiram is currently being evaluated in clinical trials for cocaine-dependent subjects who are also dependent on opioids or alcohol, as well as Phase-I and Phase-II trials for methamphetamine dependence. *Nepicastat*, a more selective DβH inhibitor, is also being evaluated for efficacy in cocaine dependence.
- *Mirtazapine*: An antagonist at serotonin 5-HT_{2A}, 5-HT_{2C}, and 5-HT_3 receptors, ▶ mirtazapine is under evaluation for treatment of cocaine and methamphetamine dependence, and for treatment of cocaine-dependent individuals with depression.
- ▶ Modafinil: The glutamate-enhancer ▶ modafinil has shown promise in clinical trials for treatment of cocaine dependence, reducing the number of cocaine positive urines in cocaine-dependent subjects. Modafinil is currently being evaluated in Phase-II and ▶ Phase-III trials for cocaine dependence and Phase-II and Phase-IV trials for methamphetamine dependence.
- *Quetiapine*: An ▶ atypical antipsychotic that acts as an antagonist at multiple receptors, including dopamine D_1/D_2, serotonin 5-HT_{1A}/5-HT_2, and α_1/α_2 adrenergic receptors, ▶ quetiapine is being evaluated for treatment of cocaine dependence, methamphetamine dependence, and cocaine/methamphetamine dependence comorbid with either ▶ bipolar disorder or schizophrenia.
- *Topiramate*: ▶ Topiramate enhances GABA-activated chloride channels, while inhibiting excitatory neurotransmission through actions on kainate and AMPA receptors. This drug is under evaluation for cocaine dependence as well as for treatment of individuals with comorbid cocaine and alcohol or cocaine and opioid dependence.
- *Vigabatrin*: Vigabatrin enhances levels of the neurotransmitter GABA by inhibiting its catabolism via GABA transaminase. Several Phase-II trials are underway with vigabatrin for treatment of both cocaine and methamphetamine dependence.

The observation that about 60% of alcohol-, opioid-, or cocaine-dependent patients who received treatment medications relapsed into drug use within one year suggests that further research and advancement of these efforts is essential in order to improve treatment efficacy. The development of new pharmacological agents for the treatment of substance-use disorders would greatly increase treatment and access options, particularly if medications to enhance abstinence, reduce craving, and prevent relapse could be perfected. This is an important quest and one ripe for with near-term therapeutic potential with positive outcomes.

Cross-References

▶ 5-HT2A Receptor
▶ Abstinence
▶ Acetylcholine
▶ Affinity
▶ Agonist
▶ Alcohol
▶ Amphetamine
▶ Amygdala
▶ Antagonist
▶ Antidepressants
▶ Attention Deficit Hyperactivity Disorder
▶ Atypical Antipsychotics
▶ Bipolar Disorder
▶ Caffeine
▶ Classification of Psychoactive Drugs
▶ Cocaine
▶ Cocaine Dependence
▶ CRF Stimulation Test
▶ Disulfiram
▶ Dopamine
▶ Dopamine Transporter

- ▶ Drug Self-Administration
- ▶ Efficacy
- ▶ Glutamate
- ▶ Hippocampus
- ▶ Methylenedioxymethamphetamine (MDMA)
- ▶ Methylphenidate
- ▶ Modafinil
- ▶ Monoamines
- ▶ Muscarinic Receptor
- ▶ Naltrexone
- ▶ Narcolepsy
- ▶ Neuroplasticity
- ▶ Neurotransmitter Transporters
- ▶ Neurotransmitter
- ▶ Nicotine
- ▶ Nicotine Agonists
- ▶ Nicotine Dependence
- ▶ Norepinephrine
- ▶ Norepinephrine Transporter
- ▶ Nucleus Accumbens
- ▶ Operant Conditioning
- ▶ Opioid Dependence
- ▶ Opioids
- ▶ Phase I
- ▶ Phase II
- ▶ Phase III
- ▶ Prefrontal Cortex
- ▶ Reinstatement of Drug Self-Administration
- ▶ Relapse
- ▶ Schizophrenia
- ▶ Serotonin Transporter
- ▶ SSRIs and Related Compounds
- ▶ Stereotypical and Repetitive Behavior
- ▶ Tricyclic Antidepressants
- ▶ Ventral Tegmental Area
- ▶ Withdrawal Syndromes

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Psychotic Symptoms

Definition

Refers to a cluster of symptoms such as: paranoia, hallucinations, delusions, and incoherent speech and behavior.

Psychotomimetics

- ▶ Hallucinogens

PTM

- ▶ Post-Translational Modification

PTSD

- ▶ Post-Traumatic Stress Disorder

Pulmonary Hypertension

Definition

Pulmonary hypertension is an increase in blood pressure in the pulmonary artery, pulmonary vein, or pulmonary capillaries, leading to shortness of breath, dizziness, fainting, and other symptoms. Pulmonary hypertension can

involve a markedly decreased exercise tolerance and heart failure. The PDE5 inhibitor sildenafil, which is used to treat erectile dysfunction, is also used for the treatment of pulmonary arterial hypertension. But it is on the market under the name of Revatio to avoid confusion with Viagra.

Cross-References

- ▶ Congestive Heart Failure
- ▶ Erectile Dysfunction
- ▶ PDE5 Inhibitors
- ▶ Sildenafil

Punished Behavior

- ▶ Punishment Procedures

Punishment

Definition

A behavioral process wherein the consequences for an operant make instances of the operant less frequent in the future. Such consequences take the form of presentations of environmental stimuli, which are thereby defined operationally as aversive (punishers). Such stimuli can either be exteroceptive (e.g., pain-inducing events such as excessive heat or pressure) or interoceptive (e.g., noxious drugs).

Cross-References

- ▶ Punishment Procedures

Punishment Procedures

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Synonyms

Conditioned emotional response; Experimental conflict; Passive avoidance; Punished behavior; Punishment; Suppressed behavior

Definition

Punishment is defined as the suppression of behavior that results from the response-dependent delivery of a stimulus (punisher). Punishment procedures in rodents and other species have been used for nearly 50 years to detect effects of classical anti-anxiety agents (e.g., benzodiazepine receptor agonists such as valium) as well as other mechanisms that are or might prove to be anxiolytic in humans. Classical anxiolytic agents including ethanol increase behavior suppressed by punishment. The punishment procedures include passive avoidance, conflict tests, and other related methods. The conflict tests have been most widely used and include the Geller–Seifter and Vogel conflict tests of which a host of variants exist. In the Geller–Seifter test, stable baselines of responding are maintained in the presence of one stimulus and suppressed by punishment in the presence of an alternate stimulus. In the Vogel conflict procedure, drinking is suppressed by drink-dependent delivery of electric shock. The two procedures differ principally in that drug effects in the Geller–Seifter conflict test are evaluated against steady-state behavioral suppression whereas under the Vogel conflict tests, drug effects are evaluated for their ability to prevent response suppression upon the introduction of shock. A related test, albeit not explicitly a punishment procedure, is the conditioned-emotional response test (CER) in which a stimulus that is temporally paired with shock suppresses ongoing responding.

Impact of Psychoactive Drugs

Preclinical evaluation of the potential efficacy of putative anxiolytic agents has relied heavily upon the use of a variety of punishment procedures in experimental animals. Punishment is operationally defined as a decrease in the future probability of behavior subsequent to the response-dependent presentation of a stimulus (punisher). Punishment procedures have been studied widely and have been used for both behavioral analyses as well as for assessing drug action, yielding a wealth of information on both behavior and pharmacology. For the most part, the behavioral procedures have employed electric shock as the punishing event, mainly because it is discrete, readily controllable, and manipulable over a wide range of intensities. Other events have been employed (e.g., blasts of compressed air, electrical brain stimulation) but these have typically yielded a similar behavioral and pharmacological outcome. One of the earliest punishment methods to be used was the so-called *passive avoidance procedure*. Under this procedure, the movement of a rodent from one portion of an apparatus to another resulted in the delivery of electric shock. Subsequent placement of the rodent in the initial portion of the apparatus resulted in a

decrease in the probability of moving to the second location. It was found that drugs with anti-anxiety effects in humans would increase this suppressed behavior (Kelleher and Morse 1968). Despite the relative simplicity of this procedure, passive avoidance is highly influenced by variables controlling memory hence, memory disruptors can be false positives (e.g., scopolamine) in this procedure when attempting to assess potential anxiolytic drug effects. Thus, due to a host of factors including the lack of discrete responses and the detection of false positives, other punishment methods have dominated the anxiolytic drug discovery process for decades. These latter methods utilize the discrete response of a lever press, nosepoke, or lick on a drinking tube; these responses are typically controlled by ► schedules of reinforcement and are not as readily influenced by memory disruption as passive avoidance responses.

Another punishment procedure that utilizes the movement of rodents as the dependent variable is the *four-plate test*. Under this procedure, rodents are placed in an open arena in which four metal squares are situated. Contact with the metal results in electric shock to the paws and subsequent suppression of behavior. As in the case of the passive avoidance procedure, anxiolytic agents can increase movement within such an environment and the probability of contact with the metal plates.

A variant of the four-plate test involves active behaviors engendered by the punisher. Exposure to electric shock can result in burying behaviors if material is made available that permits burying to occur. For example, in the *shock-probe-burying test* (sometimes referred to as defensive burying), rodents, generally rats, are placed in a chamber with bedding material in which an electrified probe exists. Contact with the probe as a result of exploratory behavior results in the delivery and an electric shock, which generally leads to *increases* in the probability of burying of the probe. Anxioltyic drugs decrease the probability of shock-induced burying (File et al. 2004). Although not a punishment procedure per se, another highly used method for screening potential anxiolytic agents is marble burying. Mice placed in a bedding filled chamber with marbles on the top of the bedding will bury the marbles and such burying behavior is reduced by anti-anxiety drugs (Borsini et al. 2002).

Although first-and second-generation anti-anxiety drugs were not developed through the use of punishment procedures, the clinical efficacy of ► meprobamate, ► barbiturates, and later ► benzodiazepine-based anxiolytics led to more refined methods capable of detecting the distinct behavioral effects engendered by these compounds. Geller and his colleagues were the first to develop and pharmacologically characterize a punishment procedure (*Geller–Seifter conflict*) that embodied several distinctive features (Geller et al. 1962). Under the Geller–Seifter or Geller conflict procedure, lever-pressing of food-deprived rats is maintained under a variable-interval 2 min schedule of food delivery in which a lever press results in food delivery on the average of every 2 min. Interspersed throughout this initial training are 3-min periods in which a tone is presented and every lever press during the tone produces food. Subsequently, foot shock is introduced during the tone periods such that each lever response produces both food and shock. Under stable conditions, a relatively constant rate of responding occurs in the unpunished component and lower rates of responding occur in the tone period associated with punishment. The effects of drugs are assessed under this stable baseline of unpunished and punished responding. Typically, drugs are studied in the same animals with a drug free period of a day to several days allowing stable pre-drug rates of responding to become reestablished. Many variations of the Geller–Seifter conflict test have been developed and utilized over the almost 50 years since its introduction into the behavioral pharmacology arena. The most common variations have involved changes in the schedule of food delivery in either the unpunished or punished components or variations in the schedule or the intensity of shock delivery. One common variation in food scheduling is one involving fixed-ratio schedules of food delivery. Under one variation, a variable-interval schedule of food delivery is used to control unpunished responding and a fixed-ratio 10 schedule control punished responding where every tenth lever-press produces food and shock. Another common variation schedules response-dependent shock delivery for only the first response in the fixed-ratio of responses required for food delivery. In all cases, if other experimental conditions are set appropriately (see below), benzodiazepine anxiolytics such as diazepam increase the rate of suppressed or punished behavior.

A great advantage of the Geller–Seifter conflict methods are the highly reproducible behavioral baselines that are maintained and the reliable sensitivity of this behavior to drug effects engendered by the judicious scheduling of reinforcing and punishing events. In addition, the control by discriminative stimuli during the unpunished and punishment periods permits a simultaneous assessment of anxiolytic-like effects and effects on behavior not controlled by punishment. In addition, there is the benefit that comes from the ability to use the experimental subjects as their own controls, which greatly minimizes variability and the need for large numbers of animals. With

these advantages, however, comes the burden of time that is needed to establish stable behavioral performances.

In an attempt to decrease training time, the *Vogel conflict test* was developed (Vogel et al. 1971). The procedure utilizes water drinking in water-deprived rodents as the response. There is little training required to develop drinking from a drinking tube. Drug testing can occur after only a day of exposure to this procedure. During the actual assessment of drug effects, the animals are allowed to drink for a brief period (e.g., 3 min), and then an unsignalled punishment period begins in which licking results in electric shock (to the sipper tube or to the grid floor). It is critical to note that the Vogel conflict test is distinct from the Geller–Seifter procedure in that in the Vogel procedure drug effects are evaluated for their ability to prevent the response suppression following the introduction of shock, whereas in the Geller models, effects of drugs attenuate the suppression of behavior resulting from shock. Despite this difference, drug effects are often comparable across methods (see Table 1 and reviews in McMillan and Leander 1976; Millan 2003).

Although all punishment procedures cannot be described due to space constraints, it is important to mention the CER method. Under this method, originally developed by Estes and Skinner in 1941, steady rates of behavior are maintained under a variable-interval schedule of food delivery. A stimulus is then presented that terminates with the delivery of electric shock independently of responding. Repeated stimulus-shock pairings eventually result in a behavioral baseline characterized by steady rates of responding punctuated by the suppression of responding in the presence of the pre-shock stimulus. Although the outcome of this CER procedure is similar to that in the Geller–Seifter method (i.e., responding is suppressed during the stimulus associated with shock), a key difference is that in the CER procedure, the shock is independent of responding, whereas under the Geller–Seifter procedure, shock only occurs following a response. Though the behavior appears to be the same, the effects of drugs on these two different types of suppressed behavior can be quite different (Kelleher and Morse 1968).

Punished behavior as described earlier has been shown to be an effective method for studying the behavioral effects of drugs across many species including mice, rats, rabbits, pigeons, fish, nonhuman primates, and humans. Various responses have been successfully employed that include lever-pressing, nose-poking, key pecking in the case of pigeons, and chain pulling. In addition to the sensitivity of punishment to the effects of anxiolytic drugs, it is important to note that this behavior is relatively insensitive to the effects of other drug classes, such as the ▶ antipsychotics and ▶ antidepressants, which typically only further reduce punished behavior, thereby making these methods valuable assays for pharmacological evaluation (Table 1). As such, these methods have been of exceptional value in drug-screening efforts to predict potential therapeutic activity in humans.

Although large variations in the experimental conditions being studied generally do not alter the effects of drugs on punished behavior, there are conditions that easily modify the quantitative effects as well as the qualitative changes in the behavioral effects of drugs. Quantitative modifications in the magnitude of drug effects occur with variations in the reinforcement schedule, the frequency, and the intensity of the punisher, as well as the deprivation levels that are used. It is important to acknowledge that the conditions under which punished behavior is established and maintained are critical to the sensitivity to drug effects as well as to the qualitative and quantitative nature of those effects (Barrett 1987; McMillan 1975; Witkin and Katz 1990). While recognizing that human behaviors are not typically punished by electric shock but rather suppressed by a variety of social and other forms of stimuli, it appears that, based on a wide range of studies, the procedures described in this section have been generous in yielding not only an insight into the effects of punishment on behavior but also on the sensitivity and selectivity of punished behavior to the effects of various drugs. In addition, these procedures have also been applied to the investigation of ▶ anxiogenic behavioral effects and behavioral effects of drugs.

As noted earlier, the Geller–Seifter and Vogel conflict punishment procedures demonstrate a fair degree of pharmacological specificity that is exemplified in Table 1. These methods are robust detectors of compounds that are positive ▶ allosteric modulators of $GABA_A$ receptors (benzodiazepine anxiolytics, barbiturates, neuroactive steroids). Other compounds known to have antianxiety effects in humans also increase punished responding in these preclinical models (e.g., (alcohol) ▶ ethanol). However, anxioltyic-like effects (increases in punished responding) are generally not observed with a host of other drug classes and mechanisms (antidepressants, antipsychotics, opiate analgesics, psychomotor stimulants, and muscarinic antagonist amnestics) although exceptions exist (Table 1). Some of the other methods described in this chapter have broader scope in detecting pharmacological effects. Marble burying, for example, can detect the effects of acutely administered ▶ selective-serotonin reuptake inhibitors (SSRIs) as well as their subacute administration (Borsini et al. 2002). Since the SSRIs are used in the therapeutic control of anxiety symptoms and

Punishment Procedures. Table 1. Effects of some pharmacological agents in Geller-Seifter conflict and Vogel conflict procedures in rodents.

Compound[a]	Mechanism(s)/Class[b]	Activity[c]	Procedure[d]	Comment[e]
▶ Diazepam	Benzodiazepine receptor agonist	++	G-S	Clinical efficacy
		++	V	
▶ Chlordiazepoxide	Benzodiazepine receptor agonist	++	G-S	Clinical efficacy
		++	V	
▶ Lorazepam	Benzodiazepine receptor agonist	++	G-S	Clinical efficacy
		++	V	
Bretazenil	Benzodiazepine receptor partial agonist	++	G-S	Clinical efficacy
		++	V	
▶ Alprazolam	Benzodiazepine receptor agonist	++	G-S	Clinical efficacy
		++	V	
DOV 51892	Alpha-1-preferring GABAA agonist	++	V	Clinical efficacy – one study
TPA023	Alpha 2/3-preferring GABAA agonist	+	V	Conditioned drink suppression
NS11394	Alpha 3/5-preferring GABAA agonist	++	CER	CER data
Allopregnanolone	Neuroactive steroid GABAA agonist	++?	G-S	No comparator molecule
▶ Pentobarbital	Barbiturate GABAA agonist	++	G-S	Clinical efficacy
		++	V	
Muscimol	Direct GABA-A agonist	–	G-S	
		–	V	
Baclofen	GABA-B agonist	–	G-S	
▶ Chlorpromazine	Dopamine antagonist/Typical antipsychotic	–	G-S	
		–	V	Mouse procedure with food
▶ Haloperidol	Dopamine antagonist/Typical antipsychotic	–	G-S	Clozapine produced small increases
		–	V	
S32504	D3/D2 agonist	+	V	
▶ Clozapine	Atypical antipsychotic	+	G-S	Clinical efficacy
		–	V	
▶ Olanzapine	Atypical antipsychotic	+	G-S	Clinical efficacy
▶ *d*-Amphetamine	Dopamine stimulant	–	G-S	
		–	V	
▶ Yohimbine	Alpha 2 antagonist	–	G-S	
		+	V	
Amibegron	Beta 3 agonist	+	V	
▶ Propranolol	Beta antagonist	+	G-S	Effect under limited conditions
▶ Scopolamine	Muscarinic antagonist	–	G-S	
		–	V	
▶ Fluoxetine	5-HT uptake inhibitor/antidepressant	–	G-S	Clinical efficacy
		–	V	
▶ Imipramine	5-HT/NE uptake inhibitor/ antidepressant	–	G-S	

Punishment Procedures. Table 1. (continued)

Compound[a]	Mechanism(s)/Class[b]	Activity[c]	Procedure[d]	Comment[e]
		–	V	
► Valproate	Mood stabilizer/anticonvulsant	+	G-S	Conditioned emotional response method
		–	V	Mixed results in a small literature
► Gabapentin	Mood stabilizer/pain	+	G-S	CER procedure
8-OH-DPAT	5-HT1A agonist	+		Literature inconsistent
		+		
Flesinoxan	5-HT1A agonist	+		
► Buspirone	5-HT1A partial agonist	–	G-S	Clinical efficacy
		–	V	Literature inconsistent
WAY100635	5-HT1A antagonist	–	G-S	
		–	V	
MDL 100,907	5-HT2A antagonist	–	V	
Ritanserin	5-HT2A/2C antagonist	+	G-S	
BW 723C86	5-HT2B agonist	++	V	
SB 206553	5-HT2B/2C antagonist	+	V	
S32006	5-HT2C antagonist	+	V	Literature inconsistent
Ondansetron	5-HT3 antagonist	–	G-S	
		+	V	Effects not dose-dependent
SB 204070A	5-HT4 antagonist	–	G-S	
SB-399885	5-HT6 antagonist	+	V	
SB 269970	5-HT7 antagonist	+	V	
► Ethanol	Anesthetic/GABAA/NMDA	+	G-S	Clinical efficacy
		++	V	
► Morphine	Mu opioid agonist	–	G-S	
► Naloxone	Mu opioid antagonist	–	G-S	
Diprenorphine	Kappa opioid antagonist	+	G-S	
Ethylketocyclazocine	Kappa opioid agonist	–	G-S	
► Phencyclidine	Uncompetitive NMDA antagonist	–	G-S	Literature inconsistent
Dizocilpine	Uncompetitive NMDA antagonist	+	G-S	Literature inconsistent
		++	V	
CGP37849	Competitive NMDA antagonist	++	G-S	
		++	V	
Ifenprodil	NR2b/Polyamine NMDA antagonist	–	G-S	
ACPC	Glycine B-site NMDA partial agonist	–	G-S	Pigeon
		++	V	
EGIS-10608	AMPA antagonist	+	V	Literature inconsistent
LY388284	Kainate antagonist	+	V	
EMQMCM	mGlu1 antagonist	–	G-S	
LY354740	mGlu2/3 agonist	–	G-S	
LY341495	mGlu2/3 antagonist	–	G-S	
Fenobam	mGlu5 antagonist	++?	G-S	Clinical efficacy; No comparator

Punishment Procedures. Table 1. (continued)

Compound[a]	Mechanism(s)/Class[b]	Activity[c]	Procedure[d]	Comment[e]
		++?	V	Clinical efficacy; No comparator
MPEP	mGlu5 antagonist	++	G-S	
SCH 221510	Nociceptin 1 agonist	+	V	
GR205171	NK1 antagonist	–	G-S	Safety-signal withdrawal procedure
		–	V	
SR48968	NK2 antagonist	–	G-S	
		–	V	
R278995/CRA0450	CRF1 antagonist	–	V	
SSR149415	Vasopression 1b antagonist	+	V	
PD 135,158	CCK-B antagonist	–	V	Literature inconsistent
SNAP 37889	Galanin 3 antagonist	++	V	
► Rimonabant	CB1 antagonist	+	V	
MCL0042	MC4 antagonist/SSRI	+	V	
► Pregabalin	Ca++ channel blocker/anticonvulsant	+	G-S	Clinical efficacy

[a]Only selected compounds are shown for purposes of comparing mechanisms/drug classes using data from two major classes of punishment procedures. Only data from systemic dosing are included. Only data from acute dosing are included. Anxiolytic-like effects of some compounds in these assays have been reported in the literature but with other procedures suggested to detect anxioltyic mechanisms (e.g., endocannabinoid uptake or enzyme inhibition; mGlu8 agonists; gabapentin). It must also be noted that sometimes the findings summarized have not been replicated.
[b]A comprehensive review of drug effects under the Vogel conflict procedure and associated mechanisms can be found in Millan (2003). General summaries of data in the Geller–Seifter procedures can be found in McMillan and Leander (1976), Kelleher and Morse (1968).
[c]Data included in this table represent results of findings from a host of sources readily accessible in the archival literature; a listing is available upon request from the authors. Data from experiments using rats are used when possible to keep the compound comparisons as uncomplicated as possible. Data are classified by activity on the basis of comparison to the maximal effect observed under the procedure. Maximal effect in each experiment was estimated on the basis of effects of a positive allosteric modulator of GABAA receptors, generally, a benzodiazepine anxiolytic. ++: maximal increase in punished responding at some dose (in comparison with a benzodiazepine anxiolytic if available); +: significant increase but less than maximal; –: no increase in punished responding or decrease at some dose; ++? An increase in punished responding was observed but the comparative magnitude of effect relative to a standard was not tested in the same study.
[d]Data from two major types of procedures are compared if available. *G-S*: Geller–Seifter conflict tests of which there are variants; *V*: Vogel conflict tests of which there are variants.
[e]Clinical efficacy is in reference to anxiety disorders. Literature inconsistent refers to both the potential qualitative differences observed with the specific compound and/or with discrpencies across compounds within a given mechanism of action.
ACPC 1-aminocyclopropanecarboxylic acid; *BW 723C86* 1-[5-(2-thienylmethoxy)-1H-3-indoyl] propan-2-amine hydrochloride; *EGIS-10608* (±) 1-(3-methyl-4-amino-phenyl)-4-methyl-7,8-methylenedioxy-4,5-dihydro-3-acetyl-2,3-benzodiazepine; *EMQMCM* ((3-ethyl-2-methyl-quinolin-6-yl)-(4-methoxy-cyclohexyl)-methanone methanesulfonate); *8-OH-DPAT* 8-hydroxy-2-(di-*n*-propyl-amino) tetralin; *GR205171* (S)-(2-methoxy-5-(5-trifluoromethyltetrazol-1-yl)-phenylmethylamino)-2(S)-phenylpiperidine; *LY341495* (2*S*)-2-amino-2-[(1*S*,2*S*)-2-carboxycycloprop-1-yl]-3-(xanth-9-yl) propanoic acid; *LY35474* (+)-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylate monohydrate; *LY388284* 3S,4aR, 6S,8aR-6-((4-carboxyphenyl)methyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid; *MCL0042* 1-[2-(4-fluorophenyl)-2-(4-methylpiperazin-1-yl)ethyl]-4- [4-(1-naphthyl) butyl]piperazine; *MDL 100,907* R-(+)-alpha-(2,3-dimethoxyphenyl)-1-[2-(4-fluorophenyl)ethyl-4-piperidinemethanol; *MPEP* (2-methyl-6-(phenylethynyl)pyridine); *NS11394* [3_-[5-(1-hydroxy-1-methyl-ethyl)-benzoimidazol-1-yl]-biphenyl-2-carbonitrile]; *PD 135,158* N-methyl-D-glucamine; R278995/CRA0450 1-[8-(2,4-dichlorophenyl)-2-methylquinolin-4-yl]-1,2,3,6-tetrahydropyridine-4-carboxamide benzenesulfonate; *S32006* N-pyridin-3-yl-1,2-dihydro-3H-benzo[e]indole-3-carboxamide; *S32504* (+)-trans-3,4,4a,5,6,10b-hexahydro-9-carbamoyl-4-propyl-2H-naphth[1,2-b]-1,4-oxazine; *SB-399885* N-[3,5-dichloro-2-(methoxy)phenyl]-4-(methoxy)-3-(1-piperazinyl)benzenesulfonamide; *SCH 221510* 8-[bis(2-methyl-phenyl)-methyl]-3-phenyl-8-azabicyclo[3.2.1]octan-3-ol; *SNAP 37889* (1-phenyl-3-[[3-(trifluoromethyl)pheny-l]imino]-1*H*-indol-2-one; *SSR149415* (2S,4R)-1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxy-phenyl)-2-oxo-2,3-dihydro-1H-indol-3-yl] -4-hydroxy-N,N-dimethyl-2-pyrrolidine carboxamide; TPA023: 7-(1,1-Dimethylethyl)-6-(2-ethyl-2H-1,2,4-triazol-3-ylmethoxy)-3-(2-fluorophenyl)-1,2,4-triazolo[4,3-b]pyridazine; *WAY 100635* *N*-[2[4(2-methoxyphenyl)-1-piperazinyl]xethyl]-*N*-(2-pyridinyl) cyclohexanecarboxamide trihydrochloride.

► obsessive–compulsive disorder (OCD) as are some antipsychotic agents, the pharmacological specificity of the punishment methods clearly do not universally detect the breadth of antianxiety mechanisms known to be medically valuable (though some variations in these methods have increased sensitivity). Nonetheless, punished responding is still widely used to evaluate potential anti-anxiety compounds and mechanisms. Table 1

illustrates that novel mechanisms sometimes display positive effects in these punishment assays.

Cross-References

- ► Alcohol
- ► Animal Models for Psychiatric States
- ► Antidepressants
- ► Anxiety: Animal Models
- ► Barbiturates
- ► Benzodiazepines
- ► Benzodiazepine Agonists
- ► Dissociative Anesthetics
- ► Elevated Plus-Maze
- ► Emotion and Mood
- ► Hypnotics
- ► Mood Stabilizers
- ► Passive Avoidance
- ► Social Anxiety Disorder
- ► SSRIs and Related Compounds

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Pure Insertion

- ► Cognitive Subtraction

Puromycin

Definition

An aminonucleoside isolated from *Streptomyces alboniger* that inhibits protein synthesis by causing premature chain termination during polipeptide translation.

Purposive Behavior

- ► Operant Behavior in Animals

Q

Q'at

► Khat

Qat

► Khat

qEEG

Synonyms

Digital EEG; Quantified (wake) EEG

Definition

First an analog-amplified EEG trace is obtained in the form of equidistant samples. To minimize errors like aliasing, the signal is in practice low-pass filtered (e.g., high cutoff at 70 Hz, steepness 24 dB/oct or 48 dB/oct commensurate with Bessel characteristics). The interval is determined by the sampling rate, usually 256 samples/s or higher. From here, PC-assisted digital filtering, artifact rejection, and quantification in the frequency domain become feasible.

Cross-References

► Digital EEG Nomenclature
► Electroencephalography
► Spectrograms

QOL

► Quality of Life

QT Interval

Definition

The *QT interval* is a measure of the time between the start of the *Q wave* and the end of the *T wave* in the heart's electrical cycle. The QT interval is dependent on the heart rate; (the faster the heart rate, the shorter the QT interval) and has to be adjusted to aid interpretation. The standard clinical correction is to use Bazett's formula (named after physiologist Henry Cuthbert Bazett). The corrected QT interval is denoted as QTc. Normal values for the QT interval are between 0.30 and 0.44 s (0.45 s for women). The QT interval is influenced by various antidepressants and antipsychotic drugs and thus caution must be exercised while prescribing these drugs particularly in vulnerable individuals with cardiac ailments.

Cross-References

► Antidepressants
► Antipsychotic Drugs

Quality of Life

Synonyms

QOL

Definition

Quality of life (QOL) is the degree of well-being felt by an individual or group of people. The perception of QOL is made up of two components: the physical and the psychological. QOL can be measured only indirectly using different rating scales or questionnaires.

Cross-References

► Quality of Life: Assessment

Quality of Life Scales

► Impairment of Functioning; Measurement Scales

Quantified (Wake) EEG

► qEEG

Ian P. Stolerman (ed.), *Encyclopedia of Psychopharmacology,* DOI 10.1007/978-3-540-68706-1,

Quazepam

Definition

Quazepam is a benzodiazepine with hypnotic and anticonvulsant properties. Clinically, quazepam is particularly effective in the short-term treatment of insomnia by inducing and maintaining sleep. Unlike other benzodiazepines, quazepam selectively targets $GABA_A$ type 1 receptors, but one of its major long-acting metabolites does not share this selectivity. Due to its long-lasting action, impairment of motor function is a significant side effect. Quazepam use is subject to tolerance, abuse, dependence, and withdrawal, although possibly with reduced severity as compared with other benzodiazepines.

Cross-References

- ▶ Benzodiazepines
- ▶ $GABA_A$ Receptors
- ▶ Insomnias
- ▶ Sedative, Hypnotic, and Anxiolytic Dependence

Querulous Paranoia

- ▶ Delusional Disorder

Quetiapine

Definition

Quetiapine is a second-generation antipsychotic that acts as an antagonist at dopamine D2 and serotonin $5\text{-}HT_{2A}$ receptors, with a generally broad receptor-binding profile. Quetiapine is indicated for the acute and maintenance treatment of schizophrenia and bipolar disorder. Because of its low propensity to cause extrapyramidal symptoms, the drug can be used to treat psychosis in Parkinson's disease. It is a dibenzothiazepine derivative that dissociates quickly from the D2 receptor. Fast-dissociating D2 antagonists have been hypothesized to allow dopamine to still interact with the D2 receptor under conditions of phasic bursts of dopamine release, thereby eliciting its normal effects in the nigrostriatal and tuberoinfundibular pathways and reducing the risk of side effects. Possibly because of these properties, the risk of extrapyramidal symptoms and effects on prolactin release is lower than for first-generation antipsychotics. Quetiapine has relatively prominent histamine H1 antagonistic effects that are likely to contribute to its sedative properties. The drug also has an active metabolite, norquetiapine.

Cross-References

- ▶ Antipsychotic Drugs
- ▶ Antipsychotic Medication: Future Prospects
- ▶ Bipolar Disorder
- ▶ Parkinson's Disease
- ▶ Schizophrenia
- ▶ Second- and Third-Generation Antipsychotics

R

Radial Arm Maze

Synonyms
Olton maze; Radial maze

Definition
The radial arm maze, originally developed by David Olton, is an apparatus that taps into natural foraging abilities of rodents and can be used to test different types of memory, including short-term (working), long-term (reference), nonspatial and spatial memory. The arena consists of a number of arms (typically ranging from 4 to 16) that extend from a central hub, and food is placed in the ends of some or all of the arms. The food cannot be seen from the central platform. Versions that test spatial memory require rats or mice to navigate through the environment using allocentric spatial cues placed around the maze. Thus, animals must recall which arms had been entered or remain to be entered using the location of each arm relative to the different cues around the maze. Numerous studies have shown that rats do indeed use a spatial strategy to solve this task, as elaborate control experiments have been used to ensure that the rats do not simply use their sense of smell either to sense unclaimed food objects or to sense their own tracks.

Cross-References
► Rodent Models of Cognition
► Short-Term and Working Memory in Animals
► Spatial Learning in Animals

Radial Maze

► Radial Arm Maze

Radioactive Tracer

► Radiopharmaceutical

Radiolabeled Probe

► Radiotracer

Radioligand

► Radiopharmaceutical
► Radiotracer

Radioligand Binding

► Receptor Binding

Radionuclide

Definition
A radionuclide is an unstable isotope that undergoes radioactive decay.

Cross-References
► Positron Emission Tomography (PET) Imaging

Radiopharmaceutical

Synonyms
Radioactive tracer; Radioligand

Definition
A radiopharmaceutical consists of a radionuclide attached to a compound of interest. In the case of a perfusion radiopharmaceutical, the compound of interest should have properties that allow distribution in proportion to brain blood flow but the compound should not have specific binding to brain components. In the case of a target molecule-binding radiopharmaceutical, the compound of interest should bind with high specificity to a target

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molecule, such as a neurotransmitter receptor or a neurotransmitter reuptake transporter.

Cross-References

► Positron Emission Tomography (PET) Imaging

Radiotracer

Synonyms

Radiolabeled probe; Radioligand; Reporting ligand; Tracer

Definition

A molecule containing a positron-emitting isotope, used as a tracer in PET imaging. Generally, a very small fraction of the molecules of the radiotracer contain the positron emitter – the majority contain the stable isotope. The decay events of the unstable isotope are recorded by the imaging system; this in turn allows the pharmacokinetic fate of the radiotracer to be inferred.

Radiotracer Imaging

► Positron Emission Tomography (PET) Imaging

Randomized Controlled Trials

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Synonyms

Controlled clinical trials; Randomized clinical trials

Definition

Randomized controlled trials (RCTs) are studies in which people are allocated at random (*by chance alone*) to receive one of two or more treatments. People who take part in an RCT are called *participants* (or *subjects*). The Consolidated Statement of Reporting Trials (CONSORT) provides readers of RCTs with a list of criteria that will be useful to assess trial validity (for full details visit www.consort-statement.org) (Altman 1996).

As quantitative, comparative studies, RCTs are one of the simplest and most powerful tools in clinical research. In the field of medicine (and, of course, in psychiatry also) RCTs are recognized as the most rigorous method of assessing the efficacy of interventions, and are designed to determine whether an association exists between treatment and outcome (Rees 1997). RCTs essentially provide evidence of causality. These clinical studies point to a link between events rather than an explanation of how or why these events may be linked.

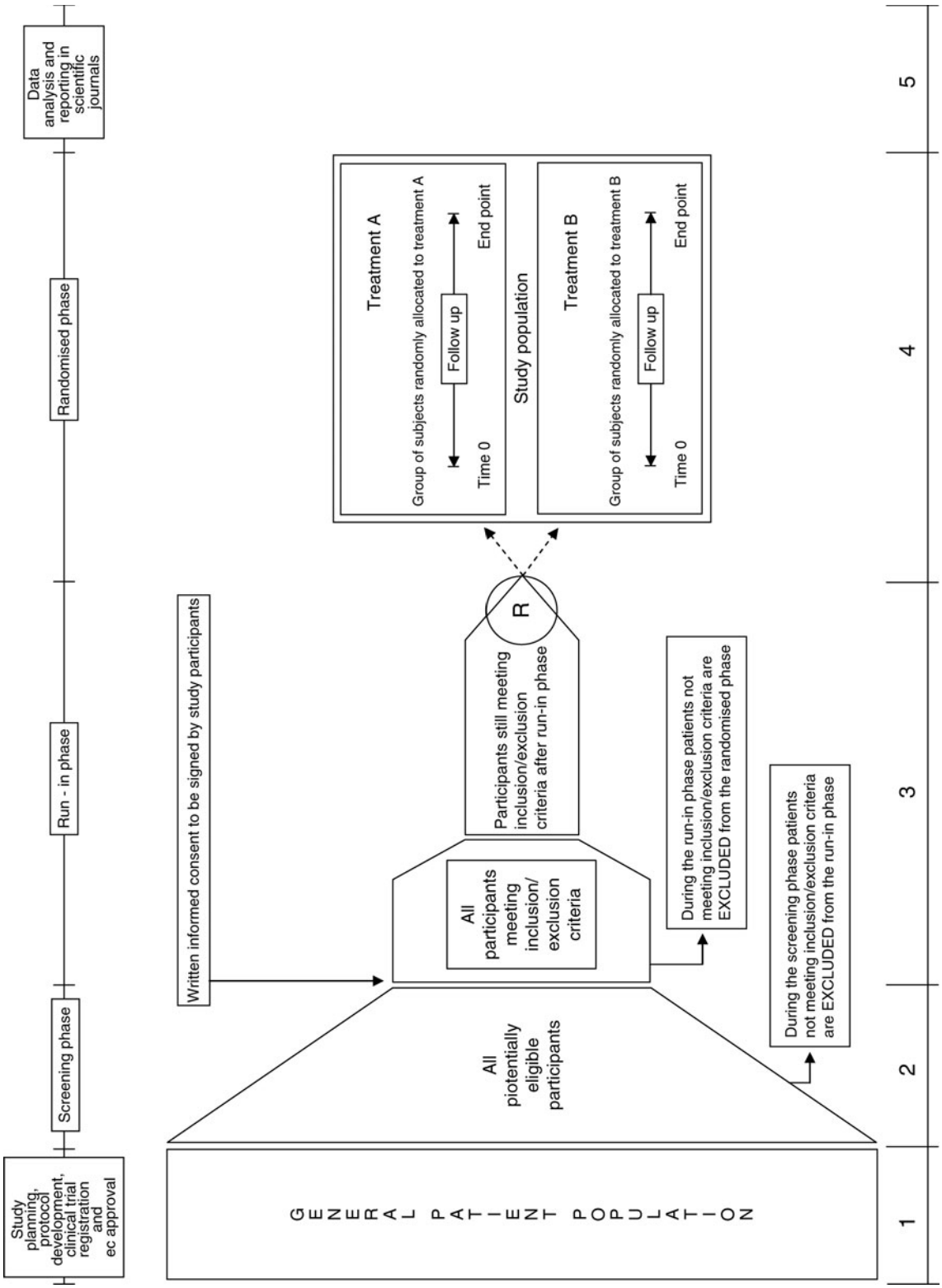
Random allocation ensures that there are no systematic differences between intervention groups in factors, known and unknown, that may affect outcome. Other study designs, including nonrandomized controlled trials, can detect associations between an intervention and an outcome; however, they cannot rule out the possibility that a third factor – or *confounder* – linked to both intervention and outcome, might have caused the association. To be convincing, observational studies need very large samples, which can provide sufficient power to control for known variables that might influence the outcome of treatment (e.g., age, sex, social class, ethnic group, and other clinically meaningful variables such as severity of illness or setting of health care). Even then, there is the risk of residual confounding, and it is impossible, of course, to control for unknown factors. Randomization is the only way of controlling for both known and unknown factors, and it is also very efficient. Nonetheless, RCTs are generally more difficult, costly and time consuming than other study designs. Careful consideration needs to be given, therefore, to their use and timing.

Current Concepts and State of Knowledge

The main phases of an RCT are shown in the Fig. 1

Study Planning and Protocol Development

Before starting to design an RCT, the two key questions to be asked are (1) whether the tested intervention is sufficiently well developed to permit evaluation, and (2) whether there is enough preliminary evidence that the intervention is likely to be beneficial (most frequently, this evidence comes from observational studies). The development of a new pharmaceutical is conventionally divided into phases, with the initial preclinical toxicity and pharmacological work leading to small preliminary trials in human volunteers (► phase I), then small (perhaps 30–50 participants), usually randomized, studies in patients, before the pivotal ► phase III RCTs of efficacy and safety. Noncommercial trials will try to replicate this approach. The retrieval of preliminary data will need to



Randomized Controlled Trials. Fig. 1. The main phases of a randomized controlled trial.

inform the estimation of the size of the likely treatment effect, dose, and safety. Such information is needed to estimate the sample size of the study and also to justify the expenses of a larger trial. When planning an RCT, it is now common for trialists to carry out a systematic review of the available evidence to answer these questions.

The trial protocol should be as detailed as possible, describing every step of the study (e.g., identification of the problem, application of the results, etc.) and answering relevant questions (Are the objectives consistent with the study question? Does the study design achieve these objectives? What is the public health impact of the findings?). In the protocol, researchers need to report all information about the conduct and analysis of the trial (e.g., criteria for the inclusion or exclusion of the study population, data handling, and data analysis plan). The lead author of the protocol needs to identify individuals with relevant experience to contribute to the protocol and to provide statistical input or technical information. All protocols must meet a standard that adheres to the principles of Good Clinical Practice, prior to being submitted to the Ethics Committee (EC) or Institutional Review Board (IRB) (for details, see the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use – ICH, available at http://www.ich.org/cache/compo/276-254-1.html). After preparation, the first draft of the protocol should be peer reviewed, ensuring that all points have been incorporated or discussed further within the review team. In parallel with finalizing the protocol, it is necessary to prepare all other necessary trial documents, such as subject information sheets and informed consent forms (an example can be found on the Web at the following address: http://www.dh.gov.uk/en/Publichealth/Scientificdevelopmentgeneticsandbioethics/Consent/Consentgeneralinformation/DH_4015950).

Ethics Committee Approval

Once the protocol and other relevant documentation are ready, applications should be made to the EC. As for experimental studies that have the potential of risk to human subjects, all related RCTs have to be approved by an EC before patient recruitment is started. All study participants must be informed about the study characteristics; they must provide written informed consent before enrollment into the trial. In some circumstances, an RCT may be ethical but difficult to carry out (or even unfeasible). One reason might be difficulties with randomization or recruitment (Fairhurst and Dowrick 1996). For example, once an intervention becomes widespread, it can prove impossible to recruit clinicians who are willing to "experiment" with alternatives. This might be true for some widespread practices in clinical psychiatry that are actually not backed by randomized evidence. For example, it is not clear whether anticholinergic drugs work better than ▶ levodopa against ▶ extrapyramidal side effects in patients with ▶ schizophrenia who take long-term antipsychotic medications; however, in daily clinical practice clinicians are reluctant to use specific antiparkinsonian drugs (such as levodopa) that might trigger psychotic symptoms. Strong patient preferences may also limit recruitment and bias outcomes if not accommodated within the study design (Brewin and Bradley 1989).

Clinical Trial Registration

The protocol should also be registered for publication in dedicated Web sites. Based on both ethical and scientific reasons, since 2000 major registries (such as ClinicalTrials.gov and Controlled Clinical trials) have been recording trial protocol information. This progress in the public registration of clinical trials worldwide is important because it allows clinicians and researchers to see in advance details about study conduct and analysis in a more transparent way. The number of registered trials increased dramatically in 2005 after the requirement for registration was introduced by several medical journals, led by the International Committee of Medical Journal Editors.

Screening Phase

All patients enrolled in the study must meet the eligibility criteria. Screening procedures are performed to determine the eligibility of participants for the study and document their baseline medical conditions. Information gathered during the screening phase is used to make decisions on participants' eligibility. Therefore, the threshold for access to assessment should be set at a low enough level to ensure people are not screened out before full information on their condition is obtained. There are usually one or two screening visits, and all screening and enrollment procedures take place within a pre-defined period (7–56 days, depending on the clinical status and diagnosis).

Run-In Phase

Run-in phases are pre-randomization periods used to select or exclude patients in a clinical trial. Run-in periods might be used to exclude non-compliant subjects, placebo responders, or subjects who could not tolerate or did not respond to active drug. For this reason, run-in periods have implications for interpreting the results of clinical trials and applying these results in clinical practice (Pablos-Méndez et al. 1998).

Run-in phases can use either ▶ placebo or active therapy, and are usually single-blind or unblinded (that is,

only the study staff is aware of the nature of the medication). A placebo run-in allows trial staff to be sure that reported side effects are not caused by treatment. By contrast, an active run-in can identify and exclude individuals who may be unable to tolerate the medication being tested in a long-term trial. For instance, the long-term treatment of ▶ bipolar disorder is supposed to be a treatment specifically intended to prevent recurrence of mood episodes. Subjects who are entering a long-term trial are asked to take the study medication (or the combined study medications) for a long period of time. In real-world clinical settings, people who are prescribed long-term treatments will usually be selected from those who have been able to tolerate the medication in the short-term – perhaps during acute phase therapy. In these studies, a run-in design (that is a run-in phase with active long-term treatments before randomization) may maximize the study power through participants' better compliance. Individuals who lose interest early on (potential "drop-outs") can then be excluded before random allocation. Similarly, subjects who become convinced about receiving the intervention treatment (potential "drop-ins") can also withdraw before randomization. This potentially lowers rates of anticipated noncompliance to allocated treatment during a trial, resulting in a smaller required sample size. Once randomized, these participants would generally be included in an intention-to-treat analysis (for details, see below).

Run-in periods can dilute or enhance the clinical applicability of the results of a clinical trial, depending on the patient group to whom the results will be applied. This approach usually enhances clinical applicability by selecting a group of study subjects who closely resemble patients undergoing active clinical management for this problem. However, compared with results that would have been observed without the run-in period, the reported results might overestimate the benefits and underestimate the risks of treatment. Because the reported results apply to subgroups of patients who cannot be defined readily based on demographic or clinical characteristics, the applicability of the results in clinical practice might be diluted. For this reason, reports of clinical trials using run-in periods should indicate how this aspect of their design might affect the application of the results to clinical practice.

Randomized Phase

RCTs have several important features:

- Randomization
- Allocation Concealment
- Blinding
- Choice of Interventions and Outcomes

Randomization

The simplest approach to evaluating a new treatment is to compare two consecutive series of patients (historical controls are undesirable because of the consistent tendency for historically controlled trials to yield more optimistic results than randomized trials). If clinicians are allowed to choose which treatment to give to each patient, there will probably be differences in the clinical and demographic characteristics of the patients receiving the different treatments. Such systematic differences are called *bias,* and bias may lead to a distortion (overestimate or underestimate) of the difference between treatments (Schulz et al. 1995). Thus, the main reason for using randomization to allocate treatments in a controlled study is to try to prevent biases. Randomization is a process that aims at producing groups that are similar in terms of clinical, demographic, and prognostic factors. Random allocation means that each patient has a known, equal chance of being given each treatment, but the treatment to be given to each patient cannot be predicted.

The process of randomization begins with the generation of a random allocation sequence. The simplest procedure to equally allocate to two treatment groups involves using a table of computer-generated random numbers. This is called simple randomization, and it is equivalent to tossing a coin. Similar lists of random numbers can be found in most statistics textbooks. From a methodological point of view, a simple randomization may remove the risk of bias from the allocation procedure; however, it cannot guarantee that the individuals in each group have a similar distribution of clinical or demographic variables. Some chance imbalance may occur, especially in small studies. An imbalance in the distribution of baseline characteristics might make the interpretation of results complicated or even impossible. There are ways to modify simple randomization, such as *block randomization* and *stratified randomization. Block randomization* ensures closely similar numbers of patients in each group; by contrast, *stratified randomization* is used to keep the groups balanced for certain important clinical or prognostic patient characteristics, producing a separate randomization list for each pre-specified subgroup based on such characteristics (each such subgroup is called a *stratum*). For instance, in multicenter studies, the stratifying variable may be the study center itself, because the patients within each center need to be equally randomized to one or the other of the two study treatments. Stratified

randomization can be extended to two or more stratifying variables, even though in small studies it is not practical to stratify on more than one (or perhaps two variables), as the number of strata can quickly approach the number of subjects. When it is really important to achieve close similarity between treatment groups for several variables, *minimization* can be used. *Minimization* is based on a different principle from randomization, and it has the advantage, especially in small trials, that there will be only minor differences between groups in those variables used in the allocation process. When using minimization, the first participant is randomly allocated to treatment, but each subsequent participant is allocated to the treatment that would lead to a better balance between the groups in the variables of interest. The chosen treatment could simply be taken as the one with the lower allocated sample (100% of probability to be allocated to this group); otherwise, a random element can be introduced (a high chance, say 80%, of probability to be allocated to the treatment that minimizes the imbalance – the so-called, *weighted randomization*). The use of a random element makes the allocation more unpredictable. Even though it may slightly worsen the overall imbalance between the groups, the balance (for the chosen variables) is usually much better than with simple randomization. Minimization is a secure allocation system when used by an independent person. In RCTs, individual patients are usually randomized to a treatment or control group, but sometimes cluster-randomized controlled trials are carried out, in which groups (or clusters) of individuals, rather than individuals themselves, are randomized. The groups may be villages, colleges, medical practices, or families. A cluster-randomized design may be used simply for convenience. One of the main consequences of a cluster design is that participants within the cluster often tend to respond in a similar manner, and thus their data can no longer be assumed to be independent of one another. In such studies, the "unit of allocation" is the cluster and not the patient. Cluster trials are increasingly common because they are often the only valid approach to evaluate certain types of interventions (such as those used in health promotion and educational or psychosocial interventions). However, cluster trials are generally more difficult to design and carry out than individually randomized studies, and some of their design features may make them particularly vulnerable to bias. A proper analysis can help overcome this risk.

Allocation Concealment

The process of randomization does not end until participants are actually assigned to their groups. Allocation concealment refers to the process used to ensure that subjects, investigators, and all other study personnel are unaware which group participants are being allocated to at the time they are enrolled in the study. Adequate methods of concealment might be centralized allocation (for instance, via telephone), computerized allocation systems (via web-based facilities) or coded identical containers (using sealed envelopes). The use of adequate methods of concealment is considered an indicator of a well-conducted study (see CONSORT Statement). There is evidence that where allocation concealment is inadequate, investigators can overestimate the effect of interventions by up to 40%. Study reports should include a description of the method used to conceal allocation, with enough technical details to let readers determine the likelihood of the success of this process.

Blinding

Blinding refers to the process whereby people are kept unaware of which treatment an individual patient has been receiving. Blinding (or "masking") is different from allocation concealment. Blinding is the prevention of knowledge of treatment assignment after randomization has been done; allocation concealment refers to the prevention of knowledge of upcoming assignment from the randomization sequence before the treatment is allocated. Allocation concealment is part of the randomization process and must always be included in the design or conduct of an RCT. By contrast, blinding, in some clinical circumstances, may not be feasible, for example in trials investigating the effect of some psychological treatments. However, blinding might be very important when the outcome for a patient has to be assessed (most of all, when using a clinician-based rating scale).

Blinding can be carried out up to four levels: (1) patient; (2) investigator (or clinical trial nurse); (3) outcome assessor; (4) biostatistician. In medical journals, the term "double-blind" is often used. This term does not have a standard definition and cannot always be relied upon to convey which groups in an RCT were truly blind (for further details, please visit www.consort-statement.org). Because of this ambiguity, descriptions of blinding in reports of RCTs ideally should be explicit, reporting precisely who was masked and how this was done.

Choice of Interventions and Outcomes

A key component of an RCT is to specify the interventions of interest and the interventions against which these will be compared (Huston and Locher 1996). These interventions are called *comparisons*. One of these treatments is a treatment commonly used in clinical practice – the

so-called *standard* (or *control*) treatment; the new treatment to be tested in the study is named *experimental* (or *investigational*) treatment. The control might be an inactive control intervention (such as placebo, no treatment, standard care, or a waiting list control), or an active control intervention (such as a different variant of the same intervention, a different drug, a different kind of therapy, or a combination treatment, when the intervention of interest is combined with another intervention). When specifying drug interventions, dosing factors such as drug preparation, route of administration, and dose, duration and frequency of administration should be considered and clearly specified in the study protocol. Regarding dose, for example, it is necessary to know whether there is a critical dose below which the intervention may not be effective. Dosing factors are important because study authors must always consider whether the characteristics of the intervention might result in substantially different effects on the participants and outcomes of interest. For instance, when comparing two drugs, it would be unacceptable to use one drug at the lower end of the therapeutic range and the second one at the higher end of the therapeutic range. This imbalance might affect the reliability of the study results, reducing the internal and external validities of the RCT. For more complex interventions (such as psychoeducational or psychotherapeutic interventions, like cognitive-behavioral or psychodynamic psychotherapy), the core features of the interventions have to be defined. In general, for psychotherapies it is useful to report exactly what is delivered, at what intensity, how often it is delivered, who delivers it, and whether people involved in delivery of the intervention need to be trained (manualized interventions).

Another key component of an RCT is the delineation of particular outcomes that are of interest. In general, an RCT should have a primary outcome (on which to base the calculation of sample size) and also include other outcomes that are likely to be meaningful to patients and clinicians. Outcomes may include survival (mortality), clinical events (recurrence, relapse, and hospitalization), patient-reported outcomes (rating of symptoms, quality of life), adverse events, and economic outcomes (costs and resource use). When planning an RCT, authors should consider how outcomes may be measured, in terms of both the type of scale to be used and the timing of measurement. Outcomes may be measured objectively (number of relapses, number of hospitalizations) or subjectively as rated by a clinician, patient, or caregiver (for instance, severity of illness scales or disability scales). In other fields of medicine, it is common to use so-called *hard outcomes* (that is, objective outcomes like mortality rates, concomitant medications, return to work). By contrast, in psychiatric trials changes in rating scale scores are more commonly reported. There are four different kinds of rating scales that can be used in psychiatric trials: (1) observer-based disease-specific rating scales, where a clinician rates a patient on items about a specific disease; (2) patient-based disease-specific rating scales, which analyze the same domains from a patient's perspective; (3) observer-based non-disease-specific scales, which are rating scales filled by clinicians and designed to measure a patient's global functioning; and (4) patient-based non-disease-specific scales of global functioning. If a psychiatric treatment really worked, one might expect the effect of treatment to show up on rating scales from all four domains of measurement. However, this often does not happen because of the complexity of psychiatric illness and because of the degree of subjectivity in assessing outcomes. This is the reason why it is important to use published or validated rating instruments. Furthermore, when defining the timing of outcome measurement, authors may consider whether all timeframes or only selected time points are to be considered.

Data Analysis and Reporting in Scientific Medical Journals

Analysis

Attrition, a ubiquitous problem in RCTs of psychotropic agents, can cause biased estimates of the treatment effect, reducing statistical power and restricting the generalizability of results. There are various approaches to data analyses in RCTs (Rennie 1999). One way is to include data only on participants, whose results are recorded, using as a denominator the total number of people who had data recorded for the particular outcome in question. Another way is to use the total number of randomized participants, irrespective of whether some participants withdrew from the study. This will involve imputing outcomes for these missing participants. There are several approaches to imputing outcome data, either for dichotomous or continuous outcomes. One common approach is to either assume that all the missing participants experienced the event, or that all of them did not. An alternative approach is to impute data according to the event rate observed in the control group, or according to event rates among completers in the separate groups (the latter provides the same estimate of intervention effect but results in an unwarranted inflation of the precision of effect estimates). The choice among these assumptions should be based on clinical judgment and should be pre-planned and clearly reported in the study protocol. Intention-to-treat analysis maintains the advantages of random

allocation, which may be lost if subjects are excluded from analysis through, for example, withdrawal or failure to comply.

Journal Reporting

When data are analyzed, results of the RCT are disseminated and published in scientific journals. To be published, study reports must undergo a peer-review process. Almost all the most important scientific journals want to see the study protocol before accepting a study for publication, in order to check the consistency between the protocol and the full report of the RCT (Gilbody and Song 2000).

The first use of an RCT in psychiatry was to demonstrate that cortisone did not work for schizophrenia. Nowadays in psychiatry, new agents are usually compared with placebo. This is because there is a high placebo response rate that varies considerably depending on chronicity, severity, and subtype of the disorder. While it has been suggested that placebo run-in periods can help to control for this, evidence is inconsistent. In an illness such as ► major depression, up to 50% of those who respond while taking a medication may improve due to placebo factors. This placebo response rate in depression RCTs varies, but is growing. In other disorders (such as ► obsessive–compulsive disorder or schizophrenia), the placebo response is much less. The use of a placebo arm in an RCT raises ethical, clinical, and methodological issues. Ethically, it may be argued that placebo is only appropriate when no established effective treatment is available. On the other hand, the dangers of marketing ineffective drugs or psychotherapies that carry risks of side effects may outweigh the modest risk associated with placebo treatment in randomized, placebo-controlled trials. A placebo group is essential to establish that a treatment is effective for any condition. However, a placebo-controlled design may also influence the outcome of the trial. For example, individuals likely to participate in a placebo-controlled trial have less severe, less chronic, and less disabling disease. Therefore, they may be the very people who are apt to respond to placebo.

One important issue for RCTs in psychiatry is the way in which the treatments are delivered. In drug trials, a dosage schedule must be specified. This can be left up to the clinician or predetermined by the investigators. Clinician titration is probably closer to clinical practice, and may reduce dropouts since sensitive patients will be maintained at lower doses and dosage increased more slowly. The exact details of treatment and comparator are also important in trials of psychotherapeutic interventions. Since different types of psychotherapies may give rise to different results, it is important to define the exact form of therapy to be given, to ensure adherence of therapists to that therapy, and to maintain its quality. In reporting the trial, it is important to describe the therapy in such a way that it can be replicated if it proves to be clinically useful. RCTs have particular problems when comparing psychotherapies, of which the most serious is that interventions do not represent distinctly different treatments (because of the many factors common to all forms of psychotherapy) and therefore violate the premise of controlled trials. Often it may not be possible to sufficiently control how treatments are conducted, leading to poor external validity of psychotherapy RCTs. In psychotherapy, for example, RCTs typically involve manual-based interventions. However, the relationship of these therapies to general practice may be unclear, since in reality most clinicians do not have the level of training and supervision provided to research therapists.

Apart from the proposed treatments under investigation in an RCT, it is important to anticipate the possibility that additional, less specific treatments will be needed during a trial. In trials for ► mania or depression, certain "rescue" medications (such as, ► benzodiazepines) may be used. The use of rescue medications may vary between study groups and could obscure a difference in outcome. This may therefore need to be considered as an actual treatment outcome. The use of additional treatments (and which medications to use) should also be predetermined and included in the protocol.

Many published trials in psychiatry have included several outcome measures. This makes it likely that at least one of them will show a difference by chance. It is not easy to decide on a single outcome measure. Differing definitions of what constitutes a response to treatment is a problem in psychiatric trials where clear outcomes, such as death or highly reliable physiological changes, are rarely suitable. In many trials of antidepressant treatment, it has been total score or change from baseline on a rating scale at a pre-defined time point. Psychiatry researchers are increasingly advocating the use of simple objective outcomes to make trials large enough (and therefore simple enough to be carried out at many sites) to show relatively small differences.

A typical psychiatric RCT has fewer than 100 subjects. Small samples are more likely to have initial group differences (despite randomization) and differential dropout rates. Statistical techniques can be used to control for differences in assignment or from dropouts, but small samples can only have adequate power to detect moderate to large treatment differences and are unlikely to detect

differences either in rare events, such as a suicide attempt, or factors that have high variability.

Randomized controlled trials often recruit different subjects from those who present to clinical services. Exclusion criteria, usually set to create a more homogeneous sample, reduce the comparability of the enrolled subjects to those in a clinical service. Excluding patients with co-occurring disorders should not occur when these comorbidities are common or they affect treatment response and prognosis. For example, in patients with major depression, comorbid Axis I and Axis II conditions are present in most patients, and may impact response to treatment. A further problem is that most RCTs are of short duration, but clinicians are interested in longer-term outcome. Many disorders are recurrent or chronic, but trials usually last between 6 and 12 weeks, and can only address short-term response or remission, since they do not deal with the clinical outcome of recovery (a sustained remission). This would not be a significant problem if short-term response was strongly predictive of recovery. However, the relationship between initial response and recovery is not consistent.

Since all treatments potentially have ► adverse effects, it is important to anticipate, measure, and report them accurately. A treatment that increases the speed of recovery from depression but gives rise to enduring side effects may not be deemed useful. This is the case with ECT, which may lead to a rapid recovery for people with severe depression, but which may lead to cognitive side effects measured in a longer-term perspective. For many conditions (for example, anorexia nervosa, somatoform disorders, or personality disorders) insufficient data are available to guide treatment. For other disorders, despite research, no consensus has been reached. RCTs are unlikely to influence practice unless they address an area of perceived uncertainty. However, RCTs are often driven by commercial interest. This leads to a focus on discrete choices, such as treatment modality or intensity, rather than practical decisions, such as when to use physical restraint or to hospitalize a patient.

To summarize, patients need individually tailored treatment. RCTs are the best way to tell clinicians what treatments are effective, but not necessarily which patients should receive them and when they should be given.

Cross-References

► Antidepressants
► Anti-Parkinson Drugs
► Antipsychotic Drugs
► Bipolar Disorder
► Ethical Issues in Human Psychopharmacology
► Mood Stabilizers
► Quality of Life: Assessment
► Rating Scales and Diagnostic Schemata
► Suicide

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Rapamycin

Synonyms

Sirolimus

Definition

A potent immunosuppressant drug that possesses both antifungal and antineoplastic properties. Sirolimus belongs to a class of macrolide antibiotics and used to prevent the rejection of organ transplants by the body. It is a type of serine/threonine kinase inhibitor.

Rapid Eye Movement Disorder

► Parasomnias

Rapid Eye Movement Sleep

Synonyms

REM sleep

Definition

REM sleep is usually associated with dreaming (also known as "dream sleep"). REM sleep is characterized by paralysis or nearly absent muscle tone (atonia; except for control of breathing and erectile tissue), periods of phasic eye movements, and a rise in cortical activity associated with dreaming. The brain however remains highly active, and the electrical activity recorded by electroencephalography (EEG) during REM sleep is similar to that seen during wakefulness. Irregular respiration and heart rate are also features. The first REM sleep period occurs 70 to 100 min after sleep onset, may last as short as 5 min and as long as 60 min (or more). In adults, about 20% of nighttime sleep is devoted to REM. In the rat, REM sleep is characterized by low-voltage fast frontal waves, a regular theta rhythm in the occipital cortex and a silent electromyogram except for occasional myoclonic twitchings.

Cross-References

► Electroencephalography
► Parasomnias
► REM-Behavior Disorder

Rapid Tryptophan Depletion

► Tryptophan Depletion

Rasagiline

Definition

Rasagiline is an irreversible monoamine oxidase (MAO) inhibitor selective for MAO-B. MAO-B inhibition reduces dopamine breakdown in nerve terminals, resulting in increased extracellular dopamine levels in the striatum. Rasagiline is indicated for the treatment of ► Parkinson's disease (PD) either as an initial monotherapy in early PD or as an adjunct to l-DOPA in advanced PD. Rasagiline and its major metabolite 1(R)-aminoindan have neuroprotective effects *in vitro*. Early treatment with rasagiline results in better clinical outcome than drugs with a delayed start, but whether such results are due to its neuroprotective effect in patients is controversial. As with other MAO inhibitors, ingestion of tyramine-rich foods can potentiate hypertensive crisis.

Cross-References

► Monoamine Oxidase Inhibitors

Rat or Mouse Models

► Rodent Tests of Cognition

Rate of Responding

► Rate-Dependency Theory

Rate-Dependency Theory

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Definition

Fixed ratio (FR) – a ► schedule of reinforcement under which the reinforcing stimulus is presented upon the completion of a fixed number of responses.
Fixed interval (FI) – a schedule of reinforcement under which the reinforcing stimulus is presented upon the first response to occur following the elapse of a fixed amount of time.
Interresponse time (IRT) – the time between two successive responses.
► Punishment – the decrease in the probability of a response in real time as a consequence of the presentation of a punishing stimulus upon a response.
Rate of responding – the number of responses per unit of time (e.g., responses/second).
Reinforcement – the increase in the probability of a response in real time as a consequence of the presentation of a reinforcing stimulus upon a response.

Impact of Psychoactive Drugs

Evolution of the Theory

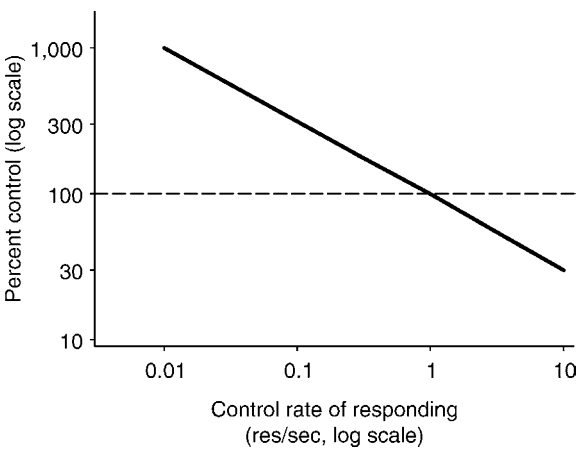
The 1950s was a time of great advances in the development of behaviorally active drugs, and a great deal of effort was spent trying to understand why drugs altered behavior in specific ways. During this period, drug action on behavior

was interpreted, for the most part, in terms of the drug's capacity to reduce a primary drive (e.g., hunger, fear, or thirst) or by the drug's capacity to interfere with a learned association between a stimulus in the environment and one of the primary drives. The work of Clark L. Hull and Neal Miller figured prominently during this period (for review see McMillan and Katz 2002). Thus, when drugs with clinically relevant effects on anxiety were examined in laboratory animals and shown to produce differential effects on behavior controlled by food presentation as compared to behavior controlled by electric shock, the observations were viewed as being consistent with the reduction of primary drives and confirmed the validity of the drive reductionist concepts of drug action. It was in this historical context that Peter B. Dews initiated a series of studies that would eventually lead to the development of what is now known as rate-dependency theory.

In 1955, Dews published the first of a series of papers in which he examined the effect of drugs in food-deprived pigeons responding under different operant schedules of food presentation (Dews 1955). In his first paper, he showed that doses of ▶ pentobarbital that produced dramatic decreases in the rate of responding under a fixed-interval 900 s (FI900) schedule did not affect the rate of responding under a fixed-ratio 30 (FR30) schedule of food presentation. Since responding under the two schedules was maintained by the same event, it was difficult to explain such profound differences based upon drive reduction theories proposed by the current theorists of the day. Alternatively, Dews suggested that rather than interacting with drive states, pentobarbital appeared to be producing the differential effect by interacting with the control of the rate of responding. In a subsequent paper, Dews showed that the effects of ▶ methamphetamine in pigeons responding under four different schedules of food presentation depended upon the length of the time between individual responses (IRT; rate of responding). When control performance was characterized by low rates of responding, low to moderate doses of methamphetamine increased rates of responding. At higher doses, methamphetamine did the same thing but it also decreased the high rates of responding (Dews 1958). Over the next several years Dews along with colleagues, William Morse and Roger Kelleher, as well as investigators from other labs showed that the control rate of responding was a key factor in determining drug effects, and that the control rate of the behavior was an important independent variable. However, it was not until 1964 that Dews formally proposed a way to express this relationship (Dews 1964). Dews argued that since one frequently had to deal with a range of doses that spanned several log units, by analogy to dose–response curves in classical pharmacology, the control rate of responding should be plotted on the abscissa using a log scale. He went on to show that if one plotted the log of the rate of responding following drug administration divided by the rate of responding under control conditions on the ordinate (Fig. 1), not only did this log–log plot aid in the uniform distribution of the data points, it yielded a linear relationship that had predictive value. As a result, one typically sees a log–log linear relationship with a negative slope. Thus, very low rates of responding tend to be increased more than moderate rates, and high rates of responding are either increased less than moderate rates or are actually decreased compared to the control rate of responding. This log–log linear relationship and the theory behind it are referred to as the rate-dependent theory of drug action.

Generality of the Theory

During the 1960s and early 1970s, numerous studies showed that the rate of responding was more important in determining the effect of drugs than the specific reinforcing event used to maintain the behavior. Furthermore, in addition to the ▶ amphetamines and ▶ barbiturates, rate-dependent drug effects were shown for many drugs including ▶ benzodiazepines, ▶ meprobamate, ▶ phenothiazines, ▶ atypical antipsychotics, anticholinergics, ▶ phencyclidine, and ▶ ketamine.



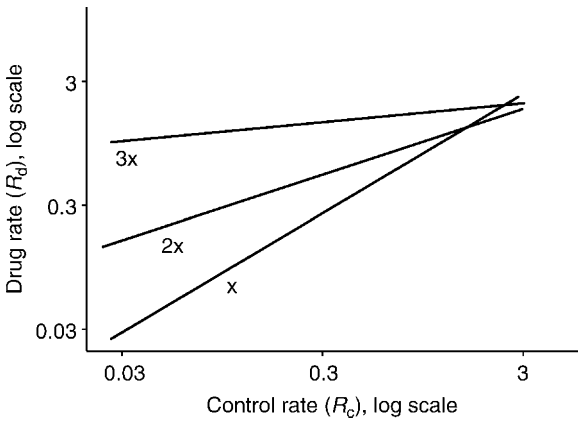
Rate-Dependency Theory. Fig. 1. Typical rate-dependency plot. *Abscissa*: control rate of responding (log scale); *Ordinate*: Rate of responding following drug administration divided by the control rate and converted to a percentage (log scale).

Although Dews and others showed that the rate-dependency theory described the actions of many drugs on schedule-controlled operant responding, a question remained about whether the rate of the ongoing behavior could account for drug effects on other behaviors (nonoperant). Looking at a wide range of behavioral effects of amphetamine in rats, Dews and Wenger (1977) could not show any separation between operant studies and nonoperant studies (e.g., locomotor activity or rearing). For the most part, data from operant and nonoperant studies fell on the same log–log regression line. Similarly, if one examined very low rates of behavior, although the variance was very high, there was no obvious break in the log–log relationship. However, there were a couple of notable exceptions for the rate-dependency of amphetamines. Control rates of behavior that were very low as a result of the presentation of an aversive event upon a response (punishment) did not appear to be increased to the same extent as equally low rates of responding in the absence of a punishment procedure. These low punished rates may, however, have their own parallel relationship between drug effect and control rate of responding. Interestingly, barbiturates, benzodiazepines, and other drugs with clinical antianxiety properties do not share this attenuated capacity of amphetamines to increase low rates under punishment situations. The barbiturates and benzodiazepines, for example, may produce an even larger increase in low rates maintained by punishment procedures compared to their effect on equally low rates maintained by procedures not involving punishment. In nonoperant experiments, there was one notable exception to the rate-dependent effects of amphetamine. The rate of licking by rats appeared to be relatively resistant to change by amphetamines. The resistance to change of licking responses has been reported for several other drug classes.

In addition to the punishment situations discussed earlier for amphetamines, there are a couple of other situations where the rate of ongoing behavior is not the sole determinant of the drug effect (for review see: McKearney 1981). As with the effect of amphetamines on low rates of behavior that have been suppressed by punishment, the ability of barbiturates to increase low rates of responding that are under strong discriminative control has been shown to be less than predicted based solely upon the rate of responding. Nevertheless, the effect of the barbiturates in this situation seemed to be strongly influenced by the control rate of responding. A third situation of note is where the rate of responding directly influences the rate of reinforcement. In many situations, the rate of responding can vary widely with minimal effect on reinforcement rate. However, in situations where an increase in rate decreases reinforcement frequency, these low rates are relatively resistant to increases by drug. Finally, although under most situations the drug effects are independent of the event maintaining the behavior, there are a few known examples where similar rates of responding are altered differently depending upon the reinforcing event. For example, the effect of ▶ morphine has been shown to alter rates of responding differentially depending upon whether the reinforcing event used to maintain the behavior is food or electric shock presentation.

Challenges to the Theory

Although a vast body of literature shows that drugs obey the rate-dependency theory of drug action as proposed by Dews, there have been several challenges and alternative theories proposed. The most significant challenge was, in part, a mathematical issue versus a biological issue, but it also raised questions about the nature of drug effects. Gonzalez and Byrd (1977) stated that the log–log linear relationship proposed by Dews (1964) can be summarized by eqn. 1. By rearranging eqn. 1 to yield eqn. 2, it can be seen that when the slope of the rate-dependency plot equals −1, then the rate following drug administration becomes independent of the control rate and all rates are equal. They further stated that, in order to make it easier to see when the rate after drug administration becomes independent of the control rate, the data should be plotted as shown in Fig. 2. As can be seen with increasing dose and increasing effect, the slope becomes less and less positive and potentially approaches zero. Furthermore, they argued that both the control rate and the rate after



Rate-Dependency Theory. Fig. 2. Rate-dependency plot according to Gonzalez and Byrd (1977). *Abscissa*: rate of responding under control conditions (R_c); *Ordinate*: rate of responding following drug (R_d). *X* dose administered.

drug administration are dependent upon the maximum possible response rate. Thus, Gonzalez and Byrd stated that the effect of a drug on the rate of responding is best considered independent of the control rate, and it is necessary to know the maximum possible rate of responding before the drug effect can be interpreted.

$$\log\left(\frac{R_d}{R_c}\right) = \log k + j \log R_c \quad (1)$$

Rearrangement yields the following:

$$\log R_d = \log k + (j+1)(\log R_c) \quad (2)$$

where, R_d – rate after drug administration
R_c – control rate
k – Y-intercept
j – slope of the regression line

In defense of Dews' position (Dews 1964), it must be remembered that drugs do not create behavior, they only modify existing behavior. Thus, the drug effect cannot be considered in the absence of a comparison to the control behavior. With respect to the contribution played by the maximum possible response rate, such a rate can only be determined experimentally, and it never will be possible to establish the true maximum rate of responding. Furthermore, there is no experimental evidence to support the need to know the maximum rate of responding (see Dews 1978).

The second major challenge to the theory was published in 1981 (Ksir 1981). Ksir's challenge can be summarized by saying that drugs tend to make the rate of responding a constant independent of the control rate of responding. Thus, with increasing doses of drug, the rate of responding approaches some constant value. If this were the case, such a nonspecific effect of a drug would be of little interest. Furthermore, few pharmacologists would accept such a conclusion. Thus, like the Gonzalez and Byrd (1977) challenge, the arguments may be mathematically correct, but they may not be correct from a biological standpoint.

Summary

In summary, a question that arises is how strongly can the theory be stated? Based upon the literature, Dews and Wenger (1977) stated that it is probably true that with all other variables unchanged, a change in the rate of responding may change the behavioral effect of a drug. It is probably also true that not only may differences in the rate of responding lead to differences in the effects of drugs, but in general, such differences will be determined by the control rate, and there will be a systematic relationship between the rate of responding and drug effect. Although there are some exceptions as noted earlier, the control rate of responding relates to the drug effect in such a manner that in most cases the log of the effect is a linear function of the log of the control rate of the behavior. However, probably it is a mistake to conclude that the control rate of responding is the sole determinant of the effect of a drug and that other factors are only important to the extent that they modify the control rate of responding.

The rate-dependency theory describes a relationship between the control rate of behavior and the rate of responding after drug administration. It was never intended to be an absolute relationship, but rather it was a way of showing order and predictability in drug effects. McKearney (1981) summarized the concept by saying rate-dependency is more of a theoretical law than it is a theory or hypothesis. It describes a predictable relationship between the control behavior and the effects of drugs. Viewed in this manner, it is not unlike the way the temperature of a tissue bath influences the response of a tissue to a drug. The temperature of the bath does not explain the action of the drug, but to consider the action of the drug without considering the bath temperature will lead to something that makes little sense. Thus, the rate of responding should be viewed not as the sole determinant of drug action, but, under the right conditions, it can assume a prime role in the determination of the response.

Although the issues and theories of the 1950s seem of little consequence today, the lessons learned need not be forgotten. For example, as we explore the role of genetics in the control of behavior and the response to drugs in newly developed animal strains, it must be remembered that ignoring the role of the control behavior in influencing drug effects is done at ones own peril.

Cross-References

- ▶ Barbiturates
- ▶ Operant Behavior in Animals
- ▶ Psychomotor Stimulants

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Rating Scales and Diagnostic Schemata

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Synonyms

Assessments; Inventories; Measures; Tests

Definition

Diagnostic precision is achieved using structured diagnostic interviews. In contrast, rating scales are not intended for diagnostic purposes. Their function is to measure the severity of a condition or symptom cluster after the diagnosis is made by independent means. Typically, in psychopharmacology research, patients are screened into studies using structured diagnostic interviews. The response to treatment over time is then assessed by measuring the severity of the primary and associated symptom clusters or domains of interest from baseline through treatment follow-up (American Psychiatric Association 2000).

Principles and Role in Psychopharmacology

Structured Diagnostic Interviews

Structured diagnostic interviews were developed to improve reliability in making psychiatric diagnoses for clinical and research purposes. Psychiatric diagnosis was very unreliable prior to the introduction of structured diagnostic interviews. Different criteria were used in different countries and within different schools of psychiatric thought. Within these groups, diagnosis varied based on the manner and on the amount of information elicited from patients. Information provided by patients was interpreted and assembled differently in reaching a diagnosis. The systems used to elicit information, to assemble this information, and to make diagnoses were too many, too varied, too inconsistent, and too divergent to permit accurate communication between large numbers of clinicians and to foster constructive and efficient international collaboration in research. The adoption of efficient and easily administered structured diagnostic interviews, that were translated into a large number of languages and used as consistent diagnostic criteria, has harnessed the energy of international research collaboration in pursuit of finding better treatments for, and understanding of, psychiatric disorders (Sheehan et al. 1998; Spitzer et al. 1992). Structured diagnostic interviews reduce variance in information gathering and reduce criterion variance in assembling this information to make a diagnosis. In this way, they improve both the reliability and quality of diagnostic decision-making.

Choice of Scales

A typical treatment-outcome study uses at least three scales: a scale to measure improvement in the symptom cluster of primary interest (Hamilton 1959, 1967; Montgomery and Asberg 1979); another scale to measure the functional impairment or disability (Endicott et al. 1993; Sheehan and Sheehan 2008); and a third scale to measure the global improvement (Guy 1976). In the past 2 years, the tracking of suicidality in psychiatric and neurological studies has also become routine and is now required by many regulatory agencies (Coric et al. 2009; Posner et al. 2007). Additional scales are frequently used to assess other secondary symptom clusters of interest, e.g., quality of sleep, ▶ cognitive impairment (Folstein et al. 1975), negative symptoms in ▶ schizophrenia (Kay 1990), anxiety symptoms in ▶ depression, or sexual symptoms. With the rise in managed care and increasing concern about cost containment, there is more inclusion of pharmaco-economic measures, especially on health care utilization and cost data. Since major drivers of costs in the management of many psychiatric disorders are poor adherence, increasing switch rates, and more augmentation with other medications, cost drivers are also increasingly tracked in long-term studies. A wide array of scales is available to assess adverse events. Examples include assessments of ▶ extrapyramidal side effects on ▶ antipsychotic medications (Barnes 1989), assessments of sexual side effects with ▶ antidepressants (Clayton et al. 1997), assessments of ▶ discontinuation withdrawal symptoms and of ▶ abuse liability, ▶ craving or "liking" with controlled substances (Selzer 1971).

Scale Metrics

Psychometric constructs may be measured in two major ways. Categorical classification (e.g., yes or no) qualitatively

assesses the presence of symptoms, signs, or attributes and is widely used in diagnostic assessment through structured diagnostic interviews. Continuous measures (e.g., height or weight) permit quantitative assessment of the severity, intensity, or frequency of symptoms, signs, or attributes. In between these two poles lie the ordinal scales that use an ordered set of categories (e.g., none, mild, moderate, and severe). Such ordinal scales are effectively treated and analyzed like continuous measures especially if they have 10 or more points. Continuous or ordinal scales that yield a total score may themselves be used for categorical classification. For example, a score of seven or less on the ▶ Hamilton Depression Rating Scale (Hamilton 1967) may be classified as a remission in depression.

A variety of scale structures or metrics are used in continuous or ordinal scales. The most common scale structure involves the use of a 5- or 10-point scale. Dichotomous categorical scales are less common and a few widely used scales have six or seven response options. Likert scaling is frequently used to measure change in symptoms in efficacy studies. Visual analog scales are popular in the assessment of pain. The DISCAN design metric is increasingly popular in scales designed to be sensitive to drug-placebo differences (Sheehan and Sheehan 2008). Although measures of frequency, e.g., of panic attacks, of seizures, or of ▶ tics are often used as outcome measures; in general, they disappoint in their ability to discriminate between active and ▶ placebo treatments. The main reason is that the frequency of most behaviors is of skewed distribution in nature. Nonparametric tests statistically punish sensitivity and this price makes them less able to discriminate drug from placebo and to be less sensitive to change.

Scale Testing

Scales and structured interviews in psychopharmacology must be subjected to proper reliability and validity testing. Validity tests the degree to which the scale or structured interview is consistent with a "gold standard" measure (e.g., how well a structured diagnostic interview maps the diagnostic classification or how a severity scale accurately reflects the severity of a disorder). The problem in psychiatry is that the "gold standard" is not really "gold." Three kinds of reliability testing are usually done on scales and structured interviews. These include inter-rater reliability, test-retest reliability, and internal consistency. Inter-rater reliability measures the agreement between two raters in rating the same subjects using the same scale or interview at the same time. It is most useful in assessing clinician-rated scales. Test-retest reliability measures the agreement between assessments done at two different points in time (e.g., the same scale done on consecutive days, but assessing the same time period). It has special value in assessing self-rated scales. Internal consistency measures the agreement among the items within a scale. It assesses the degree to which all the items measure a single dimension.

In spite of the limitations of these paper and pencil interview tests, they have performed well in guiding our search for and selection of effective treatments. Researchers in psychopharmacology continue to refine their precision and predictive value. Some day, they will be largely replaced by more precise laboratory tests.

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RBD

- ▶ Parasomnias
- ▶ Recurrent Brief Depressive Disorder
- ▶ REM Sleep Behavior Disorder

Reactive Depressions

- ▶ Adjustment Disorders

Reactive Oxygen Species

Synonyms
ROS

Definition
Reactive oxygen species (ROS) are, for example, hydroxyl radicals or superoxide radicals. They are extremely reactive in "oxidizing" membrane constituents, like lipids, thus causing membrane damage and cell death.

Cross-References
- ▶ Free Radicals

Reboxetine

Synonyms
Davedax; Edronax; Norebox; Prolift; Solvex; Vestra

Definition
Reboxetine (*R**,*R**)-2-[(2-ethoxyphenoxy)-phenyl-methyl]morpholine mesilate is an antidepressant that selectively inhibits the reuptake of norepinephrine (▶ SNRI). It is claimed to have mood-lightening effects in the elderly, but it is significantly less clinically effective against the acute phase of major depressive disorders, and less acceptable relative to other new antidepressants. It is also used in the treatment of panic disorder and ADHD.

The side effects of reboxetine derive from the anticholinergic effects of the compound, particularly antimuscarinic effects, and range from dry mouth, constipation, headache, drowsiness, dizziness, and excessive sweating to insomnia. Rare cases of seizures have been reported.

Cross-References
- ▶ ADHD
- ▶ Antidepressants
- ▶ Panic Disorder

Receptor

Definition
A protein embedded in the cell membrane or the cytoplasm, which is sensitive to a drug or chemical neurotransmitter. It docks (binds) to the drug or neurotransmitter and then generates an electrical or chemical signal in the neuron in which it is located. A given substance can have more than one type of receptor.

Receptor Activator

- ▶ Agonist

Receptor Antagonist

Definition
A receptor antagonist is a type of receptor ligand or drug that does not provoke a biological response itself upon binding to a receptor, but blocks or dampens agonist-mediated responses. Antagonists mediate their effects by binding to the active site or to allosteric sites on receptors, or they may interact at unique binding sites not normally involved in the biological regulation of the receptor's activity. Antagonist activity may be reversible or irreversible depending on the longevity of the antagonist-receptor complex.

Cross-References
- ▶ Ligand

Receptor Inhibitor

- ▶ Antagonist

Receptor Trafficking

Definition

For example, AMPA receptor trafficking; the dynamic movement of receptors in and out of the synapse from intracellular compartments.

Cross-References

► Long-Term Depression and Memory

Receptors: Binding Assays

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Synonyms

Labeled ligand binding; Ligand binding; Radioligand binding

Definition

Receptor binding refers to a technique in which a labeled compound, a ligand, which binds to a receptor, is used to detect that receptor. Usually, the ligand is labeled by means of a radioactive isotope, such as ^{3}H, ^{125}I, ^{35}S, etc., but a fluorescent moiety is also possible. The receptor can be localized in a tissue that is homogenized or sliced or in cells in culture that either have an endogenous expression of the receptor or have been transfected with a cloned receptor gene. Tissue preparations are incubated with a labeled ligand that has a high binding affinity for the target receptor. The labeled ligand bound to tissue is then collected and detected using various techniques, such as filtration techniques combined with radioactivity counting, scintillation proximity analysis and autoradiography for radioactive ligands, and time resolved fluorescence resonance energy transfer (TR-FRET) or amplified luminescent proximity homogeneous assay (AlphaScreen) for ligands labeled with a fluorescent or a chemoluminescent probe, respectively. These techniques are applied in vitro or ex vivo. In vivo receptor binding can be investigated using positron emission tomography (PET) or single photon emission computerized tomography (SPECT) imaging.

Principles and Role in Psychopharmacology

Receptor binding techniques were first introduced in the 1970s (historic reviews: Lefkowitz 2004; Snyder and Pasternak 2003). It was the first tool enabling receptors to demonstrated in tissues using biochemical means. In the early years, one had no clue about the nature or structure of receptors. Extensive research throughout the 1980s led to the cloning of receptor genes and the identification of their structure. Today, three major classes of receptors that are located in cell membranes and one class of cytosolic receptors have been identified.

1. The ► G-protein coupled receptors (GPCRs), also called "7 Transmembrane (7 TM)" receptors, are integral membrane protein monomers. With 802 known and predicted human GPCRs, derived from the human genome, this is the largest receptor family and at least 50 of them have been identified as major drug targets (Lagerström and Schiöth 2008). Sequence comparison revealed five subfamilies, all of which have a central core domain in common, which consists of 7 TM helices connected by three intracellular and three extracellular loops. The protein has an extracellular N-terminal and an intracellular C-terminal, which can be of widely varying lengths. GPCRs have diverse natural ligands comprising of small molecules (amines, amino acids, nucleotides, nucleosides, prostaglandins, peptides, lipid-like molecules, etc.), light, Ca^{++}, odorants and pheromones, and proteins (for review of the GPCR classes, structures, features, and natural ligands, see Lagerström and Schiöth 2008). Upon activation, a GPCR associates with a G-protein that further activates effectors in the cell. Various different proteins can interact with GPCRs so that receptor complexes can exist in multiple states leading to possible complex kinetics for ligand binding (Christopoulos and Kenakin 2002).
2. Ligand-gated ion channels are multimeric, often pentameric, protein complexes that form a pore in the membrane. Members of this family are e.g., the nicotinic acetylcholine, $GABA_A$, $5\text{-}HT_3$, glycine, purinergic P2X, and the NMDA, AMPA and kainate subtypes of glutamate receptors, each of itself has several subtypes.

3. Receptors that are enzymes with a ligand-binding domain that couples to an intracellular membrane-anchored enzyme such as tyrosine kinase, tyrosine phosphatase, serine/threonine kinase, and guanylyl cyclase. Members of this class are e.g., growth factor receptors, neurotrophic factor receptors, and transforming growth factor β (TGFβ) receptors.
4. Cytosolic receptors regulate transcription in the cell nucleus. Members are steroid, retinoid, and tyrode hormone receptors.

Large numbers of members of each of these receptor classes as well as (neurotransmitter) transporters have been studied with receptor binding techniques and receptor binding assays, for hundreds of different molecular targets have been described. In this chapter, in vitro and ex vivo methods used for investigating membrane-bound receptors will be discussed.

Principles

Analytical Rules

Receptor binding assays require working according to analytical rules and procedures. Water must be of freshly double distilled or milliQ quality and all chemicals (salts, metal ions, organic solvents, etc.) of analytical grade. Labeled ligands must have a purity of >98% and purity must be checked regularly (radioligands, in particular with high specific activity, suffer from radiolysis). Stability of compounds must be checked and purified where necessary (e.g., catecholamines and indoleamines are very unstable and solutions need to be purified just prior to use). (Micro)-balances, pipettes (manual and automated) must be regularly gauged. Compounds must be solubilized and diluted according to their physicochemical properties. Lipophilic compounds are best solubilized and diluted in pure dimethyl sulfoxide (DMSO) and buffer should be used only for the last dilution step, or the organic solvent solution should be added directly into the incubation mixture. However, the organic solvent concentration in the assay mixture should not exceed 0.5%. Dilution in the organic solvent is indicated to avoid the loss of lipophylic compound due to adsorption to glass or plastic ware. Plastic tubing must be avoided when using robotic devices. Hydrophilic compounds must be solubilized and diluted in buffer or water. Sometimes protecting agents such as anti-oxidants must be added. Biological materials must be kept on ice in buffer of neutral pH until the start of the incubation. Buffer pH must be adjusted to the temperature of the incubation.

Law of Mass Action

Ligand – receptor binding experiments are usually analyzed according to the simple model of law of mass action:

$$[R] + [\mathrm{L}] \underset{k_{off}}{\overset{k_{on}}{\longleftrightarrow}} [\mathrm{RL}]$$

where [R], [L], and [RL] represent the free concentration of receptor, ligand, and receptor–ligand complex, respectively, and where it is assumed that the reaction components can freely diffuse within the medium. k_{on} and k_{off} are the rate constants for association and dissociation of the ligand–receptor complex. It is assumed that after dissociation, receptor and ligand are not altered.

Association and dissociation rates are temperature dependent. The reaction is driven by the concentration of the reacting agents. Equilibrium is reached when the rate at which ligand–receptor complexes are formed and dissociate are equal. At equilibrium, the following applies:

$$[R]\,[\mathrm{L}]\,k_{on} = [\mathrm{RL}]\,k_{off},$$

The equilibrium dissociation constant, K_d, a measure for binding affinity, is defined as

$$K_d = \frac{k_{off}}{k_{on}} = \frac{[\mathrm{L}]\,[\mathrm{R}]}{[\mathrm{RL}]}$$

The constants have the following units: k_{on}: $M^{-1}{\cdot}s^{-1}$; k_{off}: s^{-1}; K_d: M, where M stands for Molar or $mol{\cdot}L^{-1}$. When receptor binding experiments are performed, [R] usually is unknown (needs to be determined), [RL] is measured in the assay, and [L] usually is assumed to be equal to the applied ligand concentration. This implies, however, that only a minor fraction (<5%) of the total applied ligand should become bound (either by specific binding, nonspecific binding or adsorption to tissue and assay container) so that the free concentration is not significantly altered.

Criteria Required by the Law of Mass Action; Can They be Met?

It is important to realize that the reaction conditions never meet the required criteria. The reaction model itself is largely simplified, as receptors can occur in different states and ligands may bind to ► orthosteric and ► allosteric sites (see Christopoulos and Kenakin 2002). "Free in solution" and "freely moving in solution" does almost never apply to biological tissue, either as an homogenate or a membrane suspension and certainly not when tissue slices, whole cells or tissue fixed on a support are used. Membrane preparations consist of membrane vesicles of varying dimension, possibly with strips of membrane suspended in aqueous medium. Surface phenomena will

inevitably take place when ligands (hydrophobic or hydrophilic) approach the membrane vesicle. Examples of surface phenomena are electrostatic interactions of ionized compounds or surface excess of lipophilic compounds. Surface phenomena, which are difficult to measure or estimate, have received virtually no attention in receptor binding research. Yet, they are a matter of fact and, for ▶ haloperidol, a 1000 x surface excess was calculated to exist in the monolayer around a membrane vesicle as compared to the concentration in aqueous medium (Leysen and Gommeren 1981).

Furthermore, reaction temperature needs to be carefully controlled. A binding reaction is temperature dependent and tissue is temperature sensitive; the transition temperature of the lipid cell membrane (usually around 15°C) must be considered. Tissue and compounds may also behave differently according to pH, in particular when they have ionizable groups with an acid association constant, pKa, between 5 and 8. Therefore, it is advised never to consider experimentally measured values for e.g., K_d or K_i as "absolute," but refer to them as "apparent" under the conditions of a particular assay. Those conditions should always be fully reported.

Types of Binding

Labeled ligands show different types of binding, depending on their physicochemical and pharmacological properties. There is specific binding to the target receptor, which occurs in a concentration range of 2 log units around the K_d value. This binding is saturable, as the number of receptors present is limited. Binding to the target receptor should be reversible and can be inhibited by a compound (competitor) that has the same pharmacological property, related to the target receptor, as the labeled ligand. Full inhibition of receptor binding is obtained at 100 x K_i of the competitor (K_i, inhibition constant, see below), provided that the labeled ligand is used at concentrations around its K_d. A particular labeled ligand (or competitor) may bind to several different receptors within a narrow concentration range. In particular agonists or antagonists for various subtypes of dopamine, noradrenaline, serotonin, histamine, and acetylcholine GPCRs can show, what is called, a "broad receptor profile" (see Leysen 2002, 2004). Binding of a labeled ligand to several different receptors can be a problem, in particular when natural tissues are investigated (this is less of an issue when cultured cells transfected with a particular receptor gene are used and high receptor expression is obtained). If required, occluding agents can be added to prevent the labeling of nontargeted receptors. Labeled ligands also show "nonspecific" binding due to adsorption to tissue, this binding is linearly proportional with the labeled ligand concentration and non-saturable, i.e., non-displaceable. Nonspecific binding can be measured in an experiment where an appropriate competitor (with high ▶ affinity for the target receptor, but preferably of a different chemical structure than the labeled ligand) is added at a concentration 100–1,000 times its K_i and incubated together with the labeled ligand and the tissue. Resulting binding represents nonspecific binding. Labeled ligands may show an additional type of binding, apparently of high affinity and saturable, hence displaceable, but related to a particular moiety in its structure and apparently unrelated to binding to a known biological target (e.g., [^{3}H] spiperone, the 5-HT_{2A} and dopamine D2 receptor ligand, labels "spirodecanone sites"); this binding can be occluded by adding a structural analogue of the labeled ligand, but which does not bind to the target receptor. When studying receptor binding in natural tissues, the various possible types of binding should be carefully investigated (Leysen 1984).

Types of Experiments

Saturation Binding Experiments or "Labeled Ligand Concentration Binding Isotherms"

Aim: determination of K_d and ▶ B_{max} (maximum number of receptor binding sites in the tissue preparation) values.

These assays are performed using a constant amount of tissue at a particular temperature (preferably 37 °C, but sometimes lower temperatures are used) and pH (around 7.4) with increasing concentrations of labeled ligand. The specific binding isotherm, according to the simple law of mass action, follows the course of a hyperbola when the labeled ligand's free concentration on the abscissa and specific binding on the ordinate are plotted using linear scales. Half-maximal binding is reached at a concentration that equals the K_d value and maximal binding is approached at four times the K_d value. Applied labeled ligand concentrations should span a range from 0.2 to 8 times K_d in a series of at least 12 points covering the rising part and plateau of the hyperbola (e.g., for a labeled ligand with K_d=1 nM, appropriate test concentrations are 0.2, 0.4, 0.6, 0.8, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0 nM). The "total binding" is measured in assays with the labeled ligand at its various concentrations, the tissue preparation and a solvent sample, the "nonspecific binding" is measured in assays with the labeled ligand (at each of its concentrations), the tissue preparation and a (non-labeled) competitor at a concentration of 100 times its K_i value. Specific binding is calculated by subtracting

nonspecific binding from total binding at each labeled ligand concentration. To date, binding isotherms are calculated by nonlinear regression analysis and computerized curve fitting, which provide the K_d and B_{max} values. In case a "one binding site model" does not fit the data, a "two binding site model" can be attempted. Curve fitting programs for labeled ligand binding are available commercially, e.g., GraphPad Prism (GraphPad Software, La Jolla, USA). The programs usually provide background on calculations with radioactivity, e.g., on converting bound radioactivity, measured in counts, into pmoles of bound labeled ligand. In the past, when computing power was not readily available, the hyperbola was transformed into a linear equation, e.g., a Scatchard plot.

Kinetic Binding Experiments

Aim: Determination of the association and dissociation rate constants.

Rate constants are relatively easy to measure for a labeled ligand.

To measure the association rate, a labeled ligand, at a given concentration (e.g., 3–4 x K_d), together with the tissue preparation, is incubated for various periods of time and for each time bound labeled ligand is measured. Association of ligands with nM affinity is fast and incubation times should be in the range from seconds up to 10 min. The maximal bound radioligand at equilibrium is usually reached within 2–4 min. Ligand–receptor association is a second-order reaction, involving two reaction partners: the free ligand and the free receptor. However, measured binding is the result of association and dissociation, and usually the free receptor concentration is small, and consequently the free ligand concentration drives the association. Therefore, the reaction proceeds according to pseudo first order kinetics. The plot of bound labeled ligand versus time is hyperbolic and can be transformed according to a pseudo first order rate equation, in a linear plot:

$$\ln\left(\frac{B_{eq}}{B_{eq}-b_t}\right) \text{versus time (s)},$$

B_{eq} and b_t are bound labeled ligand at equilibrium and at a given time. The pseudo first-order rate constant, k_{obs} (s^{-1}), is given by the slope of the line. For calculation of the association rate constant, k_{on} ($M^{-1}\cdot s^{-1}$), the dissociation rate constant, k_{off} (s^{-1}), is needed.

$$k_{on} = \frac{k_{obs} - k_{off}}{[L]}$$

The dissociation rate constant can be measured by incubating the tissue preparation with the labeled ligand at a given concentration (preferably not exceeding the K_d value) until equilibrium is reached and then either strongly diluting the reaction medium (more than 10 times) to favor dissociation and minimize re-association, or, more common, adding an excess of strong competitor to the reaction medium, which will induce displacement and hence dissociation of the labeled ligand. From that point onward a series of incubation samples is taken to measure remaining bound labeled ligand. The dissociation reaction is a first-order reaction, a semilogarithmic plot of log[bound labeled ligand] versus time is linear and the dissociation rate constant, k_{off}, is given by the slope of the line x 2.3 (transformation of $\log_{10}$ into ln). The half-life of dissociation is given by $t_{1/2}=0.693/k_{off}$. Measurement of the dissociation rate of an unlabeled competitor requires a more elaborate procedure. The approximate half-life of dissociation of an unlabeled competitor can be assessed by an indirect method. Tissue with competitor at a given concentration (not exceeding 2 x K_i) is incubated until equilibrium and filtered over a glass fiber filter. The tissue (with bound competitor) adsorbed on the filter is rinsed for various periods of time, followed by short incubation of the tissue on the filter with a labeled ligand. The amount of labeled ligand that becomes bound is then an indication of the amount of competitor that has dissociated. (Leysen and Gommeren 1986). Knowledge of the receptor dissociation rate of compounds has gained interest, in light of deriving information on factors that contribute to the duration of action of drugs and on the ease with which a drug bound to the receptor in vivo, can be displaced e.g., by the endogenous ligand for the receptor.

Competitive Binding Experiments

Aim: To determine the IC_{50} value (concentration producing 50% inhibition) of a competitor. Competitive binding experiments are used to compare different ligands acting at similar sites. The sigmoid curve obtained with a competitor should asymptotically approach the level of non-specific binding, without surpassing it. Nonlinear curve fitting programs can be used to estimate IC_{50} values. Curve fitting also yields a value for the slope (n) of the curve; $n = 1$, for competition at one binding site; $n > 1$ or $n < 1$ for multiple binding sites, binding of the competitor with different affinity to multiple states of the receptor, or involvement of cooperative binding. Curve fitting programs allow for the analysis of data for multiple binding site models. IC_{50} values are dependent on applied concentration and K_d of the labeled ligand. The Cheng Prusoff equation provides for the calculation of the equilibrium inhibition constant, K_i (equaling the

equilibrium dissociation constant), which is independent of the applied labeled ligand:

$$K_i = IC_{50}/(1 + [L]/K_d)$$

The Cheng Prusoff equation is derived from a simple model of competition at one and the same binding site; the same warnings of caution for the interpretation of K_i values as described earlier apply.

For further reading on different types of binding experiments, illustrations and details on analyses of receptor binding data, see: Keen and MacDermot 1993.

Antagonist Binding

For GPCRs and ligand-gated-ion-channels, the majority of studied labeled ligands and competitors are antagonists or ▶ Inverse Agonists. Antagonist binding to GPCRs, has appeared to be insensitive to the occurrence of the receptor in various states (e.g., G-protein coupled or uncoupled). Antagonist binding curves (labeled antagonist saturation binding and antagonist–antagonist competition) have often been found to obey apparent single site binding kinetics.

Agonist Binding

Agonist binding to GPCRs is sensitive to the state in which the receptor occurs. Agonists have substantially higher affinity for the G-protein coupled than for the uncoupled receptor. As a consequence, competition between a labeled antagonist and an unlabeled agonist often yields a shallow inhibition curve, pointing to multiple binding sites or binding to the receptor in multiple states. Inhibition curves of agonists can be influenced by additives in the incubation medium, in particular by agents that affect the coupling of the receptor to the G-Protein. Guanosine triphosphate (GTP), or a stable analogue thereof, uncouple the receptor-G-protein complex. Addition of GTP to the medium will shift an (shallow or biphasic) agonist inhibition curve to the right, make it mono-phasic, and decrease the slope to approach 1 (see Lefkowitz 2004). Agonist binding to GPCRs is also affected by divalent cations, in particular Mg^{++} or Mn^{++}, which may favor receptor-G-protein coupling and increase the agonist binding affinity. The effect of divalent cations on agonist binding should be experimentally investigated. A good example is the investigation of the effects of bivalent cations on the affinity states of the M1 ▶ muscarinic acetylcholine receptor (Potter et al. 1988). Labeled agonist concentration binding isotherms will similarly be influenced by additives in the incubation medium, and affect the measured apparent K_d and B_{max} values. When labeled agonist saturation curves are measured in a low concentration range, usually only the high affinity-binding constant of the agonist, K_H, will be detected. The B_{max} value measured with a labeled agonist may only represent the G-protein coupled portion of the receptor and, for the same tissue sample, usually will be lower than the B_{max} value measured with a labeled antagonist.

GPCRs for which labeled agonist binding hase been amply studied and for several of which agonists are used as therapeutic agents are μ−opiate, 5-HT_{1A}, 5-HT_{1B}, 5-HT_4, and various peptide receptors (e.g., NK1, NK2, NK3, CRF1). Examples of GPCRs that have been studied with both labeled agonists and antagonists are dopamine D_2, 5-HT_{2A}, 5-HT_{2C}, 5-HT_4, 5-HT_6 and muscarine M1ACh receptors, and β1-and β2-adrenoceptors.

Allosteric Competitors

The natural ligand or a synthetic agonist that binds to the orthosteric site and a compound that attaches to the ▶ allosteric binding site can concomitantly occupy the same receptor without mutual inhibition of binding. Positive ▶ allosteric modulators will enhance and negative allosteric modulators will reduce the activity/affinity of an orthosteric agonist. The allosteric receptor interaction of compounds usually is studied in functional, signal transduction assays (▶ Receptors: Functional Assays). Labeled ligand binding to an allosteric site may be used in competition binding assays to detect competitors that bind to the same allosteric site.

Ligand-gated ion channel receptors are known to have several different allosteric binding sites. The ▶ $GABA_A$ receptor was the first receptor for which the phenomenon was discovered with drugs that were in use as therapeutic agents, namely the ▶ benzodiazepines. GPCRs of family 3, the $GABA_B$ receptor, and the ▶ metabotropic glutamate receptor subtypes are amply studied for positive and negative allosteric modulators.

Methods for In Vitro Receptor Binding Using Tissue or Cell Homogenates or Membrane Preparations

Tissues and Preparation

Tissues used for receptor binding are e.g., dissected brain regions or organs, cultured cells (cell lines or primary cultures) or blood cells that express a particular receptor endogenously, or cultured cells with (abundant) expression of a particular receptor following the transfection of the cells with that receptor's cloned gene from a specific species (often human). Although, when conditions are appropriate, receptor binding can be performed on intact cells, in most cases the tissue is homogenized, and either

the whole homogenate or, more often, a membrane preparation is used for the assay. Used membrane preparations are the "total particulate fraction" (i.e., the total fraction of membranes spun down at high centrifugation speed following extensive homogenization of the tissue in buffer with a blender) or a membrane preparation from separated subcellular particles (e.g., heavy and light mitochondrial fractions, plasma membrane fraction) following careful homogenization of the tissue in 0.25 M sucrose followed by differential centrifugation (see Laduron et al. 1978). Membrane preparations are washed by re-suspension in medium and re-centrifugation. All tissue preparation steps are to be carried out at 0–4°C. Tissue preparations can be stored below −20°C.

Incubation in Tubes and Multi-Well Plates

Incubations can be performed in test tubes (volumes 0.5–2 mL) or 96 multi-well plates (0.1–0.2 mL). Incubation mixtures are composed of a sample of cells or membrane preparation suspended in buffer, an aliquot of labeled ligand to give a desired final concentration and, depending on the type of experiment, an aliquot of a competitor to give a desired final concentration (see types of experiments). The buffer has a particular pH (usually around 7.4) and can contain certain additives such as metal ions. Depending on the type of experiment, the incubation is run at a given temperature for a given time period (see types of experiments). For competition-binding experiments, the incubation time should be sufficiently long to reach binding equilibrium.

Filtration Methods

Labeled ligand, bound to the tissue preparation and free-labeled ligand, can be separated by filtration over glass fiber filters (filters are sometimes presoaked in polyethyleneimine to reduce absorption of the labeled ligand to the filters) under suction, followed by rapid rinsing with ice-cold buffer. For incubation in test tubes, a Brandel harvester (Brandel, Gaithersburg, USA) is used, for incubations in 96 multi-well plates, various harvesting devices are available (e.g., Micromate 196 and Mac II, Perkin Elmer, Waltham, USA; Brandel 96, Brandel, Gaithersburg, USA). The radioactivity of bound labeled ligand collected on the filters is counted; for β ray emitting isotopes e.g., ^{3}H-labeled ligands, the filters are dried, liquid scintillation fluid is added and radioactivity is counted in a liquid scintillation counter, for γ ray emitting isotopes (e.g., ^{125}I) radioactivity can be counted directly in a γ counter. For competition binding assays, 96 multiwell incubation, filtration, and counting methods and devices are appropriate; for saturation binding experiments with the determination of K_d and B_{max} values and the determination of ligand association and dissociation rates, incubation in test tubes and filtration over separate filters that are counted in vials in a calibrated liquid scintillation counter is advised.

Scintillation Proximity Assay (SPA)

SPA is a homogenous assay that avoids the filtration step. For SPA either poly-vinyl-toluene beads, filled with scintillant (GE Healthcare Life Sciences, Buckinghamshire, UK) or "Flashplates" or "Scintiplates" (Perkin Elmer, Waltham, USA), i.e., 96 multi-well plates with scintillant coated on the inner surface of the wells, are used. The beads or plates are coated with membrane preparation. Samples of coated beads added in 96 multi-well plates or wells of coated Flashplates are incubated with labeled ligand without or with competitor at desired concentration in buffer. Since the tissue is not "free in solution," several hours of incubation time are required to reach binding equilibrium. After incubation, the multi-well plates are counted directly in a Topcount NXT (Perkin Elmer, Waltham, USA). The scintillant will only detect radioactivity in its immediate vicinity, i.e., the radioactive ligand that is bound to the tissue coated on the beads or on the plates. The mix-and-read format technology is useful for high throughput screening, but long incubation times have to be taken into account.

Nonradioactive Proximity Assays

The burden on the environment and the inherent high cost for the removal of radioactive waste encouraged the development of nonradioactive techniques for receptor binding. TR-FRET, making use of fluorescent probes, and AlphaScreen™, which is based on chemoluminiscence, are examples that are mainly applied for high throughput competition binding assays. The technologies are based on the excitation of the "donor" probe (e.g., attached to the ligand), which triggers an energy transfer to the acceptor probe (e.g., attached to the receptor preparation) if they are within a given proximity. The acceptor probe in turn emits light of a given wave length, which is detected. The application of these techniques is limited, since it requires the development of ligands labeled with relatively large probes, resulting in a compound with a different chemical structure than the original ligand. The receptor binding characteristics of such fluorescent or chemoluminiscent ligands will be altered and need to be fully investigated. Development of apt fluorescent or chemoluminiscent ligands is a matter of trial and error.

Labeled Ligand Autoradiography

Autoradiography is a general technique allowing the visualization of the distribution of a radioactive ligand, bound to a molecular target in a tissue section. The radioactive ligand can be injected (iv) in an animal, followed by sacrifice of the animal, tissue dissection and sectioning. Otherwise, tissue sections can be incubated with radioactive ligand in vitro. Tissue (often brain) sections (20 µm thick), usually is cut with a cryostat, and mounted on a coated microscope glass support. Incubation is performed by overlaying the tissue section with a drop of incubation medium containing the radioactive ligand. After incubation, the tissue sections are quickly rinsed and dried. To "visualize" radioactive ligand bound to the tissue, different techniques have been used. The highest resolution, but requiring the longest exposure time (weeks up to several months), is obtained by exposing the tissue sections to a photographic emulsion. Shorter exposure times (several days up to one week) can be achieved by using a phosphor imager. The most recently developed device, the β-imager (Biospace Lab, Paris, France), can produce an image of the bound radioactivity, following over night counting and up to 15 microscope glass slides can be counted simultaneously. The images are analyzed and quantified by counting the number of β-particles emerging from the delineated brain areas by using the β–vision program (Biospace Lab, Paris, France).

For technical details on receptor autoradiography protocols, see: Wharton and Polak 1993.

Apart from neuroanatomical mapping, autoradiographic techniques can also be applied to measure receptor occupancy by non-labeled drugs (Schotte et al. 1993). A drug, at varying dosages, systemically is given to laboratory animals. The animals are sacrificed, tissue dissected and sectioned, and tissue sections are briefly incubated with a radioactive ligand for the target receptor. The difference in labeling in a defined area on matching tissue sections from drug-treated and non-treated animals is a measure for the occupancy of the receptor by the drug administered to the animal. This "ex vivo" incubation technique, is only applicable for drugs with a sufficiently slow dissociation rate from the receptor. Alternatively, the radioactive ligand can be injected iv to the animal that is systemically treated with the investigational drug; in this way, the competition for receptor binding between the drug and the radioactive ligand will take place in vivo. Subsequently, the animal is sacrificed, tissue dissected and sliced, followed by the quantification of the image. With the introduction of the highly sensitive β-imager in the 1990s, allowing images to be obtained in a few hours, receptor occupancy assays ex vivo, became a feasible and highly valuable drug screening technique (Langlois et al. 2001).

Application of Receptor Binding

Receptor binding data sometimes are scornfully looked at by pharmacologists with the view that binding does not say anything about function. Yet, receptor binding has contributed substantially to the field of pharmacology. It has demonstrated the existence of receptors at the molecular level. It has contributed to the isolation and purification of receptor proteins, leading to the cloning of the first receptor gene. It has allowed the study of the localization of receptors at anatomical and cellular levels and of receptor dynamics, such as receptor desensitization, receptor endo- and exocytosis, and transport of receptors along axons (see Lefkowitz 2004).

In terms of drug discovery and drug profiling, receptor binding has revolutionized the field. Drug screening with receptor binding started in the mid-1970s and soon led to high throughput, assay automation and super high throughput assays, allowing for screening thousands of compounds in one day at many different receptors with a minimum of personnel.

Receptor binding profiles of drugs have revealed that many of the drugs that were in clinical use, such as ▶ antidepressants and ▶ antipsychotics, bound to several different receptors within a narrow potency range, e.g., the antipsychotic ▶ clozapine was found to bind to more than 20 receptors with such potency, that all of them could be hit at a therapeutic dose (Leysen 2002; Leysen 2004). Receptor binding is the method of choice to investigate and demonstrate the selectivity of action versus the multiplicity of action of drugs. Measurement of receptor occupancy in the brain by drugs that are administered to animals, using ex vivo autoradiography, has become a key component of CNS drug discovery programs. It allows determination of the dose range within which central receptors become occupied and does not only provide information on the extent of receptor occupation, but also on the brain penetration of the drug.

Cross-References

- ▶ Agonist
- ▶ Allosteric Modulator
- ▶ Antagonist
- ▶ Antidepressants
- ▶ Antipsychotic Drugs
- ▶ Benzodiazepines
- ▶ Binding
- ▶ Bmax
- ▶ Cathecholamines

- ▶ Clozapine
- ▶ Corticotropin Releasing Factor
- ▶ Desensitization
- ▶ Dopamine
- ▶ Equilibrium Dissociation Constant
- ▶ $GABA_A$ Receptor
- ▶ Glutamate Receptors
- ▶ Inverse Agonists
- ▶ Ligand
- ▶ Metabotropic Glutamate Receptor
- ▶ Muscarinic Receptor
- ▶ Neurotransmitter
- ▶ Neurotrophic Factors
- ▶ Nicotinic Acetylcholine Receptor
- ▶ NMDA Receptor
- ▶ Positron Emission Tomography (PET) Imaging
- ▶ Receptor Signal Transduction
- ▶ Reversible Binding
- ▶ SPECT Imaging Receptor Activation
- ▶ Transporter

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Receptors: Functional Assays

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Synonyms

Measurement of biological effect resulting from interaction with the receptor; Measurement of receptor signaling

Definition

Psychoactive drugs generally exert their effects by binding to a specific recognition site, whether that is associated with a receptor, a transporter, or an enzyme and thereby alter the function of that receptor, enzyme, or transporter. However, receptors are the predominant targets for psychoactive drugs (Grigoriadis et al. 2009) and these may be either ▶ G-protein-coupled receptors (GPCRs) or, to a lesser extent, ion channels (the latter of which may be either ligand- or voltage-gated).

Although the actual effect produced by drugs affecting GPCRs and ion channels are very different, their mechanisms of action follow similar principles. Hence, a drug acting at a GPCR or ion channel may block the effect of an endogenous ▶ Agonist (i.e., act as an ▶ Antagonist), mimic the effect of the endogenous activator (i.e., act as an agonist), or inhibit spontaneous (nonagonist-stimulated) receptor activation (i.e., act as an ▶ Inverse Agonist). In addition, a drug may bind to a recognition site that is physically distinct from the agonist-binding site and as a result, produce allosteric changes in receptor structure that enhance or reduce the effects of the endogenous agonist; such drugs are known as positive ▶ Allosteric Modulators (PAMs) and negative allosteric modulators (NAMs), respectively.

Stated simply, a drug binds to a receptor and then "does something." It is the purpose of functional assays to measure and quantitate that "something," with the choice and design of assay being highly dependent upon the type of receptor (i.e., GPCR or ion channel), as well as the effect being studied (agonism, antagonism, inverse agonism, or allosteric modulation).

Principles and Role in Psychopharmacology

Introduction

Drugs may exert their effects by specifically interacting with receptors, enzymes, or transporters, by interfering with DNA, RNA, or ribosomal processes, by exerting physicochemical effects, or in the case of monoclonal antibodies, by targeting a variety of different proteins. With regard to receptors, this classification includes GPCRs, ion channels, and nuclear receptors. Since the latter are primarily the therapeutic focus for obesity, diabetes, and cancer, the GPCR and ion-channel family represent the main receptor targets in psychopharmacology. As a therapeutic class, GPCRs are more successful than ion channels as measured in terms of FDA-approved drugs and hence, GPCRs appear to be more "drugable" targets. However, there is little doubt that ion channels have been generally underexploited, especially as targets for CNS disorders, especially when one considers that most of the neuropsychopharmacological ion channel drugs are ▶ $GABA_A$ modulators that were discovered prior to the revolution in molecular biology and genomics.

In the search for new psychopharmacological drugs, the identification of novel chemical structures that interact with the target of interest is arguably the most crucial step in the drug discovery process. Such compounds are usually identified in the screening of large chemical collections (ranging from hundreds of thousands to up to several million) in high-throughput screening (HTS) campaigns. Accordingly, the focus of this article will be the measurement of the functional effects of compounds at GPCRs and ion channels in such HTS formats.

Functional Assays: What to Measure?

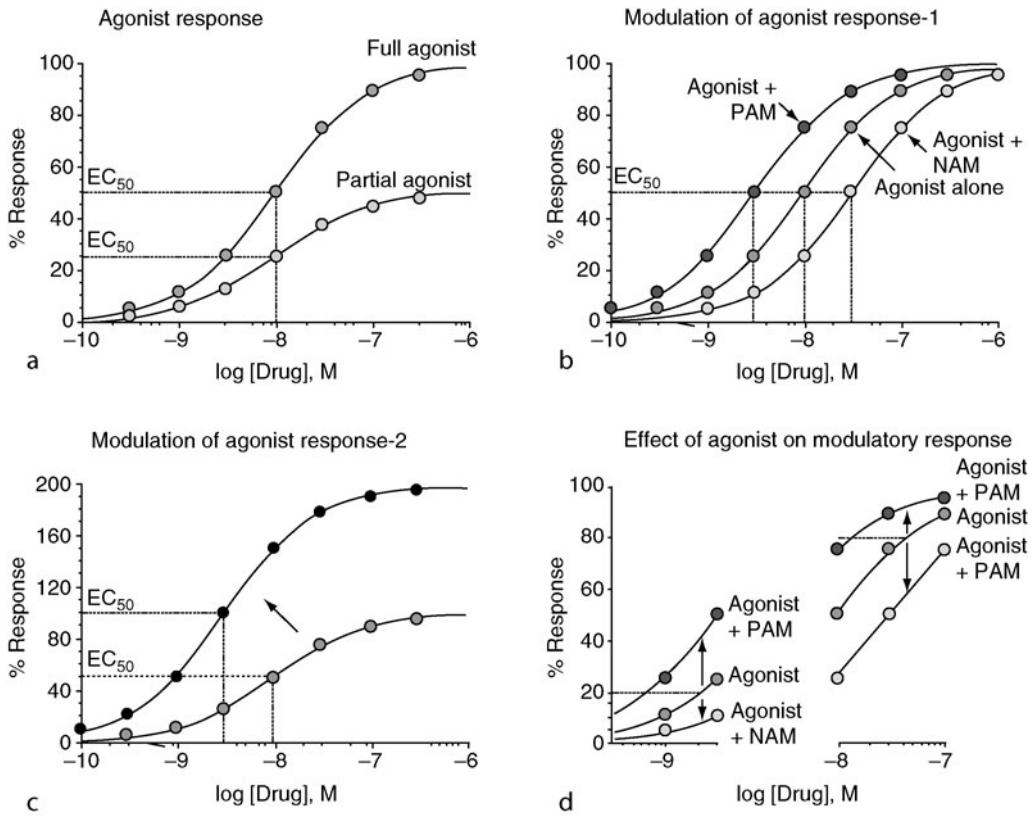
The design of an HTS-compatible functional assay is determined not only by the functional response being measured (i.e., change in ▶ second messenger or ion concentration or a downstream consequence of such changes), but also by the pharmacological profile – agonist, antagonist, and modulator – of the desired compound. The simplest type of assay is one in which the test compound is being evaluated for its agonist response. The ▶ potency of this effect is generally characterized in terms of the concentration at which a response that is 50% of the maximum (EC_{50}) is observed as well as the size of the maximum response. For instance, the response may either be of a magnitude comparable to the reference agonist or may produce a reduced response relative to the reference agonist (full and partial agonist, respectively; Fig. 1a). Compounds may also bind to the receptor and produce allosteric modulatory changes that might reduce or increase the EC_{50} (PAM or NAM, respectively) (Fig. 1b), as well as the maximal response (Fig. 1c). If an assay is being established in order to detect modulatory compounds, then the choice of agonist concentration should be picked according to whether a PAM or NAM is desired, in which case EC_{20}- or EC_{80}-equivalent agonist concentrations are usually employed (Fig. 1d). Although ▶ benzodiazepines represent a well-established class of ion-channel ($GABA_A$ receptor) PAMs, more recently allosteric modulators of GPCRs have attracted considerable attention as potential therapeutics (Conn et al. 2009).

As regards the shift toward the identification of allosteric modulators as drug targets, one of the attractive features of certain types of instrumentation is the ability to record data in real-time rather than producing just single, end-point readouts. This permits compounds to be assessed using two-addition, or sometimes even three-addition protocols. For example, in the absence of exogenous agonist, an initial addition of compound will detect direct agonist effects. If there is no direct agonist effect, then a second addition, this time of agonist, can detect a PAM (Fig. 2).

As regards antagonists, the ability of a compound to block an agonist-stimulated response is related to the functional affinity of the agonist as well as the affinity of the antagonist. For example, a low affinity antagonist will have difficulty in blocking the effects of a high affinity agonist. Although the potency of a competitive antagonist can be quantified in terms of the pA_2 derived from a Schild plot of the rightward shift of an agonist concentration-effect curve at increasing antagonist concentrations, such analyses are not suitable for an HTS screen. Accordingly, the choice of the reference agonist and the concentration and preincubation time of test compound, should be given consideration. In certain expression systems, some receptors demonstrate activity in the absence of an agonist and are therefore described as possessing ▶ constitutive activity. Compounds that block this constitutive activity are described as inverse agonists.

General Methodologies

The general principle of functional assays for receptors is that they should demonstrate that a compound binds



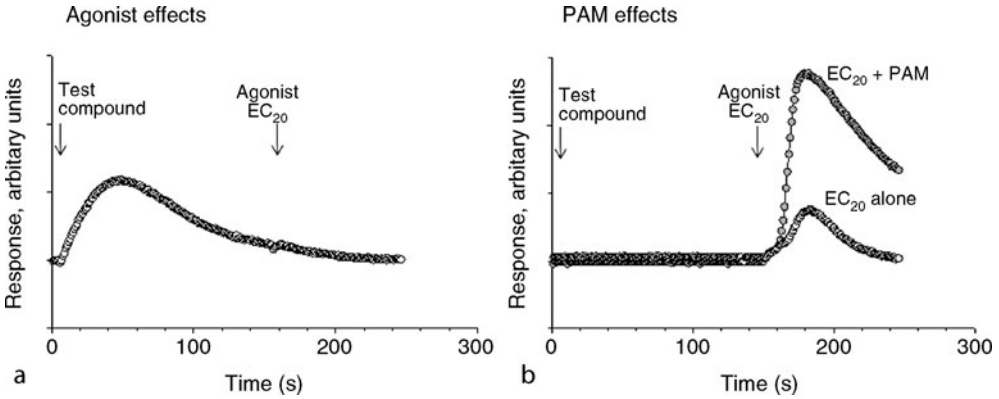
Receptors: Functional Assays. Fig. 1. Schematic representation of agonist-related responses. (**a**) Compounds may directly activate the receptor and produce a response that is comparable to or submaximal when compared with the endogenous ligand (full agonist and partial agonist, respectively). (**b**) Compound might produce a *leftward* or *rightward* shift in the agonist concentration–effect curve. Such compounds are designated positive or negative allosteric modulators (PAMs and NAMs, respectively). (**c**) In addition to shifting the EC_{50}, a compound may also have an effect on the maximal response (in this case increasing the maximum response). (**d**) An expanded view of parts of the concentration effect curves shown in Panel B illustrate how the absolute modulatory effects of PAMs and NAMs are a function of the agonist concentration. Hence, PAMs produce a proportionately greater potentiation of an EC_{20} when compared with EC_{80} response, whereas NAMs give a greater attenuation of an EC_{80} when compared with EC_{20} response.

to a receptor and "does something." Whether that "something" is direct activation, inhibition, or modulation of an agonist response, the key is being able to reliably demonstrate and quantitate a response. These methods most frequently rely upon a biosensor to detect that there has been an increase or a decrease in some component of an intracellular signaling pathway.

Some methods are unique to the class of receptor, for example [^{35}S]GTPγS is an hydrolysis-resistant analog of GTP (guanosine triphosphate). Its binding is specific for GPCRs in comparison to, for example, the measurement of ion flux which is specific for ion channels. However, some techniques are more generally applicable to the measurement of changes in intracellular molecules. These include, but are not limited to, techniques such as fluorescence resonance energy transfer (FRET) and the related technique of homogenous time-resolved fluorescence (HTRF), and bioluminescence resonance energy transfer (BRET).

Fluorescence and Bioluminescence Resonance Energy Transfer (FRET and BRET)

FRET refers to the process whereby energy is transferred from a fluorescent donor to a suitable energy acceptor, with the absorption spectrum of the acceptor overlapping the emission spectrum of the donor. Since the efficiency of this process is inversely proportional to the sixth power of the distance between the two molecules, then the acceptor



Receptors: Functional Assays. Fig. 2. Raw data traces from a real-time Ca^{2+} kinetic readout, showing the effect of a compound with (**a**) Agonist activity or (**b**) PAM activity. Ca^{2+} flux assays can be designed to identify compounds exhibiting agonist or PAM activity in one and the same assay well. Test compounds are added to cells loaded with a Ca^{2+} sensitive dye and incubated for 2.5 min. Thereafter, a submaximal (approximately EC_{20}) concentration of agonist is added. A compound displaying intrinsic agonist activity will increase the Ca^{2+} response in the first read (see *left-hand figure*), while PAMs will only show activity (i.e., a potentiation of the EC_{20} agonist effect) in the second read (see *right-hand figure*). The EC_{20} agonist effect after vehicle treatment, which was measured in a separate well of a 96-well plate, is indicated in the right panel in gray.

and donor molecules need to be in close proximity, in the region of 1–10 nm, for significant FRET to occur. The readout is a change in fluorescence emission of the acceptor, which may either increase or decrease as the proximity of the donor and acceptor also increases or decreases. The most common FRET acceptor–donor pair is the cyan fluorescent protein and yellow fluorescent protein, both of which are variants of green fluorescent protein. However, these proteins are not suitable for detecting ion-channel-mediated changes in membrane potential and therefore, special dyes are employed for this purpose (see below).

BRET is based on the same donor–acceptor energy transfer principle as FRET, with the difference being that in BRET the donor is a luminescent molecule, generally coelanterazine, which is excited by the enzyme Renilla luciferase (Rluc) rather than a fluorescent molecule; this avoids the need for the external illumination source required for FRET. The BRET-acceptor molecule can be a fluorescent protein such as green or yellow fluorescent protein.

Ca^{2+} Sensors

Fluorescent Ca^{2+}-sensitive probes linked to a fluorescence plate reader, such as the Fluorometric Imaging Plate Reader (FLIPR™, Molecular Devices, Corp.) or Functional Drug Screening System (FDSS, Hamamatsu), have become probably the gold standard for HTS of GPCRs. This is in part related to the combined liquid-handling and imaging capabilities of machines such as the FLIPR and FDSS as well as the properties of Ca^{2+}-sensitive dyes, such as organic fluorophores, fura-2, indo-1, fluo-3, fluo-4, and Calcium Green. In addition, Ca^{2+}-sensitive proteins may be used as Ca^{2+} sensors. Fluorescent proteins are generally engineered to contain the calcium-binding protein calmodulin as a molecular Ca^{2+}-sensing switch, which may be associated with either a single or two different fluorescent proteins, with the latter producing a FRET signal due to Ca^{2+} binding to calmodulin-producing conformational changes in the sensor.

Aequorin is a Ca^{2+}-activated bioluminescent photoprotein derived from the jellyfish *Aequoria victoria*, which emits luminescence as a result of the irreversible binding of Ca^{2+} ions. It comprises two components, the 22 kDa apoaequorin protein and a coelenterazine cofactor, and cells can be engineered to express apoaequorin, whereas coelenterazine needs to be added exogenously. When Ca^{2+} binds to the apoprotein, coelenterazine is oxidized to coelenteramide and this results in the emission of a blue light that is detected as luminescence.

Functional Assays for GPCRs

GPCRs activate intracellular signal transduction mechanism via either G-protein- or β-arrestin-mediated pathways, with examples of the various methodologies used to measure components of these pathways being presented in Table 1. With respect to the G-protein-mediated pathway, the binding of an agonist produces conformational changes in the GPCR which permit interaction between the C-terminal, intracellular receptor domain, and the heterotrimeric G-protein, which comprises an α, β, and γ subunit. This

Receptors: Functional Assays. Table 1. Summary of methods available for assessing functional effects at G-protein-coupled receptors (GPCRs).

Assay type	Comment
[^{35}S]GTPγS binding	Generic assay for studying interaction of G-proteins but $G\alpha_{i/o}$-linked receptors give best signal:noise ratio
cAMP measurement – direct (radioimmunoassay)	Radiometric assays not preferred for high-throughput screening (HTS)
cAMP measurement – direct (nonradiometric)[a]	High-affinity enzyme complementation (HitHunter™)
	Bioluminescence resonance energy transfer (BRET) (e.g., ALPHAscreen)
	Fluorescence resonance energy transfer (FRET) (e.g., LANCE™, PerkinElmer; HTRF®, CisBio)
	Fluorescence polarization (FP)
cAMP measurement – reporter gene assay	Reporter gene (e.g., β-galactosidase, β-lactamase, GFP, luciferase) linked to a cAMP-response element (CRE)
Ca^{2+} – direct measurement	Organic fluorophores (fura-2, fluo-3, fluo-4, etc.)
	Fluorescent proteins incorporating Ca^{2+} sensor (e.g., calmodulin)
	Bioluminescence – emission upon irreversible binding of Ca^{2+} to aequorin
Ca^{2+} – reporter gene assay	Reporter gene (e.g., β-galactosidase, β-lactamase, GFP, luciferase) linked to a calcium-sensitive element such as activator protein 1 (AP1) or nuclear factor of activated T-cells (NFAT)
β-arrestin	BRET
	FRET
	Enzyme fragment complementation (PathHunter™)
ERK phosphorylation	BRET (ALPHAscreen SureFire)
Electrical impedance or refractive index	Label-free cell-based assays (refractive index: EPIC; impedance: ECIS, RT-CES, CellKey)

results in the exchange of GDP for GTP associated with the Gα subunit, and in this activated state, the Gα subunit may, depending upon its subtype, stimulate or inhibit the production of cAMP ($G\alpha_s$ and $G\alpha_i$, respectively) or result in the $G\alpha_q$-mediated, phospholipase C (PLC)-dependent cleavage of phosphatidylinositol-4,5-bisphosphate to produce inositol trisphosphate and diacylglycerol, which mobilize intracellular Ca^{2+} stores and activate protein kinase C, respectively. These alterations in intracellular second messengers can in turn trigger cascades that result in changes in the gene expression.

Following agonist binding, GPCRs become substrates for G-protein-coupled receptor kinases (GRKs), and the resulting phosphorylated GPCRs are able to bind β-arrestins which causes the membrane trafficking machinery to internalize receptors away from the cell surface in clathrin-coated pits. In addition, the formation of the GPCR/β-arrestin complex can result in activation of the extracellular, signal-regulated (ERK)/mitogen-activated protein (MAP) kinase pathway.

[^{35}S]GTPγS Binding Assay

The nucleotide exchange process at G-proteins in cell membranes, resulting from agonist binding to GPCRs, can be measured by monitoring the binding of [^{35}S]GTPγS. The advantage of this assay is that it measures an early event in the signal transduction cascade and hence is less subject to amplification or regulation by more distal cellular processes that may compromise other functional measurements, such as reporter gene assays. The disadvantage of this assay is that it is generally more feasible for receptors coupled to the abundant G_i family of G-proteins, although several approaches have been introduced to extend its utility, such as use of immune-capture of [^{35}S]GTPγS-bound G-proteins of interest at the end of the assay, or the use of GPCR-G-protein fusion proteins (Milligan 2003).

cAMP Measurements

Historically, ► cAMP was measured based on radioisotopes using, for example, GE Healthcare SPA™ and Perkin

Elmer Flashplate™ cAMP assays; however, these methods are relatively expensive for screening large numbers of compounds, in addition to having issues with safety, and are therefore generally not the preferred option for HTS.

Alternatively, reporter gene assays are popular functional cell-based assays suitable for cAMP measurements. In order to monitor $G_{\alpha s/i}$-dependent changes in cAMP, the cAMP response element (CRE) can be used as the promoter for an easily detectable reporter gene, such as the firefly luciferase, β-galactosidase, β-lactamase, or GFP. Various detection methods are used to measure expressed reporter gene protein, including luminescence, absorbance, and fluorescence. CRE-luc assays are generally very sensitive given the low background signal and the amplification of the signal between GPCR activation and gene expression. They have the disadvantage of measuring downstream effects, and hence require a few hours of incubation to accumulate the reporter gene product in the cells. As a consequence, these assays are characterized by a high level of false positives.

Other HTS technologies for direct cAMP measurements rely on homogenous competitive immunoassays. TR-FRET combines HTRF and FRET principles and is based on the competition between an europium or terbium-labeled cAMP tracer and sample cAMP for binding sites on cAMP-specific antibodies labeled with a fluorescent dye. The formation of antibody-cAMP complex is inversely proportional to cAMP concentration in the sample. Several assay kits allowing cAMP detection based on this principle (e.g., LANCE™ and HTRF®) are commercially available.

The DiscoveRx technology platform HitHunter™ is based on high-affinity complementation of two separately inactive enzyme (β-galactosidase) fragments (enzyme donor and acceptor) to form a stable heteromeric enzyme complex capable of hydrolyzing substrates to produce a chemiluminescent or fluorescent signal. The analyte (cAMP) competes with an analyte-conjugated donor fragment for binding to an analyte-specific antibody. Upon antibody binding, the donor portion of the enzyme is incapable of association with the enzyme acceptor. Hence, the amount of cAMP-conjugated donor available for enzyme complementation is proportional to the concentration of cAMP in the sample.

Alternative assay kits include Alphascreen™, a highly sensitive bead-based chemiluminescent assay based on the competition between endogenous cAMP and exogenously added biotinylated cAMP, and fluorescence polarization (FP), which measures the parallel and perpendicular components of fluorescence emission generated by polarized light. The magnitude of the polarization signal is used to quantitatively determine the binding extent of a fluorescent cAMP tracer complex (Heilker et al. 2009; Thomsen et al. 2005).

Ca^{2+} Mobilization

If the GPCR of interest signals via PLC, then the most broadly used cell-based technique is the measurement of transient changes in intracellular Ca^{2+} concentrations using a fluorescent plate reader such as FLIPR™ or FDSS. In FLIPR-type assays, cells expressing a receptor of interest are usually incubated with a membrane-permeable fluorescent dye that after hydrolysis is converted to a Ca^{2+} sensitive, membrane-impermeable probe. Alternatively, Ca^{2+} generation can be measured with the use of Ca^{2+}-responsive luminescent photoproteins, such as aequorin. While Ca^{2+} fluxes traditionally could only be measured for G_q-coupled GPCRs, the coexpression of promiscuous G-proteins has extended the use of this technique to all GPCRs.

Reporter gene assays (using AP1 or NFAT response elements) can be used as an alternative method to measure Ca^{2+} mobilization (Heilker et al. 2009; Thomsen et al. 2005).

ERK Phosphorylation and β-Arrestin Signaling

GPCRs can generate diverse signals that activate the ERK MAP kinase pathway. Depending on the receptor and cell type, GPCR-mediated ERK activation may involve classical second messenger-dependent routes, utilize tyrosine protein phosphorylation, or involve β-arrestins as scaffolds for the MAP kinase module. A popular assay to measure ERK phosphorylation is the Alphascreen SureFire™ technology. Advantageously, ERK phosphorylation is independent of the type of G-protein linked to the receptor.

Signalling via the β-arrestin pathway is usually assessed by measuring β-arrestin translocation to receptors. This can be done via fluorescently tagged β-arrestins and either microscopic imaging of β-arrestin redistribution, or FRET or BRET assays to detect β-arrestin-receptor interactions. An HTS-suitable enzyme fragment complementation β-arrestin assay (PathHunter™) has been developed by DiscoveRx (Heilker et al. 2009).

Label-Free Functional Assays

Label-free technologies based on either electrical impedance or refractive index are novel tools for measuring cell-based, real-time, kinetic functional responses (Minor 2008).

While these assays eliminate the need for expensive and "artificial" tags, dyes, or specialized reagents, the downside of this technology is that one measures a response

"signature," and that it needs to be confirmed whether that is specific for the G-protein subtype to which the receptor is coupled. And although these systems can be configured in multiwell format, most of them lack on-board pipetting capabilities, and are therefore not yet equipped to support HTS campaigns (Table 1).

Functional Assays for Ion Channels

As their name suggests, ion channels are intramembrane proteins which when activated undergo a conformational change that results in the opening of a channel through which ions cross the cell membrane. Ion channels can be classified into two types: ligand-gated and voltage-activated ion channels, which are activated by the binding of a ligand or changes in the membrane potential, respectively, and representative technologies associated with measuring ion channel function are presented in Table 2. The relevance of ion channels as drug targets is highlighted by their pathological involvement in a variety of disorders (the so-called "channelopathies"), as well as the efficacy of drugs that target specific ion channels, most notably from a psychopharmacological view the ▶ benzodiazepines, which modulate $GABA_A$ receptor function, as well as antiepileptic drugs that target sodium and calcium channels (Camerino et al. 2007).

High-Throughput Electrophysiology

The flow of ions across the membrane is most precisely measured using electrophysiological methods, such as patch-clamp electrophysiology in mammalian cells or two-electrode voltage clamp in *Xenopus laevis* oocytes. While electrophysiology remains the gold standard for assessing ion-channel function, these methods are relatively low throughput and although higher throughput platforms have been developed, such as IonWorks (Molecular Devices), QPatch (Sophion Bioscience), Patchliner (Nanion Technologies), or PatchXpress (Axon Instuments), nonelectrophysiological, high-throughput cell-based assays using fluorescent dyes or ion flux have been widely used for HTS assays (Dunlop et al. 2008a,b).

Optical Methods: Membrane Potential Sensors

The changes in membrane potential that occur when ion channels are activated may be detected using dyes that are sensitive to membrane potential, such as the negatively charged oxonols, $DiSBAC_2(3)$ or $DiSBAC_4(3)$. These molecules are mobile and can move from the outer to inner face of the membrane according to the membrane potential. Hence, as the membrane potential changes, so does the partitioning of the oxonol across the plasma membrane. In the presence of a cell-impermeable fluorescence quencher, the dye will only produce a fluorescent signal when associated with the inner face of the membrane. FMP dyes operate on the same principle but have a faster response than the oxonol dyes.

Fluorescent probes may also be used to detect changes of membrane potential using FRET. One component, for example, a coumarin-labeled phospholipid, binds specifically to the exterior surface of the membrane whereas the other partner, typically $DiSBAC_2(3)$ or $DiSBAC_4(3)$, is mobile.

Receptors: Functional Assays. Table 2. Summary of methods available for assessing functional effects at ion-channel receptors.

Assay type	Comment
Electrophysiology	"Gold standard" for ion channel measurements. Labor intensive but recent technological advances (e.g., QPatch, IonWorks, PatchXpress) have markedly increased throughput
Optical probes – intracellular Ca^{2+}	Organic fluorophores (fura-2, fluo-3, fluo-4, etc.)
	Fluorescent proteins incorporating Ca^{2+} sensor (e.g., calmodulin)
	Bioluminescence – emission upon irreversible binding of Ca^{2+} to aequorin
Optical probes – other	Thallium-sensitive dyes as surrogate for K^+ (e.g., BTC-AM, ThalKal) MEQ for Cl^-
Optical probes – membrane potential	FRET-based – immobile donor (coumarin-linked phopholipid) mobile, voltage-sensitive oxonol acceptor (e.g., $DiSBAC_2(3)$, $DiSBAC_4(3)$)
	Fluorescence-based – voltage-sensitive oxonol or FMP dye plus quencher
Ion flux – radiometric	^{22}Na for sodium channels, ^{86}Rb for potassium channel, ^{45}Ca for calcium channels, ^{36}Cl or ^{125}I for chloride channels
Ion flux – atomic absorption spectroscopy	Lithium for Na channels; rubidium for potassium channels; chloride for chloride channels[a] (e.g., Ion Channel Reader from Aurora Biomed)

[a]Chloride ion measurement is indirect and involves precipitation with silver nitrate and measuring free-silver concentrations

Hence, as the membrane potential changes, so does the partitioning of the oxonol across the plasma membrane and as a result, the FRET between the membrane-bound donor and the mobile voltage-sensitive acceptor changes. Commercialization of this technology has resulted in the voltage-sensitive ion probe reader (VIPR; Aurora Biosciences Corp.) and the electronic-stimulation voltage ion probe reader (E-VIPR; Vertex Pharmaceuticals).

Optical Methods: Ion Flux Indicators

The use of detectors that are selective for particular ions provides a reliable means of detecting intracellular changes in ion concentrations in response to ion-channel activation. In this regard, methods for Ca^{2+}-permeable ion channels are the best established due to the wide range of well-characterized Ca^{2+}-sensitive organic fluorophores and Ca^{2+}-sensitive proteins. In contrast to Ca^{2+}, there are currently no generally accepted fluorescent indicators for K^+ suitable as primary functional assays for potassium channels, although thallium-sensitive indicators can be used as a surrogate since K^+-conducting ion channels are also permeable to other ions such as rubidium (for which no sensor currently exists) and thallium. As regards halide ions, the interaction of halide ions with 6-methoxy-*N*-ethylquinolinium iodide (MEQ) reduces the fluorescence of the latter, and this reduction in fluorescence can be used as an indicator of chloride channel-mediated Cl^- flux.

Ion Flux Indicators: Nonoptical

As an alternative to optical methods, the flux of ions through the channel may be measured either as an influx or efflux assay, depending upon the direction of ion flow. This might be using a radiometric assay in which, for example, $^{22}Na^+$ or ^{14}C-guanidinium may be used for sodium channels, $^{86}Rb^+$ for potassium channels, $^{45}Ca^{2+}$ for calcium channels, and $^{36}Cl^-$ or $^{125}I^-$ for chloride channels. However, such assays require a separation step in order to remove radioisotopes that have not been taken up into the cell and are therefore generally unsuitable for HTS. An additional factor that makes radiometric ion flux assays unattractive is that they often use high-energy radioisotopes. As an alternative, nonradioactive flux assays may be used in which highly sensitive flame atomic absorption spectrometers capable of measuring the ion content in small volumes are used to quantify ion flow (e.g., the Ion Channel Reader from Aurora Biosciences Corp.).

The disadvantages of flux methods, whether optical or nonoptical, include the possibility of large, nonspecific background fluxes or a rapid inactivation of the target ion channel. Moreover, although this latter aspect can be addressed by using mutated target proteins and/or pharmacological agents that prolong the channel open state or decrease the rate of channel inactivation, it is possible that some interactions may be missed or artifactually detected in such a modified system (Table 2).

Limitations and Other Considerations

The main caveat to most functional assays is that they are performed in artificial systems, generally using human receptors stably, or sometimes transiently, expressed in generally nonneuronal cell lines, such as Chinese hamster ovary (CHO) or human embryonic kidney (HEK) cells. Under such conditions, the functional effects of compounds can be influenced by the level of receptor expression and, in the case of GPCRs, by the efficiency of coupling to G-proteins. The level of receptor expression and G-protein coupling efficiency dictate the level of GPCR receptor reserve (i.e., the amount of "spare" receptors, in excess of those necessary to produce a maximum response when occupied by an agonist), and this may further complicate the interpretation of functional screening data. For example, a ► partial agonist in one tissue may appear to act as a full agonist in another tissue with a higher receptor reserve.

Consideration should also be given to the subunit composition of the particular receptor of interest, as well as the impact that auxiliary proteins may have upon the function of the receptor. For instance, ion channels may be heteromeric assemblies, the subunit composition of which is a key determinant of receptor pharmacology. Furthermore, an emerging area of GPCR research is that of heterodimerization of subunits which can also markedly influence the pharmacology (Waldhoer et al. 2005). However, since information concerning the physiological subunit composition and the relevance of ancillary proteins may well be absent, or at best poorly understood, a minimalistic approach is often adopted in which homomeric receptors are studied.

An emerging area of GPCR research is that of collateral efficacy, also known as biased agonism, ► functional selectivity and stimulus trafficking, in which different agonists can produce differential effects on different intracellular signaling pathways (in other words, all agonists for a particular GPCR do not necessarily produce the same effects on signaling pathways; Galandrin et al. 2007). The implication of this is that compounds that produce a functional response using a methodology based upon a GPCR-linked signaling pathway, for example, cAMP, may not necessarily produce a similar functional response in another pathway such as the β-arrestin-mediated pathway.

In summary, it is important to emphasize that there is no one-size-fits-all functional assay for GPCRs or ion channels. Hence, the choice of assay should be based upon practical considerations such as the number of compounds requiring testing, the instrumentation available, and the properties of the cell lines being used. As a result, a degree of trial-and-error evaluation of different assay formats is to be expected. Finally, while functional data obtained from recombinant model systems are crucial early on in the search for novel pharmaceuticals, it is critical that these functional effects of compounds are also evaluated at native receptors.

Cross-References

- ▶ Affinity
- ▶ Agonist
- ▶ Allosteric Modulator
- ▶ Antagonist
- ▶ Binding
- ▶ Desensitization
- ▶ Efficacy
- ▶ Inverse Agonists
- ▶ Partial Agonist
- ▶ Receptors: Ligand-Binding Assays and Their Interpretation

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Recombinant Cell Line

Definition

A cell line into which recombinant DNA has been introduced, either stably or transiently.

Reconsolidation

Definition

The process by which some types of consolidated memories are rendered stable once again after being reactivated.

Recurrent Brief Depression

▶ Recurrent Brief Depressive Disorder

Recurrent Brief Depressive Disorder

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Synonyms

RBD; Recurrent brief depression

Definition

Recurrent brief depressive disorder (RBD) is a well-defined and prevalent mood disorder with an increased risk of suicidal behavior and significant clinical impairment. The syndrome is defined by depressive episodes that occur at least monthly and last only a few days. RBD represents a distinct and frequent clinical diagnosis in ▶ ICD-10. In contrast, ▶ DSM-IV classifies RBD into the subcategory of depressive disorders "Not Otherwise Specified (NOS)" for clinical purposes, with detailed operationalized diagnostic criteria offered in the appendix

of DSM-IV for scientific use only. In both diagnostic manuals, psychopathological symptoms required for the diagnosis of RBD are the same as for ▶ major depressive disorder (MDD). Hence, RBD is primarily diagnosed by its duration criterion (episode duration <14 days) and frequency criterion (approximately 1 episode/month). The average duration appears to be 3–4 days.

The longitudinal course of mood disorders is characterized by a substantial diagnostic overlap between different diagnostic groups. However, longitudinal epidemiological studies have demonstrated that RBD is neither a prodromal nor a residual state of MDD or any other psychiatric disorder. Sometimes, RBD symptomatology might be accompanied by recurrent brief hypomania.

The concept of RBD and its clinical significance have been further delineated by studies on the patterns and consequences of a lifetime co-occurrence of both RBD and MDD, called combined depression (CD). Epidemiological and clinical studies have demonstrated a dramatic increase in ▶ suicide attempt rates and measures of impairment in cases of CD in comparison to either RBD or MDD alone. Based on this data, it has been suggested that it is important to ascertain the existence of previous recurrent brief depressive episodes in patients with current MDD, because such information contributes to the assessment of suicidal behavior risk as well as drug response, which appear to be worse for CD in comparison to RBD patients.

The differential diagnosis of RBD and MDD is based on their distinct courses of depressive episodes (1–3 days vs. weeks or months). Other psychiatric disorders with short-lived syndromes have to be ruled out, such as: (1) panic disorder, characterized by recurrent unexpected panic attacks lasting for minutes up to a few hours; (2) premenstrual dysphoric disorder (PMDD), appearing exclusively in relation to the menstrual cycle; (3) borderline personality disorder (BPD), in which affective instability can be manifested by depressive mood fluctuations that usually last for hours but can persist for days as well (although clinical studies suggest low comorbidity of RBD with borderline personality disorder, as well as different endocrine response patterns); (4) rapid cycling (RC) (>4 episodes/year), ultra-RC (episodes in a weekly rhythm) or ultra-ultra-RC (ultradian episodes) bipolar disorders, which must show at least hypomanic (or manic) episodes according to DSM-IV; (5) other affective disorders, such as minor depression, ▶ bipolar disorder, and ▶ dysthymia, which can be easily distinguished from RBD by the criterion of duration of the depressive episode; (6) drug-induced depression, such as in cocaine withdrawal; and (7) various somatic diseases which might be accompanied by brief depressive episodes, such as postictal ▶ dysphoria or the so-called interictal dysphoric disorder in epilepsy, migraine plus aura, ▶ Parkinson's disease, Fabry disease, celiac disease, and Prader–Willi syndrome.

Role of Pharmacotherapy

Two-thirds of all RBD patients seek professional help in the course of their life. Of this group, one quarter consult a general practitioner, one quarter see a psychologist, and the remaining half consult a psychiatrist or neurologist. Epidemiological studies have shown that nearly all such patients receive treatment with psychotherapy. However, RBD patients hardly ever receive pharmacological treatment in community samples. Almost two decades after the concept of RBD was introduced, data from clinical trials are still limited.

However, there are a few placebo-controlled studies and several case reports, a single-case analysis, and one open trial assessing the drug treatment of patients with RBD. The most rigorous of these studies, which have used a classical ▶ double-blind placebo-controlled two-tailed design, have not been able to demonstrate successful drug treatment for RBD. It has been suggested that the negative results in ▶ placebo-controlled studies have been due to a study design that is inappropriate for this clinical phenomenon. This suggestion is mainly supported by reported treatment responses in double-blind placebo-controlled one-tailed single-case analyses with nimodipine, verapamil, and ▶ carbamazepine. Furthermore, the controlled studies were carried out with highly selected RBD patient samples, i.e., patients with repeated suicide attempts or ▶ comorbid borderline personality disorder or somatic diseases. This might have led to a bias reflecting treatment resistance. This view is supported by case reports or open trials demonstrating successful treatment of RBD with mirtazapine, reboxetine, fluoxetine, lithium, carbamazepine, lamotrigine, tranylcypromine, and olanzapine.

The optimal treatment regime for RBD remains an open question. The aggregate of available data and clinical experience suggest that second-generation antidepressants might be appropriate. As a second-line treatment, ▶ mood stabilizers can be considered. However, longer response rates (weeks to a few months) than in MDD are characteristic for this disorder, since symptoms are occurring less regularly than in MDD.

Because available study results remain unclear and contradictory, there is a great need for additional controlled clinical trials without the methodological limitations of previous studies. Early pessimism concerning the pharmacological treatment of RBD could be due to the false-negative study results and is probably not justified.

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Re-Encoding

Definition

The fact or process whereby a memory item is again encoded after it has been retrieved. The resulting engram may or may not be identical to the one that preceded it.

Reference Electrode

Definition

Voltage potentials are only defined with respect to a reference: an arbitrarily chosen zero level. For each EEG recording, a reference electrode has to be selected in advance. Ideally, this electrode should be affected by ambient electrical activity in the same manner as all the other electrodes, such that this activity is subtracted out by the referencing procedure. In most studies, a reference on the head, but at some distance from the other recording electrodes is chosen. Such a reference can be the earlobes, the nose, or the mastoids (i.e., the bone behind the ears).

Cross-References

► Electroencephalogram
► Event-Related Potentials

Refractory Schizophrenia

► Treatment-Resistant Schizophrenia

Region-Specific Knockout

► Conditional Knockout

Reinforcement

Definition

A behavioral process whereby the probability of a response is increased because it previously produced a particular environmental consequence. Such consequences take the form of presentations of environmental stimuli, which are thereby defined operationally as reinforcers. Such stimuli can either be exteroceptive (e.g., a sweet-tasting substance) or interoceptive (e.g., an abused drug).

Reinforcement Disorders

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Definition

Reinforcement refers to the process or constellation of processes that "stamp in" learned associations and response habits, processes that enhance or establish the transfer of immediate short-term memories to relatively permanent long-term memories. The mechanisms of reinforcement remain mysteries not yet fully understood, but a variety of animal models identify reinforcement closely with the consequences of the extracellular actions of the neurotransmitter dopamine. ► Dopamine is released from nerve terminals in response to various reinforcers – the prototypical reinforcer is food for a hungry animal – and, once the association is formed, in response to conditioned stimuli that reliably predict those rewards. The habit-forming and habit-sustaining effects of most positive reinforcers are lost in animal models when the receptors for dopamine are blocked pharmacologically.

Current Concepts and State of Knowledge

Until recently in our evolutionary history, the ability to learn associations and response habits leading to sweet and calorie-dense substances has had obvious adaptive value. By learning to identify the predictors and repeat the acts that bring them in contact with sweet taste, infants learn to find the mother's nipple efficiently and adults learn to find and eat ripe fruits and to save them for another day. When the food supply has been limited, this has served us well. However, in recent decades, people in industrial societies are increasingly exposed to more tasty and abundant energy rich foods than they need for simple subsistence, and the tendency to overindulge in sweet and fatty foods has resulted in an epidemic of obesity that can be seen as a disorder of reinforcement, of reinforcement gone awry. When we have easy access to tasty energy-laden foods, our reinforcement mechanisms prove to be *too* effective, encouraging maladaptive overeating.

In the last few thousand years we have learned to store and refine ▶ alcohol and inhale the smoke of tobacco and in the last few hundred years we have learned to refine and synthesize several addictive substances, substances that can themselves serve as positive reinforcers. Easy access to these substances and to effective ways to ingest them has given rise to a more immediately knotty problem of over-reinforcement: addiction. Drugs such as ▶ heroin, ▶ cocaine, and ▶ methamphetamine can elevate dopamine levels further and more rapidly than even the most palatable of foods, and can establish drug-taking habits that are arguably more compulsive than the eating habits of the clinically obese. The smoking of tobacco and the drinking of alcohol also elevate dopamine levels much more rapidly than does food, again, often leading to compulsive and maladaptive habits. Here, again is a disorder resulting from reinforcement that is too effective, from reinforcers that are too habit-forming. Also often viewed as disorders of over-effective reinforcement are compulsive gambling, compulsive video gaming, compulsive sexual habits, compulsive thrill seeking, and other learned compulsions. Our understanding that the mechanisms of reinforcement have gone awry derives in large part from studies of addictive drugs: substances that can act directly at the various sites of action of endogenous neurotransmitters.

Drug Addiction

Almost all addictive drugs share the ability to elevate extracellular dopamine levels. ▶ Amphetamines cause dopamine to be released from nerve terminals. Cocaine blocks the reuptake of dopamine when it has been released by neuronal activity. ▶ Nicotine stimulates dopamine neurons to fire and release dopamine. ▶ Opiates also cause dopamine neurons to fire, not by stimulating them but by inhibiting neighboring cells that usually limit dopamine cell firing. Ethyl alcohol and cannabis also – through yet other mechanisms – increase dopamine cell firing and extracellular dopamine release.

Moment-to-moment changes in dopamine levels have been monitored during periods of intravenous self-administration of cocaine and heroin. This is best seen in animals trained to earn intravenous injections by lever-pressing and given limited daily access to the drug. Experienced rats initiate a drug self-administration session by earning one or more injections causing rapid elevation of dopamine levels to three or four times the normal extracellular concentration. Once dopamine levels are elevated the animals cease lever-pressing until dopamine levels fall back to about twice normal. Then they make another response, again elevating dopamine levels and again waiting to respond further until the dopamine level again falls to about twice normal. This sequence is repeated until the session ends or until the animal is exhausted, with dopamine levels maintained above the trigger point of about twice normal elevations. If the animal is given an unpredictable sequence of sometimes small, sometimes medium, and sometimes large cocaine doses, the delay between successive lever-presses will be short, medium, or long, respectively.

The regular psychomotor stimulant intake seen when animals are limited to 1–4 h of daily drug access can escalate and become irregular when animals are given prolonged access to the drug. This can be seen with many weeks of access or with more than 6 h of daily access. A variety of neuroadaptations in the reward circuitry itself have been identified and hypothesized to contribute to the escalation of intake and the increasing compulsiveness of intake at a time when the subjective perception of drug reward is decreasing. The degree to which such neuroadaptations affect other compulsive behaviors remains unclear.

In the cases of cocaine and amphetamine – drugs that appear to rely entirely on dopamine as their reinforcement substrate – the pharmacological blockade of dopamine receptors eliminates the reinforcing effects of the drugs. Lesions of the terminals of the mesocorticolimbic dopamine system can have similar effects if the lesions are large enough and are correctly placed. It is not yet clear, however, what constitutes correct placement. Large lesions of the ventral striatum are effective, but they usually include damage to dopamine fibers terminating not only at ▶ nucleus accumbens, the intended lesion target, but also to dopamine fibers of passage to the olfactory tubercle and

the medial ▶ prefrontal cortex, two sites in which cocaine is known to have habit-forming actions. Small lesions tend to implicate the core but not the shell of nucleus accumbens as the site of cocaine reinforcement, but while rats will learn to work for cocaine microinjections into the shell of accumbens (and even more readily learn to work for injections into the underlying olfactory tubercle), they do not similarly learn to work for injections into the core of accumbens. Thus extracellular dopamine plays a necessary role in cocaine reinforcement, but it is not yet clear *where* dopamine plays this necessary role.

In the cases of opiates and ▶ phencyclidine, dopamine does not appear to play an essential role. The reinforcing effects of phencyclidine appear to be in the ventral striatum, but postsynaptic to the dopamine terminals that innervate the GABAergic ventral striatal output neurons. ▶ Morphine (like dopamine) inhibits these output neurons, and morphine appears to be reinforcing because of this ventral striatal action. Phencyclidine blocks the excitatory input of glutamatergic input to the GABAergic output neurons, an input that parallels and is thought to interact with the adjacent dopaminergic input to these neurons. Nicotine and dopamine may have additional inputs to reinforcement circuitry, inputs that are also "downstream" to the dopamine synapses of the mesocorticolimbic dopamine system. The effects of dopamine antagonists and dopaminergic lesions on the self-administration of other addictive drugs are more complex and less well understood.

Compulsive Eating

Foods are the prototypical reinforcers. The most powerful food reinforcers are sugars, particularly when taken in combination with lipids (which are also reinforcers in their own right); however, even untasted vitamins and minerals can serve as reinforcers. These are substances that, once encountered, are returned to because of their reinforcing effects. Sugars and lipids result in the release of dopamine from nerve terminals in many brain regions, elevating extracellular dopamine to as much as twice normal levels. If the receptors that normally respond to dopamine are pharmacologically blocked, food is no longer habit forming. Sweet foods appear to have a double reinforcing effect; sweet taste is naturally reinforcing to many species and the post-ingestional effects of natural sugars are also reinforcing.

While compulsive food habits are usually associated with sweet and fatty foods, compulsive food habits can be entrained by unpalatable foods. Calcium-deprived institutionalized orphans, for example, were reported to compulsively eat plaster off the walls, as do many birds, despite its lack of palatability. Sodium-deprived animals and humans develop compulsive cravings for salt. A variety of such "specific hungers" have been reported in animals lacking the nutrient provided by the craved substance. Most of these hungers are learned.

Other Learned Compulsions

Many other compulsions have been labeled and likened to addiction. Compulsive ▶ gambling, compulsive sexual behavior, and compulsive thrill seeking are examples. Several investigators are pursuing the hypothesis that the brain mechanisms subserving a variety of such behaviors are shared with the brain mechanisms of drug addiction and compulsive eating.

Reinforcement Leads to Craving

While some compulsive ingestion habits like salt intake in sodium deficient animals appears to be innate, most compulsive habits result from reinforcement-based learning. Most compulsive cravings are the result of experience. Some exceptions can be attributed to reflexes, such as the reflexive approach induced by sexual pheromones or the reflexive avoidance induced in some species by fox odor and in other species by putrid smell. Some human cravings can develop through communication by language; ▶ cravings for illicit drugs, for example, can be established by language. Most cravings, however, develop as a result of the reinforcing effects of contact with the substance or event in question. Once a compulsive habit has been established, it can be sustained for long periods in the absence of reinforcement. In this case, however, even sparse intermittent reinforcement can sustain an established habit.

Extinction

Once a compulsive habit is established, many repetitions of the habit in the absence of reinforcement are required before the habit is "extinguished." Indeed, there is strong evidence that a compulsive habit is never completely extinguished even after long periods of non-reinforcement; presumably extinguished habits can always be reestablished with less reinforcement than was required to establish them in the first place.

The rate of ▶ extinction of a response habit depends on several things. If reinforcement follows every response immediately during the learning period, extinction (never to zero but to some low probability) can be fairly rapid. If reinforcement is delayed or intermittent during training, a response habit can be very resistant to extinction.

Intermittent reinforcement is termed "partial" reinforcement, and the greater resistance to extinction after partial reinforcement training is known as the "partial reinforcement extinction effect." The partial reinforcement extinction effect has important implications for the treatment of compulsive habits. Each binge after an attempt to diet, for example, results in an intermittent reinforcement that makes subsequent extinction more difficult.

Thus it takes much less reinforcement to sustain a habit than it takes to establish one. Reinforcement can become less frequent or less intense and still maintain a compulsive response habit. Thus addicts report that even when, because of drug ▶ tolerance, their drug of choice no longer seems to bring the subjective pleasure that accompanied initial use, they still seek the drug and have compulsive thoughts about it. Clinicians refer to the persistence of drug habits despite reduced reinforcement as "chasing the remembered high." Whatever form the "remembered high" takes – whether it be a conscious memory or merely a residual memory trace in the nervous system, the consequences of reinforcement in the past are of great importance for the cravings and behaviors of the present.

Potential Medications

The fact that some degree of reinforcement is required to maintain reinforcement-based response habits suggests that drugs that block reinforcement should cause extinction of those habits. Much of the evidence that brain dopamine plays an important role in reinforcement, and, indeed, drugs that block the central actions of dopamine do cause extinction-like decreases in habitual responding. However, consistent with the fact that it takes less reinforcement to maintain a habit than it takes to establish one, dopamine antagonists do not block an established response habit right away, and must be given repeatedly to cause anything approaching complete extinction. Dopamine antagonists have not been found effective in treating reinforcement disorders. First, consistent with the view that brain dopamine is important for a wide range of reinforcers, these drugs attenuate the effectiveness of many of life's pleasures and are not pleasant to take. These drugs are used effectively to treat the (seemingly unrelated) symptoms of ▶ schizophrenia, and patients do not like them and often discontinue their use when given the chance. Moreover, schizophrenic substance abusers continue to seek and use cocaine and amphetamine despite treatment with dopamine antagonists. This may be, of course, because cocaine and amphetamine are antagonists for the dysphoric effects of the dopamine blockers. It is also the case that dopamine antagonists have little if any effect on the motivational impact of reward-predictive environmental cues that contribute to drug seeking and drug euphoria. In any case, dopamine antagonists have not proven useful for the treatment of reinforcement disorders.

Two classes of drugs that are currently under study as potential medications for reinforcement disorders are opioid antagonists and cannabinoid antagonists. Exogenous opiates and ▶ cannabinoids are drugs of abuse, but endogenous opioids and cannabinoids are found in the brain and serve neurotransmitters or neuromodulators that, like other addictive drugs, have actions in the reward circuitry of the brain. ▶ Opioid antagonists are known to block the reinforcing effects of opiates and also appear to attenuate cravings for alcohol and for nicotine. Cannabinoid antagonists block the reinforcing effects of cannabinoids (marijuana, hashish) and also attenuate heroin, cocaine, and food cravings. The fact that each drug appears to affect natural reinforcers as well as drug reinforcers strengthens the evidence that drug and natural reinforcers share a common reward mechanism in the brain, but makes the search for medications that can target a troublesome reinforcer without affecting others more challenging. Over most of the course of our evolutionary history, the substances our brain finds reinforcing have been the necessities of life.

Cross-References

▶ Addictive Disorder: Animal Models
▶ Eating and Appetite
▶ Intracranial Self-Stimulation
▶ Pathological Gambling
▶ Reinstatement of Drug Self-Administration
▶ Self-Administration of Drugs

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Reinforcer

Definition

An event that maintains or strengthens a behavioral response that produces it. For example, cocaine can function as a reinforcer because when an animal is allowed to self-administer it by means of pressing a lever, the animal will continue to press the lever again and again. The act of pressing the lever was reinforced by cocaine.

Reinforcer Efficacy

► Subjective Value

Reinstatement

Definition

A procedure used to examine drug-seeking behavior, typically in rodents or nonhuman primates. Animals are first trained to self-administer drug (or other reinforcer) and then the response is extinguished by omitting the reinforcer. Following extinction, the animal receives a drug prime (typically by injection) or drug-associated cue and is allowed to respond, but without any contingent delivery of the reinforcer. Reinstatement is reflected as an increase in non-reinforced responding relative to the last day of extinction.

Reinstatement of Drug Seeking

► Reinstatement of Drug Self-Administration

Reinstatement of Drug Self-Administration

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Synonyms

Reinstatement of drug seeking; Reinstatement of drug-taking behavior

Definition

In the learning literature, the term "reinstatement" refers to the resumption of a learned response that occurs when a subject is exposed non-contingently to the unconditioned stimulus. In the addiction field, "reinstatement of drug self-administration" in experimental animals (typically termed "reinstatement of drug seeking") refers to the resumption of a previously drug-reinforced behavior by non-contingent exposure to drugs, different types of drug cues, or stressors after the ► extinction of the drug-reinforced behavior. The animal model that addiction researchers use to study the reinstatement of drug seeking is termed the "reinstatement model" (Shaham et al. 2003).

Impact of Psychoactive Drugs

Background

A major problem in the treatment of drug addiction is the high rate of relapse to drugs of abuse following a prolonged abstinence period. Results from studies in humans suggest that in drug-free individuals, relapse to drug use during periods of forced or voluntary abstinence can be triggered by acute exposure to the self-administered drug, stimuli previously associated with drug taking, or stressors. Acute exposure to the self-administered drug or related drugs, ► drug-associated cues, or ► stress also reinstates drug seeking in laboratory rats and monkeys (Shaham et al. 2003). Because of the similarities between the human condition and the laboratory animal model, many investigators currently use the reinstatement model to study mechanisms underlying relapse to drug use. Conceptual issues related to the validity of the reinstatement model as an animal model of relapse to drug use are discussed by Epstein et al. (2006).

Experimental Procedures

In the ► drug self-administration version of the reinstatement model, which is based on an ► operant-conditioning

procedure, laboratory animals (rats, mice, and monkeys) are initially trained to self-administer drugs by lever pressing (or another operant response such as nose-poking) for intravenous drug infusions (or for oral delivery of alcohol). Subsequently, the drug-reinforced behavior is extinguished by substituting the drug solutions with saline or by disconnecting the infusion pumps. After the extinction of the drug-reinforced behavior, the ability of acute noncontingent exposure to drugs (termed "drug-priming"), drug-associated cues, or stress to reinstate lever responding is measured under extinction conditions (Shaham et al. 2003). The non-reinforced responding on the "active lever" – the lever that previously delivered the drug – is interpreted to reflect the reinstatement of drug seeking. The responding on the "inactive lever" – the lever that has not been associated with drug injections – is often interpreted to reflect nonspecific activity, but it may also reflect response generalization.

In laboratory animals, the reinstatement of drug seeking has been studied using the "between-session," "within-session," and "between-within session" variations of the reinstatement model (Shalev et al. 2002). In the between-session procedure, training for drug self-administration, the extinction of the drug-reinforced behavior and tests for reinstatement are conducted on different daily sessions. In the within-session procedure, all three phases are conducted within a daily session. This daily session consists of 1–2 h of drug self-administration that is followed by 3–4 h of extinction of the drug-reinforced behavior; after extinction of lever responding, a test for reinstatement is conducted. In the between-within procedure, the laboratory animals are trained daily for drug self-administration; subsequently, the extinction of the drug-reinforced lever responding and tests for reinstatement are conducted on the same day. In addition, researchers also assess the reinstatement of drug seeking in variations of the reinstatement model that are based on the ► runway and ► conditioned place preference procedures. Shalev et al. (2002) provide a detailed description of the different procedural variations of the reinstatement model and discuss the advantages and disadvantages of using them for assessing the reinstatement of drug seeking.

Neuropharmacology of Reinstatement of Drug Seeking

In this section, we summarize the extant literature on the neuropharmacology of the reinstatement of drug seeking induced by exposure to the self-administered drug or related drugs (drug-priming), drug-associated cues, or stress. Due to space constraints, we often do not differentiate between results obtained from studies in which rats were trained to self-administer cocaine and other psychostimulants, heroin and morphine, or alcohol. A detailed description of the neuropharmacology of the reinstatement of drug seeking is provided by Shalev et al. (2002) and Bossert et al. (2005).

Drug-Priming-Induced Reinstatement

Results from studies on drug-priming-induced reinstatement of drug seeking indicate that this reinstatement is primarily mediated by dopaminergic and glutamatergic neurotransmission in the mesocorticolimbic system (Kalivas and McFarland 2003; Schmidt et al. 2005; Self 2004). This system consists of dopamine cell bodies in the ► ventral tegmental area (VTA) that project to limbic areas, including ► nucleus accumbens, ► amygdala, and bed nucleus of stria terminalis (BNST), and cortical areas, including medial ► prefrontal cortex (mPFC) and orbital frontal cortex (OFC).

Regarding dopamine, systemic injections of either D1-family dopamine receptor agonists or antagonists decrease cocaine-induced reinstatement; D1-family dopamine receptor antagonists also decrease heroin-priming-induced reinstatement. On the other hand, systemic injections of D2-family receptor antagonists decrease heroin- or cocaine-priming-induced reinstatement, while injections of D2-family receptor agonists reinstate drug seeking. The effect of cocaine priming on reinstatement is also attenuated by systemic injections of selective D3 receptor antagonists. Additionally, injections of D1-family or D2-family receptor antagonists into the dorsal mPFC, accumbens shell (but not core), and amygdala (both central and basolateral subregions) decrease cocaine-priming-induced reinstatement. Accumbens core injections of D1-family or D2-family receptor antagonists decrease heroin-priming-induced reinstatement. Finally, activation of VTA dopamine neurons by local injections of morphine reinstates heroin and cocaine seeking, while local inhibition of these neurons by a mixture of $GABA_A + GABA_B$ receptor agonists (muscimol+baclofen) decreases cocaine-priming- and heroin-priming-induced reinstatement.

Regarding ► glutamate, systemic injections of metabotropic glutamate receptor 5 antagonists or group II metabotropic glutamate agonists (which decrease evoked glutamate release via a presynaptic autoreceptor mechanism) decrease cocaine-priming-induced reinstatement. Additionally, local injections of nonselective ionotropic glutamate receptor antagonists into the VTA, selective ► AMPA receptor antagonists into the accumbens, or reversible inactivation of the glutamate projection from the dorsal mPFC to the accumbens decrease heroin or

cocaine-priming-induced reinstatement. Finally, there is evidence that cocaine self-administration and subsequent withdrawal leads to long-lasting neuroadaptations in glutamatergic transmission in the mPFC–accumbens pathway, and that the pharmacological reversal of these neuroadaptations prevents cocaine-priming-induced reinstatement.

Results from studies in which investigators used reversible inactivation manipulations (the sodium channel blocker tetrodotoxin or muscimol+baclofen) suggest a role of the ventral pallidum in cocaine- and heroin-priming-induced reinstatement. In the case of heroin-priming-induced reinstatement, there is also evidence for a role of the BNST (dorsal and ventral subregions), dorsal striatum, substantia nigra, and ventral mPFC. Additionally, there is evidence from pharmacological studies that other neurotransmitter systems, including ► endocannabinoids, ► serotonin, and ► GABA contribute to drug-priming-induced reinstatement. However, the brain sites involved in these effects are unknown. Finally, there is evidence for a role of accumbens protein kinase A and calcium–calmodulin dependent kinase II signaling pathways in cocaine-priming-induced reinstatement.

Cue-Induced Reinstatement

In humans, relapse-provoking drug-associated stimuli can be divided into two general categories: discrete drug cues (e.g., drug paraphernalia) that are associated with the acute rewarding effects of the drug, and contextual drug cues (e.g., a specific environment such as a local bar) that predict drug availability. In laboratory animals, procedures to assess cue-induced reinstatement of drug seeking are classified into three types according to the type of the conditioned cue: discrete-cue, discriminative-cue, and contextual-cue.

► Discrete-cue-induced reinstatement: Results from pharmacological studies suggest a role of several neurotransmitters and receptors in discrete-cue-induced reinstatement (Feltenstein and See 2008). Systemic injections of D1-family receptor antagonists, selective D3 receptor antagonists, nicotinic cholinergic antagonists, several serotonergic agents, group II metabotropic receptor agonists, cannabinoid 1 (CB1) receptor antagonists, and mu opiate receptor antagonists decrease the discrete-cue-induced reinstatement of drug seeking. In the case of D1-family receptors, two brain sites are critical for their effects: the amygdala (both central and basolateral subregions) and the accumbens core (but not shell). The brain sites involved in the modulation of the discrete-cue-induced reinstatement by the other neurotransmitter systems are unknown. Additionally, results from studies in which reversible inactivation manipulations were used suggest a role of the dorsal mPFC and dorsal striatum in the discrete-cue-induced reinstatement. In heroin-experienced rats, there is evidence that discrete-cue-induced reinstatement also involves the ventral mPFC, the dorsal BNST, the ventral pallidum, and the substantia nigra.

► Discriminative-cue-induced reinstatement: Results from pharmacological studies suggest a role of several neurotransmitter system in discriminative-cue-induced reinstatement (Weiss 2005). Systemic injections of D1-family and D2-family receptor antagonists, selective D3 receptor agonists, group II metabotropic receptor agonists, metabotropic glutamate receptor type 1 or type 5 antagonists, CB1 receptor antagonists, sigma 1 receptor antagonists, 5-HT2B/2C receptor agonists, and mu opioid receptor antagonists decrease the discriminative-cue-induced reinstatement. The discriminative-cue-induced reinstatement is also attenuated by ventricular injections of the opioid peptide nociceptin/orphanin FQ (the endogenous ligand for the opioid-like orphan receptor). In the case of CB1 receptor antagonists, two brain sites are critical for their effects: the mPFC and the accumbens. The brain sites involved in the modulation of discriminative-cue-induced reinstatement by the other neurotransmitter systems are unknown. However, in the case of dopamine receptor antagonists, likely brain sites are the amygdala, the accumbens, and the mPFC. Thus, exposure to cocaine discriminative cues increases dopamine release in the accumbens and amygdala. Additionally, discriminative-cue-induced Fos (a neuronal activity marker) expression in the basolateral amygdala and prefrontal cortex is decreased by systemic injections of a D1-family receptor antagonist.

► Context-induced reinstatement: Results from pharmacological studies suggest a role of several neurotransmitter systems in context-induced reinstatement (Crombag et al. 2008). Systemic injections of D1-family and D2-family receptor antagonists, group II metabotropic receptor agonists, CB1 receptor antagonists, and 5-HT2B/2C receptor agonists decrease context-induced reinstatement. In the case of D1-family receptors, a critical brain site is the accumbens shell. In the case of group II metabotropic receptors, the critical brain sites are the accumbens shell and VTA. The brain sites involved in the modulation of the context-induced reinstatement by the other neurotransmitter systems are unknown. Results from studies in which reversible inactivation methods were used suggest a role of the dorsal mPFC, the dorsal striatum, the basolateral amygdala and the dorsal hippocampus in context-induced reinstatement. Results from studies on the

effect of context-induced reinstatement testing on Fos expression in the brain suggest a role of the lateral hypothalamus in this reinstatement.

Stress-Induced Reinstatement

The phenomenon of stress-induced reinstatement of drug seeking was initially demonstrated in studies in which investigators used an intermittent footshock stressor. The effect of this stressor generalizes to certain other stressors, including swim stress, acute food deprivation, ► social defeat, and several pharmacological stressors: the stress neurohormone ► corticotropin-releasing factor (CRF), the anxiogenic drug ► yohimbine (an alpha-2 adrenoceptor antagonist), and agonists of the kappa opioid receptor.

Evidence from studies in which pharmacological agents were used suggests a role of several neurotransmitter systems in stress-induced reinstatement. The ► stressor used in most of the neuropharmacological studies is intermittent footshock. Systemic injections of nonselective CRF antagonists, selective CRF1 receptor antagonists, alpha-2 adrenoceptor agonists (which decrease ► noradrenaline cell firing and release), ► hypocretin 1 receptor antagonist, non-selective dopamine receptor antagonist, ► selective serotonin reuptake blockers (SSRIs), and $5HT_3$ receptor antagonists decrease stress-induced reinstatement. The stress-induced reinstatement of alcohol (but not cocaine) seeking is attenuated by ventricular injections of nociceptin/orphanin FQ.

The effect of CRF antagonists on stress-induced reinstatement is independent of the activity of the ► hypothalamic-pituitary-adrenal axis (HPA) and the effect of these antagonists on the stress hormone corticosterone. The critical extrahypothalamic brain sites and projections for CRF's role in footshock-induced reinstatement are the BNST, VTA, and a projection from the central amygdala to the BNST. Within the VTA, footshock causes local CRF release, which leads to increased glutamate transmission; this enhanced glutamate transmission is critical for stress-induced reinstatement, presumably via an activation of the mesocorticolimbic dopamine system. Support for this notion is provided by the findings that injections of D1-family receptor antagonists into the dorsal mPFC or OFC, or preferential D3 receptor antagonists into the accumbens decrease stress-induced reinstatement. The critical brain sites and projections for noradrenaline's role in footshock-induced reinstatement are the central amygdala and BNST, and the noradrenergic projection from the lateral tegmental nuclei to these brain sites.

Finally, results from studies in which reversible inactivation methods were used confirm the findings on the role of the dorsal mPFC, the BNST, the central amygdala, the accumbens, and the VTA in stress-induced reinstatement, and further suggest a role of the ventral pallidum in this reinstatement. Finally, as in the case of drug-priming-induced reinstatement, the glutamatergic projection from the mPFC to the accumbens plays an important role in stress-induced reinstatement.

Acknowledgment

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Cross-References

► Conditioned Place Preference
► Contextual Cue-Induced Reinstatement
► Discrete-Cue-Induced Reinstatement
► Discriminative-Cue-Induced Reinstatement
► Drug Self-Administration
► Extinction
► Runway Procedure
► Stress

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Reinstatement of Drug-Taking Behavior

► Reinstatement of Drug Self-Administration

Reinstatement Procedure

Definition

In reinstatement procedures, the laboratory animals are trained to self-administer drugs and are then subjected to extinction training, during which lever presses are not reinforced with drugs. Reinstatement of extinguished lever responding (the operational measure of drug seeking) is determined after manipulations such as noncontingent ► priming injections of the drug, exposure to cues associated with drug intake, or exposure to different ► stressors. During testing for reinstatement, extinction conditions remain in effect (the drug is not available).

Relapse

Definition

In drug dependence, to regress back to a level of drug use at or comparable to use prior to a quit attempt following a period in which reduced use or abstinence was attained.

Cross-References

► Addictive Disorder: Animal Models
► Drug Self-Administration
► Reinstatement of Drug Self-Administration

Relapse Prevention Studies

Definition

The standard approach to assessing the potential value of continued treatment in mood and anxiety disorders. Patients who have responded to open treatment are randomized to either continue with that compound, or to be switched to ► placebo, and followed up over 6–18 months, monitoring for signs of relapse, that is, the reappearance or significant worsening of symptoms. Efficacy is assessed through examining the mean time to relapse and the proportion of patients who relapse, in both groups.

Relapse Prevention Study Design

Definition

A study design that randomizes open-label responders to ongoing active or ► placebo treatment and follows them over several weeks under double-blind conditions to observe relapse rates.

Cross-References

► Double-Blind
► Open-Label

Relative Validity

Synonyms

Degraded contingency; Partial reinforcement

Definition

A relative reduction in associative learning (compared with what would ordinarily be supported) arising because the reliability with which an ► unconditioned stimulus (UCS) is predicted depends on the level of contingency between the UCS and the preceding ► conditioned stimulus (CS) at issue. To the extent that this informational relationship or contingency is partial, associative learning to the nominal CS will be reduced and alternative available stimuli, including those provided by the context, are likely to gain associative strength. Relative validity is a term applied to classical (Pavlovian) conditioning and a constraint on the general importance of temporal coincidence as the sole determinant of new learning.

Cross-References

► Classical (Pavlovian) Conditioning

Release Probability

Definition

Quantal release probability refers to the likelihood of vesicular release events of quanta of neurotransmitter occurring in a population of nerve terminals or a single nerve terminal, usually during invasion of an action potential. Drugs that have presynaptic actions on nerve terminals either increase or decrease quantal release probability.

REM Sleep

► Parasomnias
► Rapid Eye Movement Sleep

REM Sleep Behavior Disorder

Synonyms
RBD

Definition
In REM sleep behavior disorder, the paralysis that normally occurs during REM sleep is only partially present or may be absent altogether, thus enabling the affected individual to act out his/her dreams. Most frequently, the type of dreams that are acted out during RBD are vivid, intense, and violent. Examples include talking, yelling, punching, kicking, sitting, jumping out of bed, flailing arms about, and grabbing nearby objects, including the bed partner. A highly focused or acute form of RBD may occur during withdrawal from alcohol or sedative-hypnotic drugs.

Remeron

► Mirtazapine

Remission (From Depression)

Definition
Remission from depression is essentially the complete elimination of all symptoms for at least 6–12 months. In clinical trials, it may be defined according to the achievement of a particular score on a depression rating scale (e.g., a score of 7 or less on the Hamilton Depression (HAM-D) Rating Scale).

Cross-References
► Depression

Remission (From Obsessive–Compulsive Disorder)

Definition
The concept of remission for OCD is debatable, and there is no universally accepted definition. It has been described as a brief period during which sufficient improvement has occurred so that the individual no longer suffers with OCD. Studies have chosen varying remission criteria based on the Y-BOCS scale. A score of 16 on Y-BOCS is generally considered too high to meaningfully represent true remission, and a score of 7 too low to be achieved by all but a very few cases. In a recent analysis, a Y-BOCS score of 7 did not discriminate between active and control treatments, whereas in two recent multicenter extended SSRI (SSRI and related compounds) studies a score of 10 did. Therefore, for the purposes of definition a reduction in OCD symptoms such that the individual no longer suffers with OCD and has a total score of 10 on the Y-BOCS is usually accepted as remission.

Cross-References
► CGI-I
► SSRI and Related Compounds
► Y-BOCS

Repetitive Behavior

► Motor Activity and Stereotypy

Repetitive Thoughts

► Obsessions

Reporting Ligand

► Radiotracer

Reproduction Protocol

Definition
Reproduction protocol refers to a protocol in which subjects are presented with an event and required to reproduce a sequence of behavior compatible with the estimated duration of the event. Reproduction protocols avoid verbalizing the durations.

Reproductive Behavior

► Sexual Behavior

Reserpine

Definition

Reserpine is an indole alkaloid with antipsychotic and antihypertensive properties. It is currently not in clinical use for psychiatric conditions. Reserpine was isolated in 1952 from the dried root of *Rauwolfia serpentina* (Indian snakeroot), which was used in India for centuries to treat insanity and high blood pressure. Reserpine blocks the vesicular monoamine transporter, thereby acutely inhibiting the reuptake of the monoamines into the synaptic vesicles and increasing monoamine concentrations in the synaptic cleft, but eventually leading to depletion of vesicular monoamine stores in synaptic nerve endings upon chronic use, as the neurotransmitters that cannot reenter the vesicles will be degraded by monoamine oxidase. Chronic treatment can lead to ▶ depression, possibly due to depletion of these neurotransmitter stores. The drug can cause a range of additional side effects, for example, in the gastrointestinal tract (ulcerations, cramps, diarrhea) or the cardiovascular system (hypotension, bradycardia), all of which make it obsolete as an antipsychotic for today's treatment of ▶ schizophrenia or other psychoses. It was also used as a tool in experimental pharmacology, to deplete stored neurotransmitters and thus allow tests of their roles in pharmacological reactivity; this usage ended when more selective drugs became available.

Cross-References

▶ Antipsychotic Drugs
▶ Depression
▶ Schizophrenia

Resistance

▶ Tolerance

Respondent Conditioning

▶ Classical (Pavlovian) Conditioning
▶ Pavlovian Conditioning
▶ Pavlovian Fear Conditioning

Response Conflict Task

▶ Go/No-Go Task

Response Inhibition or Behavioral Inhibition

▶ Impulsivity

Response Inhibition Task

▶ Stop-Signal Task

Responsiveness

▶ Behavioral Flexibility: Attentional Shifting, Rule Switching and Response Reversal

Restlessness

▶ Hyperactivity

Retaining Current

Definition

In neurophysiological studies, a current (either positive or negative) that reduces or blocks the spontaneous efflux of charged transmitters, drugs, or other compounds of interest from the iontophoretic pipette into the extracellular environment.

Retardation of Acquisition Test

Synonyms

Retardation test

Definition

The retardation of acquisition test is one of two widely accepted tests for whether a stimulus functions as a conditioned inhibitor (see summation test for the other). In the retardation test, a stimulus is first trained as a putative conditioned inhibitor. Once complete, the stimulus is then repeatedly paired with the unconditioned stimulus (US). If the stimulus functions as a conditioned inhibitor, acquisition of an excitatory

conditioned response should be impaired (retarded) relative to controls. Because alternative accounts remain for delayed acquisition, the strongest case for a stimulus functioning as a conditioned inhibitor also requires the use of the summation test.

Cross-References

- ► Blocking, Overshadowing, and Related Concepts
- ► Classical (Pavlovian) Conditioning
- ► Occasion Setting With Drugs
- ► Pavlovian Fear Conditioning

Retardation Test

► Retardation of Acquisition Test

Retention

Definition

The process that allows an engram (memory) to be retrieved over a protracted time span. Retention performance, which depends on memory recall, is influenced by the ability of the subject to retrieve contextual stimuli. Distinctions between a failure of retention and one of recall are difficult, especially in animal subjects. A dissociation may exist between memory and performance, since the subject may not be able to properly express a learned response.

Cross-References

- ► Consolidation
- ► Short-Term and Working Memory in Animals
- ► Short-Term and Working Memory in Humans

Retrieval

Definition

The fact or process whereby learned information or response changes are expressed, or remembered.

Rett's Disorder

Definition

Rett's disorder is defined by normal development for the first 5 months of life in female infants. Between 5 and 48 months, there is a deceleration of head growth, loss of previously acquired purposeful hand skills with the development of stereotyped hand movements, and loss of social interaction, coordination skills, and expressive and receptive language skills.

Cross-References

- ► Autism Spectrum Disorders and Mental Retardation

Reverse Genetics – Targeted Mutagenesis

► Forward Genetics/Reverse Genetics

Reverse Tolerance

- ► Sensitization
- ► Sensitization to Drugs

Reversible Binding

Definition

The mode of interaction with receptors undergone by most neuroreceptor imaging tracers. Reversible means that the radiotracer will dissociate from the receptor-ligand complex with some regularity during the course of the imaging experiment, that is, that the ratio of the "on" rate of binding to the "off" rate of dissociation is not exceedingly large.

ReVia

► Naltrexone

Reward Intensity

Definition

The subjective strength of a reward, for example, the subjective attractiveness of different concentrations of sucrose to a hungry rat.

Rewarding

Definition
A drug is said to be rewarding if an animal behaves as if he likes it or wants more of it. In humans, we often think of rewarding as meaning that the drug produces a pleasant euphoria.

Reward-Related Incentive Learning

Synonyms
Incentive learning

Definition
Reward-related learning occurs when biological relevant (rewarding) stimuli are presented to an organism and involves the acquisition by neutral stimuli of an increased ability to elicit approach and other responses.

Reye's Syndrome

Definition
A rare but potentially fatal syndrome targeting the liver and brain; changes in behavior and cognitive state can be seen as a result of encephalopathy and chemical alterations in the blood derived from liver damage. Other symptoms include vomiting, seizures, hyperventilating and coma. It primarily presents in children and adolescents as the result of consuming acetylsalicylic acid during a viral infection such as chickenpox or influenza.

Modified from the Diagnostic and Statistical Manual of the American Psychiatric Association, Fourth edition (► DSM-IV) and the NIH-NLM MedlinePlus Encyclopedia (online).

Rhythmicity

Synonyms
Frequency of oscillation

Definition
In describing rodent behaviors that are expressed with a relatively invariant approximately sine wave-like regularity, "rhythm" and "rhythmicity" are used as descriptors to avoid the ambiguity associated with the word "frequency," which can mean "oscillations in cycles/s (Hz)" in physical contexts, but in statistical contexts refers to frequency of occurrence of events that have no synchronous relation to one another.

Cross-References
► Motor Activity and Stereotypy

9-β-D-Ribofuranosyladenine

► Adenosine

Ribozyme

Synonyms
Catalytic RNA molecule

Definition
Ribozymes are RNA molecules of viral, prokaryotic, or eukaryotic origin that possess catalytic activity. The term "ribozyme" was coined by Thomas R. Cech upon the discovery of a self-splicing intron in the ciliate protozoan *Tetrahymena thermophila*. Most commonly, ribozymes catalyze sequence-specific endonucleolytic cleavage, but also other catalytic activities, such as RNA polymerization, have been described. Similar to antisense oligonucleotides and siRNA, ribozymes find frequent application in the knockdown of expression of selected genes. There are several different classes of ribozymes, with the "hammerhead" ribozyme being the most widely studied, in recent years.

Cross-References
► Antisense Oligonucleotides
► siRNA

Rights

► Ethical Issues in Animal Psychopharmacology
► Ethical Issues in Human Pharmacology

Rigidity

Definition
Involuntary resistance to passive movement.

Rilmazafone

Definition
Rilmazafone is a benzodiazepine prodrug. Its activity is due to an active metabolite that is a benzodiazepine with sedative, hypnotic, and anxiolytic properties. It is a long-acting compound used in the short-term treatment of insomnia. Like most similar compounds, its use is subject to tolerance, abuse, dependence, and withdrawal.

Cross-References
► Benzodiazepines
► Insomnias
► Sedative, Hypnotic, and Anxiolytic Dependence

Rimonabant

Synonyms
SR141716

Definition
Rimonabant was the first selective CB_1 ligand introduced into clinical practice. This CB_1 receptor antagonist (with ► inverse agonist action) was found to be efficacious as a treatment for obesity and for improving dyslipidemias and metabolic disorders. There was also some promise for treatment of nicotine dependence and cannabis addiction. However, due to some increased rates of depression and anxiety and cases of suicide related to drug use, it was withdrawn from the market. It is used in experimental psychopharmacology as a probe for the involvement on CB_1 receptors in physiological and pharmacological phenomena.

Cross-References
► Appetite Suppressant
► Inverse Agonists

Risk Assessment (animals)

Synonyms
Stretched-attend posture

Definition
Risk assessment comprises a range of defensive behaviors displayed when animals are confronted with a novel and/or threatening stimulus. The biological function of these behaviors is to gather information about the potential threat by cautiously approaching it or by scanning the surrounding area. As rodents may display an increase in stretched-attend postures even when not avoiding an unprotected area, it has been advocated that risk assessment, thus representing the most enduring behavioral expression of anxiety, may even be more sensitive to anxiety-modulating drugs than avoidance behavior.

Cross-References
► Anxiety
► Defensive Behavior

Risk Taking

Synonyms
Adventuresome; Thrill seeking

Definition
Selection of alternative associated with lower probability of occurrence but, usually, larger subjective return. Unlike novelty seeking, the alternative selected is not necessarily unfamiliar to the individual. Sensation seeking incorporates both novelty seeking and risk taking.

Risperidone

Definition
Antipsychotic drug of the first generation, atypical category with combined dopamine D2/serotonin2 receptor-blocking properties.

Ritalin

► Methylphenidate
► Methylphenidate and Related Compounds

Ritual Uses of Psychoactive Drugs

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Definition

Substances, mainly plants that provoke an altered state of consciousness, have been used ritually for several thousand years throughout the globe in a wide variety of cultures. Their use has included religious, recreational, and healing aspects.

Current Concepts and State of Knowledge

Cultural anthropologists with interest in these substances document their important role in all continents among hunter/gatherers, incipient horticulturalists, advanced agricultural societies and pristine state societies as well as contemporary cultures. Over time, as societies became more complex, the use of plant ► hallucinogens changed from open access and widespread experiences to the usurpation of such use by elite segments of society. As societies became more complex, access to drug-induced altered states of consciousness became part of sumptuary laws, as fewer individuals were permitted entry to these states. This contrasts with societies of hunters/gatherers, for example, whereas many as one third of adult men might use plant psychedelics in ritual ceremonies for spiritual purposes. With cultural change, wars and conquest, much of our information about historical and prehistorical use of these substances was lost, only to be reformulated since the l960s. We can suppose that the abrogation of such drug access was related to the supposed power of the hallucinogenic state and the power believed to be conferred upon the user to control or harm others through magical means or witchcraft. There is a cultural evolutionary movement from exoteric rituals, open and accessible to all adults, to esoteric rituals, much like the Eleusinian mysteries of ancient Greece. Unauthorized drug use under these circumstances may have become a crime against the commonwealth. Cross-cultural studies of thematic materials linked to societies where these substances have been utilized and reported upon enable us to make a reasonable connection, however (Dobkin de Rios 1984). One illustrative example has been through the careful examination of ancient Mayan art, which has revealed that the water lily, found more frequently than the rain god, contained aporphine, which after causing heavy vomiting provided the user with a languid state conducive to visual ruminations, influencing the art and architecture of this ancient civilization.

Societies for which we have excellent data on the ritual use of plant hallucinogens include the Chumash Indians of Santa Barbara, the Tsogana Tsonga of East Africa and the Australian Aborigines (see Dobkin de Rios 1974; Dobkin de Rios and Kaz 1975; Mckenna et al. 1998; Siegel 1989). The examination of these tribal societies have identified that there existed managed altered states of consciousness where plant hallucinogens were given by elders to youth as part of an intensive short-term socialization for religious and pedagogical purposes. The use of hypersuggestibility as a cultural technique to "normalize" youth in these societies can be compared to the role of pathology of drug ingestion patterns among Euro-American adolescents (Dobkin de Rios and Smith 1977; Grob and Dobkin de Rios 1991).

In tribal societies for which we have good data, these plants have been used mainly as facilitators for religious ecstasy and to permit individuals to come into firsthand contact with spirit or divinity. In hunter/gatherer societies, male hunters used hallucinogens in shamanistic religious rituals to divine the future and to locate the animals they hunted. The chief focus in these societies was on power and its exercise by religious practitioners. These substances, however, have been viewed as a two-edged sword. On the one hand they have been utilized by different societies over time and space due to their perceived ability to access spiritual realms. The obverse is a faulty wiring hypothesis that argues that plant chemicals deceive and trick. These substances however have been seen by serious scholars as a psychotechnology that allow tribal elders to manage the altered states of consciousness of their adolescents through hypersuggestibility, utilizing the properties of the plant hallucinogens to decondition youth and to heighten religious experiences deemed important for social survival.

A major theme among traditional societies ritually utilizing plant hallucinogens is that of shape shifting. The transformation of human being into animals is found associated with plant drugs where the shamans, technicians of ecstasy, are metamorphosed into animal familiars. This action symbolized the power source of the individual who calls upon his animal familiar to do his bidding. The shaman is believed to be able to control and beckon a series of familiars for his own personal use in curing or bewitching. The concept of morphing, a phenomenon where one image remains in the mind's eye while a second is superimposed upon it, with the first then fading away, can be cited to explain this

common occurrence. Animal familiars are viewed as an empowering element. The religion of hunters and gatherers, shamanism, has a focus on personal ecstasy and direct knowledge of the preternatural. Human beings appear to be wired for the ability to experience ecstasy and the ability to have unordinary experiences to apprehend the divine, what psychiatrists call dissociative or potentially therapeutic transpersonal states. Hallucinogenic ingestion for purposes of religious ecstasy has been reported in all segments of human society.

Under the effects of the plant hallucinogens, perception of time changes. There is a circularity and reversible element of time, in which an eternal mythical present exists which is periodically reintegrated into the religious rites of tribal peoples. One of the characteristics of hallucinogenic drug use entails the perception of time which slows up almost to an imperceptible flow or else is experienced as indescribably fast.

A second theme deals with animals that appear to have played a vital role in teaching or revealing to human beings the properties of plant hallucinogens. Animals seek out psychotropic experiences and several societies that incorporate plant hallucinogens into their rituals report learning about drug plants from deer, reindeer or wild boars in their environment. Despite the apparent nonadaptive aspects of such animal behavior as they are likely to be placed in danger of predators, this is widespread and may point out the antiquity of hallucinogenic use in human society since hunters and gatherers are most likely to have been the ones to observe animal plant use most carefully and imitate this behavior.

The spiritual animation of hallucinogenic plants is another theme of interest. Many tribal groups believe that animated spirits of hallucinogenic plants exist that are either minuscule or gigantic in size, called micropsia or macropsia. Cultures across the world report this phenomenon.

Music is very important in ritual use of hallucinogens. Music is deemed by healers or sorcerers to evoke stereotypic visions. Music which is generally of a percussive nature, may be viewed as necessary for the individual to attain certain cultural goals, such as seeing an individual deemed responsible for bewitchment, to help in healing, to foresee the future, etc. Sudden access to the unconscious by means of hallucinogenic use, despite the esthetic and expressive dimensions, is a dangerous space for human beings to enter. Psychodynamically-oriented researchers stress the emotional response to such entry in terms of somatic stress registered by nausea, vomiting, diarrhea, tachycardia, and elevated blood pressure. The role of music with its implicit structure, may be to provide a substitute psychic structuring during periods of ego dissolution. Music does not simply create mood within the drug setting. Given the change in ego structure and the anxiety, fear and somatic discomfort attendant upon unexpected access to unconscious materials, the shaman guide also creates a corpus of music which some investigators have called the jungle gym in consciousness whose intrinsic structure provides the drug user with a series of paths and banisters to help him negotiate his way during the actual experience. Shamans themselves claim that the music created under their guidance provokes specific, highly valued patterned drug visions that permit their clients access to particular supernatural entities, to view the source of witchcraft, to permit contact with ancestor forces, etc. This goes along with death and resurrection themes reported in tribal societies where powerful hallucinogens are used in rituals. When used in adolescent rituals, the youth is seen to die in his social status of a child, and reborn and returned to social life as a new person with a new name, responsibilities and knowledge of the supernatural world. The psychedelic states heightened the learning of sacred knowledge and created a bonding among members of the cohort group.

Psychiatric/Psychological Implications

Cross-cultural research has shown is that at the most private and personal level of being – the hallucinogenic experience-cultural membership determines the nature of the visionary experience. Among ayahuasca users in the Peruvian Amazon (various *Banisteriopsis* sps.), beliefs hold that the mother spirit of the plant is a boa constrictor, which appears in visions overseen by the rural and urban healers. When Westerners take ayahuasca, they often report idiosyncratic visions that go along with the lack of hallucinogenic traditions in their own culture. These substances, drawing upon enhanced suggestibility, have a long history in the transformation of adolescent boys and girls into fully participating members of adult society. Legal constraints of use in Euro-American society contrast with the ritualistic use of such plant drugs in traditional tribal societies of the world. With indigenous traditions, we find managed altered states of consciousness where tribal elders provide a didactic experience to prepare youth for new adult roles. The psychedelic states heighten the learning of youthsand create a bonding among the cohort members so that individual psychic needs are subsumed to the needs of the social group. The youth may undergo austerities and rituals with painful activities such as genital mutilation, sleeplessness, and beatings. This results in an aboriginal boot camp where a youth would share and identify with his cohorts upon

whom survival success might often depend. Docility and bounded rationality is a mechanism for social selection and is implicated in the voluntary success of altruistic behavior. This docility – receptivity to social influence – contributes greatly to fitness in the human species. Plant hallucinogens used ritually create docility states in adolescents in tribal society for the purpose of maturity preparation and is widely found in the anthropological record.

Drug use patterns have also changed over time and some observers have documented controversies in recent years with foreigners seeking out ayahuasca experiences in the Peruvian rain forest, unfortunately with some abuses occurring on occasion with unscrupulous practitioners.

Modern Syncretic Religions and Ayahuasca

During the twentieth century, the use of ayahuasca was incorporated into a number of new syncretic churches in Brazil. By the late l980s, the Brazilian government sanctioned the use of this powerful Amazonian plant hallucinogenic decoction discovered from indigenous plant medicinal traditions for use as a ceremonial sacrament in the structure of modern religions. In 2006, the US Supreme Court also ruled, by unanimous vote, to protect the legal rights of the Brazilian syncretic church, Uniao do Vegetal, to practice its religion and ritual use of ayahuasca within the context of religious ceremony in the USA. Similar legal advances have been made in Europe by another Brazilian syncretic church, Santo Daime, allowing formal ayahuasca ceremonies. The origin of the Brazilian ayahuasca religions lie in the first half of the twentieth century when their respective founders, Maestre Gabriel of the Uniao and Maestre Irrianeu of the Daime churches, during expedition to the remote regions of the forest, encountered indigenous Amazonian people who used ceremonial ayahuasca for healing and divination. Bringing back knowledge of these ancient plants, they created the necessary religious doctrine and rituals for modern church structures that utilized this powerful psychoactive sacrament (Dobkin de Rios and Grob 2005).

A critical series of issues examined during proceedings to determine the legality of ayahuasca have focused on its effects on the health and safety of its users. After an extensive examination of the available evidence, all court rulings have accepted that there are safe parameters of ayahuasca use within the context of the groups studied. In the l980s, representatives of the Brazilian Confen (Narcotics Commission) tasked to investigate the use of ayahuasca by syncretic religions, conducted extensive examination of the Uniao do Vegetal in particular and determined that the responsible administration of ayahuasca in Uniao religious ceremonies caused no apparent harm to participants and should be provided legal status. The US Federal Courts investigation of ayahuasca also emphasized the importance of data provided by the medical section of the Uniao do Vegetal as well as published reports in the medical and neuroscience literature of an international multidisciplinary research investigation of the short and long-term effects of ayahuasca in subjects recruited in Manaus, Brazil in the early l990s (Grob et al. 1996).

Findings from these studies supported that the human use of ayahuasca, administered within the context of the Uniao do Vegetal, appears to be tolerated without evident negative consequence. Indeed, a number of subjects evaluated for this research investigation reported dramatic improvements in psychological and physical health, including most notably a number of cases of abolition of dangerous addictive and antisocial behaviors. Overall mood regulation, cognitive acuity, and responsible behavior all appeared to improve. An intriguing neuroscience finding from this project was the increased density of ▶ serotonin transporters in the blood ▶ platelets of long-term ayahuasca users compared to ayahuasca naïve controls, which may provide the biological substrate for the observed positive and potentially therapeutic outcomes (Callaway and Grob 1998). A cautionary note should be provided, however, regarding adverse interactions between ayahuasca and other biologically active prescription and non-prescription medicines. One example has been the reports of serious and potentially life threatening ▶ serotonin syndrome in individuals administered ayahuasca who were already taking selective ▶ serotonin re-uptake inhibitor (SSRI) antidepressants. Another concern is with individuals combining ▶ psychostimulants with ayahuasca. Given the ubiquity of stimulants in modern society, from legally prescribed Ritalin for attention deficit disorder to illegal cocaine and methamphetamine, there is a risk if combined with ayahuasca of causing serious cardiovascular problems as well as sustained adverse psychiatric reaction.

In the early 2000s, the Brazilian judiciary requested a formal research evaluation of the health and well-being of adolescents who participated with their parents in religious ceremonies of the Uniao do Vegetal. In collaboration with Brazilian psychological and psychiatric colleagues, an investigation was conducted of ayahuasca-exposed youth contrasted with a matched control group of young people without a history of ayahuasca use. Results included no differences between the two groups of neuropsychological function with ayahuasca-exposed adolescents demonstrating fewer psychiatric symptoms and less use of alcohol and other psychoactive recreational drugs. Indeed, one Brazilian medical authority of the Uniao do Vegetal, Glacus de Souza

Brito, has described the use of ayahuasca by young people within the Uniao as "prophylaxis against drug abuse" (Dobkin de Rios and Grob 2005).

In forming an understanding of the relative safety of ayahuasca within the context of the modern syncetic religion, Uniao do Vegetal, it is important to appreciate the contributions of both the psychobiological effects of the plant compound as well as the socio-cultural context within which it is taken. Ayahuasca, a decoction of native plants of the Amazon forest, *Banisteriopsis caapi* and *Psychotria viridis*, contain biologically active harmala alkaloids and dimethyltryptamine (DMT). When DMT is administered orally, its potent psychedelic effects are entirely neutralized by the monoamine oxidase (MAO) enzyme system in the gut. However, when the brew is infused with monamine oxidase inhibiting (MAOI) harmala alkaloids, the DMT is absorbed through the gut allowing for the intense activation of the central nervous system. Such precise knowledge of the native plant pharmacopeia of the Amazon forest was passed down over millennia from the earliest inhabitants through the indigenous tribal people to the founders of the syncretic religions (Callaway et al. 1994, 1996). The Uniao do Vegetal in particular has developed a scrupulous process of evaluating prospective participants in their ayahuasca ceremonies, screening for individuals with medical and psychiatric vulnerabilities. For those who pass the screening process, careful monitoring of their reaction to the ayahuasca experience is established. The relative care the Uniao takes with novice participants and vulnerable long-term members, along with the relative safety of ayahuasca when administered under ideal conditions, has led to a very low incidence of adverse health reaction. Indeed, the Brazilian syncretic ayahuasca religions represent an illustrative modern example of the value of ritual in establishing an essential structure that will minimize the potential adverse effects and maximize the therapeutic and positive transformative values of the psychedelic experience (Dobkin de Rios and Rumrrill 2008).

Conclusion

Two major themes emerge from a study of the ritual use of hallucinogens. The first is the reluctance of Western scholars to acknowledge the important role of plant hallucinogens in human history and expressive behavior. In the hallucinogens, hallucinophobic westerners see the forbidden and irrational. Yet in tribal societies, access to supernatural power and the unitive experience (so-called oceanic experience in psychoanalytic discourse) was highly valued. Psychedelic plants were used to enhance perception and intuition and played an important role in healing (Winkelman and Roberts 2008). The second area of interest is the enormous potential of these plants to create hypersuggestible states. These can reinforce religious and spiritual beliefs in their communities and can also be used to control and direct youth while contributing to the survivability of the social group.

Cross-References

► Ethnopharmacology
► Hallucinogens

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Rivastigmine

Definition

Rivastigmine is an anti-dementia drug used for the treatment of mild to moderately severe ► Alzheimer's disease

as well as for dementia in ► Parkinson's disease. Clinical trials have indicated that it produces a very modest improvement in symptoms but appears to be particularly effective in patients with either type of dementia who suffer from hallucinations. Rivastigmine is a high-potency anticholinesterase (inhibiting both acetylcholinesterase and butyrylcholinesterase), the clinical effectiveness of which is based on its ability to enhance central cholinergic function by increasing the availability of ► acetylcholine. However, with the progression of the disease and further loss of functional cholinergic neurons, its effectiveness is reduced. The most common side effects of rivastigmine are nausea, vomiting, and diarrhea. However, recently developed transdermal rivastigmine patches reduce the incidence of unpleasant side effects without the loss of clinical effectiveness.

RNA Editing

Definition

RNA editing is a molecular process changing the information contained in the coding region of the primary RNA transcript. Editing can occur in tRNA, rRNA, and mRNA molecules of eukaryotes and takes place in the nucleus and in mitochondria. Mechanisms of RNA editing includes nucleoside modifications such as C to U and A to I deaminations but could also be non-templated nucleotide additions and deletions. RNA editing in neuronal iGluR transcripts is catalyzed by adenosine deaminase that recognizes partially double-stranded primary RNA transcripts, modifying adenosines to cause A to I, an editing process that results in this case in codon changes.

RNA Interference

Synonyms

RNAi

Definition

RNA interference (RNAi) is a surveillance system in most living eukaryotic cells that assists to regulate gene activity and to control expression of endogenous and parasitic genes, for example, viral genes or transposable elements. RNAi was discovered in 1998 by Andrew Z. Fire and Craig C. Mello in the nematode worm *Caenorhabditis elegans*. Mechanistically central to the RNAi system are small RNA molecules, such as siRNA (and also micro RNAs). Long double-stranded RNA, cleaved and processed by the RNase III family enzyme Dicer, are the typical precursors of siRNA molecules; shRNA (short- or small-hairpin RNA) introduced to cells by recombinant expression vectors is frequently used precursors in experimental gene-silencing studies (Fig. 2). One of the two strands of each siRNA fragment, known as the guide strand, gets incorporated into the multiprotein RNA-induced silencing complex (RISC). This complex specifically binds to and efficiently cleaves single-stranded RNA, for example, mRNA transcripts, which match the siRNA bound by RISC (Fig. 2B). Thus, RNAi represents a natural mechanism to knock down the expression of selected genes, which is more potent than conventional antisense oligonucleotides or ribozyme approaches because it is assisted by an efficient cellular defense machinery and also offers multiple turnovers. In addition, most eukaryotic cells possess RNAi-related pathways also recruited by siRNA (and micro RNA, to some extent), including activation of cellular antiviral defense mechanisms (e.g., the interferon response) or interference with the chromatin structure of the genome.

siRNA can also be used for pharmacological target validation by inhibiting target gene expression, thus representing an alternative strategy to pharmacological tools including antisense oligonucleotides, antagonists, and knockout mice.

siRNA can either be cellularly expressed by appropriate vectors or chemically synthesized and transfected into cells or whole animals, which is associated with technical challenges similar to the delivery of standard antisense oligonucleotides.

Cross-References

► Antagonists
► Antisense Oligonucleotides
► Gene Expression and Transcription
► Genetically Modified Animals
► Ribozyme
► siRNA
► Small Interfering RNA

RNAi

► RNA Interference

Ro 4-4602

► Benserazide

Ro-15-1788

► Flumazenil

Rodent Behavioral Test Paradigms or Procedures

► Animal Models for Psychiatric States
► Rodent Tests of Cognition

Rodent Models of Attention, Memory, and Learning

► Rodent Tests of Cognition

Rodent Models of Autism

► Autism: Animal Models

Rodent Models of Cognition

► Rodent Tests of Cognition

Rodent Tests of Cognition

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Synonyms

Rodent behavioral test paradigms or procedures; Rodent models of attention, memory, and learning; Rodent models of cognition

Definition

Rodent tests of cognition are behavioral means of assessing different components of cognition, including memory, learning, and attention, for evaluating the ability of drugs to remediate impaired cognitive functions or to produce cognitive enhancement.

Principles and Role in Psychopharmacology

Cognition is currently a much-employed term in psychopharmacology, referring to a collection of higher-order processes that intervene between sensory processing and motor output to produce behavior. Cognition is thus not a unitary construct and has to be carefully decomposed into its constituents, which can be modeled in terms of well-designed procedures that provide objective measures with good test–retest reliability. These constituents are derived from theories that provide operational definitions of constructs such as perception, attention, working memory, associative learning, and executive control. Further requirements are for tests that are validated in terms of their presumed psychological processes, neural basis, and sensitivity to drug effects. The ultimate requirement is to find procedures that can predict cognitive enhancing effects in humans with neurological or neuropsychiatric disorders. A secondary consideration is for the procedures to be sensitive to detrimental effects of certain drugs, neurotoxins, or other manipulations to provide models that can be remediated by appropriate drug treatments. The final, and perhaps key, consideration is that the tests have some translational validity for humans (McArthur and Borsini 2008a,b). The last is a contentious issue, as it is of course unclear to what extent cognitive functions in rodents might map onto functionally homologous processes in humans. Nevertheless, there has been an excellent degree of translatability thus far in certain domains, which bodes well for the further development of this discipline.

Although cognition can be segregated into its different aspects, it is important in any evaluation to measure a range of functions to be best able to define the functional selectivity of any drug effect; for example, is an effect on a memory or learning test in fact dependent on a perceptual or attentional effect of the drug? Moreover, one has to be certain that basic sensory, motor, motivational, or sedative actions are not in fact responsible for any behavioral change. This can be achieved by a battery approach, in which performance on several tests with different requirements are compared, or by the more elegant and economic method of incorporating "control" tests of such factors as motivation and sensorimotor capacity within a test of a cognitive construct such as attention or working memory.

Several examples of this will be provided later. The possibility of preclinical cognitive test "batteries" are currently popular in the wake of such approaches to measure cognition in clinical trials and experimental studies in humans, embodied, for example, by the ► MATRICS battery for schizophrenia and more generally by the ► CANTAB battery.

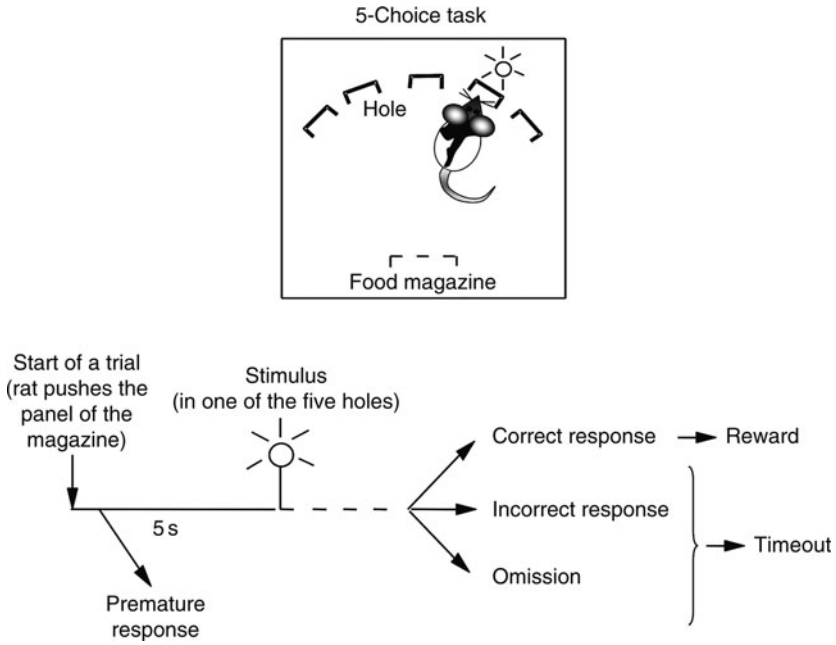
Perception

This is generally best tested by means of discrimination learning or performance, whereby responding in the presence of one stimulus is reinforced, whereas the other is not. The stimuli have to be presented randomly across two locations to avoid a confound by spatial factors. The test can be made more sensitive by varying the degree of similarity of the stimuli, and also using a titration method to determine the limits of discrimination (by which the stimuli are made more similar following a correct response and less so by an incorrect one). By this means, it may be feasible to determine a psychological ► threshold for detection. Of course, one has to rule out other factors such as motivation that might produce possible changes (often deficits) in perceptual function as a result of a drug effect. If a deficit, for example, occurs regardless of level or type of motivation, then a perceptual impairment is more likely. Comparison of different types of discrimination performance, for example, in the visual, auditory, or olfactory modalities will also serve to test the specificity of a perceptual explanation. Similarly, learning factors are also ruled out if the deficit occurs following training to asymptotic performance. It is quite difficult however to distinguish between an effect on perception or attention, unless special manipulations are used to influence the latter. A useful quantitative technique for separating sensory/perceptual from motivational or other response biasing factors is ► signal detection theory, which has been applied with success to determine whether drugs affect primarily perceptual/sensory factors (d') or response bias (ß) (Appel and Dykstra 1977). Finally, operant psychologists tend to avoid using such terms as "perception" in such tasks and prefer the more theoretically neutral term, "stimulus control." However, a loss of stimulus control is not necessarily due to perceptual factors.

Attention

There are many forms of human attention, including ► selective attention (focusing on one input or feature, while ignoring the rest), ► sustained attention (maintaining attention over a long period), vigilance (detecting rare inputs) and ► divided attention (maintaining attention to more than one input or task). Most, if not all, of these can be measured in experimental animals. Continuous performance tests measure the capacity to sustain attention and generally reveal impairments in disorders such as ► schizophrenia or ► attention deficit hyperactivity disorder. A simple analogue of this in experimental animals is the ► five-choice serial reaction time task (Robbins 2002), based on a paradigm once used to assess attention in human volunteers in a variety of experimental situations, including stress, distracting white noise, and following drug treatment. The five-choice task (Fig. 1) measures the accuracy (errors of commission) and latency of detecting visual targets, as well as errors of omission and impulsive responding (i.e., responding prior to target onset). The latency to collect food pellets provides a control measure of motivation. The difficulty of the task can be enhanced in various ways, including shortening of the duration of the visual target, varying its rate of presentation and temporal predictability, and also the occurrence of defined distractors, such as burst of white noise interpolated into the inter-trial interval. This task has now been widely used in rats, and more recently, mice to measure effects of drug, regional brain lesions, and manipulations of the central neurotransmitters or genetic mutations. Its major uses have been to reveal beneficial effects on response accuracy of some putative "cognitive enhancing" drugs such as dopamine D1 agonists, and also to characterize the neuropharmacology of impulsive behavior, which has also been shown to predict escalation of cocaine self-administration. There are several variants of this standard task, the main one of which requires the rat to make an observing response into a central location to detect a peripheral target, and has also been used to quantify the "attentional neglect" that can occur after unilateral manipulations of cortico-striatal brain regions. A rather different form of test requires the cross-modal integration of auditory and visual stimuli.

Some tests of rodent selective attention appear to mimic strongly specific tests in humans that are sensitive to frontal lobe damage, involving the formation and shifting of attentional "sets" and the capacity to avoid a prepotent response to one aspect of a stimulus in order to respond to another (Birrell and Brown 2000). The attentional set-shifting task is based on the use of compound visual stimuli (i.e., that vary in at least two perceptual dimensions). Humans or nonhuman primates are trained to attend to one dimension on the basis of reinforcement and to ignore the other one, including tests of reversal (where the two stimuli within a dimension have their reinforcement contingencies reversed), and intra-dimensional shifting (where novel stimuli are introduced, but the



Rodent Tests of Cognition. Fig. 1. Schematic of the rodent five-choice task (See Robbins 2002; Figure provided by courtesy of Dr. Christelle Baunez).

same dimension is reinforced). Finally, an extra-dimensional shift is arranged in which novel stimuli are again introduced, but now the previously irrelevant dimension is reinforced. This latter stage is analogous to the category shift on the ▶ Wisconsin Card Sort Test, which is much used to assess cognitive flexibility in human patient populations, especially those with presumed damage to the prefrontal cortex. In the rodent version (being available for mice as well as rats), the test is implemented using olfactory cues and texture in a "digging for food" test paradigm. Performance across the various stages is qualitatively comparable to that seen in primates; the extra-dimensional shift is the most sensitive stage to drug effects, performance at other stages usually being employed as internal controls. There are now various versions of these tests of "cognitive flexibility," which use similar logic for shifts between, for example, responding according to body turns or to space on a cross-maze, or alternatively attending to discrete (e.g., visual) cues versus contextual cues on a maze. These tests do not use different stimuli at each test and so are also confounded by any response to interference. However, they do exemplify the general requirements of tests of executive function (see below).

Another major source of tests of attention comes from animal learning theory, in which the repeated non-reinforced presentation of stimuli retards subsequent learning about them, a process called ▶ latent inhibition. One theory of latent inhibition ascribes the loss of salience of the preexposed stimuli to a loss of attention, although it is possible that an associative account might suffice. However, a particular advantage of latent inhibition paradigms, which are very sensitive to dopamine D2 receptor antagonists (i.e., ▶ antipsychotic drugs) is that impairments are indexed subsequently by successful learning, in drug-free state, thus controlling for many other explanations of impairment.

Learning (see Gluck et al. **2007**)

Both ▶ Pavlovian and ▶ instrumental conditioning are now considered to have cognitive aspects, given that the basis for the former is prediction and expectancy, and for the latter, cognitive control over environmental contingencies. The detection of instrumental contingency, in particular, can be thought of as a higher-order cognitive process, which plays an important component of our ability to make voluntary actions that form part of goal-directed behavior. Disruptions of aspects of Pavlovian and instrumental learning almost certainly underlie all of the major forms of neuropsychiatric disorder, including drug addiction. However, these forms of conditioning will be considered elsewhere in more detail under specific entries.

Learning is generally measured in simplified chambers or operant settings (especially for rats); however, maze learning is often employed when spatial cognition is the main subject of study, being especially compatible with the well-developed foraging tendencies of rodents.

Memory (see Gluck et al. 2007; Morris 2007)

This section serves to overview the many distinct forms of memory paradigms used in rodents, which are considered in greater detail under individual entries. Memory can be divided in many ways; a basic distinction is between relatively transient short-term memory and long-term or more permanent memory. Memory "traces" are thus hypothesized to be "consolidated" into long-term memory. Another distinction that has been made in human long-term memory by Tulving, ► "episodic" (generally autobiographical, the "what, where and when" of memory), versus ► semantic memory (memory for meaning) has not been exploited so far to any great extent in rodents.

Perhaps the greatest contribution made to the study of memory from rodent studies has been the post-trial or post-training paradigm popularized by McGaugh (McGaugh and Roozendaal 2009). Here, what is generally a single trial or training session is *followed* immediately by a drug treatment that can either be amnestic (e.g., protein synthesis inhibitors) or promnestic (e.g., amphetamine). ► Retention is tested on a subsequent trial, perhaps 24 h or 3d later. The post-training manipulation is thus designed to influence ► consolidation, either beneficially or adversely. The procedure most often used is of aversive memory; the rodent is punished for stepping down from a platform or through a door by presentation of electric foot-shock. Memory is expressed on the retention trial by a longer response latency to step down or through the door. The great advantage of this design is that the drug cannot be said to have affected memory indirectly by its actions on perceptual, attentional, or motivational mechanisms, as it is administered at a time when these no longer impinge on learning. It is necessary however to perform controls with longer post-trial treatments to check that the drug effects are not affecting retention proactively (i.e., by being active at the time of retention and affecting memory retrieval). Studies of the consolidation of appetitive memory are also feasible, but are used less often because of the unreliability of one trial appetitive learning. The post-trial paradigm has been employed for example to demonstrate the contribution of noradrenergic, opioidergic, and GABAergic mechanisms to emotional memories laid down in the ► amygdala.

Reference memory is a form of long-term memory, which refers to rodent task requirements that stay constant from trial to trial. This definition was originally applied by Olton to rats remembering the constant location of the food-baited arms in an eight-arm ► radial maze. However, it can also be applied to the ► Morris water maze, a notable assay of hippocampal function, in which rodents are required over a number of learning trials to learn the location of a hidden platform in order to escape from a vat of water (D'Hooge and De Deyn 2001; Morris 2007). The rodent is allowed to swim the maze beginning from different vantage points, and so successful learning depends on the construction of a "cognitive map" to navigate the environment. In contrast, the term ► "working memory" in the Olton maze refers to the requirements of another memory test procedure in which rodents are required to visit each of the eight arms once and once only in order to retrieve a maximum of eight pellets. So, the animals have to remember only where they have recently been, and this memory is irrelevant to performance on subsequent test days. It can be argued that this form of "working memory" is not quite the same as that defined by human memory theorists such as Baddeley, where there is a coordination of different, modality specific short-term memory buffers for use in various tasks such as planning, linguistic discourse, and logical reasoning. However, it does seem to overlap the human form of working memory in some important respects (see also Ko and Evenden 2009).

Olton's working memory tasks are strongly reminiscent of the tests of ► spatial delayed response and delayed alternation that have been used to establish the role of the primate ► prefrontal cortex in working memory. Delayed alternation in rodents is easily implemented in a maze or operant chamber, where it is often referred to as "delayed non-matching to position." Nonmatching is an easier task for rodents than matching because of their preexisting foraging tendency to alternate spatial choices. The operant versions of the task allow the systematic variation of delay intervals, which can extend from 0–60s. A "delay-dependent" effect in such a task is generally taken as evidence of a specific memory effect, independent for example, of attention. However, for that inference to be valid it is necessary for performance on the task at zero seconds to be shown not to be similarly susceptible when the perceptual difficulty of the task is enhanced. An additional artefact that is difficult to surmount in the operant task is that of mediating responses, by which the rodent adopts postures or positions that minimize the memory requirement of the task. One way of overcoming this

problem is to use sensitive touch screens to record responding and which can more precisely vary the spatial requirements of the memory tasks, as in the ▶ CANTAB battery for humans and nonhuman primates.

Recognition memory tasks have a superficial resemblance to those employed for working memory. A commonly used variant is that of object recognition (devised by Aggleton and others based on the paradigm of Delacour) in which a rodent explores a novel object during a sample trial, and is then given a choice between this familiar object and a novel object, in terms of the amount of time it allocates to exploring both objects. Lesser exploration of one object indicates greater familiarity and hence recognition of it (in some, restricted sense). The test can also be adapted to measure ▶ "social recognition" by using experimental animals as the "object." Recognition memory is generally manifested over long delays, up to 24 h, although it can be tested at much shorter intervals also and has been shown to depend on structures such as the rodent perirhinal cortex. What distinguishes such tasks from those used to test working memory, apart from the precise test material, is that recognition memory tasks generally employ stimuli only once, so that the test is "trial unique." If the same set of objects were to be used over many trials (as occurs in the spatial delayed alternation or delayed response task), this would produce considerable proactive interference, and the test therefore becomes one of recency memory (how *recently* the stimulus has been experienced) rather than one of recognition memory. In that case, the test also becomes one more of frontal rather than temporal lobe function.

Recognition memory is a less sensitive test of memory than either cued or free recall, in which the memory has to be generated from long-term memory store. Unlike recall, recognition is not particularly sensitive to hippocampal damage, and nor is it the earliest manifestation of ▶ Alzheimer's disease, where amnesia for episodic memories is more evident. Some human and primate data indicate that the hippocampus is implicated in forms of associative memory, particularly in animals involving space, for example, remembering the location of objects. Recent advances have begun to focus on these forms of associative memory, building on the classical Morris water maze. For example, recent touch-screen tests have been developed for mice and rats of their ability to remember the location of objects, and also to form associative memories of tastes with specific locations (Bussey et al. 2008).

Recognition and recall correspond to what Squire has denoted for humans as ▶ "declarative memory" as distinct from "procedural memory" (memory for "how," or for "skill"). We have not discussed procedural memory in any detail in this article, but it may readily be tested in rodents in motor-learning situations such as the rotor-rod test, or as memory for "habits," being part of the process of instrumental learning.

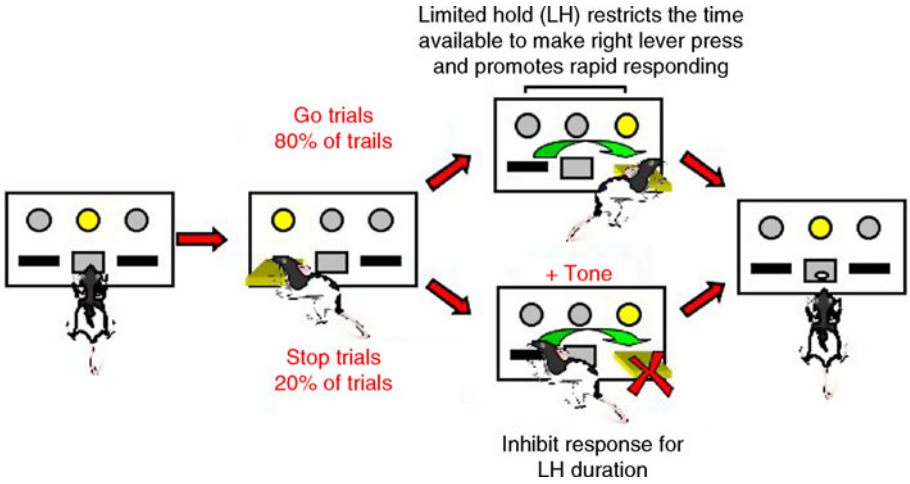
Executive Functions

In human cognitive neuropsychology, this term refers to that set of cognitive processes that serve to optimize performance. The term embraces a number of functions already described earlier, including cognitive flexibility (e.g., attentional set shifting), response inhibition, working memory, planning, ▶ decision making, and aspects of social cognition, some of which are difficult to test in rodents.

A recent development has been a rodent analogue of Logan's ▶ "stop-signal" task, which is much used in the testing of patients with ▶ Attention Deficit Hyperactivity Disorder, for assessing their impulsivity. The stop-signal task requires the cancellation or termination of a motor response that has already been initiated by a "Go" cue, by a less frequently occurring "Stop" cue. It is feasible to measure a stop signal reaction time, as well as a conventional (go) reaction time. The rodent stop signal task (Fig. 2), so far has shown a similar pharmacology to that of the human task, both being sensitive, for example, to the beneficial effects on stopping of the selective noradrenaline uptake blocker ▶ atomoxetine (Eagle et al. 2008). Intriguingly, the classical ▶ Go/No Go task, which has formal similarities with the Stop task, appears to be differentially sensitive to certain drug effects in a manner suggesting the mechanisms of stopping a motor response to be distinct from those of selecting it (Eagle et al. 2008).

Until recently, it was considered difficult to implement a version of the human Stroop task for rodents. The human Stroop requires subjects to resist responding to the dominant aspect of a colored word stimulus (the word itself) and to report the color. A similar conflict has been achieved in rats by training them on two different conditional discriminations with different rules for responding to each ▶ discriminative stimulus, and then placing the rat into conflict by presenting combinations of the discriminative stimuli that are either congruent (i.e., both stimuli indicate the same response or incongruent, both stimuli indicating opposing options) (Haddon and Killcross 2006).

Decision-making cognition has attracted considerable recent interest, in the context of both neuropsychological studies of human patients and in neuroeconomics. This



Rodent Tests of Cognition. Fig. 2. Schematic of the rodent stop-signal reaction-time task (See Eagle et al 2008; Figure provided by courtesy of Dr. Dawn Eagle).

trend is followed in rodent studies by the provision of tests of important component processes, including the discounting of rewards over time, as well as time perception itself. Recently, rat analogues of the ► Iowa Gambling Task, as used to show deficits in patients with lesions of the ventromedial prefrontal cortex, have begun to be implemented, but there are, as yet, few pharmacological studies.

Cross-References

► Animal Models for Psychiatric States
► Attention
► Attention Deficit Hyperactivity Disorders: Animal Models
► Behavioral Flexibility: Attentional Shifting, Rule Switching, and Response Reversal
► Blocking, Overshadowing, and Related Concepts
► Declarative and Nondeclarative Memory
► Delay Discounting Paradigms
► Instrumental Conditioning
► Latent Inhibition
► Long-Delay Learning
► Long-Term Depression and Memory
► Long-Term Potentiation and Memory
► Primate Models of Cognition
► Protein Synthesis as a Mechanism of Memory
► Rate-Dependency Theory
► Schizophrenia: Animal Models
► Short-Term and Working Memory in Animals
► Spatial Learning in Animals
► Spatial Memory

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Rolipram

Definition

Rolipram is a PDE4 inhibitor. It is being widely researched as a possible alternative to current antidepressants. In addition, it might be beneficial to improve memory in patients with mild ► Alzheimer's disease either directly or via a neuroprotective mechanism. Like most PDE4 inhibitors, it also has anti-inflammatory properties. However, till now neither rolipram nor any other developed PDE4 inhibitor made it to the market due to emetic side effects.

Cross-References

► PDE4 Inhibitors
► Phosphodiesterase Inhibitors

Ropinirole

Definition

Ropinirole is a non-ergoline D2, D3, D4 dopamine agonist with preference for D3 receptor. It is approved for the treatment of ► Parkinson's disease (PD) and restless leg syndrome (RLS). Ropinirole can be used either as a monotherapy or as an adjunct to l-DOPA for PD. The mechanism for the treatment of PD is thought to be stimulation of the postsynaptic D2 receptor in the caudate-putamen. The mechanism for RLS is unknown. It is associated with rare side effects such as hypersexuality and compulsive gambling. Other side effects include hallucination, orthostatic hypotension, and somnolence, especially in Parkinson's disease patients.

Cross-References

► Dopamine Agonists

ROS

► Reactive Oxygen Species

Rotigotine

Definition

Rotigotine is a non-ergoline D3, D2, D1 dopamine agonist approved by the United States Food and Drug Administration for the treatment of ► Parkinson's disease. It comes as a transdermal delivery system designed for continuous release over 24 h period. Exact mechanism of action is unclear but is believed to result from its ability to stimulate D2 receptor in the brain. Major side effects include somnolence. Its availability in the USA ceased after April 2008.

Cross-References

► Dopamine Agonists

RSA

Synonyms

Hippocampal EEG domain; Theta rhythm

Definition

RSA is the acronym of rhythmic slow activity, seen in various mammalian species for intra-hippocampal recordings. Upon visual inspection, one can recognize easily these quasi-sinusoidal field potentials that are in the range from 4 to 7 Hz, somewhat higher in rodents (in the rat, e.g., up to 12 Hz), named commonly theta rhythm.

Cross-References

► Electroencephalography

Runway Procedure

Definition

In the form of these procedures used in connection with the ► Reinstatement of drug self-administration, the dependent measure is the *run time* from a *start box* to a *goal box* associated with a reward (e.g., food or drug). During daily training sessions, food-restricted rats are given food pellets when they reach the goal box, and over sessions they decrease their run time. During the subsequent extinction sessions, food is not available in the goal box, and over daily sessions the rats' run time progressively increases (reflecting extinction). A single exposure to

food pellets during extinction leads to a faster run time on the subsequent daily session; this decrease in run time is the operational measure of food-priming-induced reinstatement. A unique feature of the runway reinstatement procedure is that the effects of pharmacological manipulations are assessed on a subsequent, drug-free day. This helps rule out the possibility that any observed effects of pharmacological manipulations on reinstatement are due to locomotor activation or sedation during testing.

S

σ-Receptor

Synonyms
Sigma-receptor

Definition
One of two subtypes of receptor for several opioid drugs that was thought (originally) to be a type of opioid receptor but has subsequently been shown to be unrelated. Although one type of σ-receptor (type 1) has been isolated, it is not a GPCR and its biological function is still being resolved.

Saccaddes

► Eye Movement Tasks

Salaciaceae

► Celastraceae

Sandostatin

► Octreotide

Saporin

Definition
A neurotoxin that is used in conjugation with different ligands to selectively deplete target neurons.

Satiety

Definition
The end state of satisfaction after consumption of a meal. The further suppression of the drive to consume post-meal (*between-meal inhibition*).

Cross-References
► Hunger
► Satiation

Saturation Binding Curve

Synonyms
Labeled ligand concentration binding isotherm

Definition
Isotherm: a line that connects points of equal temperature or points of measurements performed at equal temperature. The specific binding of the labeled ligand to tissue samples is measured at a given temperature at various concentrations of the labeled ligand. The values of the specific binding, on the ordinate, are plotted versus the labeled ligand's free concentration on the abscissa; connecting the points results in a curve with the form of a hyperbola. At a certain concentration of the labeled ligand, all available specific binding sites in the tissue sample will be occupied by the labeled ligand and specific binding will not further increase with increasing labeled ligand concentration; saturation of specific binding is reached.

Cross-References
► Receptors: Binding Assays

Scalar Property

Definition
Scalar property refers to the linear relationship between the estimation error and the estimated duration. In most

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species investigated, including humans, the estimation error increases linearly with the estimated duration across a large range of intervals (see Gibbon et al., 1997).

Schedule I

Definition

A category of controlled substances outlined in the U.S. Comprehensive Drug Abuse Prevention and Control Act of 1970. Schedule I drugs:

- Have a high potential for abuse
- Have no currently accepted medical use in treatment in the USA
- Have a lack of accepted safety for use under medical supervision

Examples of Schedule I drugs include: crack cocaine, GHB, Heroin, LSD, MDMA

Cross-References

► Comprehensive Drug Abuse Prevention and Control Act of 1970
► Crack
► GHB
► Heroin
► LSD
► Methylenedioxymethamphetamine (MDMA)

Schedule II

Definition

A category of controlled substances outlined in the U.S. Comprehensive Drug Abuse Prevention and Control Act of 1970. Schedule II drugs:

- Have a high potential for abuse
- Have a currently accepted medical use in treatment in the USA or a currently accepted medical use with severe restrictions
- May lead to severe physiological or physical dependence

Examples of Schedule II drugs include: amphetamine, cocaine, morphine, oxycodone, methylphenidate (Ritalin).

Cross-References

► Amphetamine
► Cocaine
► Comprehensive Drug Abuse Prevention and Control Act of 1970
► Methylphenidate
► Morphine
► Oxycodone

Schedule of Reinforcement

Definition

Describes the relationship between responding by a subject and the delivery of a reward to that subject, for example, a reward is delivered after every ten responses.

Schedule-Induced Polydipsia

Synonyms

Adjunctive behavior; Adjunctive drinking

Definition

Schedule-induced polydipsia is excessive drinking induced by a particular schedule of reinforcement. Typically, the schedule involves the delivery of a food pellet at predictable intervals (e.g., fixed-interval 60 s).

Cross-References

► Operant Behavior in Animals

Schizoaffective Disorder

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Definition

There is no agreement about how schizoaffective disorders could be defined. According to the World Health Organisation (WHO) and its International Classification of Mental and Behavioral Disorders (► ICD-10), schizoaffective disorders are "episodic disorders in which both affective and schizophrenic symptoms are prominent but which do not justify a diagnosis of either schizophrenia or depressive or manic episodes." The diagnostic criteria are the following:

G1	The disorder meets the criteria of one of the affective disorders (F30, F31, F32) of moderate or severe degree, as specified for each category.
G2	Symptoms from at least one of the groups listed below must be clearly present for most of the time during a period of at least 2 weeks: Thought echo, thought insertion or withdrawal, thought broadcasting. Delusions of control, influence or passivity, clearly referred to body or limb movements or specific thoughts, actions or sensations. Hallucinatory voices giving a running commentary on the patient's behavior or discussing the patient between themselves, or other types of hallucinatory voices coming from some part of the body. Persistent delusions of other kinds that are culturally inappropriate and completely impossible, but not merely grandiose or persecutory, e. g. has visited other worlds; can control the clouds by breathing in and out; can communicate with plants or animals without speaking. Grossly irrelevant or incoherent speech, or frequent use of neologisms. Intermittent but frequent appearance of some forms of catatonic behavior, such as posturing, waxy flexibility and negativism.
G3	Criteria G1 and G2 above must be met within the same episode of the disorder, and concurrently for at least part of the episode. Symptoms from both G1 and G2 must be prominent in the clinical picture.
G4	*Most commonly used exclusion clause.* The disorder is not attributable to organic mental disorder or to psychoactive substance-related intoxication, dependence or withdrawal.

ICD-10 defines three different types of schizoaffective disorders: manic type (F25.0), depressive type (F25.1) and mixed type (F25.2).

The American Psychiatric Association (APA) in the fourth revision of its Diagnostic and Statistical Manual of Mental Disorders (► *DSM-IV*) defines the following diagnostic criteria for schizoaffective disorder:

A	An uninterrupted period of illness during which, at some time, there is either a Major Depressive Episode, a Manic Episode, or a Mixed Episode concurrent with symptoms that meet Criterion A for Schizophrenia.
B	During the same period of illness, there have been delusions or hallucinations for at least 2 weeks in the absence of prominent mood symptoms.
C	Symptoms that meet criteria for a mood episode are present for a substantial portion of the total duration of the active and residual periods of the illness.
D	The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

DSM-IV specifies two subtypes: bipolar type, if the disturbance includes a manic or a mixed episode (or a manic or a mixed episode and major depressive episodes), and depressive type, if the disturbance only includes major depressive episodes.

While the main problem with the ICD-10 definition of schizoaffective disorders is their ► longitudinal aspect, the problem with DSM-IV concerns both – ► cross-sectional and longitudinal aspects. The problem with the cross-sectional definition of DSM-IV concerns the time span indicated in criterion B (during the period of illness there have been ► delusions or ► hallucinations for at least 2 weeks in the absence of prominent mood symptoms). Obviously, that is an attempt of DSM-IV to separate schizoaffective disorders from psychotic ► mood disorders. The DSM-IV definition of mood disorders is broad, including even those with mood incongruent symptoms (even ► first-rank schizophrenic symptoms). The chronological criterion, however, is rather arbitrary (2 weeks of psychotic symptoms without mood disorders is schizoaffective; less than 2 weeks is psychotic mood disorder!). Yet, the beginning of a psychotic episode is hard to assess exactly. Every clinician knows that there is usually a gap of many days, weeks, or months between the beginning of a psychotic episode and admission to hospital. Reconstruction of the psychopathological picture, retrospectively, is fraught with difficulties. Given the likelihood that the psychotic period is underestimated, many patients who are really schizoaffective could be diagnosed as schizophrenic or as having psychotic mood disorder.

Furthermore, the intensity of both concurrent syndromes (mood and schizophrenic syndromes) can vary enormously during an episode; hence, it seems arbitrary to give chronological priority to the psychotic symptoms over the mood component. It is strange that DSM-IV rejected Jasper's hierarchical diagnostic principle, which suggested a diagnostic superiority of schizophrenic symptoms over affective symptoms, but, regarding the chronological criterion of the schizoaffective definition, obviously made an exception!

Considering what is known so far about schizoaffective disorders (see overviews in Marneros and Tsuang 1986, 1990), we suggest that the definition of

schizoaffective disorders should contain two components: a cross-sectional and a longitudinal aspect.

The *cross-sectional* definition should be the definition of an episode; while the longitudinal definition should be that of a disease or disorder. The cross-sectional definition of a schizoaffective episode should be based on the simultaneous occurrence of symptoms of a schizophrenic and a mood episode, independent of the chronological manifestation. Thus, we agree with the definition of ICD-10, which yields three types of schizoaffective episodes: schizodepressive, schizomanic and mixed ones.

The *longitudinal definition* of schizoaffective disorder should consider the sequential occurrence of mood and schizophrenic episodes during course. The longitudinal research demonstrates that the course of schizoaffective disorders can be very unstable because schizoaffective episodes, pure mood episodes, and pure schizophrenic episodes can each occur at different points in the patient's longitudinal course.

What are such disorders when viewed longitudinally? Are they considered to be mood disorders because of the pure mood episodes, or schizophrenic disorders because of some pure schizophrenic episodes, or schizoaffective disorders because of some schizoaffective episodes? Relevant to this question is the finding that there are no differences between patients who have only had schizoaffective episodes, and those in whom schizoaffective episodes occur along with pure mood and schizophrenic episodes. There are therefore no differences between the "*concurrent*" and the "*sequential*" type of schizoaffective disorder. Patients, who change from pure mood episodes to pure schizophrenic episodes and vice versa, do not differ from patients having schizoaffective episodes. In this sense, Marneros et al. suggest a longitudinal definition of schizoaffective disorders, including a concurrent and a sequential type, the "*concurrent type*" being characterized by the coincidence of schizophrenic and affective episodes and the "*sequential type*" being characterized by the longitudinal change from schizophrenic to affective episodes and vice versa (Marneros et al. 1989).

How essential it is to have a longitudinal definition of schizoaffective disorder is illustrated by the Halle Bipolarity Longitudinal Study (HABILOS), in which the investigators tried to allocate disorders with manic symptomatology to "pure mood disorders" or to "schizoaffective disorders" according to DSM-IV, ICD-10 and the "empirical definition" as described above. Applying the ICD-10 definition, only 8.3% of the 277 patients could longitudinally be allocated to schizoaffective bipolar disorder and 36.1% to affective bipolar disorder, while the majority of patients (55.6%) could not be allocated longitudinally due to the occurrence of different types of episodes (schizophrenic, schizoaffective, affective) at different times.

Using the empirical definition with its cross-sectional and sequential aspects, however, all patients can be allocated: 36.1%, as in the ICD-10 categorization, could be allocated to bipolar mood disorder, and 63.9% could be allocated to schizoaffective disorder.

Recent research has confirmed earlier assumptions that schizoaffective disorders occupy a position between affective and schizophrenic disorders with regard to relevant sociodemographic and premorbid features, as well as with regard to patterns of course, outcome, treatment response and prophylaxis (Marneros et al. 1988, 1989).

It seems certain that schizoaffective disorders are not simply a type of schizophrenic disorder, although in some cases that are ▶ schizo-dominant the relationship to schizophrenia is quite clear. With respect to the relationship between schizoaffective and mood disorders, the similarities are more compelling than the differences (Marneros and Tsuang 1986, 1990).

Role of Pharmacotherapy

Although the clinical relevance of schizoaffective disorders is - inspite of controversies - meanwhile well established their treatment has received less attention in pharmacological studies, especially ▶ double blind studies, than other psychotic or non-psychotic major mental disorders. One of the main reasons might be the problem of their definition and, most important for the pharmaceutical industry, the clinical fact that schizoaffective disorders usually need a combined treatment with more than one substance, for example, with ▶ antipsychotics, ▶ antidepressants and ▶ mood stabilizers. Pharmacological studies dealing with schizoaffective disorders mostly investigated them as a subgroup of schizophrenia and seldom as a subgroup of mood disorders. Pharmacological studies only on schizoaffective disorders are rare. Nevertheless it can be said that schizoaffective disorders are the domain of antipsychotics and mood stabilizers (Baethge 2003; Jäger et al. 2009; Levinson et al. 1999; McElroy et al. 1999; Mensink and Slooff 2004).

All antipsychotics seem to be efficient in the treatment of schizoaffective disorders, but some atypical antipsychotics like ▶ olanzapine, ▶ quetiapine, ▶ risperidone, or ▶ ziprasidone are superior or have some advantages in comparison to typical ones. The heterogeneity of the studies and the investigated populations do not permit a science-based statement on the topic. The clinical

effectiveness of mood stabilizers like ► lithium, ► carbamazepine or ► valproate was reported in some, however, heterogeneous studies. Clinical reality is compatible with such a conclusion.

Pharmacotherapy depends from the type of schizoaffective disorder. The official types of schizoaffective disorder registered in ICD-10 are: manic type, depressive type, mixed type, and those in DSM-IV are bipolar type and depressive type. Empirical work and longitudinal investigations considering a course of the disorder over many years, however, support some more subtypes:

(a) Schizo-dominant type
(b) ► Affective dominant type
(c) Bipolar type
(d) Unipolar type
(e) Sequential type

In the schizo-dominant type the main medication must be an antipsychotic one. In the affective dominant type mood stabilizers and antidepressants or antipsychotics are effective. The bipolar type is treated with antipsychotics combined with mood stabilizers, whereas the unipolar type needs to be treated with antipsychotics and antidepressants. The sequential type is totally ignored. The reasons are given at the beginning of this chapter. It is characterized by the occurrence of schizophreniform or mood episodes during course. The treatment focuses on the treatment of the particular disorder. The longitudinal treatment is a prophylactic one, mainly with mood stabilizers and antipsychotics (McElroy et al. 1999; Mensink and Slooff 2004).

Clinical studies reported also a positive effect of electroconvulsive treatment (Swoboda et al. 2001). Other treatments like augmentation with l-thyroxine found only small benefit (Bauer et al. 2002). The role of psychological treatment in schizoaffective disorders has not yet been systematically investigated.

Conclusions

Schizoaffective disorder is a very common diagnosis in clinical practice, but not sufficiently investigated, especially with regard to treatment.

Cross-References

► Antidepressants
► Antipsychotic Drugs
► Bipolar Disorder
► Lithium
► Mood Stabilizers
► Schizophrenia

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Schizo-Dominant

Definition

Type of schizoaffective disorder dominated by schizophreniform symptoms.

Schizophrenia

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Synonyms

Dementia praecox

Definition

Schizophrenia is a severe and persistent debilitating psychiatric disorder consisting of disturbances in thoughts, cognition, mood, perceptions, and relationships with others. According to ► DSM-IV-TR (American Psychiatric Association 2000), the patient must have experienced at least two of the following symptoms: delusions, hallucinations, disorganized speech, disorganized or catatonic behavior, or negative symptoms. Only one symptom is required if the delusions are bizarre or if auditory hallucinations occur in which the voices comment in an ongoing manner on the person's behavior, or if two or more voices are talking with each other. The patient must experience at least 1 month of symptoms during a six-month period, and social or occupational deterioration problems occur over a significant amount of time. These problems must not be attributable to another condition for the diagnosis of schizophrenia to be made.

By contrast, *schizophreniform disorder* is a short-term type of schizophrenia with the characteristic symptoms (including prodromal, active, and residual phases) being present for at least one month but not for the full six months required for the diagnosis of schizophrenia. In contrast to schizophrenia, the onset of schizophreniform disorder can be relatively rapid and the individual's level of functioning may or may not be affected. According to the American Psychiatric Association, about two-thirds of people with schizophreniform disorder do not recover and are subsequently diagnosed with schizophrenia.

Current Concepts and State of Knowledge

Historical Aspects

The clinical picture of schizophrenia was described for the first time by the German physician Emil Kraepelin who used the term "dementia praecox" to define a disorder with early beginning, a uniformly deteriorating course and a poor prognosis (Kraepelin 1893). Subsequently, Eugen Bleuler coined the term "schizophrenia" and distinguished between fundamental and accessory symptoms of the disease (Bleuler 1908, see Table 1). He believed that the fundamental symptoms were present in all patients and were unique to the disorder while the accessory symptoms could also occur in other disorders. Bleuler realized that the condition was not a single disease and referred to a whole "group of schizophrenias". Some decades later, Kurt Schneider established the differentiation between first- and second-rank symptoms (Schneider 1959, see Table 2), representing a preliminary stage of contemporary operationalized classification systems.

Schizophrenia. Table 1. Fundamental and accessory symptoms of schizophrenia (Bleuler 1908).

Fundamental symptoms	Accessory symptoms
Loosening of associations	Hallucinations
Disturbances of affectivity	Delusions
Ambivalence	Catatonic symptoms
Autism	Speech abnormalities (e.g., mutism, neologisms)

Schizophrenia. Table 2. First-and second-rank symptoms (Schneider 1959).

First-rank symptoms	Second-rank symptoms
Voices heard arguing	Other forms of hallucinations
Voices heard commenting on one's actions	Sudden delusional ideas
Audible thoughts	Perplexity
Thought insertion	Depressive or euphoric mood changes
Thought withdrawal	Emotional blunting
Thought diffusion	
Delusional perception	

In 1980, Timothy Crow postulated two dimensions of pathology underlying schizophrenia. According to his concept, the type I syndrome is mainly characterized by positive symptoms, potentially neuroleptic-responsive and reversible while the type II syndrome is mainly characterized by negative and cognitive symptoms, sometimes progressive and relatively irreversible (Crow 1980, see Table 3).

The concepts described above have used a categorical approach, thereby indicating homogeneous, mutually exclusive subtypes of the disease. Essentially, schizophrenic disorders are heterogeneous and consequently, Peter Liddle has introduced a dimensional approach comprising three neuroanatomically classifiable syndrome clusters: psychomotor poverty, disorganization, and reality distortion (Liddle 1987, see Table 4).

Psychopathology

Disorders of Thinking and Speech

Basically, thought processes may be disordered in form and content. Common ► formal thought disorders observed in schizophrenia patients include ► incoherent thinking. The patient's thoughts are illogical and confused up to a defect in processing and organizing language

Schizophrenia. Table 3. Two-syndrome concept of schizophrenia (Crow 1980). (Reproduced with permission)

	Type I	Type II
Characteristic symptoms	Hallucinations, delusions, thought disorders (positive symptoms)	Affective flattening, poverty of speech, loss of drive (negative symptoms)
Type of illness in which most commonly seen	Acute schizophrenia	Chronic schizophrenia, the "defect" state
Response to neuroleptics	Good	Poor
Outcome	Reversible	? Irreversible
Intellectual impairment	Absent	Sometimes present
Postulated pathological process	Increased dopamine receptors	Cell loss and structural changes in the brain

Schizophrenia. Table 4. Dimensional approach (Liddle 1987).

Neuroanatomical dysfunction	Left dorsolateral prefrontal cortex	Medial temporal lobe	Right ventrolateral prefrontal cortex
Syndrome	Psychomotor poverty	Reality distortion	Disorganization
Symptoms	• Poverty of speech • Blunted affect • Slowness	• Delusions • Hallucinations	• Formal thought disorder • Distractibility • Incongruous affect

("schizophasia"). During *thought block* thinking is decelerated and stagnant, and the patient's language is sagging accordingly. Thought content may be diminished as well. On the other hand, the term *flight of ideas* describes excursive and uncontrollable thinking, associations become loose and mental activity is generally accelerated. Furthermore, *improper responding to questions*, ▶ perseverations, ▶ paralogism, ▶ neologisms, and ▶ concretism are commonly observed in schizophrenia patients.

Essentially, ▶ content-disordered thought processes are equivalent to delusions. They are characterized by abnormal, apparently unreasonable interpretations of one's own experiences and perceptions to which the person concerned adheres despite refutation by others (▶ Delusional disorder). According to Karl Jaspers, these interpretations fulfill three main criteria: certainty, incorrigibility, and impossibility (Jaspers 1913). The most frequently observed delusions in schizophrenia patients are delusions of reference, of persecution and guilt as well as megalomania, nihilism, and delusions with religious content.

Many patients experience prepsychotic states and prodromal symptoms before the first episode of schizophrenia is apparent. For example, this stage of the illness includes attenuated psychotic symptoms (APS) or brief limited intermittent positive symptoms (BLIPS) (▶ Prepsychotic states and prodromal symptoms).

Disorders of Affect and Mood

Schizophrenia is characterized by abnormalities of affect, emotional response, and mood. In this context, the profound disturbance of emotional rapport perceived in an intuitive way by an experienced psychiatrist interacting with a schizophrenia patient was named "praecox feeling." Due to fluctuations in attention and misinterpretation of stimuli, schizophrenia patients might be confused, depressed, and anxious. Sometimes, even situations of minimal novelty cause anxiety (novophobia), e.g., unfamiliar people, items, conversations. Common objects might take on undue significance and therefore scare patients. A further fundamental symptom of the schizophrenia-related affective disorder is parathymia, the inappropriateness of facial expression, gesture, and speech, which is contrary to the patient's real experience.

Affective flattening becomes manifest as a diminution of emotional response and indifference to events or topics that normally evoke such a response (Andreasen 1987, see Table 5).

Anhedonia refers to a pervasive and refractory reduction in the capacity to experience pleasure, which becomes apparent in reduced leisure activities or sexual interest.

Ambivalence is characterized by simultaneous, conflicting feelings toward a person or thing, e.g., love and hate or happiness and fear. These contradictory

Schizophrenia. Table 5. Symptoms of affective flattening (Andreasen 1987).

Unchanging facial expression
Decreased spontaneous movements
Paucity of expressive gestures
Poor eye contact
Affective nonresponsivity
Inappropriate affect
Lack of vocal inflections

impulses are usually unconscious and uninterpretable for other people.

Depressive symptoms can be found in up to 50% of schizophrenia patients. On the other hand, some patients develop ► manic conditions characterized by hyperactivity, a reduced ability to think critically and an overestimation of their own capabilities.

Hallucinations

► Hallucinations are conscious perceptions affecting the different senses in the absence of external stimuli. ► Auditory hallucinations are perceived as noise, words, sentences, whisper, or voices. They are apparent in about 70% of schizophrenia patients and mainly become manifest in thoughts becoming aloud as well as commenting, dialogic or imperative voices, respectively. ► Visual hallucinations occur relatively infrequently. ► Tactile hallucinations create the sensation of tactile sensory input and are perceived as touch, burning, or electrifying sensations. Coenesthesia is characterized by abnormal bodily sensations, e.g., parts of the body that are perceived as being changing their shape or size. ► Olfactory and gustatory hallucinations are quite uncommon in schizophrenia patients but can be associated with delusions of poisoning.

Disorders of the Ego

Patients with schizophrenia experience themselves in a disordered manner and often believe that they are affected by external forces. Accordingly, the term "disorders of the ego" comprises various symptoms. For example, patients experiencing thought diffusion are convinced that other people know their thoughts. Other symptoms belonging to this category are thought withdrawal, thought insertion, ► depersonalization, and ► derealization.

Disorders of Psychomotor Functioning

Many patients with schizophrenia experience psychomotor disturbances already at an early stage of the illness. Accordingly, changes in facial expressions, gestures, posture, voice, and speech are often observed. Everyday activities have to be reconsidered (loss of automatisms), which is why patients appear mannered.

Catatonic phenomena comprise disorders of movement, speech, and autonomic function. These motor disturbances consist of hyper- or hypokinesias (excitement and inhibition, respectively) and parakinesias (abnormal postures, mannerisms, grimacing, stereotypies). Catatonic speech disorders include perseveration, echolalia, mutism, et cetera. Characteristic autonomic signs are dilatation of pupils, seborrhea, sweating, and alterations in muscle tone (rigidity or hypotonia, respectively). Catatonic stupor and excited states represent the extreme ends of the spectrum.

Cognitive Symptoms

► Cognitive impairment is a cardinal feature of schizophrenia, which is found in 60–80% of patients. Generally, it is assumed that schizophrenia patients show deficits across a large number of neurocognitive domains including ► attention, ► executive functioning, memory, and fine motor skills. Performance has been reported to be two standard deviations below the mean of healthy control subjects. Cognitive variables have been related to the heterogeneity of functional outcomes, with difficulties in profiting from rehabilitation programs, and with quality of life. Evidence suggests that cognitive deficits may be of equal or greater importance in predicting functional outcome as positive or negative symptoms.

Such cognitive disturbances are present both in children who have a schizophrenic parent ("high risk children") and in first-degree relatives of patients, who do not suffer from a schizophrenic disorder. Furthermore, these deficits are apparent long before the onset of psychotic symptoms and they endure after a psychotic episode when patients are in remission. Therefore, cognitive deficits represent a possible trait marker of schizophrenia.

Next to neurocognitive impairment, schizophrenia has consistently been associated with deficits in the recognition, ► discrimination and experience of emotional stimuli. Impairments in affect perception have been demonstrated in chronic and first-episode patients and their unaffected siblings but not in high-risk individuals with initial prodromes, and it has been suggested that the initial psychotic episode represents a critical point for the emergence of emotion perception deficits in schizophrenia spectrum illnesses. Several studies have shown that these deficits in emotion recognition are associated with illness-related measures such as duration of illness, symptomatology, symptom severity, and cognitive

disturbances but are not influenced by age or antipsychotic treatment.

Other studies have shown significant and stable "theory of mind" (ToM) impairments in patients with schizophrenia. ToM refers to the ability to perceive other people's opinions, beliefs, and intents, and to establish a connection between these mental states and a person's behavior. These deficits are probably independent of neurocognitive dysfunctions and they might contribute to social and behavioral deviations in schizophrenia patients.

Subtypes

Depending on the combination of symptoms, different subtypes of schizophrenia have been defined:

► Paranoid schizophrenia is characterized by relatively stable, often paranoid delusions, usually accompanied by (auditory) hallucinations and perceptual disturbances. Disturbances of affect, volition and speech, and catatonic symptoms are not prominent.

Hebephrenic schizophrenia is dominated by affective changes with shallow and inappropriate moods. Thought is disorganized leading to incoherent and rambling speech, whereas delusions and hallucinations are fragmentary if present at all.

Catatonic schizophrenia is mainly determined by psychomotor disturbances with alterations between extremes such as hyperkinesias and stupor.

Undifferentiated schizophrenia meets the diagnostic criteria for schizophrenia but does not conform to any of the above subtypes or exhibits the features of more than one of them without a clear predominance of a particular set of diagnostic characteristics.

The diagnosis of ► post-schizophrenic depression (► Postpsychotic depressive disorder of schizophrenia) should be made if the patient has had a schizophrenic illness meeting the general criteria for schizophrenia within the past twelve months and some schizophrenic symptoms are still present. Depressive symptoms must be prominent and distressing, fulfilling at least the criteria for a depressive episode, and have been present for at least 2 weeks.

The term "residual schizophrenia" describes a chronic stage in the development of a schizophrenic disorder in which there has been a clear progression from an early stage (comprising one or more episodes with psychotic symptoms meeting the general criteria for schizophrenia described above) to a later stage characterized by long term, though not necessarily irreversible, negative symptoms, i.e., psychomotor slowing, underactivity, blunting of affect, passivity and lack of initiative, poverty of quantity or content of speech, poor nonverbal communication by facial expression, eye contact, voice modulation, posture, poor self-care, and social performance.

► Simple schizophrenia represents an uncommon disorder characterized by a slowly progressive development of negative symptoms without any history of hallucinations, delusions, or other manifestations of an earlier psychotic episode, and with significant changes in personal behavior, manifest as a marked loss of interest, idleness, and social withdrawal.

Epidemiology, Risk Factors, and Course of Symptoms

The incidence of schizophrenia in industrialized countries ranges from 10–70 new cases/100,000, whereas prevalence rates range from 1.6 to 12.1/1,000. The lifetime risk is 0.5–1%. Both "social drift" and environmental risk factors (e.g., drug abuse, migration) might account for an increased prevalence in the lower socioeconomic classes.

Epidemiological studies have shown gender differences in the age of onset of schizophrenia. The peak age of onset is 10–28 years for men and 26–32 years for women. However, there is a second peak of onsets in women after the menopause, resulting in an equal lifetime incidence for both genders. Affected men make contact with the psychiatric services at an average of five years earlier than women do.

Both twin and adoption studies indicate genetic effects in the liability to schizophrenia. Although the mode of transmission has not been clarified, several studies corroborate the so-called multifactorial polygenic model that involves an interaction between many contributing genes and environmental factors (obstetric complications, prenatal infection, neurodevelopmental abnormality, substance misuse, social and psychological factors).

Approximately 20% of patients with schizophrenia improve without relapse and 40% achieve a clinically stable residual state and are socially integrated, whereas approximately one-third of patients suffer from continuous psychotic symptoms and/or increasing social disability. Factors affecting prognosis are listed in Table 6.

Treatment Considerations

The discovery of ► chlorpromazine in the early 1950s introduced an era of effective pharmacological treatment for schizophrenia. Today, antipsychotics of different chemical structures, ranging from tricyclic ► phenothiazines to thioxanthenes, ► butyrophenones, dibenzazepines, substituted benzamides, benzioxazole derivatives, and chinolones are considered to form the backbone of treatment (► Antipsychotic drugs, ► First-generation

Schizophrenia. Table 6. Factors affecting prognosis.

Favorable prognosis	Unfavorable prognosis
Acute onset of illness	Insidious onset of illness
Positive symptoms	Negative symptoms
Lack of family history of schizophrenia	Family history of schizophrenia
Inconspicuous premorbid personality	Poor premorbid personality
Average IQ	Low IQ
High social class	Low social class
Social integration	Social isolation
Lack of comorbidities	Comorbid drug abuse
Female sex	Male sex
Being married	Single marital status

antipsychotics, ► Second-and third-generation antipsychotics, ► Future of antipsychotic medication). They shorten the length of an acute episode of the illness and reduce the risk of relapse. Clearly, modern concepts of schizophrenia management include psychosocial and rehabilitative measures, and pharmacotherapy should always be embedded in integrative treatment procedures.

Essentially, the prognosis of schizophrenia depends on when pharmacological treatment is started and on the number of psychotic episodes. Two-thirds of patients experiencing a first episode of the illness experience symptomatic remission within half a year if antipsychotic treatment is started immediately. In addition, consistent prophylaxis with antipsychotic medication results in a reduction of the one-year relapse rate from 75 to 20%. Since less than 50% of patients with schizophrenia in long-term treatment take their medication according to the physician's recommendations, interventions to enhance compliance should be implemented at the beginning of treatment (Fleischhacker et al. 2007).

The parenteral administration of rapid-acting antipsychotics should be confined to emergencies, where acute agitation and lack of insight lead to a high risk of patients harming themselves or others. In contrast, the administration of long acting depot antipsychotics is an important treatment option for the long-term management. The advantages of these injectable drugs include dose reduction due to avoidance of the first-pass-effect, the fact that patients do not need to take medication every day, and the facilitation of management due to certainty concerning compliance. The disadvantages of this type of treatment include the fact that some patients refuse intramuscular injections or develop irritations at the injection site. Another problem is that the dose of a depot antipsychotic cannot be reduced once administered.

Despite continuous new findings in the field of psychopharmacology, there are no reliable predictors for individual drug response/tolerability. Therefore, the choice of medication depends on an individual risk–benefit analysis. In patients who do not adequately respond to two antipsychotic drugs of different chemical classes, switching to ► clozapine is indicated. This compound has been shown to have unique efficacy in so far as it reduces symptoms in 30–60% of treatment refractory schizophrenia patients (Fleischhacker 1999) (► Antipsychotic drugs). However, although pharmacological agents have substantially advanced the treatment of schizophrenia and have had a significant impact on the lives of patients in terms of relapse prevention, ► quality of life, and resocialization there are still considerable unmet needs in the management of these patients.

Cross-References

► Antipsychotic Drugs
► Delusional Disorder
► First-Generation Antipsychotics
► Future of Antipsychotic Medication
► Hallucinations
► Postpsychotic Depressive Disorder of Schizophrenia
► Prepsychotic States and Prodromal Symptoms
► Second-and Third-Generation Antipsychotics

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Schizophrenia: Animal Models

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Definition

Animal models for schizophrenia refer to animal preparations which attempt to mimic aspects of the human disorder, schizophrenia. In general, these animal models are subdivided into screening models, in which the therapeutic effects are modelled, and simulation models, in which the emphasis is on the symptoms of schizophrenia.

Current Concepts and State of Knowledge

Screening Models

In screening models, sometimes referred to as animal models for antipsychotic action, the focus is on the pharmacology of schizophrenia (Arnt 2000). The principal aim is to predict the therapeutic effects of novel drugs, based on the efficacy of antipsychotic drugs that have already been in clinical use. Such clinically successful drugs are often referred to as "gold standard." The development of a screening model therefore starts with the identification of an appropriate gold standard. In the early years, this gold standard was usually ▶ chlorpromazine or ▶ haloperidol. In more recent years, screening models often use two gold standards, a so-called classical (most often haloperidol) and an atypical antipsychotic drug (most often ▶ clozapine). The rationale behind this approach is that many clinical studies have shown differences between these two (classes of) antipsychotic drugs. Most notably, while classical antipsychotic drugs induce severe neurological (so-called extrapyramidal) side effects, ▶ atypical antipsychotic drugs do not, or to a much lesser extent. Having two gold standards might help identify which aspects of the screening models are more related to the therapeutic efficacy of antipsychotic drugs (i.e., those aspects in which both gold standards show similar effects) and those that are more related to the side effects (i.e., those aspects that are induced by the classical but not by the atypical gold standard).

After having selected the appropriate gold standard (or standards) the drug is given to an animal, usually a rat or a mouse. In many cases this is a normal, naïve, and untreated animal, but in some cases the animal is trained before hand (such as in the conditioned avoidance response) or treated with a specific drug (such as a dopamine agonist or a glutamate antagonist) to induce a specific behavioral response. Table 1 lists the most often used screening models for schizophrenia.

The effects of the gold standard are then evaluated in this behavioral setup and if a clear reproducible response

Schizophrenia: Animal Models. Table 1. A summary of the most important screening models for schizophrenia and their validation on the basis of the criteria discussed in the text.

Screening test	No false positives	No false negatives	Potency correlation	Anticholinergic	Chronic treatment
Spontaneous behavior					
Paw test	+	+	+	+	+
Learned behavior					
Conditioned avoidance response	−	+	+	−	±
Intracranial self stimulation	−	+	±	−	+
Drug-induced behavior					
DA agonist–induced hyperactivity	−	±	+	±	Ø
DA agonist–induced stereotypy	−	−	−	−	−
DA agonist–induced prepulse inhibition deficit	±	+	+	−	+
NMDA antagonist–induced prepulse inhibition deficit	−	±	−	Ø	+

+ indicates that there is convincing evidence that the criterion is fulfilled; − indicates that there is convincing evidence that the criterion is not fulfilled; ± indicates that contradictory evidence exists in the literature regarding this criterion; Ø indicates that there is not enough literature to assess this criterion

is obtained, the model can go into the next and most important phase of model development: the validation phase. In this most crucial phase of the model development, the validity of the model is established on the basis of clinical evidence. ► Antipsychotic drugs have been in clinical practice since the 1950s and therefore a vast knowledge about their clinical effects now exists. From this knowledge base, several criteria can be formulated that can be used to validate a screening model (Ellenbroek 1993). The two most obvious criteria are the absence of ► false negatives and ► false positives. False negatives are drugs that in the model do not resemble the gold standard but in clinical practice are effective antipsychotic drugs. False positives, on the other hand, are drugs that act like the gold standard in the model, but in clinical practice are not effective. Especially this criterion is difficult to test, since there are thousands of compounds available most of which have not been extensively tested in patients. Moreover, it was common practice that many pharmaceutical companies did not publish negative results from phase II or phase III studies, and in several instances contradictory data have been published. The evaluation of this criterion is therefore usually based on a selection based on similarity in chemical structure or drugs with a known influence on motor activity (such as ► diazepam or ► morphine), since such drugs can interfere with behavioral performance in general. Another general criterion is that there should be a correlation between the potency of the antipsychotic drugs in the clinic and in the model. Finally, several other criteria can be specifically deduced from the clinical literature on antipsychotic drugs. One of the most interesting criteria is the lack of effect of anticholinergic drugs. The rationale behind this criterion is that while anticholinergic drugs do not influence the therapeutic effect of antipsychotic drugs, they do diminish the extrapyramidal side effects. Thus, anticholinergic drugs can be useful to distinguish between parameters modelling the therapeutic and the unwanted side effects. The same holds true for chronic treatment with antipsychotic drugs. It is well known that the therapeutic effect usually increases with prolonged treatment, whereas the ► extrapyramidal side effects usually wane with repeated administration. Table 1 tries to summarize the vast literature on the validation of the screening models for schizophrenia (Ellenbroek 1993).

Once the validation phase has (satisfactorily) finished, the model goes into the final stage in which novel compounds can be evaluated and compared to the gold standard(s). Once a promising new drug candidate has been identified (that also shows a good ► pharmacokinetic and safety profile) it can then be tested in clinical trials.

Although most of the currently available treatments for schizophrenia have been developed using screening models, they have received much less attention in recent years. The principal reason for this is that such screening models, how predictive they may be, will always produce drugs similar to the gold standard (often referred to as a "me too" approach). Indeed, this probably explains why there are so few differences between the currently available drugs. However, in spite of this disadvantage, screening models are still being used because they are usually quick and easy, but also because they can help us to understand the mechanism of action of antipsychotic drugs and especially the differences between classical and atypical antipsychotic drugs.

Simulation Models

Since screening models will unlikely lead to a major breakthrough in the treatment of schizophrenia, attention has in recent years shifted more and more to simulation models. This shift was aided by the increasing clinical knowledge of the disease. In simulation models, one tries to mimic as many aspects of a disease as possible. In its simplest form, this requires two steps: (1) the induction of the disease and (2) the measurement of the symptoms. Unfortunately, both steps have proven to be very difficult in the case of schizophrenia. With respect to the symptoms, most of the cardinal symptoms (especially the so-called positive symptoms such as ► hallucinations and ► delusions) in humans can only be assessed in a psychiatric interview. Since such symptoms can not be modelled in animals, researchers have resorted to negative symptoms (such as anhedonia and social withdrawal) and symptoms within the cognitive domain (such as ► attention and ► (working) memory). In addition, much attention has recently been paid to so-called ► endophenotypes and potential biomarkers for schizophrenia. It is beyond the scope of this chapter to discuss all the aspects of endophenotypes, but in general, they are physiological or psychological phenomena that have a genetic basis and are associated with the specific disease. The idea behind such endophenotypes is that they may be more related to specific brain structures and neurotransmitter functions than the symptoms of the disease. Moreover, they are usually easier to model in animals. In the case of schizophrenia, several endophenotypes have been proposed, such as smooth eye pursuit movement, P_{50} sensory gating and ► prepulse inhibition. Especially the latter two can also quite easily be assessed in animals. Biomarkers are also increasingly considered to be of great value for diseases, although the traditional peripheral (for instance blood or urine) analyses may not be very relevant for

central nervous system disorder such as schizophrenia. However, with the advent of modern functional imaging new possibilities have occurred. For instance, using ► PET and ► SPECT scan analyses, it has been shown that psychotic patients have an increased basal as well as amphetamine-enhanced dopamine release in the basal ganglia. Using ► microdialysis techniques such changes in dopamine release can also be measured in freely moving animals. Thus, although the cardinal symptoms of schizophrenia seem to be beyond modelling in animals, other symptoms, biomarkers, and endophenotypes can be assessed in humans and animals often with more or less identical techniques and offer the possibility to assess vital aspects of schizophrenia in rats and mice.

However, even though we can measure social behavior, prepulse inhibition, dopamine release and other phenomena, the crucial step in animal modelling is to induce a disturbance in these phenomena that resemble the disturbance in the disease. There are several different approaches to achieve this and those approaches will be discussed in the following sections.

Spontaneous Models

One way of identifying a potentially interesting model is to compare different strains of rats or mice, to see whether certain strains have deficits in specific signs or symptoms of a disease. In the case of schizophrenia for instance, Brown Norway and Brattleboro rats show deficits in prepulse inhibition compared to Sprague Dawley and Lewis rats respectively. Interestingly, these animals also show other abnormalities related to schizophrenia and have thus been suggested to represent "spontaneous models" for schizophrenia.

An alternative to investigating different strains of animals is to investigate individual animals within one strain to identify extremes within a normal population. Once such individuals have been identified, the next step is usually to try to breed these extremes selectively in order to establish a colony of high and low responders to a specific situation. For instance, there have been several approaches to selectively breed animals with a poor performance in the prepulse inhibition. Many years ago, we started to select Wistar rats on the basis of their gnawing response to ► apomorphine. After only a few generations, there was an almost complete separation in susceptible (APO-SUS) and unsusceptible (APO-UNSUS) animals. Further experiments showed that the APO-SUS animals shared a large number of symptoms with schizophrenic patients (such as enhanced sensitivity to ► stress, enhanced dopamine release, reduced prepulse inhibition, etc.).

Thus, the spontaneous approach has led to several potentially interesting models. However, very few have been investigated in detail (for instance with respect to their validity) and the lack of a clear link (even if it is only theoretical) to the etiology of schizophrenia has limited the widespread use of them. In this respect, it is important to emphasize that none of the symptoms of schizophrenia are pathognomic, and that deficits in prepulse inhibition, for instance, occur in many diseases. Thus an animal with a deficit in prepulse inhibition does not immediately constitute an animal model for schizophrenia.

Pharmacological Models

It has long been known that certain drugs can induce symptoms resembling those seen in psychiatric or neurological disorders. Thus, ► antipsychotic drugs can induce a parkinsonian like ► rigidity and ► akinesia, and ► reserpine can induce depressive-like symptoms. Likewise, dopamine agonists such as ► amphetamine and NMDA antagonists such as ► phencyclidine can induce schizophrenia-like symptoms. Whereas amphetamine induces predominantly (positive) psychotic symptoms (though it can induce negative or cognitive deficits too), phencyclidine seems to be able to induce the full spectrum of schizophrenia. Such pharmacological tools have very often been used in animal modelling as well, and both drugs induce a large number of schizophrenia-like abnormalities in animals. Hence, amphetamine increases dopamine release, reduces prepulse inhibition, P_{50} gating and social behavior (especially in monkeys). Phencyclidine induces virtually the same symptoms as amphetamine, but several pharmacological studies have shown that this model is mediated via different mechanisms. For instance, all known antipsychotic drugs can reverse the amphetamine-induced deficits in prepulse inhibition, whereas most of these drugs do not reverse the phencyclidine-induced prepulse inhibition (Geyer et al. 2001). A more fundamental problem with these pharmacological models is that they induce only very short-lived symptoms, and the validity for the schizophrenic process (which is a chronic process probably already starting before birth, see below) is questionable. Indeed models such as the amphetamine or phencyclidine-induced deficit in prepulse inhibition are now often regarded more as screening models (similar to amphetamine-induced hyperactivity) than as simulation models (see also Table 1).

Etiological Models

The most interesting class of simulation models are those in which one tries to mimic the etiology of schizophrenia. Unfortunately, schizophrenia is a highly complex disorder

with a multifactorial etiology, in which genetic and environmental factors interact. Moreover, the nature of most of the genetic and environmental factors is still largely unknown. Fortunately, clinical genetic research is increasing rapidly and there is now more and more evidence for certain candidate genes associated with schizophrenia. It would go beyond the limits of this chapter to discuss the evidence in favor of each of these genes but the most often associated ones are DISC-1 (disrupted in schizophrenia-1), dystrobrevin, neuregulin-1and regulator of G-protein signalling-4 (Harrison and Weinberger 2005). Although such association studies have led to the development of specific transgenic mice, it should be noted that in different studies, different ► polymorphisms have been linked to schizophrenia and the functional consequence of these polymorphisms is in most cases still unknown, leading to intriguing results. For instance, whereas the heterozygous neuregulin knock-out mouse shows a reduction in prepulse inhibition, patients with the schizophrenia associated neuregulin ► haplotype seem to have increased mRNA and protein levels of neuregulin.

The search for specific environmental factors associated with schizophrenia is even more complicated than the search for genetic factors, since they often predate the onset of the disease by many years (if not decades) and are often only indirectly measurable, as an association between a specific event and the occurrence of the disease. For instance, several studies have reported that exposure to the 1958 influenza pandemic increased the risk of the schizophrenia in the offspring. However, whether this was due to the influenza virus, the medication, the stress of the situation, or other factors is impossible to deduce. Nonetheless, there is quite a large group of environmental factors that can increase the risk of developing schizophrenia. These include winter birth, migration, prenatal malnutrition, pre- and postnatal stressors, perinatal infection, and obstetric complications (Tandon et al. 2008). Some of these factors have also been modelled in animals, such as prenatal stress, prenatal protein restriction, Caesarean section, ► maternal deprivation, and ► isolation rearing (Carpenter and Koenig 2008). Although few of these models have been investigated in great detail, yet some of these manipulations seem to induce quite a variety of the schizophrenia-like signs and symptoms (see Table 2).

In addition to these etiologically based simulation models there are a few additional environmental models where one can argue whether they are really etiologically based, especially the ► early ventral hippocampal lesion model and the ► prenatal MAM model. Both models certainly aim to induce a neurodevelopmental disorder, but there is no evidence that patients with schizophrenia have an early hippocampal lesion nor that neurogenesis was blocked for some time during gestation. Nonetheless, both treatments induce a variety of schizophrenia like signs and symptoms.

The inspection of Table 2 shows several interesting points. Firstly, in contrast to clinical studies, much less data are available for the genetic models than for the environmental models. Secondly, of the signs and symptoms, most interest has focussed on prepulse inhibition, presumably because of the ease of measurement and the similarity to the clinical situation. In contrast, P_{50} gating and anhedonia have received much less attention.

Validation of Simulation Models

As with screening models, simulation models also have to be validated. Although this is often done using the same criteria used for screening models, it is important to note that there is much less clinical evidence that these criteria can be applied. For instance, most of the signs and symptoms in Table 2, including memory, social withdrawal, and anhedonia are related to the cognitive and negative symptoms of schizophrenia, i.e., domains that generally do not respond to antipsychotic drugs. Even with respect to prepulse inhibition, there is insufficient evidence from longitudinal studies whether (some or all) antipsychotic drugs improve this information-processing deficit. Thus, with a lack of clinical data on these signs and symptoms, the validity of simulation models is difficult to assess.

Gene – Environment Models

The models described earlier and in Table 2 are based on either genetic or environmental factors. However, there is a vast amount of evidence that schizophrenia results from an interaction between genetic and nongenetic factors (Van Os et al. 2008). So far, this interaction has received little attention in animal modelling. Some of the environmental manipulations have been performed in different strains of rats, such as early hippocampal lesions, isolation rearing, and maternal deprivation, but extensive gene – environment interactions still need to be performed. Nonetheless, some interesting findings have already been reported. Thus, compared to Sprague Dawley or Wistar rats, Lewis rats seem to be much less sensitive to early hippocampal lesioning, isolation rearing, and maternal deprivation (Ellenbroek and Cools 2000; Lipska and Weinberger 1995; Varty and Geyer 1998). This finding suggests that the genetic make-up of the Lewis rats may somehow be protective to these different manipulations. It would be of great interest to try to identify the underlying protective mechanism.

Schizophrenia: Animal Models. Table 2. An overview of the most widely used etiologically based simulation models for schizophrenia.

Etiologically based simulation models	DA hyperactivity	PPI deficit	P_{50} gating deficit	Memory impairment	Social withdrawal	Anhedonia
Genetic models						
DISC-L100P	Ø	+	Ø	+	−	−
DISC-Q31L	Ø	+	Ø	+	+	+
DISC−/−	+	+	Ø	Ø	+	Ø
Sdy Mutant Rat (DTNBP1−/−)	−	−	Ø	Ø	+	Ø
III-Neuregulin$^{\pm}$	Ø	+	Ø	+	Ø	Ø
TM-Neuregulin$^{\pm}$	Ø	+	Ø	−	Ø	Ø
CRD-Neuregulin$^{\pm}$	Ø	+	Ø	+	Ø	Ø
Environmental models						
Prenatal stress	+	+	+	+	+	Ø
Prenatal polyI:C	+	+	Ø	+	Ø	Ø
Caesarean section	+	+	Ø	Ø	Ø	Ø
Maternal deprivation	+	+	+	Ø	±	Ø
Isolation rearing	+	+	+	±	±	±
Early ventral hippocampal lesion	+	+	Ø	+	+	+
Prenatal MAM treatment	+	±	Ø	+	+	Ø

+ the sign or symptoms is observed in the animal model; − the sign or symptoms is not observed in the animal model; ± there is contradictory evidence whether the sign or symptoms is observed in the animal model; Ø the sign or symptom has not been investigated in the animal model
PPI prepulse inhibition; *DISC* disruption in schizophrenic; *DTNBP1* dystrobrevin binding protein 1; *MAM* methylazoxymethanol

Summary

Schizophrenia is a severe psychiatric disorder with an unknown etiology and complex symptomatology. This has severely hindered the development of appropriate animal models. In the past, most therapeutic agents were developed using so-called screening models, in which novel compounds were compared to known therapeutic agents. Although these models are still in use nowadays, it is highly unlikely that they will lead to a major breakthrough in therapy. With the identification of specific signs and symptoms, including biomarkers and endophenotypes that could also be assessed in animals, the field of animal modelling obtained the boost it needed. Moreover, genetic and epidemiological studies have started to identify specific genes and environmental factors that contribute to the disorder. This has led to a wealth of novel simulation models in the last decade, most of which are still in a very early exploratory phase and have not yet been properly validated. The most important challenge for the coming years will be to merge the two types of etiologically based simulation models in order to investigate the gene – environmental interaction, which is crucial for the occurrence of schizophrenia.

Cross-References

- ▶ Animal Models for Psychiatric States
- ▶ Antipsychotic Drugs
- ▶ Future of Antipsychotic Medication
- ▶ Genetically Modified Animals
- ▶ Latent Inhibition
- ▶ Prepulse Inhibition
- ▶ Rodent Models of Cognition
- ▶ Schizophrenia

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Schizophrenia Prodrome

Definition
Subthreshold psychotic symptoms that emerge prior to meeting full criteria for schizophrenia (or before relapse after remission of symptomatology).

Cross-References
► Pre-psychotic States and Prodromal Symptoms
► Schizophrenia

Scopolamine

Synonyms
Hyoscine; Levo-duboisine

Definition
A tropane alkaloid drug that acts as an antagonist at the ► muscarinic subtype of acetylcholine receptor. It is named after the plant genus *Scopolia*. It acts as a nonselective competitive antagonist. In addition to its use in experiments as a disruptor of cognitive functioning, its main medical uses are in the treatment of nausea and motion sickness, intestinal cramping, as an antiemetic, and for ophthalmic purposes to induce pupil dilation and paralysis of the eye-focusing muscles.

Cross-References
► Animal Models of Psychiatric States
► Muscarinic Agonists and Antagonists

Screening Models

Synonyms
Animal model with predictive validity

Definition
An animal model focused on drug development. The principle aim is to predict the therapeutic effects of unknown drugs, based on their comparison, in animals, with drugs with a proved therapeutic efficacy.

Cross-References
► Abuse Liability Evaluation
► ADHD: Animal Models
► Anxiety: Animal Models
► Autism: Animal Models
► Dementias: Animal Models
► Depression: Animal Models
► Eating Disorder: Animal Models
► Predictive Validity
► Schizophrenia: Animal Models

SDLP

Definition
Standard deviation of lateral position.

Secobarbital

Synonyms
Secobarbitone

Definition
Secobarbital is an intermediate- to short-acting (half-life 15–40 h) barbiturate drug that is used primarily as a hypnotic agent to treat insomnia. It is also used as a premedication before surgery and for the emergency management of seizures. Secobarbital is an agonist at ► $GABA_A$ receptors thereby increasing inhibitory ► GABAergic transmission in the CNS. It binds to a distinct site upon the $GABA_A$ receptor ion channel complex increasing the duration of time for which the Cl^- channel is open. Secobarbital, like other barbiturate drugs, has a narrow therapeutic window, that is, a small difference between the minimum effective dose for sedation and maximum tolerated dose producing coma and death. Long-term use of this drug is

contraindicated because of its ability to produce tolerance and dependence, and abrupt withdrawal from chronic treatment precipitates a life-threatening withdrawal syndrome. It is used illicitly for the purposes of getting high, to reduce anxiety, to counteract the effects of stimulant drugs, for example, cocaine, ecstasy, and in suicide.

Cross-References

► Barbiturates
► Hypnotics
► Withdrawal Syndromes

Secobarbitone

► Secobarbital

Second and Third Generation Antipsychotics

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Synonyms

Atypical antipsychotics; Novel antipsychotics

Definition

This class of antipsychotics, with clozapine as the prototype, are distinguishable from their first generation counterparts by a lower liability for ► extrapyramidal symptoms (EPS) and claims of improved efficacy that extend to other domains beyond psychosis (e.g., cognition, negative symptoms). These drugs have been designated "atypical" when compared to the older "typical" or conventional antipsychotics like ► chlorpromazine, ► haloperidol, ► perphenazine and ► fluphenazine.

The distinction between second and third generation antipsychotics has been made based on mechanistic differences. Specifically, aripirpazole is the first approved antipsychotic that is a partial ► dopamine agonist and, as such, has been designated a ► third generation antipsychotic. This presumes that all other atypical compounds to this point, including clozapine, share some common attribute(s) pharmacologically that account for their unique clinical profile. However, beyond dopamine D_2 antagonism, which characterizes all antipsychotics including ► aripiprazole, this is not the case. For example, the ► serotonin 5-HT_2/dopamine D_2 model does not adequately represent all of these compounds (see *Atypicality: Mechanisms of Action*, below). Thus, as a partial dopamine agonist aripiprazole is unique amongst the atypical antipsychotics but the distinction between second and third generation agents may misrepresent the homogeneity of all other atypicals.

Pharmacological Properties

First Generation Antipsychotics and Limitations

Antipsychotics were introduced for clinical use in the 1950s. At the time, descriptive terminology included "► major tranquilizers" (because of their sedating/calming effect) and "► neuroleptics," literally meaning "to take the neuron" and reflective of their liability for motor side effects (i.e., EPS). They rapidly became the treatment of choice for psychotic conditions such as schizophrenia although it was initially unclear as to what aspect of their diverse pharmacology accounted for this effect. Within the next years, it was established that dopamine D_2 binding seemed critical to the antipsychotic effect and this generated an additional subgroup of these drugs characterized by high affinity for the dopamine D_2 receptor, drawing a distinction between low-potency (e.g., chlorpromazine) and high-potency (e.g., haloperidol) neuroleptics. A liability for EPS, both acute (e.g., parkinsonism) and chronic (e.g. ► tardive dyskinesia or TD) characterized all these drugs and represented a substantial burden to their use in the clinical setting.

Clozapine

Clozapine, developed in the 1960s, was notable for its antipsychotic efficacy in the face of minimal EPS at therapeutic doses. It was introduced for clinical use in the early 1970s but soon withdrawn in a number of countries because of a cluster of deaths, subsequently linked to its associated risk of agranulocytosis. Work in the late 1980s, though, underscored this drug's superiority in ► treatment resistant schizophrenia and suggested it might also have broader efficacy (i.e., negative as well as positive symptom improvement). By the 1990s it was reintroduced in different countries with the associated requirement of regular hematologic monitoring.

Atypicality

Atypicality has been defined as lack of EPS at therapeutic doses (Meltzer et al. 2003). At the time of clozapine's development, it was unique amongst existing antipsychotics in this regard, establishing it as the prototype of atypicality. Over time, a new class of antipsychotics

(second generation) was developed to mirror clozapine's clinical benefits while circumventing its adverse side effects, in particular risk of agranulocytosis. In this process, it was assumed that these drugs would also mirror clozapine in other regards (e.g., greater efficacy in treatment resistant schizophrenia, improvement in negative as well as positive symptoms). With a new class of antipsychotic available, the previous medications came to be designated "first generation" (vs. second generation), "typical" (vs. atypical) or "conventional" (vs. novel).

Atypicality: Mechanisms of Action

Several aspects of clozapine's diverse pharmacology were highlighted as possibly contributing to its unique clinical profile. These included its low binding affinity for the dopamine D_2 receptor in addition to comparatively high binding at the serotonin 5-HT_2 receptor. An elegant body of pre-clinical work led Meltzer et al. to postulate that the profile of greater serotonin 5-HT_2 versus dopamine D_2 binding accounted for clozapine's atypical features (Meltzer et al. 2003), a model that was rapidly embraced in drug development and one that describes most second generation antipsychotics including ▶ olanzapine, ▶ paliperdione, ▶ quetiapine, ▶ risperidone, ▶ sertindole, ▶ ziprasidone and ▶ zotepine. Critical to this model is the ratio of serotonin 5-HT_2 versus dopamine D_2 binding; earlier antipsychotics demonstrated combined serotonin 5-HT_2/dopamine D_2 antagonism but did not meet this identified ratio and were not seen as unique clinically.

Clozapine's low affinity for the dopamine D_2 receptor also called into question the longstanding argument that dopamine D_2 antagonism is absolutely critical for antipsychotic efficacy. This encouraged efforts to look at non-dopaminergic strategies and, following the importance this model ascribed to serotonin, led to work investigating the notion that serotonin 5-HT_2 antagonism alone might be sufficient (e.g., ritanserin, MDL-100907, fanaserin). While this was not substantiated, there continues to be interest in the pursuit of antipsychotic development that is not hinged on dopamine blockade.

Although the serotonin 5-HT_2/dopamine D_2 model was widely embraced, there was reason to pursue other explanatory models. In countries outside of North America, ▶ amisulpride and ▶ sulpiride (substituted benzamides) are accessible clinically and seen as atypical; however, their pharmacological profile precludes an explanation based on serotonin 5-HT_2/dopamine D_2 antagonism. At least two other models have since been posited to account for the atypical features of newer antipsychotics. The "low affinity-fast dissociation" model (Kapur and Seeman 2001) holds that clinical benefits such as decreased EPS, lack of prolactin elevation, and possible improvement in cognitive and negative symptoms may occur as a result of transient binding at the dopamine D_2 receptor, which mitigates against impairment of phasic dopamine release. Thus, while all drugs depress tonic dopamine release, those with more rapid dissociation (i.e., fast K_{off} drugs) are less likely to alter phasic dopamine release, essential for dopamine to exert its physiologic effects in the course of daily activities. There is, for example, abundant evidence linking dopamine to reward and goal-directed behaviors, as well as cognition (Berridge 2007). This line of thinking suggests there may be clinical gains through what these drugs *don't do* (i.e., sustained dopamine blockade) rather than by unique gains attributable to some other aspect of their rich receptor-binding profiles (e.g., concomitant serotonin 5-HT_2 binding).

A second hypothesis ascribes the clinical gains associated with atypicality to limbic selectivity (Bischoff 1992) and support for this comes from several lines of investigation (Remington and Kapur 2005). Looking at early gene expression (c-fos and c-jun) as a marker of synaptic activity, it has been noted that as a class the newer antipsychotics are associated with regional differences (e.g., increased c-fos expression in limbic versus striatal regions). Similarly, more recent opportunities to examine D_2 binding extrastriatally have provided evidence that atypical antipsychotics demonstrate preferential binding for extrastriatal structures, for example temporal cortex. This could account for the diminished risk of EPS and ▶ hyperprolactinemia, as well as a more direct effect on other brain regions. Of note, while the atypicals as a class are associated with decreased EPS and a diminished risk of hyperprolactinemia, this is variable; risperidone, paliperidone, and the substituted benzamides carry a greater liability. It has been suggested that the limbic selectivity model is, at least in part, a variation of the low affinity-fast dissociation hypothesis in that the decreased binding in striatal regions reflects competitive displacement by endogenous dopamine at dopamine D_2 receptors in dopamine-rich regions.

The distinction between aripiprazole and other atypical antipsychotics is, in contrast, clearer and draws upon a shift in thinking regarding dopamine's role in schizophrenia. For decades, the most widely held biochemical model for schizophrenia posited a disorder of hyperdopaminergic activity. However, by the 1980s a clearer distinction was drawn between positive and negative symptoms, and subsequently our conceptualization of schizophrenia has broadened even further to include other domains (e.g., cognition). In the context of these changes, dopamine's role has been reframed to accommodate its differential

involvement in this expanded model, suggesting more complex feedback loops involving various dopamine receptors and other neurochemical systems. For example, while limbic structures, dopamine D_2/D_3 receptors, and hyperdopaminergic activity have been implicated in the positive symptoms, cognitive and negative symptoms have been linked to prefrontal regions, a role for dopamine D_1 receptors, and hypodopaminergia.

In this context, drugs that affect dopamine differentially may have distinct clinical advantages and aripiprazole's proposed dual action on dopamine fits with this line of thinking. A partial dopamine agonist acting on postsynaptic D_2 receptors as well as presynaptic dopamine autoreceptors, its effects are linked to whether dopamine activity is high (i.e., mesolimbic) or low (i.e., mesocortical). Thus, through its antagonist properties it diminishes positive symptoms (mesolimbic), while its agonist profile results in improved negative and cognitive symptoms (directly at the mesocortical level and indirectly at the nigrostriatal level in the form of attenuated EPS).

The popularity of each of these models speaks to the importance of dopamine and serotonin in explaining the unique clinical benefits of the newer antipsychotics, but these drugs are characterized by diverse pharmacological profiles that impact a variety of receptors and systems (e.g., acetylcholine, norepinephrine, histamine, glutamate) (Remington and Kapur 2005). Although the currently available newer antipsychotics can each be characterized by one of the aforementioned models, the potential role (s) of these other systems remains a subject of investigation, both in terms of therapeutic efficacy as well as side effects. The involvement of other receptors and systems has taken on added interest with the growing body of evidence conceptualizing schizophrenia as a disorder of multiple symptom domains (e.g., positive, negative, cognitive, affective), paralleled by increased awareness regarding the clinical and functional importance of these other nonpsychotic features. The potential benefits of an effective antipsychotic without direct dopamine blockade remains alluring, ensuring the search for new antipsychotics focused on other systems thought to play an important role in schizophrenia.

Atypicality: Second/Third Generation Antipsychotics

While Meltzer et al. defined atypicality as absence of notable EPS at therapeutic doses (Meltzer et al. 2003), evidence clearly indicates that the newer antipsychotics are not the same in this regard. For example, risperidone has been identified as having a greater liability for EPS than many other atypical agents, a risk that is dose-dependent – this also distinguishes it from other atypicals such as clozapine and quetiapine. It must also be noted that the benefits of the atypical antipsychotics, particularly agents like risperidone, in terms of EPS have been challenged on methodological grounds; often comparator trials with first generation antipsychotics have used haloperidol, which has a notable propensity for EPS, and at doses in excess of what are currently recommended. It remains, though, that as a class the atypicals have been associated with diminished risk of EPS and it is this defining feature that best distinguishes atypical antipsychotics from their conventional counterparts.

Although classifying medications based on presence or absence of a particular side effect may seem misguided, it has occurred again more recently with the growing recognition that the newer antipsychotics, in particular agents like clozapine and olanzapine, demonstrate a substantially greater risk for weight gain and associated metabolic disturbances. At least some regulatory bodies have chosen to identify this as a class effect characterizing all atypicals although evidence clearly indicates that, as with EPS, there are marked differences between these drugs on this dimension. For example, at the other end of the continuum from olanzapine and clozapine are drugs like ziprasidone and aripirazole that are considered to be "weight neutral" (Newcomer 2007).

Other definitions, for example based on mechanism(s) of action, are even less homogeneous. While the serotonin 5-HT_2/dopamine D_2 hypothesis dominated initial efforts to replicate clozapine's clinical advantages, agents now classified as atypical cannot be collectively grouped within this model. Clozapine, olanzapine, paliperidone, quetiapine, risperidone, sertindole, ziprasidone and zotepine can be categorized as serotonin 5-HT_2/dopamine D_2 antagonists but this is not the case for amisulpride and sulpiride, where their benefits might best be explained by the low affinity-fast dissociation model. In fact, it has been argued that this same model could as readily explain the benefits of drugs that meet criteria for serotonin 5-HT_2/dopamine D_2 antagonists although this is the subject of ongoing debate. As a partial dopamine agonist, aripiprazole currently stands alone pharmacologically, which has led some to suggest that it represents a third generation antipsychotic. This is, of course, a misnomer if we are to use serotonin 5-HT_2/dopamine D_2 antagonism as the mechanism of action that categorizes all other newer antipsychotics (given the substituted benzamides). The low affinity-fast dissociation explanation might better capture other antipsychotics, but this debate itself speaks to the pitfall of classifying such diverse pharmacological agents on models that are hypothetical and singularly

focused. It is very likely that the clinical gains we are seeking to achieve can be attained through different pathways, and that benefits may be accrued through a combination of pharmacological manipulations.

Attempting to collectively group these agents based on clinical similarities faces similar challenges, (Tandon et al. 2008), made more difficult by the rapid expansion in purported benefits that occurred in parallel to the development of the different atypicals.

The fact that the atypical antipsychotics differ on various measures of efficacy and side effects, in combination with evidence that clinical differences between them and first generation antipsychotics may not be as prominent as once thought, has challenged the utility of terminology like "second generation" (Leucht et al. 2009). As an alternative, it has been argued that this "all or none" approach to categorization should give way to a strategy that allows individual drugs to be defined across a number of relevant measures (i.e., different clinical measures and side effects) (Waddington and O'Callaghan 1997).

Formulations

All atypical antipsychotics are available in oral preparations that call for once daily administration. There are examples where it is recommended that the dose be twice daily, based on shorter elimination half-life (e.g., quetiapine, ziprasidone), although extended-release oral formulations have been developed to address this (e.g., quetiapine). There is some question as to the value of establishing daily dosaging based on peripheral ► pharmacokinetics, as in vivo neuroimaging techniques such as positron emission tomography (► PET) have demonstrated that central kinetics do not necessarily mirror what is observed peripherally.

With certain atypical antipsychotics, variations in formulations have been marketed to ease administration and adherence. These include rapidly dissolving, oral formulations (e.g., risperidone, olanzapine), short-acting intramuscular for acute treatment (e.g., risperidone, olanzapine, ziprasidone), and longer-acting depot formulations for maintenance treatment (e.g., risperidone, administered every 2 weeks). At least some of the first generation antipsychotics had also developed shorter and longer acting injectable formulations, but the rapidly dissolving oral formulation is unique to the newer medications.

Pharmacokinetics

(see ► Antipsychotics)

Efficacy and Effectiveness

Central to antipsychotic development was the goal of more tolerable agents from the standpoint of EPS, but limitations in the efficacy of first generation antipsychotics also represented an impetus. As many as 25–30% of individuals treated with these drugs were designated treatment-resistant or refractory, with an additional subgroup deemed only partially responsive. Furthermore, these drugs, while at least reasonably effective in treating positive symptoms (e.g., ► delusions, ► hallucinations), were not particularly useful in controlling negative symptoms (e.g., amotivation, alogia).

With clozapine there was evidence that it was superior to first generation antipsychotics on both these domains, in addition to its improved EPS profile. Thus, implicit in the development of other antipsychotics that were intended to mirror clozapine was the assumption of similar clinical benefits. As the list of new agents expanded so too did the purported benefits though, with suggestions that these drugs demonstrated clinical superiority on other symptoms (e.g., cognitive, affective) and outcome measures (e.g., quality-of-life, adherence).

Initial efficacy trials generally demonstrated superiority of the different atypical agents versus a first generation antipsychotic on total clinical (e.g., Brief Psychiatric Rating Scale (BPRS), Positive and Negative Syndrome Scale (PANSS)) and positive symptoms scores, and frequently negative symptom scores as well. However, many of these efficacy studies were subsequently challenged methodologically; not only were the trials relatively short (i.e., 6–8 weeks), they often employed haloperidol as the comparator, a typical antipsychotic with notable propensity for EPS, at doses in excess of what are currently recommended.

Similarly, questions arose over claims of superior efficacy in other symptom domains. These followed two lines of thinking: (a) the magnitude of change and extent of difference between the atypical agents and first generation antipsychotics; and (b) factors underlying such changes. With regard to the former, claims regarding the extent of improvement on neuropsychological measures were tempered over time, with current thinking that at best these changes are modest and not of a magnitude that would translate to notable differences in ► functional outcome. For negative symptoms as well, subsequent evidence fostered a rethinking of how much different atypical antipsychotics were. In both cases, initial claims implicated unique aspects of these new drugs and their pharmacology (e.g., greater serotonin 5-HT_2 antagonism). However, an alternative explanation suggested that methodological issues, discussed earlier, favoring the atypicals could account for much of these differences. Further, the possibility was raised that gains could be explained, at least in part, not by what these drugs did through different receptors and systems compared to first generation antipsychotics, but by what they didn't do (i.e., invoke high and sustained

levels of dopamine D_2 binding). Evidence demonstrated that this was associated with various adverse effects beyond motor and endocrine problems (EPS and hyperprolactinemia), including dysphoria, amotivation, and cognitive impairment.

More recently, the research focus shifted from an assessment of atypical antipsychotics in the context of smaller and circumscribed efficacy trials to larger ▶ effectiveness studies thought to be more representative of "real world" clinical practice. Once again, results have suggested that differences between atypicals and first generation antipsychotics are notably smaller than once thought. They have also provided further evidence that clozapine is clinically superior, even amongst other atypicals, in treating treatment resistant schizophrenia. Of note, there is some suggestion that amongst other atypical antipsychotics there may be clinical differences, a position that has been supported through other larger scale approaches such as meta-analytic studies. As of yet, such differences are not well established, with methodological issues (e.g., dosing) making conclusions of this sort difficult (Leucht et al. 2009; Tandon et al. 2008).

Treatment Algorithms

Current guidelines advocate atypical antipsychotics as first-line treatment for schizophrenia and related psychotic conditions. There is a lack of evidence that these drugs are more effective in this population, although decreased liability for EPS, including TD, and hyperprolactinemia, in combination with improved tolerability represent advantages from the standpoint of side effects. However, the increased risk of weight gain and metabolic disturbances that can be observed with at least some of the atypicals, in conjunction with their higher cost and lack of clear clinical superiority, have more recently challenged this position.

Clozapine is generally advocated as treatment of choice following suboptimal response to two antipsychotic trials. This is in line with evidence that it is superior to all other antipsychotics in the treatment resistant population, and that treatment resistance can be seen quite soon after the illness' onset. There is no consistent evidence that combinations of antipsychotics, including those that include clozapine, offer superior clinical efficacy in individuals who have not responded to monotherapy (i.e., one antipsychotic).

Paralleling the increased number of atypical antipsychotics has been a rise in off-label use of these medications and efforts to expand their indications. Their efficacy in a variety of psychiatric disorders is being examined (e.g., ▶ pervasive developmental disorder; ▶ generalized anxiety disorder; psychotic depression), and as a result their approved indications has grown (e.g., ▶ autism; ▶ bipolar disorder, manic and mixed states), depending on agent and regulatory body.

Side Effects

As a class, the atypical antipsychotics continue to be seen as better from the standpoint of EPS, although such a distinction is less clear depending on a variety of factors that include specific agent, comparator first generation antipsychotic, and dose. Current evidence, albeit limited, does favor the atypicals as well in terms of TD risk (Correll and Schenk 2008), a significant clinical advantage should this finding hold true. There is also an indication that as a class the atypical antipsychotics might be better tolerated. While there was an expectation that such benefits would translate to improved adherence, this has not been confirmed, a reminder that non-adherence is complex and multi-factorial.

Atypical antipsychotics, to varying degrees, also share side effects that were identified with their first generation counterparts (e.g., sedation, postural hypotension). In general, the atypicals have a lower risk of hyperprolactinemia, although this is variable; risperidone, paliperidone, and the substituted benzamides carry a greater liability. There was anticipation that ▶ neuroleptic malignant syndrome (NMS), a potentially fatal adverse event that can occur with all first generation antipsychotics, would be diminished or even absent with the atypical agents; however, all of the newer drugs to date, including clozapine, appear to carry this risk and it is not yet clear as to whether the overall liability has been reduced.

Although the atypical antipsychotics appear superior from the standpoint of movement disorders, concern has been raised about their increased liability for weight gain and associated metabolic disturbances, including dyslipidemia and type 2 diabetes. This, in turn, translates to a greater risk of metabolic syndrome, cardiovascular risk and associated mortality. There is added concern because schizophrenia has already been associated with a shortened lifespan (independent of suicide) which may be related to various factors (e.g., economic, lifestyle, access to medical care). Moreover, there is some evidence to suggest that schizophrenia itself may be a risk factor for diabetes. As with EPS, the atypicals vary in risk of weight gain, with olanzapine and clozapine identified as carrying the greatest risk, while at the other end of the spectrum aripiprazole and ziprasidone have been identified as "weight neutral" (Newcomer 2007).

In the geriatric population, atypical antipsychotics have been associated with increased risk of death (in the range of 1.6 fold) from varied causes (e.g., cardiovascular, infectious). In fact, though, both typical and atypical

antipsychotics have been linked to increased mortality rates in schizophrenia (Weinmann et al. 2009). Data regarding safety and efficacy in the pediatric population are limited.

Conclusions

With clozapine as the prototype, a number of new antipsychotics have been developed. Collectively, they have been termed "atypical" and further distinguished as "second" or "third generation" antipsychotics. Atypical differentiates these drugs from their conventional counterparts based on clinical profile, specifically diminished risk of EPS, although this definition subsequently broadened to include a variety of other measures. The distinction between second and third generation antipsychotics is mechanistic, with aripiprazole (third generation) the only atypical antipsychotic to date that is a partial dopamine agonist.

The difference between these newer drugs and so-called typical antipsychotics may not be as notable as once thought, with the exception of clozapine's clinical superiority to all other antipsychotics in treatment resistant schizophrenia. Further, "atypical antipsychotics" implies a homogeneity amongst these newer drugs and separation from first generation antipsychotics that may be both misleading and confusing. There are differences between atypicals on a variety of clinical/biological measures, and even the distinction between second and third generation antipsychotics implies two distinct mechanisms of action. However, this belies the complexity of pharmacological features that may underlie clinical differences.

This said, the atypical antipsychotics represent a clinical advance and the first notable shift in schizophrenia's pharmacotherapy since chlorpromazine. Moreover, they have stimulated numerous lines of research that have substantially impacted our understanding and conceptualization of schizophrenia. The clear limitations of these medications as well in terms of clinical response and side effects, though, underscore the need for better drugs. The widespread claims of atypical antipsychotics were in keeping with a "magic bullet" approach, where a single drug could be effective across the multiple symptom domains now defining schizophrenia. However, it may well be that a multi-dimensional approach, premised on the notion that each domain reflects different pathophysiologic mechanisms, proves a more useful strategy.

Cross-References

- ▶ Atypical Antipsychotic Drugs
- ▶ Effectiveness Studies
- ▶ Extrapyramidal Motor Side Effects
- ▶ Functional Outcome
- ▶ Hyperprolactinemia
- ▶ Serotonin (5-HT)
- ▶ Tardive Dyskinesia (TD)
- ▶ Treatment Resistant Schizophrenia

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Second-Generation Anticonvulsants

Synonyms

Newer anticonvulsants

Definition

This category includes all compounds introduced after 1990.

Cross-References

- ▶ Gabapentin
- ▶ Oxcarbazepine
- ▶ Pregabalin
- ▶ Tiagabine
- ▶ Topiramate
- ▶ Zonisamide

Second-Generation Antipsychotics

Definition

Clozapine was the first medication with good antipsychotic effects and a minimal risk for ► extrapyramidal motor side effects. It is therefore considered to have started a second generation of antipsychotics. Other drugs in this category include

Cross-References

► Amisulpride
► Olanzapine
► Paliperidone
► Quetiapine
► Risperidone
► Sertindole
► Ziprasidone
► Zotepine

Second Messenger

Synonyms

Secondary messenger molecule

Definition

Intracellular substance like Ca^{2+}, cAMP, inositol phosphates, or nitric oxide, the concentration of which is controlled by the activation of membrane receptors. Second messenger production relays downstream intracellular receptor events like protein phosphorylation or neurotransmitter release.

Cross-References

► Agonist
► Antagonist
► G Protein-Coupled Receptors

Second-Order Schedules

Definition

In a second-order schedule of reinforcement, a contingency arrangement under which a series of responses under a schedule of conditioned reinforcement is treated as a unit response under a second schedule that is simultaneously in effect. For example, under a second-order fixed-ratio 10 schedule of food delivery with fixed-ratio 5 units, every fifth response produces a conditioned reinforcer (e.g., a visual stimulus) and the completion of the tenth fixed-ratio 5 units produces the conditioned reinforcer accompanied by food delivery.

Cross-References

► Operant Behavior in Animals
► Schedule of Reinforcement

Secondary Amine Tricyclic Antidepressants

Synonyms

TCAs

Definition

Secondary amine TCAs result from the metabolism of tertiary amine TCAs, during which there is loss of one methyl group on the nitrogen side chain. They include ► nortriptyline, protriptyline, and desipramine. Secondary amine TCAs are better tolerated than tertiary amine TCAs due to decreased histaminic, cholinergic, and alpha-1 adrenergic receptor blockade.

Secondary Depression in Schizophrenia

► Postpsychotic Depressive Disorder of Schizophrenia

Secondary Messenger Molecule

► Second Messenger

Secondary Reinforcer

► Conditioned Reinforcers

Secondary Reward

► Appetitive Responses

Sedative

► Minor Tranquilizer

Sedative Dependence

► Sedative, Hypnotic, and Anxiolytic Dependence

Sedative, Hypnotic, and Anxiolytic Dependence

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Synonyms

Anxiolytic dependence; Benzodiazepine dependence; Hypnotic dependence; Sedative dependence

Definition

Benzodiazepines are widely prescribed for sedative, hypnotic, and anxiolytic purposes. In this chapter, I focus on benzodiazepine dependence, although similar considerations may pertain to certain nonbenzodiazepine hypnotics (e.g., ► zolpidem, ► zopiclone), and even to ► alcohol dependence (although I will not discuss this here). Criteria for substance dependence are provided in the most recent editions of the *Diagnostic and Statistical Manual of Mental Disorders* (fourth edition-revised) (American Psychiatric Association 1994) and the *International Classification of Disease* (tenth edition) (World Health Organizaion 1992). These criteria include ► tolerance (as defined by either a need for markedly increased amounts of the substance to achieve the same clinical effect, or markedly diminished effect with continued use of the same amount of the substance), withdrawal (as defined by either the characteristic ► withdrawal syndrome for the substance, or by the same or similar substance taken to avoid withdrawal symptoms), escalation of dosage, and various features indicative of impairment (e.g., unsuccessful attempts to cut down or control substance use, time spent in activities necessary to obtain the substance, important activities are given up or reduced, continued use despite knowledge of having a problem).

Background

Benzodiazepines were introduced in the 1950s, and over subsequent decades, became widely prescribed for various psychiatric symptoms, including agitation, ► insomnia, and ► anxiety. There has long been a controversy about whether such widespread use of ► benzodiazepines is appropriate (Ashton 1989; Lader 1983). On the one hand, these agents appear to be effective for the short-term treatment of several anxiety disorders and insomnia, and are far safer than the older ► barbiturates. On the other hand, the benzodiazepines are not effective for all anxiety disorders, have important ► adverse effects, and may be difficult to withdraw. Although the nonbenzodiazepine hypnotics, or "z-drugs" (e.g., zolpidem, zopiclone) may have a more advantageous adverse event profile, similar concerns again arise (Lader 1997). The animal behavioral literature is consistent with the relevant clinical observations (Lader 1994).

Soon after the introduction of the ► selective serotonin reuptake inhibitors for depression, many of these agents received extensive study for the treatment of several anxiety disorders (► generalized anxiety disorder, ► obsessive-compulsive disorder, ► panic disorder, social phobia). These agents are effective for a broader range of anxiety disorders than are the benzodiazepines, and their robust antidepressant effects are valuable, given the high prevalence of comorbid depression in anxiety disorders. Further, they are relatively safe agents, and withdrawal is not typically problematic. Thus, they are widely advocated as the first line of pharmacotherapy for most anxiety disorders, for both acute symptoms, and for maintenance management (Bandelow et al. 2008).

Although there is clear support for the SSRIs in the treatment of anxiety disorders, there remains ongoing debate about the specific role of the benzodiazepines in these conditions. A number of studies indicate that when prescribed together with the SSRIs, the benzodiazepines may facilitate early ► efficacy and tolerability. However, by 6 or 8 weeks of treatment, no advantage is seen in patients initially co-prescribed benzodiazepines. Similarly, many clinicians would recommend benzodiazepines only in the short-term for patients with psychotic disorders, depression with anxiety, and other psychiatric disorders where acute sedation, hypnosis, or anxiolysis is useful. A number of treatment guidelines and consensus statements have emphasize that benzodiazepines should be reserved for short-term use in minimal dosage (Ashton 2005; Lader and Russell 1993).

The issue of whether medium-to-long term prescription of benzodiazepines can be appropriate under any

circumstances remains contentious. There are clinicians who argue that there is a role for long-term benzodiazepine prescription; not all patients respond to other agents such as the SSRIs. There is some evidence of the value of long-term treatment in disorders such as panic disorder, and certain features of dependence (e.g., dose escalation, tolerance) are rarely present. Although the benzodiazepines may not be highly robust antidepressants, they may have some antidepressant effects. However, some authors emphasize the significant adverse events associated with benzodiazepines (with no change over time in cognitive impairment or vulnerability to accidents), argue that long-term prescription inevitably leads to benzodiazepine dependence (with inefficacy and impairment), and conclude that there is rarely a place for such treatments.

Given the availability of the SSRIs for anxiety disorders, and of a range of treatment options for insomnia, it is reasonable to be cautious about medium-to-long-term prescription of benzodiazepines. Certainly, both clinicians and patients should be aware of the associated adverse effects, and the potential difficulties of withdrawal. Particular caution is required in certain populations (e.g., the elderly and those with a prior history of substance dependence). Although dose escalation is not very common, and although there are perhaps patients in whom long-term use of benzodiazepines is useful, given data that benzodiazepine discontinuation is associated with psychiatric and cognitive improvements, it may be useful to consider benzodiazepine withdrawal at regular intervals in those who are on longer-term treatment (Ashton 2005; Lader and Russell 1993).

Role of Pharmacotherapy

The pharmacological mechanisms underlying benzodiazepine tolerance and withdrawal have received considerable study, and may include both desensitization of inhibitory ► GABA receptors and sensitization of excitatory glutamatergic receptors. Benzodiazepine withdrawal symptoms include symptoms of anxiety states (e.g., anxiety, insomnia, ► dysphoria), as well as a range of other characteristic symptoms (e.g., perceptual distortions, depersonalization, confusion). Withdrawal symptoms may be somewhat different in younger patients, and relevant scales have been developed specifically for this population.

As above, some authors have emphasized that few patients on long-term dependence show tolerance, that not all meet criteria for dependence, and that, in some cases, long-term treatment is needed for chronic symptoms. Nevertheless, given data that reduction of benzodiazepines is accompanied by decreased psychiatric and cognitive symptoms, it also seems reasonable to consider benzodiazepine discontinuation in those who are taking it long-term. Certainly, tapering of benzodiazepines is indicated when there are concerns about cognitive impairment or other adverse effects of long-term benzodiazepines, when there is loss of efficacy, or where there is recreational abuse and dependence. Several strategies are useful for encouraging such benzodiazepine withdrawal.

First, gradual dose tapering is important. Rapid tapering can precipitate benzodiazepine withdrawal symptoms, including the more severe ones (e.g., convulsions, psychotic symptoms, ► delirium). A reasonable approach may be to decrease the dose by around one tenth every 1–2 weeks. There has been surprisingly little work comparing different withdrawal regimens (Lader et al. 2009). Thus, a reasonable approach is to individualize the withdrawal regimen; while some patients may be able to discontinue benzodiazepines over 6–8 weeks, others may require many months.

Second, switching to a benzodiazepine with a longer half-life prior to tapering may be useful. This may be particularly necessary in patients using high potency benzodiazepines (e.g., ► lorazepam, ► alprazolam), where trials indicate a higher drop-out rate during attempts at discontinuation (Voshaar et al. 2006). Diazepam, for example, has a slow elimination, allowing a gradual fall in blood concentration. Furthermore, it is available in low dosage forms, including liquid formulations, which allows gradual tapering. Equivalent doses of diazepam can be determined for each of the benzodiazepines.

Third, psychological support can be useful. A range of simple interventions, including clinical audit, information sheets, letter from the GP, reminder cards, or brief consultations have been shown to be effective in controlled studies (Lader et al. 2009). Similarly, elements of cognitive-behavioral therapy, such as psychoeducation and providing support, appear important. Furthermore, CBT may address comorbid disorders, and may be particularly useful in preventing relapse. Patients with high-dose benzodiazepine abuse may require more intensive management, including hospitalization.

Fourth, treatment with concurrent psychotropics may be considered. ► Anticonvulsants, ► antidepressants, ► beta-blockers, ► buspirone, ► flumazenil, and ► gabapentin have all been investigated. A Cochrane review suggested that only ► carbamazepine was useful in assisting in benzodiazepine discontinuation (Denis et al. 2006). However, the available data are insufficient to suggest routine

administration of this agent in benzodiazepine withdrawal. Antidepressants may be useful for pre-existing or emergent comorbid depression.

In general, a stepped approach, beginning with simple interventions, and then proceeding to more intensive ones is appropriate when attempting benzodiazepine discontinuation (Lader et al. 2009). There is a growing database of information about predictors of response to attempts to discontinue benzodiazepines, which may be useful in guiding future interventions (Mol et al. 2007). In the interim, however, it is reassuring to note the relative success of benzodiazepine discontinuation, and the positive effects that this has for many patients.

Cross-References

► Benzodiazepines
► Selective Serotonin Reuptake Inhibitors

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Sedative–Hypnotics

► Barbiturates
► Benzodiazepines
► Meprobamate
► Non-Benzodiazepine Agonists

Selective Association

Definition

Selective association refers to the fact that not all classically conditioned associations can be acquired. Specifically, animals appear better able to associate specific stimuli, for example, tastes and toxicosis, than others, for example, audiovisual cues and toxicosis. These selective associations are thought to be shaped by evolution and to prepare animals for the acquisition of stimulus associations important for survival.

Selective Attention

Definition

This is the cognitive process by which we can select certain things in the environment to concentrate on, for example, a specific object, specific spatial location, a category of objects etc. and ignore others.

Cross-References

► Attention

Selective Breeding

Definition

Selective breeding occurs when individual animals with specific behavioral (or anatomical or physiologic) traits are bred with animals with similar characteristics. The traits selected are extremes (such as high responders or low responders in a specified task) and are determined by some criterion of deviation from the group mean (e.g., behaviors that are two standard deviations above or below the mean).

Selective Learning

► Blocking, Overshadowing and Related Concepts

Selective Noradrenergic Reuptake Inhibitors

► NARI Antidepressants

Selective Serotonin Reuptake Inhibitors

Synonyms

SSRIs

Definition

Selective serotonin reuptake inhibitors (SSRIs) are a group of antidepressants that selectively inhibit the reuptake of serotonin into the presynaptic cell. This leads to an increased concentration of serotonin available to bind to postsynaptic receptors. Before the introduction of the SSRIs, the pharmacologic treatment of depression was mainly based on ► tricyclic antidepressants that inhibit the reuptake of serotonin and noradrenaline into the presynaptic cell.

Cross-References

► SSRIs and Related Compounds

Selegiline

Synonyms

L-deprenyl; Eldepryl; Emsam patch; Zelapar

Definition

Selegiline or L-deprenyl is a phenylethylamine, specifically (*R*)-*N*-methyl-*N*-(1-phenylpropan-2-yl)prop-2-yn-1-amine. It is an antidepressant that selectively inhibits the enzyme monoamine oxidase (MAO), preferentially the type B isoenzyme in the recommended low doses. Unlike other MAOIs, selegiline is less likely to interact adversely with the consumption of tyramine-containing food, the so-called cheese reaction. In 2006, the FDA approved this compound for the treatment of major depression in the form of a transdermal patch (Emsam Patch). It is most often used in the treatment of ► Parkinson's disease in interaction with L-DOPA.

The side effects of selegiline are similar to those of amphetamine-like stimulants and may comprise cardiovascular, respiratory, motor, and perceptual problems.

Cross-References

► Antidepressants
► Monoamine Oxidase Inhibitors

Self-Administration of Drugs

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Synonyms

Drug seeking; Drug taking; Self-injection

Definition

"Self-administration" is an experimental technique which gives subjects, to some extent, control over the ingestion of a drug. In essence, the method is an ► operant conditioning procedure in which drug delivery is made contingent on a particular response emitted by the subject. A variety of species have been tested in self-administration procedures including human; however, the vast majority of published self-administration studies have examined oral or intravenous drug intake in rats or nonhuman primates. Self-administration techniques are used to study the reinforcing effects and underlying neurobiology of different classes of reinforcing drugs, to evaluate ► abuse liability of specific agents and to model the addiction process.

Impact of Psychoactive Drugs

History

There was a time when human intelligence was considered an essential requirement for the voluntary ingestion of drugs of abuse, such as ► heroin or ► cocaine. Given this bias, it was considered unlikely that any animal would self-administer psychoactive drugs.

In one of the earliest reports to challenge the prevailing dogma that drug addiction was exclusively a human condition. Spragg (1940) reported that chimpanzees would "work intentionally" to receive a ► morphine injection. The chimps received daily injections of morphine until there was clear evidence that ► physical dependence had developed (i.e., the appearance of withdrawal signs when the drug was withheld). Spragg then showed that chimps would engage in a sequence of responses that resulted in a morphine injection. If the animal were drug deprived, it would select the correct "key" (a colored wooden stick), turn, walk to a particular box, open it with the key, remove a syringe containing morphine and hand it to the investigator who would deliver an intramuscular injection of morphine. When not drug-deprived the

chimp would select a different key which provided access to food inside a different box.

Spragg wrote

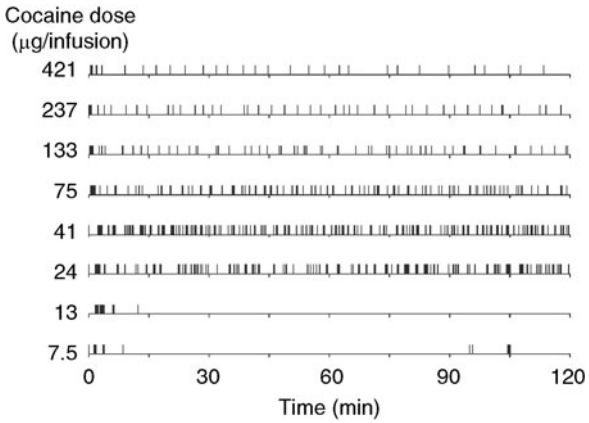
> ...since morphine addiction seems to depend essentially upon forming an association between the administration of the drug and the alleviation of withdrawal symptoms, and since this sequence involves a time lag of 10–15 min or more, the value of using subjects high enough in the phyletic scale to be able to make a delayed association of this nature is obvious. By this token, animals such as the rat, for example, could probably never become addicted to morphine, simply because they are not capable of forming associations of this order... (p 126)

The quote illustrates two important presumptions of the early literature. The first is the notion that drug taking is phylogenetically biased toward primates and the second is that ► physical dependence is a necessary precondition of drug self-administration in animals. These assumptions went unchallenged for two decades.

Weeks (1962) of the Upjohn Company published a seminal paper which marked the beginning of modern self-administration studies. By combining operant conditioning techniques, a pump mechanism that delivered precise amount of drug and a chronically indwelling jugular catheter that allowed animals to move freely within a cage, Weeks demonstrated that rats learned to respond on a lever which resulted in the delivery of an intravenous injection of morphine. Clearly rats were capable of making the correct associations and were able to self-administer morphine. Weeks' initial demonstration used animals that were first made physically dependent. Later, however, it was shown that physical dependence was not a necessary precondition for drug self-administration. Readers are referred to the 1978 NIDA Monograph No. 20, Self-Administration of Abused Substances: Methods for Study (http://www.drugabuse.gov/pdf/monographs/20.pdf) for a collection of reviews which summarize the foundational work in the field.

Patterns of Intake

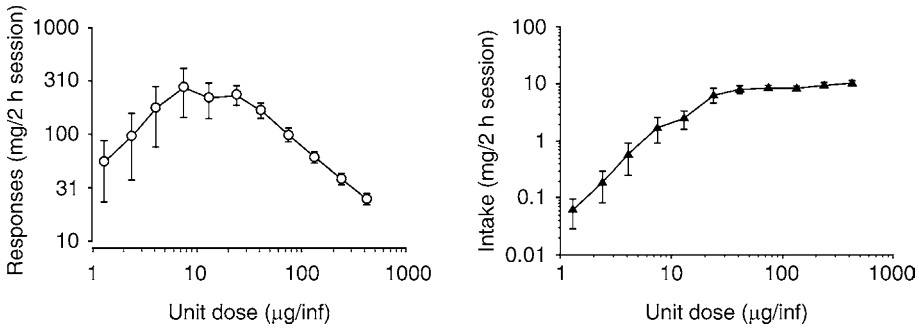
The pattern of drug self-administration depends on the pharmacological class of the drug as well as experimental factors such as dose, price, and availability. Figure 1 shows the pattern of ► cocaine self-administration in a rat using the most basic schedule, a ► Fixed Ratio 1 (FR1). Note the brief burst of responding in the first few minutes of the session; for the remainder of the session the interval between each injection is relatively consistent. As the unit dose is reduced, the number of self-administered injections increase within the 2-h session until, at some point, the dose no longer supports sustained responding (bottom two event records). This dose–response relationship for a group of animals is shown in Fig. 2 (*left*). The gradual ascending limb apparent to the left of the apex is an artifact of averaging across a group of animals and does not reflect the fact that the behavior of an individual animal shows an abrupt change from a non-reinforcing to a threshold reinforcing dose (see Fig. 1). To the right of the apex is a descending limb with a very small variance surrounding the mean rate at each dose. Figure 2 (*right*) shows the same data plotted according to total drug intake during the session. This graph illustrates that above some threshold dose animals tend to self-administer similar amounts or show a slight increase in intake at each supra-threshold doses.



Self-Administration of Drugs. Fig. 1. Examples of a rat self-administering various doses of cocaine on an FR1 schedule. Each line is an event record of a daily 2 h session with each injection indicated by an *upward* tick. The unit dose for each daily session is indicated to the *left*. The figure illustrates that (above some threshold) lower doses are self-administered more frequently.

Appetitive Versus Consummatory Responses

It is important to distinguish between two related concepts in drug self-administration: appetitive versus consummatory responses. A consummatory response is determined by the route of administration. For example, the consummatory response for ► alcohol might involve opening a bottle and drinking from it. For smoking tobacco or ► crack cocaine, it is the act of preparing and lighting a cigarette or pipe and inhaling the smoke. For intravenous drug use, it is filling the syringe and injecting the drug into a vein. Such consummatory behaviors can become extremely ritualistic and powerful habits.



Self-Administration of Drugs. Fig. 2. The effect of manipulating dose on rate of responding (*left*) and total intake (*right*) for a group of rats. Each rat in the group was implanted with an IV catheter and trained to self-administer cocaine. Each animal was then tested using a descending series of doses as illustrated in Fig. 1. The graph on the *left* illustrates that above a mean threshold dose (apex) the rate of self-administration deceases as the unit injection dose is increased. The graph on the *right* illustrates that in spite of the decrease in the number of injections self-administered, the amount consumed within a session increased gradually with dose (Oleson and Roberts 2009).

By contrast, appetitive responses serve to make the drug available. In humans, appetitive responses might involve working for money to buy the alcohol, tobacco product, or drug; in a laboratory situation it could be pressing on a lever and completing a response requirement. The difference between appetitive and consummatory responses is relatively straightforward in humans; however, the distinction becomes blurred in animals receiving drug via intravenous catheters. The appetitive response is obvious – animals can be shown to work quite hard to receive an injection. But since the drug is infused automatically via a catheter the consummatory act is harder to define. It might be argued the consummatory act is the last response on the lever prior to the injection. With that being the case, the single operant response on an FR1 schedule is both appetitive and consummatory.

Schedules will be reviewed below which attempt to address separately the appetitive and motivational factors which influence drug seeking. For the moment it is assumed that responding on an FR1 is largely consummatory and that the rate and pattern of responding reflects the preferred level of consumption.

Factors Affecting Drug Consumption

The pattern shown in Fig. 1 has been taken as evidence that animals regulate (or titrate) their intake around some preferred blood or brain level. The early burst is a "loading phase," during which blood levels of cocaine increase presumably to a preferred plateau. The subsequent regular pattern reflects a maintenance phase with each post-infusion pause determined by the ► half-life of the unit injection dose. Longer acting drugs, such as ► amphetamine, produce longer post-infusion pauses.

Independent variables such as session length and timeout periods can dramatically affect the daily pattern and rates of consumption. An examination of these factors illustrates the qualitative differences between stimulant and opiate drug use. Subjects given 24 h/day access to cocaine or other stimulant drugs on an FR1 schedule tend to "► binge" for many hours or days. It is unclear what actually terminates a binge; however, animals generally do not eat or sleep during this period so that a deterioration of their physical health probably contributes. A drug binge inevitably resumes after some recuperative drug-abstinence period. Unlimited access to stimulant drugs, therefore, results in a series of binge–abstinence cycles. Toxic effects can accumulate with repeated cycles resulting in an increased likelihood of convulsions. The probability of lethal overdose is extremely high virtually for all psychostimulants tested including cocaine, amphetamine, and ► methamphetamine. This is true for every species tested. By contrast, unlimited access to ► opiates results in a very different outcome. Heroin and morphine intake is relatively circadian rather than binge-like. Drug intake increases gradually over days as ► tolerance and physical dependence develops. The danger of lethal overdose is far less for opiates than for stimulants. Instead, a severe withdrawal reaction during experimenter-imposed opiate deprivation becomes a concern.

Any examination of extended access to stimulant drugs must necessarily limit intake in some fashion to avoid toxicity. The majority of cocaine and amphetamine studies constrain intake by restricting the daily session to 1 or 2 h a day. This produces a very consistent pattern of intake from day to day. Longer sessions (6 h) have been shown to produce an escalation of intake across days

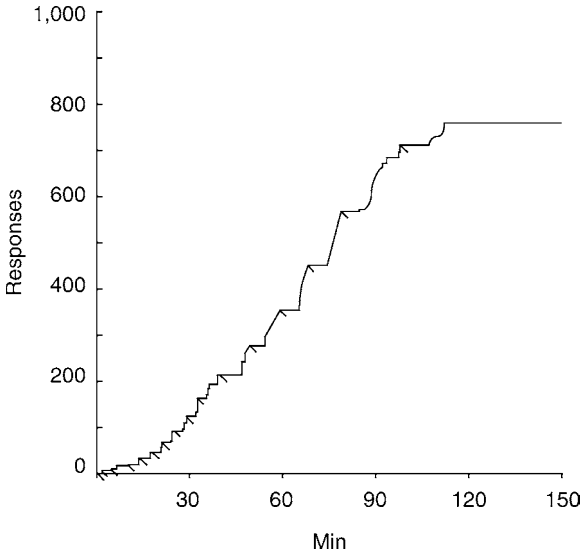
(Ahmed and Koob 1998), modeling an important aspect of the addiction process. Another method of constraining daily drug intake is to restrict the number of injections offered each hour. For example, four discrete trials per hour effectively restrict hourly intake (and the danger of drug overdose or toxicity), while permitting round-the-clock access to drug. When the number of trials and the dose is chosen so as to cap cocaine intake at 3 mg/kg/h, self-administration generally becomes restricted to the active part of the light–dark cycle and will remain circadian over many weeks (Roberts et al. 2002). Binge–abstinence cycles (without lethality) are engendered by higher hourly access (7.5 mg/kg/h).

Factors Influencing Appetitive Responding

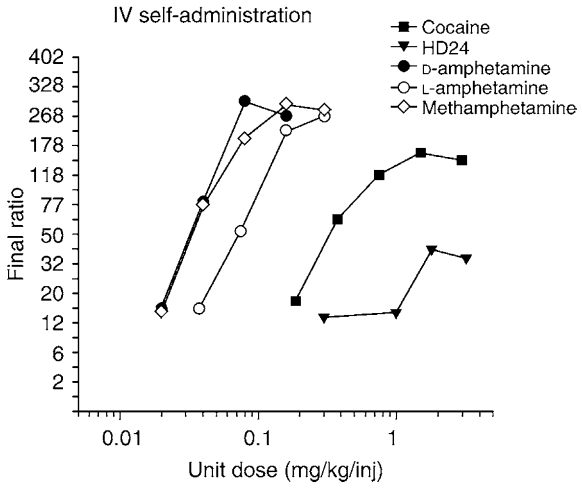
A variety of ► schedules of reinforcement have been used in order to directly address appetitive responding. It is important to recognize that different drug classes can have potent direct effects on rates of responding; therefore, once the first injection is delivered the response rates are "contaminated" by having the drug on board. ► Second order schedules have provided a useful method to circumvent this problem. A second order schedule, for example [FR5 (FR10:S)], might have an initial component wherein every tenth response results in the delivery of a stimulus light; completion of five of these components results in the delivery of the stimulus light and a drug injection. Relatively high rates of responding over prolonged periods can be maintained prior to the delivery of the first drug injection. Second order schedules have demonstrated that stimuli associated with drug injections can become potent ► conditioned reinforcers and brief presentations of these stimuli can effectively maintain drug seeking behavior. Second order schedules have been particularly useful in evaluating pharmacological treatments for drug addictions in nonhuman primates and for evaluating the neural mechanism in rats (Schindler et al. 2002). There has been a recent trend for an appetitive and consummatory phase to be formally incorporated into an experimental design. A second order schedule might be used in the initial phase of the session. Completion of the second order requirement then results in access to drugs, perhaps on an FR1. The two phases are designed to assess "drug seeking" versus "drug taking."

Choice procedures offer another way of assessing reinforcing efficacy of a drug. Typically, a subject is offered a choice between a particular dose of drug and a nondrug reinforcer such as food. Such methods, together with an assessment using ► drug discrimination techniques, have been used to evaluate abuse liability. Drugs that are abused by humans are almost invariably self-administered by rats and nonhuman primates, indicating self-administration procedures provide a good predictor of abuse liability for new therapeutic agents being considered for the clinical market (Bergman and Paronis 2006).

The ► progressive ratio (PR) schedule has been used extensively to assess the reinforcing strength of a variety of drugs. The distinguishing feature of the PR schedule is that the response requirements increase following the delivery of each reinforcement. In a typical self-administration study in rats, the first injection "costs" only one response, but with each injection the response requirement escalates through an exponential series (1, 2, 4, 6, 9, 12, 15, 20, 32, 40, 50, 62, 77, 95, 118, 145, 178, 219, 268, 328, 226 402, 492, 603). Studies in nonhuman primates have used the same or similar series except that the initial ratio often begins at 50. Figure 3 shows a cumulative record from a session in which a rat was self-administering cocaine on a PR schedule. Note that at some point in the session responding ceases. The last completed ratio (termed a ► breakpoint) is considered an index of the reinforcing value.



Self-Administration of Drugs. Fig. 3. A cumulative record illustrating the response pattern of a rat self-administering cocaine on a progressive ratio schedule. *Upward* movements of the record represent responses; *downward* angle ticks indicate a drug injection. The first response resulted in an injection. The response requirements for subsequent injections escalated through an exponential series. In this case, the animal self-administered 16 injections. The final ratio was 145.



Self-Administration of Drugs. Fig. 4. Graph shows the dose–response relationship in rats for a variety of drugs self-administered on a PR schedule. Groups of rats were first trained to self-administer cocaine. Various doses of test drug were then evaluated. The dependent measure was the final ratio (or breakpoint). HD24 is an experimental tropane compound synthesized by Dr. H. M. L. Davies. Note that the selected drugs have a range of reinforcing efficacies and potencies.

Figure 4 shows the dose–response curves for several different stimulant drugs. Higher unit doses are associated with higher breakpoints. The large range of breakpoints across various drugs suggests a wide spectrum of reinforcing efficacies.

Whether responding is measured while drug is on board is a critical theoretical issue. In some cases, it is imperative that drug seeking be measured in a drug-free state. However, it has become clear that blood levels of drug can greatly affect responding and in fact may be one of the most important factors which drives further drug taking once it has started. In this context, it is important to emphasize that the breakpoint on a PR schedule measures the motivation to continue a binge and not necessarily the motivation to start a binge.

In the past decade there has been a pronounced increase in the number of studies examining "relapse" to drug taking. In relapse experiments, animals are tested either in a drug-free state or under the influence of an experimenter delivered drug. Typically rats are trained to self-administer (e.g., cocaine or heroin) and in many cases, responding is then extinguished. The effect of a ▶ priming drug injection or ▶ conditioned stimuli are then assessed on lever responding. The term relapse is perhaps a misnomer, since animals do not self-administer during these test sessions; however, the procedure has provided a robust model to examine important influences on drug seeking. It has been shown that conditioned stimuli, ▶ stress, or a priming injection of drug can reinstate responding (Shaham et al. 2003).

Another important trend in the self-administration literature has been the application of behavioral economic principles. The theoretical constructs of supply, demand, consumption, and price have been usefully applied to the analysis of drug intake. Price can be manipulated by changing the response requirement for a fixed unit dose of drug. Alternatively, the response ratio can be fixed (e.g., FR1) and the unit injection dose reduced as might occur in an assessment of threshold (illustrated in Fig. 1). Either way the theoretical issues are the same. A behavioral economic analysis of the relationship between consumption and price offers a relatively new way of assessing reinforcing strength (Hursh 2000).

As stated previously, the majority of self-administration studies have used the intravenous route of administration. Studies of alcohol intake have quite naturally used the oral route. Rodents are generally reluctant to drink alcohol without some encouragement. ▶ Schedule-induced polydipsia has been used to induce higher levels of alcohol intake. Similarly, intake can be increased by sweetening the alcohol solutions. After a reasonable intake level has been established then the sweetener is faded out over days. The neurobiology of both appetitive and consummatory aspects of alcohol intake is currently being assessed in rodent studies through analysis of different strains, knockout mice, and through ▶ selective breeding programs for alcohol preferring animals.

Intragastric, inhalation, intraventricular, and intracerebral routes have all been used in self-administration experiments. The ▶ pharmacokinetics of each route is different; the rate of drug delivery to the brain necessarily affects the reinforcing efficacy.

Self-administration by the intracrerebral route is a special case which offers a unique perspective on brain circuitry involved in drug reinforcement. Since the first report by Olds et al. (1964) there have been about 50 papers describing self-administration of drugs into various brain regions. Interestingly, nondrugs of abuse have been reported to support operant responding. Because drugs are introduced directly into circumscribed brain regions, they can have a purely local effect which is quite different from a systemic injection. For example, Liu and Ikemoto (2007) have shown that muscimol (a $GABA_A$ agonist which would produce local inhibition) is self-administered into the median raphe nucleus. By contrast, picrotoxin (a $GABA_A$ antagonist which would produce neuronal

disinhibition) is self-administered into the ▶ ventral tegmental area. Thus, the brain region (and presumably the local circuit) determines whether a drug has a reinforcing effect. Note that, neither muscimol nor picrotoxin is self-administered when offered systemically.

Cross-References

▶ Abuse Liability Evaluation
▶ Behavioral Economics
▶ Cocaine
▶ Cocaine Dependence
▶ Inhalant and Solvent Abuse
▶ Nicotine
▶ Opioids
▶ Psychomotor Stimulant Abuse
▶ Psychomotor Stimulants
▶ Reinstatement of Drug Self-Administration
▶ Withdrawal Syndromes

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Self-Control Failure

▶ Impulsivity

Self-Destructive Behavior

▶ Suicide

Self-Immolation

▶ Suicide

Self-Injection

▶ Self-Administration of Drugs

Self-Monitoring

Definition

Self-monitoring is the ability to recognize that actions such as inner speech are initiated by the self.

Semantic Memory

Definition

Our memory for language, concepts, and facts about the world.

Sensitive Delusion of Reference

▶ Delusional Disorder

Sensitization

Synonyms

Reverse tolerance

Definition

Sensitization, in relation to ▶ Pavlovian conditioning, is an incremental change in the response to a stimulus in the absence of any associated contingency. In psychopharmacology, sensitization is more frequently used as the name

for the progressive enhancement of an ► unconditioned response to a drug when it is administered on two or more occasions. It regularly occurs with ► psychostimulant and ► opioid drugs and is believed to involve enhanced function of dopaminergic neurons projecting from the ► ventral tegmental area to the ► nucleus accumbens.

Sensitization to Drugs

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Synonyms

Behavioral augmentation; Behavioral facilitation; Behavioral sensitization; Reverse tolerance

Definition

The word "sensitization" is used to refer to a number of different, but related effects. For example, in immunology, sensitization refers to the hypersensitivity to an antigen (often an allergen) that can develop upon repeated exposure to the antigen. In the study of learning, sensitization refers to a form of nonassociative learning whereby exposure to a stimulus (an ► unconditional stimulus, US) increases subsequent responsiveness to the same or other stimuli, even though they were not explicitly paired. Similarly, in pharmacology, the word sensitization has come to refer to an increase in a drug effect upon successive exposures to a drug, or, hypersensitivity to a drug in animals that were exposed to the drug in the past (Fig. 1). For example, one unconditional effect of drugs such as ► amphetamine or ► cocaine is to produce *psychomotor activation*, often measured as an increase in forward locomotion. Under some circumstances, the repeated administration of ► psychostimulant drugs results in a progressive increase in this drug effect, whereby successive injections of the same dose produce greater and greater psychomotor activation. Furthermore, exposure to one drug (e.g., amphetamine) can also render animals hypersensitive to the locomotor activating effects of other drugs (e.g., cocaine or ► morphine). When exposure to one drug (or another stimulus, such as ► stress) renders an animal hypersensitive to another drug or stimulus, this is called "cross-sensitization" (Kalivas and Barnes 1988; Robinson and Becker 1986; Stewart and Badiani 1993).

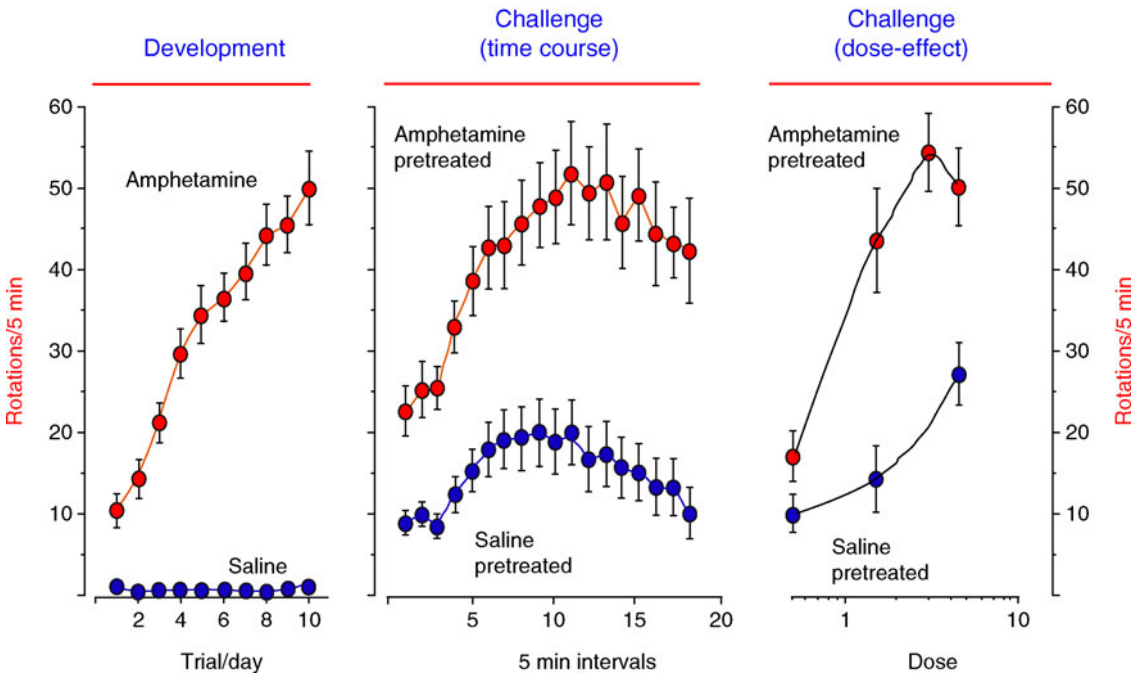
Impact of Psychoactive Drugs

Behavioral Sensitization

By itself, with no adjective, the word sensitization provides no information about the nature of the drug effect that is changed or about the underlying mechanisms. Indeed, it is not very useful to refer to "drug sensitization" or to just say an animal is "sensitized," because sensitization (or tolerance) does not develop to the drug itself. Specific drug *effects* show sensitization or tolerance. Drugs produce many different effects, and with repeated administration some effects may show sensitization while at the same time other effects show ► tolerance and yet others do not change. In fact, the same drug effect may show tolerance or sensitization depending on the conditions under which the drug is administered (e.g., if it is given continuously or intermittently – intermittent injections favor sensitization). Thus, an animal that is "sensitized" may also be "tolerant" – depending on which drug effect is under consideration.

It is important to ask, therefore, which effects of drugs tend to show sensitization, and under what conditions is sensitization induced and expressed. Most studies on sensitization involve some behavioral measure, and if a behavioral effect of a drug increases with repeated drug administration, this may be called *behavioral sensitization* (Fig. 1). In other studies, a neurobiological effect of a drug may be measured, and if increased by prior drug exposure, this may be referred to as *neural sensitization*, although again, these terms provide no information about the exact effect that is changed. Therefore, unless one wants to just refer to the general phenomenon, it is best to use terms that convey information about the specific drug effect under study, because most of them are dissociable.

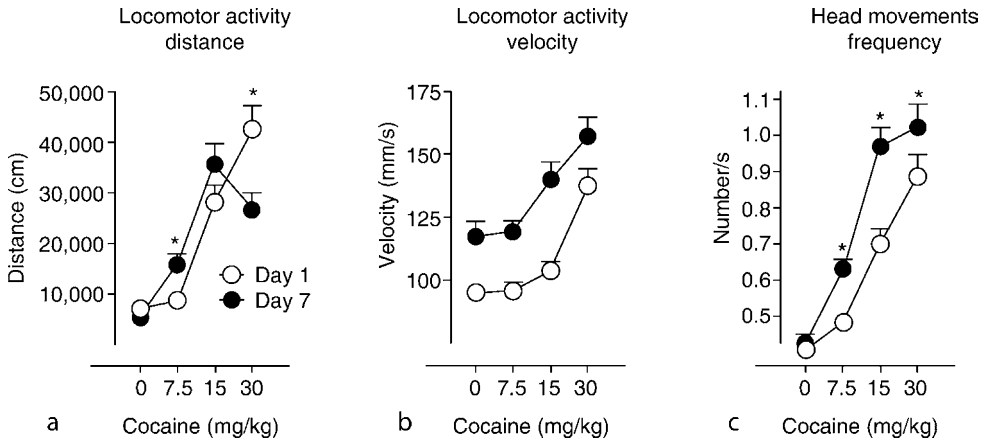
In many studies of behavioral sensitization, the drug effect measured is a psychomotor effect (*psychomotor sensitization*; Fig. 1 and 2). But the psychomotor-activating effects of drugs represent a very complex set of different behaviors, and they can compete with one another, making the accurate assessment of psychomotor effects a complicated endeavor (Flagel and Robinson 2007; Robinson and Becker 1986). The most frequent psychomotor effect studied involves some measure of locomotor activity (e.g., beam breaks, crossovers, distance traveled, etc.). To the extent that locomotor activity increases with repeated drug administration, this can be called *locomotor* sensitization. But drugs can produce many other psychomotor effects, including complex patterns of repetitive motor actions (stereotyped behaviors), including rearing, head movements, limb movements, sniffing, oral



Sensitization to Drugs. Fig. 1. An illustration of the different ways of viewing psychomotor sensitization. The specific behavior quantified is amphetamine-induced rotational behavior in rats with a unilateral 6-OHDA lesion. The dose-effect function for this behavior is linear over a much wider range of doses than for locomotor activity (see Fig. 2). *Left panel: a within-subjects* measure of sensitization, in which rats were given an injection of 3 mg/kg of D-amphetamine (or saline) once every 3–4 days for a total of ten injections. Amphetamine produced more and more rotational behavior ("psychomotor activation") with successive injections, whereas the response to saline did not change. The increase in behavioral effect is called behavioral or psychomotor sensitization. *Middle panel: a between-subjects* measure of sensitization, in which rats that were previously treated with saline or amphetamine both received a challenge injection of amphetamine (1.5 mg/kg). The behavioral response in rats that previously received ten injections of amphetamine (left panel) is much greater than in those that previously received saline, and the magnitude of the group difference indicates the degree of sensitization. *Right panel: dose-effect analysis*, in which rats previously treated as in the left panel received a challenge injection with different doses of amphetamine. In this case the degree of sensitization is indicated by the magnitude of the shift to the left in the dose-effect function. (Data are from Anagnostaras S, Robinson TE (1996) Sensitization to the psychomotor stimulant effects of amphetamine: modulation by associative learning. Behav Neurosci 110:1397–1414).

movements (licking and biting), rotational behavior, etc. Which psychomotor effect dominates behavior depends on many factors, including the drug, dose, the test environment, the time after drug administration, and many others. For example, in animals previously exposed to amphetamine a subsequent injection may initially increase locomotor activity, which then decreases and is replaced by complex patterns of stereotyped behaviors performed "in place," and then this followed by the re-emergence of locomotor hyperactivity ("post-stereotypy hyperactivity"). What is critical to realize is that each of these different psychomotor effects can be dissociated, and they do not all change uniformly as a function of repeated drug treatment (see Fig. 2). Repeated drug administration does not have the same effect on each of these behaviors, presumably in part because they are mediated by different neural systems that are changing in different ways, and in part because of the competitive relationship between different behaviors.

For this reason, negative findings can be very difficult to interpret in studies of sensitization. If a given manipulation is reported to not produce, or to prevent the expression of "sensitization" – one must immediately ask – by what measure? It could be that the manipulation influenced the induction or expression of locomotor sensitization, but had no effect on some other measure of psychomotor sensitization, or on other psychological processes that undergo sensitization (see below). Or, it could



Sensitization to Drugs. Fig. 2. Different measures of psychomotor activation in a within-subjects study of behavioral sensitization. On the first day of treatment, rats were given three injections of cocaine in ascending doses (0, 7.5, 15, and 30 mg/kg), with 45 min between each treatment. For the next 6 days, they received one injection of 15 mg/kg each day. Then, on the seventh day they again received multiple doses, as on day 1. The graph show three different behavioral measures on day 1 and day 7 of testing, obtained from video. *Panel A* shows a measure of locomotion (distance traveled in cm). Between day 1 and 7 the animals showed an increase in locomotor activity when given 7.5 mg/kg, no change when given 15 mg/kg, and a decrease in locomotor activity when given 30 mg/kg. This highlights the complexity of the dose-effect function when using locomotor activity as a measure of psychomotor activation (compare with Fig. 1). For example, under the conditions of this study, if only a dose of 15 mg/kg were used, one would conclude that the animals did not sensitize. However, other measures of psychomotor activation reveal robust sensitization. *Panel B* shows the average velocity of each bout of locomotion, and there is a large effect of repeated drug treatment on this measure (the effect at a dose of zero also reveals a conditioned effect not evident in the distance traveled). *Panel C* shows the average frequency of head movements, and again this measure reveals robust psychomotor sensitization, at all doses. These data illustrate the importance of using multiple measures of psychomotor activity in studies of sensitization, especially if negative findings are obtained. (Data are from Flagel and Robinson 2007).

be that the measure of locomotion was not the most appropriate measure under the conditions of the study. For example, repeated exposure to cocaine may have no influence on one measure of locomotion, such as distance traveled, while at the same time dramatically increasing the velocity of each individual bout of locomotion and the frequency of stereotyped head movements (Flagel and Robinson 2007; Fig. 2). Thus, the apparent absence of locomotor sensitization may not allow one to conclude no effect on "sensitization," but only on one behavioral measure. Unfortunately, in many studies only one measure is provided making it nearly impossible to interpret negative results.

It is also important to remember that many other behavioral effects of drugs can sensitize, besides just psychomotor effects. Other behaviors that have been reported to sensitize include acoustic ▶ startle, drinking behavior, lick rate, discriminative effects, and the disrupting effect of amphetamine on ▶ latent inhibition and ▶ selective attention, to name a few (Badiani and Robinson 2009; Kalivas and Barnes 1988; Robinson and Becker 1986; Stewart and Badiani 1993). In humans the psychotomimetic effects of psychostimulant drugs also sensitize (Featherstone et al. 2007; Robinson and Becker 1986). In addition, there is considerable evidence that repeated exposure to a variety of drugs of abuse increases some aspect of their rewarding or incentive motivational effects (Vezina and Leyton 2009). Repeated exposure to a number of potentially addictive drugs facilitates the later acquisition of ▶ drug self-administration behavior and a ▶ conditioned place preference, facilitates the learning of S-R habits, increases motivation for drug based on performance on a ▶ progressive ratio schedule and running in an alley, and increases the incentive salience attributed to stimuli associated with drug and nondrug rewards. This latter form of sensitization – *incentive sensitization* – may be especially important in the development of addiction because it may result in people being maladaptively attracted to drugs and cues associated with drugs, thus instigating and maintaining drug-seeking behavior even when there is a desire to remain abstinent (Robinson and Berridge 2008).

Neural Sensitization

Presumably the reason that so many different behaviors and psychological functions can be sensitized by repeated exposure to drugs is that drugs change many different neural systems, neural systems that mediate the behaviors and psychological functions that sensitize (Thomas et al. 2008). Many studies of neural sensitization have focused on ► mesotelencephalic dopamine systems, and a number of sensitization-related changes in dopamine systems have been described, including an increase in stimulated dopamine release and striatal D2 receptors (Robinson and Becker 1986; Robinson and Berridge 2008). However, sensitization-related changes have been described in nearly every neurotransmitter system within the relevant mesencephalic-striatal-amygdala-cortical circuitry, including glutamate, GABA, serotonin, acetylcholine, norepinephrine, etc. systems, and in a host of intracellular ► signaling cascades. Indeed, sensitization has been associated with changes in patterns of synaptic connectivity in these circuits, suggesting a level of reorganization that may fundamentally and persistently change their operation. Despite considerable research on neural sensitization, cause-effect relations are not well understood. What changes in what neural systems are causally-related to what changes in behavior and psychological function remains a topic of active investigation.

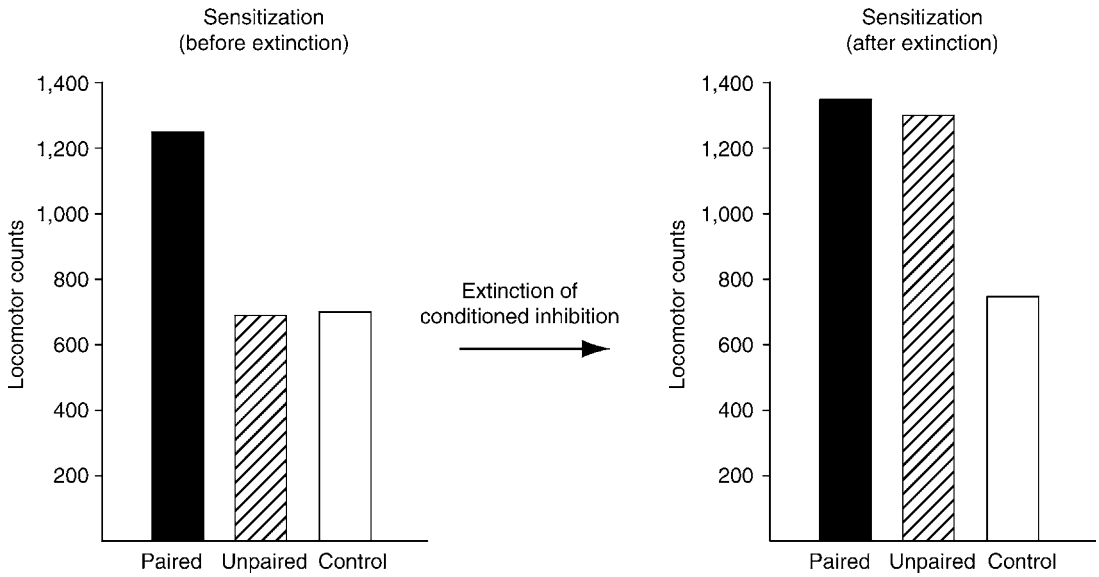
The Induction Versus the Expression of Sensitization

Most major drugs of abuse are capable of inducing sensitization, including psychostimulants (amphetamine, cocaine, ► MDMA, cathinone, fencamfamine, ► methylphenidate, phenylethylamine, etc.), opiates, ► phencyclidine, ► alcohol, and ► nicotine. Direct agonists that act on the D2 receptor also produce robust psychomotor sensitization, although it is not clear the mechanism is the same as with ► drugs of abuse, which influence dopaminergic activity indirectly. In addition, repeated intermittent exposure to stress can produce cross-sensitization to drugs, and vice versa (Kalivas and Barnes 1988; Stewart and Badiani 1993).

For some drugs it is thought that an action at the level of dopamine cell bodies in the midbrain is necessary to induce sensitization. However, once induced, sensitization may be expressed by drug actions in structures that receive dopaminergic inputs (Vezina and Leyton 2009). Whatever the case, one remarkable feature of sensitization is that, once induced, it can persist for very long periods of time in the absence of any further exposure to the drug – for weeks, months, or years. The persistence of sensitization depends on many factors, including the drug, the dose, the number of exposures, and the pattern of exposure. Furthermore, sensitization can be induced when a drug is administered by an experimenter, or when it is self-administered, including when it is self-administered under conditions that promote the development of symptoms of addiction (i.e., under extended access conditions).

Modulation of Induction and Expression

Although the repeated, intermittent administration of a number of drugs of abuse may produce sensitization, it is important to emphasize that there are a host of factors that modulate both the induction and expression of sensitization. Whether a given dose of a drug *induces* sensitization, or how robust the effect, is dependent on many factors beside dose and the treatment regimen, including, the strain of the animal, its sex (females generally sensitize more), hormonal status, past experience with ► stress, age, the rate of drug delivery (faster rates produce greater sensitization), and the context in which the drug is administered, amongst others (Badiani and Robinson 2009; Kalivas and Barnes 1988). Indeed, there are large individual differences in susceptibility to sensitization. After neural sensitization is induced there are also a number of factors that determine if it is *expressed* in behavior at any particular place or time. For example, when an animal that has developed psychomotor sensitization is re-exposed to drug in a context where it has never before experienced drug, sensitization may not be expressed in behavior (this is so-called context-specific sensitization; Fig. 3). Exactly, how contextual factors modulate the expression of sensitization is not well understood. The available data suggest that contexts *not* associated with drugs may act to actively inhibit expression, perhaps through a kind of inhibitory ► occasion-setting type mechanism. This is because specific ► extinction procedures and ECS can "release" this inhibition so that sensitization is now expressed in a nondrug context (Stewart and Badiani 1993; Vezina and Leyton 2009; Fig. 3). Of course, drug-associated contexts can also elicit drug-like conditioned responses that may add to sensitization effects, but this kind of conditioned response appears to be a different process than contextual modulation of sensitization. Indeed, it may be misleading to speak of "context-specific sensitization" versus "context-independent sensitization" as if they represent two different forms of sensitization. It appears there is one form of sensitization, a nonassociative increase in responsiveness to various stimuli because of changes in the relevant neural systems. However, the *expression* of sensitization can be powerfully modulated by associative learning, and if it is,



Sensitization to Drugs. Fig. 3. Context-specificity of sensitization (adapted from Vezina and Leyton 2009). Paired rats received amphetamine in the test environment on one day and saline in the home cage (or somewhere else) the following day. Unpaired animals were subjected to the opposite configuration while Control animals received saline in both environments. After repeated treatments, all animals were then administered a challenge injection of the drug in the test environment to assess the expression of sensitization. The results on the left illustrate that sensitization was only expressed in Paired animals. Rats that received the same number of drug injections but explicitly Unpaired with the test environment showed levels of responding similar to animals receiving the drug for the first time (controls). Evidence that this is due to Conditioned Inhibition of the expression of sensitization in Unpaired rats comes from the finding that after these rats were subjected to a procedure known to extinguish Conditioned Inhibition (but spare conditioned excitation), they now expressed sensitization (right panel). This suggests that the failure of unpaired animals to express sensitization in the first test was due to some form of conditioned inhibition (see Vezina and Leyton 2009 for further discussion).

sensitization may be expressed only under specific conditions. How contextual factors (and other stimuli) modulate the expression of sensitization is an important (but little investigated) topic, because of the potential importance of such factors in relapse. Addicts are much more prone to ► relapse in contexts associated with drugs than in other contexts. This may be related not only to the ability of drug-associated contexts to evoke conditioned responses, which is well-documented, but also because context can gate the expression of sensitization. Thus, conditions that promote the expression of neural sensitization in behavior may also promote relapse, whereas conditions that inhibit the expression of sensitization may inhibit the propensity to relapse. For this reason a better understanding of factors that modulate the induction and expression of sensitization (especially incentive sensitization) may prove useful in developing treatments for addiction (Robinson and Berridge 2008; Stewart and Badiani 1993; Vezina and Leyton 2009).

Sensitization in Humans

By necessity, most research on sensitization has involved preclinical studies in nonhuman animals. However, it is worth noting that similar effects have been described in humans (Leyton 2007). As mentioned above, it has long been recognized that the psychotomimetic effects of psychostimulant drugs sensitize, as does their ability to produce complex stereotyped behavioral patterns (in humans this is called "punding"). Indeed, sensitization of psychotomimetic effects has been interpreted as involving sensitization of incentive salience, whereby otherwise innocuous stimuli in the environment acquire pathological importance (Featherstone et al. 2007). In addition, there are now a number of reports that repeated exposure to amphetamine induces both behavioral sensitization (e.g., increased eye-blink responses, vigor, and energy ratings), and neural sensitization (e.g., an increase in evoked dopamine "release" as indicated by raclopride displacement). Finally, as in nonhuman animals, the expression of

sensitization in humans appears to be highly modulated by the context under which drugs are experienced (Leyton 2007; Robinson and Berridge 2008; Vezina and Leyton 2009).

In conclusion, the sensitization produced by repeated exposure to many drugs of abuse turns out to be a very complex form of neurobehavioral plasticity that can alter many different neural systems, and thus be manifest as a change in many different behaviors and psychological processes. Some of these changes may be related to why, in addicts, drugs and drug-associated stimuli come to acquire such inordinate control over behavior (Robinson and Berridge 2008).

Cross-References

► Psychomotor Stimulants
► Substance Use Disorders (Including Addictions)
► Tolerance

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Sensorimotor Behavior

Definition

Motor responses that immediately follow sensory stimulation.

Sensorimotor Gating

► Prepulse Inhibition

Sensory Gating

► Prepulse Inhibition

Sentient

Definition

The ability of an organism to perceive or feel things. Sentient animals have higher-order nervous systems and behaviors.

Separated

► Independents

Separation Calls

► Distress Vocalization

Serazide

► Benserazide

Serotonin

Synonyms

5-HT; 5-Hydroxytryptamine

Definition

A monoamine (► indoleamine) neurotransmitter found in the brain, ► platelets, and the gastrointestinal tract. Serotonin is synthesized from the amino acid ► tryptophan, and is involved in a wide range of behavioral, physiological, and cognitive functions, including mood, emotion, appetite, sleep, memory, temperature

regulation, platelet aggregation, vascular tone, intestinal secretion, peristalsis, and bone metabolism. Serotonin is well known for its role in psychiatric and behavioral disorders such as ► depression, ► anxiety, ► obsessive compulsive disorders, ► eating disorders, and ► addiction. This neurotransmitter may also be involved in physiological disorders such as irritable bowel syndrome and cardiac arrhythmias. The actions of serotonin (5-HT) are mediated through at least 16 receptor subtypes grouped into seven families (5-HT_1–5-HT_7) according to their structural and functional characteristics, and include 13 distinct ► G-protein-coupled receptors, coupled to various effector systems, and three ligand-gated ion channels (the 5-HT_3 receptors). The drugs targeting the 5-HT system that are in the widest clinical are the selective serotonin reuptake inhibitors that are used for the treatment of depression and other disorders.

Cross-References

► Antidepressants
► Anxiety
► Depression
► Monoamine
► Neurotransmitter
► Obsessive Compulsive Disorder
► SSRIs and Related Compounds

Serotonin Antidepressants

► SSRIs and Related Compounds

Serotonin-Norepinephrine Reuptake Inhibitors

► SNRI Antidepressants

Serotonin Syndrome

Definition

Serotonin syndrome is the result of an excessive amount of serotonin in the brain, usually the consequence of a drug interaction or overdose, and is potentially fatal. Symptoms range from mild to severe, and include cognitive (confusion, agitation, ► hallucinations), autonomic (changes in temperature, tachycardia, nausea), and somatic effects (tremor, clonus).

Cross-References

► Monoamine Oxidase Inhibitors
► SSRIs and Related Compounds

Serotonin Transporter

Definition

A presynaptic membrane protein that transports the neurotransmitter ► serotonin from the synapse back into the presynaptic neuron, thereby "recycling" serotonin.

Seroxat

► Paroxetine

Sertindole

Definition

Sertindole is a second-generation antipsychotic that acts as a dopamine D2 and serotonin 5-HT_{2A} antagonist. A phenylindole derivative, sertindole has been reintroduced as a second-line drug treatment after it had been voluntary withdrawn from the market because of concerns over cardiac arrhythmias and sudden deaths. However, the risk for cardiovascular mortality was found not to differ from that by other atypical antipsychotics, while it may be useful for patients in whom other antipsychotics have failed. Sertindole also lacks the sedative properties inherent to many other antipsychotic drugs. However, ECG monitoring is required before and during the treatment.

Cross-References

► Antipsychotic Drugs
► Future of Antipsychotic Medication
► Schizophrenia
► Second- and Third-Generation Antipsychotics

Sertraline

Definition

Sertraline is a naphthalenamine derivative and acts as a ► selective serotonin reuptake inhibitor (SSRI) that is used as an antidepressant. Its effects are mostly typical for the class of SSRIs, sharing their therapeutic effects and side-effects although some studies have found a particularly favorable balance between benefits, acceptability, and cost. A recent systematic review and meta-analysis found evidence favoring sertraline over several other antidepressants for the acute phase treatment of ► major depression. Among side effects, there was a higher rate of diarrhea with sertraline than some other SSRIs. It is absorbed slowly after oral administration and there are several metabolites including N-desmethyl-sertraline, which has weak pharmacological activity. The elimination half-life is in the range of 22–36 h. Sertraline has little inhibitory effect on the ► cytochrome P450 enzymes, with the result that interactions with other drugs are less likely than with some other SSRIs.

Cross-References

► Antidepressants

Setiptiline Maleate

Definition

Setiptiline Maleate is a tetracyclic antidepressant that has been used in the treatment of depression. It has antihistamine and hypnotic–sedative effects, but almost no ► anticholinergic effects. It is a weak inhibitor of norepinephrine reuptake *in vitro* and strongly stimulates the release of central ► norepinephrine by blocking presynaptic α_2-adrenoceptors similar to mianserin. It also acts as a 5-HT_{2A}, 5-HT_{2C}, and 5-HT_3 receptor antagonist. Unlike most conventional antidepressants, it has no efficacy as a serotonin reuptake inhibitor. It can induce drowsiness and thirst, but it displays low toxicity.

Cross-References

► Depression
► Mianserin
► Tetracyclic Antidepressant

Set-Shifting Test

► Wisconsin Card Sorting Test

Sex Differences in Drug Effects

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Synonyms

Gender differences; Sexual dimorphism

Definition

In the 2001 National Academy of Sciences report (Exploring the Biological Contributions to Human Health: Does Sex Matter?) *sex* is defined as "the classification of living things, generally as male or female according to their reproductive organs and functions assigned by their chromosomal complement, and *gender* as a person's self-representation as male or female, or how that person is responded to by social institutions on the basis of the individual's gender presentation." The term "sex differences" is used to explain biological differences between males and females while "gender differences" imply differential effects of social and cultural milieu on males and females; in other words, gender can be considered as a psychosocial construct. In nonhuman animal research, "sex differences" is the preferred term. Because of the complex interplay between biological and environmental factors, it is hard to define a clear-cut distinction between sex- or gender-based differences between males and females. Furthermore, recent findings from ► epigenetic research show that the biological factors are influenced by the environment. In either case, there is a variation in the characteristic associated with either the male or female sex. Morphological characteristics or features that are different in males and females of the same species are referred to as "sexual dimorphism" (two forms).

Sex differences are not limited to reproductive function and endocrine systems, but are also observed in brain and behavior. As a result of these distinctive features between males and females, their biological responses to drugs are not the same.

Current Concepts and State of Knowledge

Until recently, women were excluded from many experiments with drugs, and, therefore, information about appropriate treatment of diseases and reactions to drug therapy was based on studies conducted only on men. Without systematic research, it was assumed that sex

differences in responses to drugs might be attributed to differences in height, weight and hormones. The exclusion of women from drug trials was, in part, the result of the thalidomide tragedy of the 1950s. Subsequently, in 1977 FDA recommended that women of childbearing potential be excluded from drug research. It was assumed that studies conducted in adult males could be extrapolated to other patient populations, including women, children, and the elderly. For example, a 1989 study, excluding women, suggested the use of aspirin as the first-line treatment of cardiovascular disease, but in 1992 two studies showed that the benefits of aspirin were greater in men than in women. In 1993, the FDA withdrew the rule against including women of childbearing potential in clinical trials and went forward to ensure that women were included in all future drug research. The newer studies reveal that drug researchers are showing increased awareness of gender specific responses to drugs and are including more women in clinical trials.

The chemical structure and dose of a drug are important factors in producing the expected effects, but the actual amount of drug which binds to its target sites, in other words ▶ bioavailability, is critical. The primary target site for ▶ psychoactive drugs is the brain. Dynamic factors (e.g., absorption, distribution, metabolism, and excretion) that determine the bioavailability of a drug (▶ pharmacokinetics) are not the same in males and females. Gastric acid secretion and gastrointestinal blood flow are lower and gastric emptying time is longer in women; on average, women weigh less and have a higher percentage of body fat; activity of enzymes that metabolize drugs are sexually dimorphic; women have a lower glomerular filtration rate and a lower creatinine clearance compared with men.

The composition of the body, more specifically the ratio of fat and water, is an important factor in determining the plasma levels of a drug and in females the adipose tissue is more and the water content is less than in males. Therefore, as the proportion of water is smaller in females than males, the same dose of a drug would be expected to result in a higher blood level in females than males; subsequently, more concentrated drug levels would result in greater effects in females, even if the dose was corrected for body weight. On the other hand, because there is more adipose tissue in a women's body (approximately 25%) and most of the ▶ antipsychotic drugs are ▶ lipophilic, some antipsychotic drugs may accumulate in the adipose tissue and result in extended bioavailability in women. The endocrine milieu of women is much more variable than that of men; the gonadal (▶ Gonad) hormones fluctuate during the menstrual cycle, pregnancy, postpartum period, lactation, menopause, and while using oral contraceptives. Ovarian hormones have substantial modulatory roles on central neurotransmission. In case of a challenge such as an epileptic seizure, the permeability of the ▶ blood brain barrier is slightly elevated in females compared to males. This difference may impact the rate of drug entry to the brain and result in a stronger effect. Drug metabolism is another factor where sex differences are observed. Liver is the major site of drug inactivation and sexual dimorphisms in the liver may partly account for different metabolism of drugs in women and men. Sex-specific differences in enzyme activity can lead to sex differences in drug response. For example, women wake from general anesthesia several minutes before a man, given an equivalent dose. Gastric enzymes which metabolize ▶ alcohol before it reaches the bloodstream are weaker in women than men, thereby after ingesting similar amount of alcohol, women will have higher blood concentrations than men. Several ▶ cytochrome P450 isoenzymes are responsible for the metabolism of many drugs. For example, certain cytochromes which break down ▶ nicotine to its inactive metabolites are significantly higher in women than men and higher metabolism is related to nicotine dependence.

Although the ▶ activational effects of ▶ sex hormones cannot fully account for all sex differences observed in the adult brain, and though many sex differences persist in the absence of these hormones, they have a substantial impact on brain, behavior, and response to drugs. Ovarian hormones affect ▶ pharmacokinetics properties of a variety of drugs. Changes in the menstrual cycle are related to differential ▶ absorption and bioavailability of certain drugs. Gastric emptying is slower during the luteal phase of the menstrual cycle compared to the follicular phase. Gastrointestinal transit time is prolonged during the luteal phase compared to the follicular phase, allowing for greater drug absorption. Sodium retention, water content, and urinary volume may also vary with the menstrual cycle in women and influence the distribution of drugs.

Overall, rates of side effects to most drugs are reported to be higher in women than in men and sex differences in drug metabolism may be involved in these adverse reactions. Additionally, increasing age, polypharmacy, liver and renal disease may have sexually dimorphic impacts on side effects.

Dopaminergic System

Central dopaminergic systems are the target of many psychoactive drugs, including abused substances. Males and females differ in the functioning of the dopaminergic system and therefore, sex differences are observed in response to drugs which act primarily through this system.

► Dopamine neurotransmission mediates the reinforcing effects (reward system) of ► drugs of abuse and may underlie neuropsychiatric disorders such as ► schizophrenia, ► Parkinson's disease, and ► attention deficit disorder, where sex differences have been reported in incidence, prevalence, clinical course, and treatment outcome. Addiction to some abused ► psychostimulants such as ► cocaine and nicotine is more severe in women, the age of onset of schizophrenia is later in women than men and the prevalence of Parkinson's disease is lower in women than men. Sex differences in the baseline activity of the dopaminergic system may underlie these observed differences as well as responses to dopaminergic drugs.

Dopamine release and uptake rates, which regulate extracellular dopamine levels, are higher in females than males in some brain regions such as the striatum. Women have higher levels of ► dopamine transporters in the striatum, lower striatal dopamine D2 receptor affinity and higher dopamine 2 (D2) receptor levels in the frontal cortex compared to men; this may result in elevated levels of dopamine in these brain regions in women. In fact, postmortem and neuroimaging studies in human subjects suggest that dopamine release in women is higher relative to men. In human subjects, d-amphetamine-induced dopamine release in striatal and extrastriatal regions is higher in women suggesting sex differences in cognitive function and sensation-seeking behavior. The decline observed in DA receptor levels with age is also slower in women than men. In rats, indirect dopamine agonists like ► cocaine, which block the dopamine transporter, induce greater behavioral and neuroendocrine effects in females than males. Female rats acquire self-administration of cocaine faster than males. Responses to direct acting dopamine D2 ligands display sex differences with females being more sensitive than males.

Ovarian hormones underlie some, but not all sex differences observed in drug abuse, suggesting qualitative and quantitative sexual dimorphisms in neural systems. Estrogen enhances the response to the psychomotor stimulants ► amphetamine or cocaine; this effect is observed both during estrogen replacement following ovariectomy and during the estrus phase of the estrus cycle in rats.

In studies on rodents, estrogen is reported to increase dopamine synthesis, and baseline dopamine release in the striatum, and to increase neuronal firing in substantia nigra. Estrogen inhibits gamma-aminobutyrate (► GABA) neurons in the striatum and accumbens, which subsequently increase dopaminergic activity. Another established effect of estrogens is the down regulation of dopamine receptors. Dopaminergic transmission varies with estrous cycle phase. For example, amphetamine-stimulated dopamine release is greatest during the estrus phase of the cycle, a time when the behavioral response is also greatest. Estrogen plays an important role in modulating sex differences in neurochemical responses to ► psychomotor stimulants.

► Stress, negative mood, and exposure to drug-related cues predict relapse in cocaine dependence. The effect of stress is more significantly associated with relapse in women and drug cues in men. Estrogen and progesterone have opposite effects on behavioral responses to cocaine, while the former increases the effects, the latter decrease it and the effects are more pronounced in females than males. Stress and cocaine enhance the stress response, mainly through the ► corticotrophin releasing factor (CRF) and central noradrenergic pathways, both of which activate the mesolimbic dopaminergic systems involved in the rewarding effects of cocaine. Progesterone also plays a key role in stress regulation and D2 receptor function, which results in an increase of DA release. On the other hand, in male rats, the density of dopamine D1 receptors is higher than in female rats in the ► nucleus accumbens, a brain region implicated in reward.

Sex differences observed in behavioral responses to one drug cannot be generalized to all behaviors because neurobiological mechanisms controlling different behaviors can be dissociated. For example, in rats, while the locomotor responses to amphetamine and ► methamphetamine show sex differences with females being more sensitive than males, no sex differences are reported for conditioned place preference. Alternatively, sex differences are observed in responses to nicotine both in locomotor activity and in ► conditioned place preference, albeit in different directions: The effect of nicotine on locomotion is more pronounced in females, but unlike males, females do not show nicotine induced place preference. Similar to nicotine, ► LSD induces place preference in male but not in female rats. On the other hand, female rats are reported to be more sensitive to the conditioning effect of cocaine.

► Sensitization of behaviors such as rotation, stereotyped grooming, head bobs, and forelimb movements observed following chronic exposure to ► psychostimulants is greater in female rats than in males.

Methamphetamine, another abused drug like cocaine, increases dopamine levels in some brain regions but through different mechanisms: while cocaine blocks reuptake, methamphetamine induces release from nerve terminals. The sex differences observed in the effects of methamphetamine are similar to cocaine: Females are more sensitive to the locomotor activating effects, but the effect gradually declines with repeated treatment in rats.

Drug Abuse

Until recently, preclinical (► Addictive disorder: animal models) and clinical research on drug abuse has been conducted mainly on male subjects. Drug abuse was generally accepted as a male problem and males were thought to be more vulnerable to drug abuse (► abuse liability evaluation). However, this view did not take into consideration the opportunity for use. There is growing evidence that points to sex differences the effects of abused drugs. Biological and environmental predictors of drug use such as ► depression, conduct disorder, physical and sexual abuse, prenatal drug exposure, and family dysfunction affect males and females differently. Therefore, treatment strategies that are effective in one sex may not be equally successful in the other. Sex differences in sensitivity to abused drugs and in drug self-administration is also observed in laboratory animals, and during different stages of the addiction process (i.e., acquisition, maintenance, and relapse). Females appear to be more vulnerable than males to the reinforcing effects of psychostimulants, ► opiates, and nicotine as revealed by their behavioral, neurological, and pharmacological responses to these drugs. Women take less time to progress to dependence (tobacco, ► caffeine, alcohol, ► cannabinoids, opiates, ► sedatives, cocaine, inhalants, amphetamine, ► hallucinogens, and ► phencyclidine) than men. Furthermore, in many cases, women appear to be more sensitive to the adverse health effects of drugs than men, pointing to the importance of developing gender-specific prevention and treatment programs in drug-related health problems. Methamphetamine (► amphetamine derivative) abuse may be an exception. It is reported that women begin to use methamphetamine at their earlier ages, and appear to be more dependent, but also they also respond better to treatment than men do. In women, use of methamphetamine is associated with depression, suggesting a type of self-medication.

Epidemiological studies indicate that during adulthood, men outnumber women in using illicit substances (except prescription medications), alcohol and tobacco, and that men are more likely to have a ► drug abuse/dependence disorder or an alcohol use disorder than women. However, this gender difference in prevalence is not observed among adolescents; in fact, some studies point to a slightly higher prevalence of smoking among girls than boys. Nonetheless, ► alcohol abuse and dependence is higher in males than females at all age groups.

Women are more sensitive to the physiological effects of alcohol than men, have higher blood levels following similar doses of alcohol and report feeling more intoxicated. However, negative mood-induced craving for alcohol is greater in women than men.

Following different routes of cocaine intake, women detect the subjective effects of cocaine later than men and report less euphoria and dysphoria, but feel more "nervous" compared to men. Women show greater reactivity than men to cocaine-related cues and the ► craving during abstinence is significantly higher in women.

Women have greater vulnerability for smoking-related diseases (specifically myocardial infarction and lung cancer) than men, but are less successful in quitting smoking. Men benefit from nicotine replacement therapy more than women. Studies on rodents point to similar sex differences, suggesting the involvement of underlying sexual dimorphisms in biology. Females may take a shorter time to become dependent than males, they make fewer quit attempts and can stay abstinent for shorter periods than males; the rate of relapse is higher in females than males. Sexually dimorphic pharmacokinetics that causes variance in blood/brain levels of nicotine or the effects of gonadal hormones may underlie some of the sex differences observed in nicotine/tobacco addiction.

There are established sex-dependent differences in ► opiate reward. Female rats are more sensitive to the rewarding effects of ► morphine, and work more than males to self-administer morphine, and acquire conditioned place preference at lower doses than males. Additionally, there are also sex-related differences in the effect of morphine on locomotor activity, cardiovascular system, temperature, stimulus discrimination, ► physical dependence, and analgesia.

The cyto-architecture of male and female brains is not the same; for example, the dendritic arborization in the anterior cingulate cortex, implicated in craving, is greater in male rats than in females. ► Psychoactive drugs modify the action of various neurotransmitter systems at the cellular and molecular levels and impact synaptic structure and function. There are clearly established sex differences in the action of neurotransmitters, with specific characteristic. The organizational and ► activational effects of ► gonadal hormones underlie some of the sex differences in brain and behavior. Since sex steroids, and especially estrogens, modify the binding of ligands to their receptor sites, sex differences in the action of pharmaceuticals deserve attention.

Antipsychotics

The response and end-organ sensitivity to antipsychotic treatment, similar to other drugs, are influenced by genetics, age, height, weight, lean–fat ratio, diet, exercise, concurrent disease, smoking and alcohol, and the

administration of concomitant drugs. There are sex differences in all of these factors and taken together, these factors are estimated to contribute to a tenfold variability in responses to medication.

Sex differences in response to ► antipsychotic agents have been reported in both animals and humans. In drug-naive subjects, response to antipsychotic drugs is reported to be superior in women. In chronically ill patients with ► schizophrenia or related psychoses, men require twice as high a dose as women for effective maintenance. Recommendations for prescribing antipsychotic medication to women include using lower doses for women than men, longer intervals for women when depot doses are used, and careful modulation of drug dose in aging women. In general, schizophrenic women have higher degree of symptom improvement, but also of ► extrapyramidal symptoms.

Until recently, women have been underrepresented in clinical trials of ► second generation antipsychotics, and therefore, there are limited data on possible sex differences in drug efficacy and side effects. A main reason for this underrepresentation was the fear of potential ► teratogenicity. Currently, sex-specific analysis of efficacy and safety data is a requirement and therefore an increasing number of studies are now available concerning sex differences in pharmacokinetics or ► pharmacodynamics of second generation antipsychotics.

There are reported sex differences in pharmacokinetics for second generation antipsychotics ► clozapine, ► olanzapine and ► sertindole, and CYP1A2 activity has been implicated in these differences. Women have higher plasma levels of all these second generation antipsychotics than men. On the other hand, no sex differences were observed for ► quetiapine. However, as the studies involve relatively small number of patients, larger samples are required before generalizations can be made on sex differences in responses to novel antipsychotics.

Recent reports suggest that women on olanzapine have a significantly better treatment response than men, and premenopausal women have a better treatment response than postmenopausal women. Overall, schizophrenic women under 40 years of age require lower antipsychotic doses than men regarding both acute response and maintenance.

Because of important side effects of antipsychotic medication, regular monitoring of weight gain and body mass index, plasma glucose level, lipid profiles, signs of prolactin elevation and ► hyperprolactinemia, or sexual dysfunction are recommended. Cardiac side effects and extrapyramidal symptoms should be considered as well. However, despite established sex differences in response to antipsychotic medication, these effects do not receive much emphasis in prescribing these drugs to men or women. Women, perhaps because of the influence of sex hormones, have a lower risk of sudden cardiac death, but a higher risk of acquired ► long QT syndrome from antiarrhythmic drugs. Estrogens may facilitate bradycardia-induced prolongation of the QT interval. Patent antipsychotic drugs were likely to block cardiac voltage-gated potassium channels, prolong the QT interval, and result in ventricular arrhythmias. Subsequently, women may be at a higher risk of cardiac side effects of antipsychotic medication. Older antipsychotics like ► butyrophenone and ► phenothiazine derivatives, and some of the second generation antipsychotics elevate prolactin levels (hyperprolactinemia) and result in sexual dysfunction, which in turn results in non-compliance with treatment, particularly in men. In the long run, hyperprolactinemia also causes galactorrhoea, amenorrhea, breast engorgement, and osteoporosis. In women, the elevation of prolactin concentrations is generally noted to be higher than in men. On the other hand, ► aripiprazole which has a different profile from second generation antipsychotics by being a partial D2 receptor agonist is reported to lower prolactin levels.

Antidepressants

Although, the prevelance of major depression is twice as much in women than men, sex differences observed in ► antidepressant medication is not overwhelming. Women experience more vegetative and atypical symptoms, ► anxiety, and anger than men, and report higher severity of depression on self-report measures; however, no significant sex differences are observed in the course of the illness and treatment response. The efficacy of ► bupropion and ► selective serotonin reuptake inhibitors (► SSRI), appear to be equally effective in treating depression, anxious/somatic symptoms, and ► insomnia; there is a slight sex difference as greater improvement was seen in women during SSRI treatment regarding anxious/somatic symptoms of depression. Additionally, the efficacy of antidepressants is more pronounced in younger patients. On the other hand, a recent study suggests that women with ► generalized anxiety disorder, particularly those with a later age of onset, may have a poorer response to the SSRI ► fluoxetine compared to men. Although women have higher plasma levels than men, no sex differences are reported in response to ► tricyclic antidepressants.

Analgesics

Pain management by pharmacotherapy is another important medical problem where sex differences are noted. Furthermore, there may be gender differences in pain

tolerance. Women report suffering from migraine and arthritis, more intensely than men do. Men have a better response to non-steroidal anti-inflammatory analgesics (NSAIDS) than women, and women benefit more from narcotics than men do. Therefore, over-the-counter analgesics do not help women as much as men, and lower doses of narcotics which are effective on women are not as effective on men.

Males and females respond differently to drugs acting at ▶ opioid receptors; these quantitative and qualitative differences are not restricted to the ▶ analgesic and antinociceptive properties of opioids, but are also present in opioid-induced side effects (i.e., effects on respiration, locomotor activity, learning/memory, addiction, and cardiovascular system). However, the direction and magnitude of sex differences regarding the potency of opioids depend on the interacting variables which are specific to the drug (i.e., dose, pharmacokinetics and pharmacodynamics, route and time of administration) or to the subject (i.e., species, type of pain, genetics, age, gonadal/hormonal status, and psychological factors). The differential organizational and/or ▶ activational effects of gonadal steroid hormones in males versus females have received emphasis in explaining sex differences in opioid antinociception. There are sex differences in response to drugs acting on ▶ kappa-opioid receptors: Women respond more robustly than men to ▶ kappa-opioid agonists and antagonists with analgesic and hyperalgesic properties, respectively. When drugs acting at different receptors are compared, women have better pain scores with kappa-opioid agonists (butorphanol) than mu-opioid agonists (morphine). However, rodent data from laboratory pain models contrast with human data.

Conclusion

Recent studies on both animals and humans clearly indicate that many normal physiological and pathological functions are influenced by sex-based differences in biology, either directly or indirectly. Males and females are not only different regarding reproductive function, but sex differences exist in brain and behavior, including emotion, memory, vision, hearing, processing faces, pain perception, navigation, neurotransmitter levels, stress hormone action on the brain, and disease states. Sexual dimorphisms are observed in many neurotransmitter systems, including monoamines, serotonin, GABA (gama-aminobutyric acid), acetylcholine, vasopressin, and opioids. Furthermore, dynamic factors that influence the bioavailability of drugs, body composition, gastrointestinal, renal and liver function, hormonal status, and activity of enzymes involved in drug metabolism, are not the same in males and females. Subsequently, it is clear that there are sex and gender differences in response to neuropsychopharmacological treatments. Sex is an important variable that should be considered when designing and analyzing studies in all areas of biomedical and health related research.

Cross-References

▶ Abuse Liability Evaluation
▶ Addictive Disorder: Animal Models
▶ Alcohol Abuse and Dependence
▶ Analgesics
▶ Antidepressants
▶ Antipsychotic Drugs
▶ Blood-Brain Barrier
▶ Caffeine
▶ Cannabinoids and Endocannabinoids
▶ Cocaine
▶ Conditioned Place Preference and Aversion
▶ Epigenetics
▶ Hallucinogens
▶ Inhalant and Solvent Abuse
▶ Insomnias
▶ Nicotine
▶ Opioids
▶ Pharmacokinetics
▶ Psychomotor Stimulants (Psychostimulants)
▶ Schizophrenia
▶ Second and Third Generation Antipsychotics
▶ Sedative, Hypnotic, and Anxiolytic Dependence
▶ Sensitization to Drugs
▶ Sex Hormones
▶ SSRIs and Related Compounds

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Sex Hormones

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Synonyms

Gonadal hormones

Definition

The brains of mammals are sexually dimorphic due to the actions of testosterone and estradiol during sensitive periods of development. Additionally, males and females produce different sex ► hormones, so the circulating hormonal milieu is also sexually dimorphic. The ► gonadal hormones act in the brain at both intracellular and membrane receptors to induce changes in brain and behavior. One of the things that the ovarian hormones, estradiol and progesterone, do is modulate the response to cocaine and amphetamine by acting at membrane receptors in the striatum and nucleus accumbens. These effects of the ovarian hormones result in sex differences in the behavioral responses to these drugs. While ► androgens are reinforcing in their own right, they do not seem to modulate the behavioral response to cocaine or amphetamine.

Pharmacological Properties

Background

The brains of mammals undergo sexual differentiation during sensitive periods of development. In rodents, this occurs during the perinatal period and again during the peripubertal period. In humans, this occurs during the second trimester and, then again, during the peripubertal period. Exposure to testosterone (which is converted to estradiol in some areas of the brain) during early brain development influences neuronal survival, differentiation, and connectivity. During the peripubertal period, less is known about the extent of hormonal influences, but neuronal and dendritic pruning, as well as neuronal reorganization, are thought to occur when the brain is exposed to ovarian or testicular hormones at the onset of puberty. As a result of these periods of hormone exposure, the brains of adult males and females are sexually dimorphic (Becker et al. 2005, 2008).

In concert with the sexual dimorphisms caused by the processes involved in sexual differentiation, there may also be sex differences in brain function produced in response to exposure to gonadal hormones in the adult. This second type of sex difference can be either due to the effects of gonadal hormones acting on sexually dimorphic brain regions or as a result of the different effects induced by ovarian versus testicular hormones, which in some neural regions may decrease differences between the sexes.

Gonadal hormones are by definition sexually dimorphic, since males have testes that produce androgens and females have ovaries that produce ► estrogens and ► progestins. They are also dimorphic in their patterns of secretion. Testicular hormones are secreted in a tonic pattern, and feedback of testosterone to the brain maintains the rate of pituitary hormone secretion that sustains a constant rate of spermatogeneisis in the testes. Ovarian hormones are released in a cyclic manner. First, estradiol is released gradually during the development of the follicle that nourishes the development of the egg (follicular phase). Then, a rapid increase in estradiol induces the hormonal trigger to induce ovulation (periovulatory phase). Finally, in some species, estradiol and progesterone are released to prepare the womb for implantation of a fertilized egg (luteal phase) (Becker et al. 2005, 2008).

Unlike many pharmacological agents, in general, gonadal hormones do not activate or inhibit specific behaviors; instead, they prepare an individual to be able to engage in a particular behavior should the appropriate conditions arise (e.g., sexual behavior) or modulate the behavior that is exhibited (e.g., the behavioral response to ► amphetamine in females). One exception to this rule is the anxiolytic effects of progesterone and its 5α-reductase-derived metabolites, which are produced in the brain and are known as ► neurosteroids.

Mechanisms of Action

Gonadal hormones are steroidal in chemical structure, so they are lipophillic and act at both intracellular and membrane-associated receptors. The primary intracellular receptors have been well characterized. When bound to the ligand the receptor-ligand complex dimerizes and then binds to the DNA to initiate transcription. Activation of this receptor mechanism requires hours to days for a response to be observed. There are two forms of the

estradiol receptor (ER), known as ERα and ERβ. One of the products of ER activation is the progesterone receptor (PR) which has two isoforms, PR-A and PR-B (Mani 2008). Only one form of the intracellular androgen receptor (AR) has been identified to date. Males and females tend to express intracellular ER, PR, and AR in the same brain regions, but there are sex differences in the number of receptors expressed, with females expressing more ER and PR than males, and males expressing more AR than females.

Membrane receptors for the gonadal hormones have been identified only recently. In the case of progesterone, a novel receptor with seven transmembrane domains that activates a G-protein-mediated intracellular signaling pathway has been identified in vertebrates with two isoforms. The nuclear PRs are also thought to be found at the cell membrane after palmitylation, which anchors the nuclear receptor to the membrane. The nuclear PRs at the membrane also activate G-protein-mediated intracellular signaling pathways, but the exact nature of the interaction is not yet known (Mani 2008). For estradiol, two novel membrane receptors have been identified, GPR30 and Gq-mER; both activate G-protein-mediated, intracellular signaling pathways. As was seen with progesterone, nuclear ERs are also found at the cell membrane to activate G-protein-mediated intracellular signaling pathways. In the case of the ERs, palmitylation may also be involved, and the ERs are thought to associate with caveolin-1 and/or caveolin-3 as well to maintain their position in association with the membrane (Boulware et al. 2007; Micevych et al. 2009). It is not yet clear how the nuclear ERs (or PRs) are positioned relative to the membrane so that the ligand can be bound and intracellular pathways activated. In some brain regions, it is thought that ERs associate with ► metabotropic glutamate receptors to gain access to intracellular signaling pathways (Boulware et al. 2005). The rapid actions of androgens have been well documented in the brain and other tissues. The nuclear AR is implicated in many of these effects, and it is likely that there are also novel membrane ARs yet to be discovered.

Gonadal Hormone Modulation of Drug Effects in the Brain

Stimulant Drugs

In both rats and humans the behavioral effects of ► drugs of abuse, and the ► psychomotor stimulants in particular, are both sexually dimorphic and modulated by the gonadal steroid hormones. With repeated intermittent exposure to ► cocaine or ► amphetamine, the behavioral response exhibited is enhanced with each drug exposure. This is referred to as behavioral ► sensitization, is different in males and females, and is differentially affected by gonadal steroid hormones. For example, intact females exhibit more robust sensitization than do intact males. Following ovariectomy (OVX) of female rats, the expression of sensitization to amphetamine is attenuated or suppressed altogether relative to intact female rats. Estradiol treatments in OVX rats enhance sensitization of locomotor activity induced by amphetamine or cocaine (Becker and Hu 2008; Carroll et al. 2004).

These effects of gonadal hormones are relevant to addiction, where sex differences have been reported during all phases of the addiction process. Women tend to become addicted to drugs more rapidly than men and to escalate drug use at a greater rate. In animal models, when a low dose of a drug is used, female rats acquire cocaine ► self-administration at a faster rate than do males. The role of gonadal hormones can be seen when estradiol is given just before a self-administration session, as estradiol treatment enhances acquisition of cocaine self-administration in OVX female rats and treatment with the estradiol antagonist, tamoxifen, inhibits acquisition in intact females. In male rats, estradiol does not enhance acquisition or cocaine intake, so the brains of males and females are sexually dimorphic in this regard (Becker and Hu 2008; Carroll et al. 2004; Walker et al. 2006).

During maintenance conditions, when given a choice between two doses of cocaine, female rats in estrus preferred higher doses of cocaine when compared with females in other phases of the estrous cycle or male rats. When the role of estradiol in "binge" cocaine intake and subsequent motivational changes is examined, estradiol treatment increases the initial binge length and total levels of cocaine self-administration. Another way to assess motivation is to use a ► schedule of reinforcement in which the number of responses required to obtain a cocaine infusion progressively increases with each dose received. Under this "► progressive ratio schedule," intact female rats reach much higher final ratios than do males, indicating that females are more motivated to obtain cocaine. Females also work harder for access to cocaine during the phase of the estrous cycle when estradiol is elevated, indicating that ovarian hormones modulate the motivation to obtain cocaine. In fact, estradiol treatment enhances responding for cocaine on a progressive ratio schedule. These results show that estradiol influences acquisition of cocaine self-administration, and that there are motivational effects of estradiol on cocaine intake (Becker and Hu 2008).

In contrast to estradiol, progesterone treatment given concurrently with estradiol counteracts the effect of estradiol on acquisition of cocaine self-administration behavior. We have recently confirmed this finding and

understand that progesterone not only affects cocaine self-administration, but also enhances cocaine intake in estradiol-primed OVX rats. Taken together, ovarian hormones contribute to sex differences in cocaine self-administration, and estradiol in particular is a key factor influencing the reinforcing effects of cocaine in female rats. So, over the course of the estrous cycle, there are peaks and valleys during which females are more or less susceptible to the reinforcing properties of cocaine and other drugs of abuse.

As discussed above, our understanding of the mechanisms mediating the effects of estradiol and progesterone in the areas of the brain that mediate the response to drugs of abuse is evolving rapidly. For the most part, we believe that the effect of drugs of abuse on the ascending ► mesotelencephalic dopamine (DA) system is necessary for the addictive and motivational properties of these drugs. The acute administration of estradiol to OVX rats induces a rapid increase in amphetamine- or cocaine-induced DA release in ► nucleus accumbens or striatum. Estradiol also induces an increase in striatal DA turnover and downregulates D2-class DA receptors. These effects have been shown to be due to the direct effect of estradiol on the striatum and nucleus accumbens, presumably at membrane receptors for estradiol. Finally, estradiol induces an increase in PRs in the striatum, and progesterone also acts directly on the estradiol-primed striatum to modulate DA release (Becker and Hu 2008; Walker et al. 2006).

In terms of androgens, castration (CAST) of males has been reported to enhance sensitization of amphetamine- or cocaine-induced psychomotor behavior, although this result has not been found consistently. It has been hypothesized that if CAST enhances the induction and/or expression of behavioral sensitization, that testosterone treatment should reverse this effect. This is not the case, however, as testosterone treatment has not been found to affect behavioral sensitization in CAST males. Furthermore, there is no effect of CAST on acquisition of cocaine self-administration behavior, and a dose of estradiol that enhances self-administration in female rats has no effect on cocaine self-administration behavior in males. So, it does not seem that androgens play a role in modulating the motivational effects of drugs of abuse, even though hamsters, rats, and humans self-administer testosterone and other anabolic steroids all by themselves (Becker and Hu 2008).

Other Psychoactive Drugs

Gonadal hormones can also affect the response to drugs other than the stimulants, but the mechanisms mediating the effects are not as well worked out as for the psychomotor stimulants. Nevertheless, menstrual cycle effects and sex differences in the effectiveness of antidepressants and analgesics suggest that the gonadal hormones can modulate a wide variety of drug effects. In addition, the effects of gonadal hormones on the pharmacokinetics and pharmacodynamics of a drug's action must always be considered (Becker and Meisel 2007).

Conclusion

In summary, the gonadal hormones act in the brain at both intracellular and membrane receptors to induce changes in brain and behavior. The ovarian hormones, estradiol and progesterone, modulate the response to cocaine and amphetamine by acting at membrane receptors in the striatum and nucleus accumbens. These effects of the ovarian hormones result in sex differences in the behavioral responses to these drugs.

Cross-References

► Addictive Disorder: Animal Models
► Adolescence and Responses to Drugs
► Analgesics
► Antidepressants
► Behavioral Tolerance
► Cocaine
► Cocaine Dependence
► Motor Activity and Stereotypy
► Neurosteroids
► Psychomotor Stimulants
► Psychomotor Stimulant Abuse
► Self-Administration of Drugs
► Sensitization to Drugs
► Sex Differences in Drug Effects
► Stress: Influence on Drug Action

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Sexsomnia

► Parasomnias

Sexual Behavior

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Synonyms

Mating behavior; Reproductive behavior

Definition

Anaphrodisiac; any compound reducing the intensity of sexual behavior.

Aphrodisiac; any compound enhancing the intensity of sexual behavior or the pleasure derived from such behavior. The term is sometimes used to designate anything that increases sexual urges, like in "visual aphrodisiacs," referring to sexually exciting pictures or movies.

Lordosis; a concave dorsiflexion associated with lifted rump and the tail moved to one side. This posture exposes the vaginal orifice, and is the basic female copulatory posture in many mammals. The ease by which lordosis is activated is frequently called receptivity.

Proceptive behavior; stereotyped motor patterns, in rodents mainly ear wiggling and hop-darting, typical of many female mammals and supposed to indicate a high propensity to engage in copulatory behavior.

Sexual behavior; any action leading to sexual reward. Sexual reward is a state of positive affect activated by the physical stimulation of the genitalia or mental representations of such stimulation.

Sexual motivation; a concept referring to a set of central nervous processes determining the likelihood of display of sexual behaviors, and their intensity if displayed.

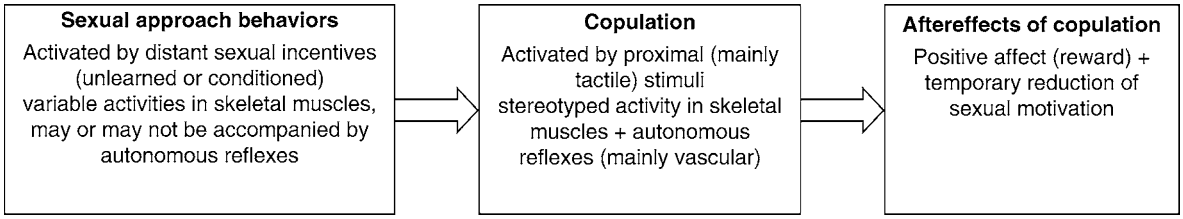
Impact of Psychoactive Drugs

A Long Tradition

The human seems to have been interested in manipulating sexual urges through pharmacological means since the dawn of history. There is anecdotal mention of plants and herbs purportedly stimulating or reducing the interest in sexual activities in many ancient sources. The search for and use of aphrodisiacs have attracted much attention, but there has also been made efforts to find ways to diminish sexual desire. In the classical Chinese Empires, this was achieved by a simple procedure modifying the availability of androgens through castration. Eunuchs were favored as high state officials during many centuries. Likewise, some men of faith, like the Egyptian theologian Origen, castrated themselves in order to be relieved from sexual temptations. During the Dark Ages, castration was no longer an approved practice, but monks are said to have prepared and consumed extracts of a plant, the common rue (*Ruta graveloens*), supposed to inhibit sexual desire. Despite the existence of occasional efforts to reduce sexual behavior, it can safely be stated that the main interest has been directed toward ways to enhance it. Unfortunately, none of the many suggested aphrodisiacs has been shown to have any reliable effect, although most of them have never been subjected to clinical or experimental tests. This, by the way, is also the case for the vast majority of anaphrodisiacs. However, it is conceivable that plants causing a strong sensation of ill-being, as *Ruta graveloens*, temporarily reduce or eliminate interest in sexual activity. Nevertheless, it is only with the advent of modern pharmacology that scientifically sound studies of the effects of xenobiotics on sexual functions have been performed (see Riley et al. 1993; Crenshaw and Goldberg 1996, for classical reviews of the pharmacology of human sexual behavior).

Essential Notions About Sexual Behavior

Any discussion of drug actions on sexual behavior becomes difficult without having some basic notions about this behavior. A schematic representation of the basic elements of sexual behavior is found in Fig. 1. Prominent among these is copulation. In all nonhuman animals, copulation is highly stereotyped. Some would even maintain that the copulatory acts basically are a series of somatic reflexes. However, copulation requires at least two individuals in



Sexual Behavior. Fig. 1. The elements of sexual behavior. Distant sexual incentive stimuli, emitted by a potential mate, activate approach behaviors. The specific motor patterns involved are determined by the context. If successful, the approach behaviors will lead to the establishment of physical contact with the potential mate. Eventually a sequence of stereotyped copulatory motor patterns (such as mounting and lordosis in rodents) may be activated. These motor patterns will bring the male genitals in contact with the female genitals and normally continue until the deposit of sperm in the female reproductive tract has been accomplished. Sperm deposit (ejaculation in the male) is followed by a state of positive affect. Every part of this sequence may be modified by drugs. The reactivity to sexual incentives may be enhanced or reduced, having as consequence increased or decreased likelihood for the display of sexual approach behaviors. Even the incentive properties of an individual may be altered through pharmacological means. However, very little is known about this. The stereotyped copulatory motor patterns themselves are rarely affected by drug treatments, but their frequency or number may be affected. Finally, the hedonic consequences of sexual activity may be enhanced or reduced by drugs. There are few experimental studies of drug-induced modifications of postcopulatory affective states. However, the opioid antagonist ► naloxone has been shown to block the postcopulatory hedonic state in male and female rats. See Ågmo (2007) for an extensive discussion of the sequence of sexual behaviors.

physical proximity. In fact, behaviors leading to approach to a potential mate always precede the execution of copulatory behaviors. Approach behaviors are extremely variable, and determined by the prevailing context. The intensity of approach to a potential sexual partner is an exquisite indicator of the intensity of the urge to engage in sexual activities, or sexual motivation. In nonhuman animals, the display of copulatory reflexes is as dependent on sexual motivation as sexual approach and proceptive behaviors are. However, the human may engage in copulatory behaviors because she/he is forced to do so (the term for most such activities is rape), or as part of a business arrangement (often called prostitution), even in the absence of sexual motivation. It is not entirely clear whether nonhuman animals also may engage in sexual behaviors without an active sexual motivation. In the case of rodents, all available data suggest that sexual motivation is a requisite for the display of sexual behaviors. With these rare exceptions, the intensity of sexual motivation determines the likelihood of display of sexual approach behaviors and their intensity as well as the likelihood of display of copulatory acts and their intensity. It can be maintained that all drug actions on sexual behaviors are, in fact, actions on motivation. It must be noted that different neurobiological processes underlie different aspects of sexual behavior. The neural systems crucial for sexual approach may be different from those controlling seminal emission and ejaculation, for example (Ågmo 2007). This means that a drug may affect the latter without modifying the former. No effort will be made to present a comprehensive list of drugs that may affect sexual behaviors. The following brief review is limited to compounds that has attracted more than occasional attention, and for which reasonably consistent and sound experimental data are available. A short summary of the effects of manipulations of the most studied neurotransmitters is found in Table 1.

Drugs Enhancing Sexual Motivation

Any increase in sexual motivation leads to an increase in one or more of the sexual behaviors. However, not all increases in the intensity of sexual behaviors should be attributed to an increment of sexual motivation. In males, including men, penile erection is a requisite for sexual behavior in the form of penile–vaginal intercourse and for some other forms of penetrative sex. Thus, the frequency of copulation is by necessity low in males suffering from ► erectile dysfunction. Such males will display more sexual behavior when using ► sildenafil, tadalafil, or some other of the phosphodiesterase-5 inhibitors than when treated with ► placebo. This is also the case for men using intra-penile treatments or centrally acting, erection-enhancing drugs such as ► apomorphine. Nevertheless, drugs facilitating erection, regardless of their site of action, are usually not considered as stimulating sexual motivation. This also holds for treatments promoting vaginal lubrication, although such treatments well may

Sexual Behavior. Table 1. Effects on sexual behaviors of manipulations of the activity in major neurotransmitter systems.

Transmitter	Drug action	Effect in males	Effect in females
Acetylcholine	Muscarinic agonists Muscarinic antagonists	Facilitation Inhibition	Facilitation[a] Inhibition
Dopamine	Nonselective or selective agonists Nonselective or selective antagonists	Stimulation or no effect Inhibition	Inhibition or no effect Facilitate lordosis
GABA	Agonists Antagonists	Inhibition Facilitation	Inhibition Inhibition or facilitation[a,b]
Noradrenaline	α_2 antagonists	Facilitation	Facilitation
Endorphins/enkephalins	Agonists Antagonists	Inhibition No reliable effect	Inhibition or facilitation[b] Inhibition or facilitation[b]
Oxytocin	Agonists Antagonists	Facilitation Inhibition	Facilitation
Serotonin	Precursor 5-hydroxytryptophan (5-HTP) Synthesis inhibition (PCPA) Neurotoxin(5,7-dihydroxytryptamine) 5-HT_{1A} agonists 5-$HT_{2A/C}$ agonists	Inhibition Stimulation Facilitation Facilitation Inhibition	Inhibition Stimulation Facilitation Inhibition Facilitation

Only the most consistently reported effects are mentioned. Facilitation includes enhanced receptivity and/or increased proceptivity in females, and reduced latencies to mount, intromit, or ejaculate in males. Inhibition includes reduced receptivity and/or reduced proceptivity in females and enhanced latencies to mount, intromit, or ejaculate in males. Many other effects on subtle details of sexual behaviors have been described in addition to those mentioned, but they are ignored here (see Argiolas 1999; Paredes and Ågmo 2004; Hull and Dominguez 2006, for reviews). Several additional transmitters/modulators have been shown to modify sexual behaviors, but our knowledge about these is at a very preliminary stage, making it too adventurous to summarize their actions

[a]Facilitation observed in partly receptive rats

[b]Depending on site of intracerebral infusion

enhance the frequency of intercourse. A drug considered as stimulating sexual motivation should not render sexual activity possible. Instead, it should enhance the urge to engage in sexual activity and/or improve the performance of copulatory acts.

► *Acetylcholine*. It has been reported that muscarinic agonists facilitate ejaculatory mechanisms in male rats. The number of intromissions necessary to trigger ejaculation has repeatedly been found to be reduced after treatment with oxotremorine. Muscarinic agonists have also been found to facilitate lordosis in females injected with a low dose of estradiol, by itself producing a low level of sexual behavior.

► *Dopamine*. Agonists reliably facilitate copulatory behavior in males with a low baseline level of sexual activity, but their effect in males with a normal activity level is highly variable from one study to another, and frequently it is none. A few studies have evaluated the intensity of sexual approach behaviors in male and female rats after treatment with drugs facilitating dopaminergic neurotransmission, such as ► amphetamine or apomorphine, usually without finding any consistent effect. To the contrary, dopamine antagonists have been found to facilitate lordosis in female rats. Strangely enough, apomorphine administered directly into the ventromedial nucleus of the hypothalamus has been found to facilitate lordosis in estrogen primed, ovariectomized females.

► *Noradrenaline*. Adrenergic α_2 antagonists such as ► yohimbine and atipamezole have been reported to facilitate copulation and sexual approach in male rats, but these studies needs to be extended before a firm conclusion can be proposed. There are also some data showing facilitated sexual behavior in both male and female stump-tail macaques after treatment with atipamezole.

Peptides. Among the peptide neurotransmitters, ► oxytocin stands out as producing the most reliable stimulatory effects on male and female sexual behavior. In the case of the female, it is known that estrogens enhance the expression of the oxytocin receptor gene as well as the oxytocin gene at brain sites relevant for female sexual behavior. This has led to the hypothesis that oxytocin is involved in the physiological control of female sexual behaviors. There are also data from male rats suggesting that oxytocin may enhance sexual behavior.

Several other peptides, such as ► orexin, ► leptin, and galanin-like peptide, have been reported to facilitate different aspects of copulation in rats after intracerebroventricular or intracerebral administration, but the number of studies is still too low for any firm conclusion. A melanocortin-4 agonist, bremelanotide, has been reported to stimulate some aspects of copulatory behavior in female rats. The compound was also subjected to clinical trials in the human as a treatment for ► sexual dysfunctions, but these trials have now been abandoned.

► *Serotonin*. Drugs reducing serotonergic neurotransmission generally stimulate copulatory behavior in both males and females. In male rats, a particularly consistent effect has been reported after treatment with 5-HT_{1A} agonists. The numbers of preejaculatory intromissions and of the time needed to achieve ejaculation are much reduced after such diverse drugs as ► buspirone, lisuride, and 8-OH-DPAT. These effects are usually explained as a consequence of actions at serotonergic autoreceptors within the raphé nucleus, leading to reduced serotonin release in the forebrain. Despite the clear-cut effects of the agonists, a 5-HT_{1A} antagonist failed to modify copulatory behavior although it reliably blocked the effects of agonists. This observation suggests that there is no tonic inhibitory activity at 5-HT_{1A} receptors in male rats. A 5-HT_{1A} agonist/5-HT_{2A} antagonist, flibanserin (BLMT-17), is currently being tested as a treatment for hypoactive sexual desire disorder in the human female. In vivo data suggest that the compound is mainly acting as an agonist at the 5-HT_{1A} receptor. The possible effects of other receptor subtype specific 5-HT agonists are less clear. Some data suggest that an agonist ((+/−)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane, DOI) acting at the 5-$HT_{2A/2C}$ receptor may facilitate both lordosis and proceptive behaviors in female rats.

Drugs Reducing Sexual Motivation

In contrast to the mostly failed efforts to enhance sexual motivation with drugs, many compounds reliably inhibit it. In fact, almost any drug will inhibit sexual motivation if the dose is large enough. Sedation, gross motor disturbances, stereotypies, or other drug actions will eventually interfere with sexual behaviors. Therefore, the present discussion is limited to drugs that appear to reduce sexual functions without having dramatic effects on other behaviors.

Acetylcholine. ► Muscarinic antagonists have generally an inhibitory action on male and female copulatory behavior. There are also some data showing that ► scopolamine reduces sexual approach behaviors in female rats and proceptive behaviors in monkeys.

Dopamine. Antagonists reduce copulatory behavior in males. Whether the inhibitory effects in males are specific to sex behavior or consequences of a generally reduced arousal is a matter of debate. Agonists are known to inhibit lordosis in females when given in high doses. The role of dopamine-dependent activation of competing behaviors, in any case, should not be ignored. In moderate doses, dopamine agonists have no effect in fully receptive females.

► *GABA*. Systemic treatment with GABA agonists are always inhibitory in both males and females, but the doses needed are almost always of such a magnitude that motor functions are compromised, and effects on sexual behavior may be secondary to motor effects. The intracerebral administration of GABAergic compounds has variable effects, again depending on the site of infusion. It is most likely so that GABA agonists will reduce nervous activity at the site of infusion, while the antagonists will have an excitatory effect. Indeed, the effects of locally infused GABA agonists are similar to those of a lesion, and GABA antagonists have effects similar to those of electrical stimulation.

► *Opioids*. Chronic use of opiates is known to reduce sexual behaviors in human males, and acute as well as chronic treatment reduces it in male rats. Since opiates inhibit gonadotropin release, it is possible that the deleterious effects of chronic opiate use are caused by reduced testosterone availability. In male rats, acute treatment with an opiate agonist that does not penetrate the ► blood-brain barrier blocks sexual behavior as efficiently as morphine, suggesting that peripheral actions may be of importance. However, the intracerebral administration of large doses of opioid receptor agonists also reduces male sexual behavior. In females, studies employing the intracerebral infusion of compounds acting at opioid receptors have provided evidence for both facilitation and inhibition of lordosis. Facilitation was observed after infusion into the ventromedial nucleus of the hypothalamus while inhibition was observed when drugs were infused into the medial preoptic area. Both effects may be mediated by the δ opioid receptor.

Peptides. Oxytocin receptor antagonists or ► antisense oligonucleotides directed against the oxytocin receptor consistently reduce lordosis. ► Neuropeptide Y has also been reported to inhibit sexual behavior in male and female rats.

► *Serotonin*. Compounds facilitating serotonergic neurotransmission inhibit copulatory behavior and sexual approach behaviors in rodents. These effects do not seem to be secondary to drug actions on other behaviors. Efficient drugs range from the serotonin precursor

5-hydroxytryptophan (5-HTP) through the ► selective serotonin reuptake inhibitors (SSRIs) to several receptor agonists. Lordosis is consistently inhibited by 5-HT_{1A} agonists. It should be observed that the effects of 5-HT_{1A} agonists are completely different in males and females. 5-$HT1_A$ antagonists usually fail to facilitate lordosis , suggesting that there is no tonic inhibitory activity at 5-HT_{1A} receptors. The inhibitory effects of serotonin agonists are not limited to rodents. In the clinical use of the SSRI antidepressants, one of the main adverse effects is reduced sexual function, both in men and women. The specific serotonin receptor involved in this effect is unknown. However, in male rats a 5-HT_{1B} antagonist blocks the inhibitory effect of 5-HTP, suggesting that the 5-HT_{1B} receptor is crucial for the inhibitory actions. Other serotonin receptors may also inhibit sexual behavior. For example, a selective 5-HT_{2C} antagonist has been found to reduce sexual motivation in female rats tested in a procedure similar to the natural mating situation. There is also some evidence suggesting that DOI inhibits copulatory behavior in male rats through actions on the 5-HT_{2A} receptor. It should be noted that DOI facilitates female copulatory behavior. Here we might have another example of the opposite actions of serotonergic drugs in males and females.

Conclusion

It is certainly too simplistic to imagine that a complex behavior like sex is controlled by a single neurotransmitter. This proposal holds both for sexual approach behaviors and for the copulatory reflexes. As well it is probably too simplistic to imagine that a particular aspect of sexual behavior, for example, lordosis, is controlled by a single transmitter. Likewise, although the medial preoptic area is required for the performance of all elements of male sexual behavior and the ventromedial nucleus of the hypothalamus is necessary for all aspects of female sexual behavior, it is too simplistic to believe that drug actions within these structures can explain the effects observed after systemic drug treatments. Manipulations of one transmitter system will certainly modify the activity of a host of other transmitter systems, and alterations within a particular structure will alter the activity of other structures. Finally, receptor agonists may have actions that the endogenous ligand never has, because of a mismatch between receptor localization and sites of endogenous transmitter release. All these facts make it extremely risky to try to elucidate the physiological control of the sexual behaviors through pharmacological means. However, if we are interested in finding compounds that can enhance or reduce some particular aspect of the sexual behaviors, then there is no need to consider whether the drug's action is part of the physiological control of sex behaviors or not. A pure description of drug effects is sufficient and interesting by itself.

Cross-References

► Muscarinic Agonists and Antagonists
► Sex Differences in Drug Effects
► Sex Hormones
► Sexual Disorders
► SSRIs and Related Compounds

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Sexual Dimorphism

► Sex Differences in Drug Effects

Sexual Disorders

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Definition

Sexual disorders are common in the general population and have a high prevalence in certain psychiatric populations. The Diagnostic and Statistical Manual of Mental Disorders, fourth edition (► DSM-IV-TR), divided sexual disorders into two groups: (1) sexual dysfunctions, defined as psychophysiological impairment of sexual desire and/or

of sexual response cycle and (2) paraphilias, defined as recurrent, intense sexual urges or behaviors that cause marked distress and involve unusual objects or activities.

Sexual Dysfunctions

Sexual dysfunction is best understood by having knowledge of the stages of the normal sexual response, which vary with age and physical status. The five-step model of Masters and Johnson has been elaborated into phases of excitement (arousal), plateau (maximum arousal prior to orgasm), orgasm (involving muscular contractions at 0.8 s intervals), resolution (return to baseline), and refractory period (a recovery stage during which another orgasm is not possible; in men this stage increases with age, whereas women have no refractory period). The triphasic model of Kaplan includes desire, excitement (arousal, a vascular phenomenon, mediated by innervation of the parasympathetic nervous system, specifically the second, third, and fourth sacral segments of the spinal cord), and orgasm (a muscular reaction, mediated by innervation of the sympathetic nervous system, whose reflex center is in the lumbar cord).

Changes in sexual response are associated with aging. In females, having decreased levels of estrogen leads to less vaginal lubrication and narrowing of the vagina. Males are slower to achieve an erection and need more direct stimulation of the penis to achieve an erection. Sexual dysfunction can be primary (life-long) or secondary (acquired), and it may be generalized (occurring in all circumstances) or situational (limited to certain types of stimulation, situations, or partners). Medications, ► drugs of abuse, diseases, injuries, and psychological conditions can affect the sexual response in any of its component phases and can lead to different dysfunctional syndromes. The emphasis on biological treatment in this chapter is not intended to minimize the importance of psychological interventions.

In DSM-IV-TR, sexual dysfunctions are categorized as follows:

1. Desire phase disorders in males and females
   - *Hypoactive sexual desire disorder* denotes persistently deficient sexual fantasies and an infrequent desire for sexual activity.
   - *Sexual aversion disorder* reflects a persistent and extreme aversion to, and avoidance of, all or almost all genital sexual contact with the sexual partner.
2. Arousal phase disorders
   - *Female sexual arousal disorder* involves a persistent inability to attain or maintain the lubrication/swelling response of sexual excitement until completion of the sexual act.
   - *Male erectile disorder* consists of the inability to attain or maintain a satisfactory erection until completion of sexual activity.
3. Orgasm phase disorders
   - *Female orgasmic disorder* is a condition in which there is a persistent delay in, or absence of, orgasm following normal excitement.
   - *Male orgasmic disorder* involves a persistent delay in, or absence of, orgasm following a normal sexual excitement phase. It is infrequent and usually restricted to failure to reach orgasm in the vagina during intercourse, although orgasm can occur with masturbation and/or with a partner's manual or oral stimulation (retarded ejaculation). This condition must be differentiated from retrograde ejaculation, where the bladder neck does not close off properly during orgasm, causing semen to spurt backward into the bladder, which can cause infertility.
   - *Premature ejaculation* is comprised of persistent ejaculation with minimal stimulation before or after penetration and before the person wishes it. It is the most common male sexual disorder.
4. Sexual pain disorders
   - *Dyspareunia* involves persistent genital pain before, during, or after sexual intercourse in either the male or the female. If the pain is caused solely by vaginismus or a lack of lubrication, the diagnosis of dyspareunia is not made.
   - *Vaginismus* denotes persistent involuntary spasm of the musculature of the outer third of the vagina that interferes with intercourse. It can be life-long with an abrupt onset following the first attempt at penetration, or occur suddenly following a sexual trauma or a medical condition.

Paraphilias

DSM-IV-TR delineates eight categories of paraphilias, all involving recurrent, intense, sexually arousing fantasies, sexual urges, or behaviors occurring over a period of at least 6 months:

1. *Exhibitionism* involves exposure of one's genitals to an unsuspecting stranger.
2. *Fetishism* denotes the use of nonliving objects.
3. *Frotteurism* consists of touching and rubbing against a nonconsenting person.
4. *Pedophilia* describes sexual activity with prepubescent children.

5. *Sexual masochism* reflects the act of being humiliated, beaten bound, or otherwise made to suffer.
6. *Sexual sadism* denotes acts in which the psychological or physical suffering of the victim is exciting to the person.
7. *Transvestic* fetishism consists of cross-dressing.
8. Voyeurism involves the act of observing an unsuspecting person who is naked, in the process of disrobing, or engaging in sexual activity.

Role of Pharmacotherapy

Treatment of Sexual Dysfunction in Women

When education, lifestyle, communication, and behavioral changes do not achieve the desired level of success, pharmacological therapy can be utilized to treat sexual dysfunction in women.

Estrogen

Estrogen replacement therapy (ERT) may positively affect sexual function in a number of ways. Estrogens rapidly restore the superficial cell layer of the vaginal epithelium, reestablish elasticity, restore the balance in vaginal pH, improve mood, and increase blood flow to enhance lubrication. Short-term studies of estrogen replacement therapy have confirmed a benefit in some postmenopausal women with sexual dysfunction. However, not all studies have demonstrated positive results, possibly because women most likely to respond are those with symptoms of hypoestrogenism. Any short-term positive effect of oral estrogen may diminish in long-term use because of increasing sex hormone binding globulin (SHBG) levels, which lead to reduced estrogen and androgen bioavailability, and consequent decreased desire and activity. The increase in SHBG appears to be less significant in women who use non-oral delivery system for ERT. Vaginal estrogen is highly effective for treating genitourinary atrophy symptoms, in particular, the vaginal dryness and dyspareunia. Water-soluble lubricants are also helpful for continued sexual activity.

Progestin

Progestin agents downregulate the estrogen receptor, a desired result in the endometrium, but potentially undesirable in the brain, heart, bone, and genitalia. Progestins generally have an overall negative effect in the central nervous system (CNS) with respect to depression and mood, and have been shown to decrease sexual desire and diminish vaginal blood flow. Available options include micronized progesterone (MP) and 19-nortestosterone derivatives, norethindrone acetate (NA), and norgestimate (NGM). When estrogen is given with progestin, the effect on SHBG depends upon the type of progestin used. 19-nortestosterone-derived progestins decrease the SHBG levels. Newer studies in progress with more modern combinations of progestin with estrogen and androgens will provide better insight into the progestational effects on sexuality.

Androgens

Androgens play an important role in physiologic aspects of the female sexual response. However, the effect of androgen therapy on sexual function in women is controversial. Some studies have reported improvements in libido, sexual arousal, and the frequency of sexual fantasies with testosterone therapy in a variety of forms. The observation that testosterone therapy may result in improvement in mood and well-being is felt by some researchers to be most important. The central sex steroid's effect on mood may be what underlies sexual function in both women and men. Potential side effects of androgens include a decline in serum high-density lipoprotein (HDL) cholesterol with oral preparations and mild cosmetic side effect such as hirsutism and acne. Testosterone preparations include creams, gels, and tablets that can be taken orally or used sublingually. They are not approved in the US FDA, but one product approved in Europe for postmenopausal women is a transdermal testosterone patch. Many clinicians have tried creams that are used for vulvar dystrophies made up with 2% testosterone propionate. Others have tapered down the potency using micronized testosterone 0.5% up to 1%, and rarely 2%. Creams were applied first on the inside of the forearms or thighs, while later paraclitoral use became common. The creams seemed to work better paraclitorally in patients with sexual arousal disorder than in those with hypoactive sexual desire disorder. Studies on the use of dehydroepiandosterone (DHEA) have shown an increase in energy level, well-being, sexual satisfaction, and sexual function only in women with primary and secondary adrenal insufficiency. There are no receptors for DHEA and side effects occur due to conversion to testosterone and then to estrogen. Combination therapy with oral estrogen and methyltestosterone also improved sexual interest/desire in postmenopausal women who were experiencing hypoactive sexual desire. The data that androgen therapy significantly improves sexual functioning are suggestive, but not conclusive. No guidelines for androgen therapy for female sexual dysfunction are available. Women most likely to benefit from androgen therapy are probably

those who have undergone bilateral oophorectomy with hysterectomy. Women with hepatic disease, a history of breast cancer, uncontrolled hyperlipidemia, acne, or hirsutism should not be treated. Baseline free and total testosterone levels, liver function tests, and lipid profile should be obtained prior to initiating therapy. Liver function tests and lipids should be monitored every 6 months during therapy. Women should be current on cervical and breast screening.

Herbal Therapies

► Yohimbine has been reported to enhance desire, arousal, and orgasm in women with sexual dysfunction secondary to ► selective serotonin inhibitors (SSRIs), but results are inconclusive. Side effects of yohimbine can be serious and include dizziness, anxiety, hyperstimulation, nausea, renal failure, and seizures. Yohimbine should not be taken together with ► tricyclic antidepressants, ► phenothiazines, clonidine, or other drugs or supplements for lowering blood pressure.

L-arginine, an amino acid, has been touted as the natural sildenafil due to the claimed ability to release nitric oxide, causing increased vasoconstriction in the genitalia of both sexes. It causes side effects such as hypotension, dizziness, headache, and nausea.

Future Therapies

Tibolone is a synthetic hormone, currently available in Europe and Australia. Tibolone is used in women to relieve symptoms of menopause and to prevent osteoporosis. It has not been approved by the US FDA. Its metabolites have estrogenic, androgenic, and progestational effects. Oral tibolone is found to increase vaginal lubrication, arousability, and sexual desire.

► Sildenafil, a phosphodiesterase-5 inhibitor, in preliminary findings demonstrated positive effects in the areas of sexual arousal and orgasm in appropriately selected women, but several large studies have yielded inconclusive results. It has been reported to reverse anorgasmia associated with SSRIs.

► Apomorphine SL, a non-ergoline dopamine agonist, has been reported to improve sexual desire and function in premenopausal women with hypoactive sexual desire. Apomorphine SL is not FDA approved for this indication. Its side effects include hypotension, dizziness, bradycardia, headache, sedation, and nausea.

Treatment of Sexual Dysfunction in Men

The three major forms of male sexual dysfunction are erectile dysfunction, ejaculatory dysfunction, and decreased libido.

Erectile Dysfunction

Therapy in men with ► erectile dysfunction is aimed at restoration of the two vital sexual functions: the capacity to acquire and sustain penile erection and to reactivate libido. Erectile dysfunction can also be a side effect of antidepressant and antipsychotic therapy. Optimal treatment varies with the cause of the erectile dysfunction.

For first-line therapy, the ► phosphodiesterase-5 (PDE-5) inhibitors are recommended because of their efficacy, ease of use, and favorable side effect profile. The three ► PDE-5 inhibitors, sildenafil, vardenafil, and tadalafil, appear to be equally effective, but tadalafil has a longer duration of action. The rationale for the use of PDE-5 inhibitors is based upon the role of nitric oxide-induced vasodilatation. Nitric oxide release triggers the production of cyclic guanosine monophosphate (cGMP), which leads to decreased intracellular calcium, smooth muscle relaxation, and penile erection. All available PDE-5 inhibitors work by inhibiting the degradation of cGMP. They are highly specific, vary somewhat in selectivity for other phosphodiesterase enzyme types, and differ in duration of action. Common side effects include dyspepsia, flushing, rhinitis, and headache. The use of PDE-5 inhibitors with nitrates is contraindicated by the risk of severe hypotension. PDE-5 inhibitors should be used cautiously with alpha-blockers (because of the risk of hypotension) and in men with aortic stenosis, recent myocardial infarction, unstable angina, heart failure, arrhythmias, degenerative retinal disease, or poorly controlled hypertension. The rare possibility of priapism exists, and patients should be instructed to seek emergent medical attention if erection persists for more than 4 h without sexual stimulation. Cases of sudden loss of vision or hearing have been associated with PDE-5 inhibitors. Sildenafil also causes blue vision in 3% of men. This effect usually lasts for 2–3 h and disappears spontaneously. For maximum effectiveness, sildenafil should be taken orally about 1 h before a planned sexual encounter. The initial dose should be 50 mg, reduced to 25 mg if side effects occur. If the drug is well tolerated but the erectile response is not fully satisfactory, the dose can be increased to 100 mg. The duration of action is approximately 4 h. Vardenafil shares a similar structure, onset of duration of action and side effect profile with sildenafil. It is available as 10 and 20 mg doses. Tadalafil differs in chemical structure, has an equally rapid onset but longer duration (24–36 h) and does not cause blue vision, but otherwise shares a similar side-effect profile with the other two PDE-5 inhibitors. The recommended starting dose for as-needed use is 10 mg, increasing to 20 mg if necessary. Lower

doses of tadalafil (2.5 mg, 5 mg) are available for once daily administration. This approach appears to be as effective as taking higher doses on an as-needed basis. Sildenafil and vardenafil must be taken on an empty stomach, while tadalafil can be taken without regard to food.

Intrapenile injection therapy with alprostadil (prostaglandin E), papaverine, and phentolamine has been used to induce erection. Since the advent of PDE-5 inhibitors, these approaches are rarely used. In the early days of penile self-injection therapy, papaverine proved to be more reliable than phentolamine in producing an erection. Papaverine is a parenteral vasodilator with marginal efficacy in peripheral vascular disease, while phentolamine is an alpha-adrenergic blocker. Alprostadil and papaverine are still used in monotherapy, and all three drugs can be given together. Intrapenile injection is recommended 10–20 min before intercourse and may require additional penile stimulation. Limitations of these agents include penile pain, lack of efficacy and need for self-injection. Priapism occurs in 6% of men who use intrapenile alprostadil and about 11% of those who use intrapenile papaverine.

Intraurethral alprostadil provides a less invasive alternative to intrapenile injection. After insertion of the alprostadil into the urethra 5–10 min before intercourse, the penis should be massaged for up to 1 min to ensure equal distribution in the corpora cavernosae. The drug can be used twice daily. It is not recommended with pregnant partners. Systemic effects are uncommon and complications such as priapism and penile fibrosis are less common than after alprostadil given by penile injection.

Off-label use of some other agents may be moderately effective in treating erectile dysfunction in men who do not respond adequately to PDE-5 inhibitors. Efficacy has been reported for ► cabergoline, a dopamine D2 receptor agonist used to treat hyperprolactinemia and ► Parkinson's disease; valvular heart disease has been observed at higher doses of this drug. Yohimbine, a presynaptic alpha 2-adrenergic blocking agent, has been used for men with psychogenic erectile dysfunction. Treatment is considered only in those who respond and also tolerate the drug's side effects, which include dizziness, flushing, nausea, headache, anxiety, insomnia, hypertension, and seizures. Melanocortin receptor agonists, which act on the CNS rather than on the vascular system, are being developed as a possible new therapy for erectile dysfunction. PT-141, an intranasal preparation, appears to be effective as monotherapy or in combination with PDE-5 inhibitors. However, significant side effects, including flushing and nausea, may limit its clinical utility. This agent is not commercially available.

Premature Ejaculation

Locally applied anesthetic creams, such as prilocaine/lidocaine mixtures, have been found to increase ejaculatory latency by approximately 7–10 min. Their major side effect is penile hypoanesthesia. The man also must use a condom or wash off the cream before vaginal penetration to minimize vaginal absorption.

Although no medications are FDA-approved for this indication, case reports have described the use of ► monoamine oxidase inhibitors, ► tricyclic antidepressants, and ► antipsychotics for this off-label use. ► Clomipramine, a tricyclic antidepressant with strong serotonergic activity, has been shown in ► double-blind trials to be effective in treating premature ejaculation on an as-needed basis. Clomipramine usually is taken 4–6 h before coitus in doses of 25–50 mg. Common side effects are dry mouth, nausea and fatigue. The SSRIs ► paroxetine, ► sertraline, and ► fluoxetine also delay ejaculation. Most trials have found that the dose needed to delay ejaculation is similar to the dose necessary to treat depressive disorders. SSRIs require chronic dosing to be effective. Among the SSRIs, paroxetine appears to have the greatest effect on ejaculatory latency. Paroxetine 20 mg daily can be started as initial treatment. Low-doses (0.5– 1 mg) of the benzodiazepine ► lorazepam, taken 30 min before coitus, also can be effective in some men. Lorazepam has the common side effect of sedation.

Decreased Libido

For men with sexual dysfunction and low serum testosterone levels, testosterone replacement therapy should be the initial treatment. If sexual dysfunction is associated with testosterone deficiency, testosterone therapy to restore normal-range testosterone levels can be achieved with transdermal gels, patches, or injections. Current recommendations are to attempt to restore serum testosterone to mid-normal range. A variety of therapeutic approaches are possible. These include 75–100 mg of testosterone enanthate or cyproate administered weekly, one to two 5 mg patches nightly, 5–10 mg of testosterone gel applied daily, or a 30 mg bioadhesive buccal testosterone tablet applied every 12 h. Potential side effects of testosterone replacement therapy include prostatic hypertrophy, increased erythropoiesis, worsened sleep apnea, gynecomastia, and fluid retention possibly worsening hypertension and cardiac failure. Follow-up care should include routine prostatic specific antigen (PSA), hematocrit and serum testosterone levels.

Pharmacological Treatment of Paraphilias

Pharmacological interventions for paraphilias are symptom-focused and directed toward ameliorating or managing comorbid conditions. The number of medications used to treat paraphilias has been steadily increasing. Pharmacological interventions fall into three primary categories: antiandrogens (testosterone-lowering agents), antidepressants, and neuroleptics and other agents.

Antiandrogens or Testosterone-Lowering Agents

Use of these drugs in treating paraphilias usually must be long-term. Relapse is common upon cessation of the medication. Testosterone-lowering agents are the gold standard for treating any paraphilic disorder in which sex-drive reduction is a desirable component.

Medroxyprogesterone acetate (MPA) is the most commonly used hormonal agent for the reduction of sex drive. It reduces levels of testosterone by inducing hepatic testosterone reductase. The goal of this strategy is to reduce baseline testosterone to 50% of initial value. Common dosages are 50–300 mg orally or 300–400 mg weekly via intramuscular injections. Depot preparations of MPA are also available.

Cyproterone acetate (CPA) blocks androgen receptors, directly decreasing the biological effect of testosterone. CPA can be given orally 100 mg daily or 200 mg every other week via intramuscular injections. CPA is not available in the USA.

Side effects of treatment with MPA and CPA include reduced sexual drive and erectile ability, fatigue, depression, liver dysfunction, gynecomastia, weight gain, hyperglycemia due to an exaggerated insulin response to a glucose load, headaches, and increased risk of deep vein thrombosis.

Leuprolide and triptoreline are long-acting luteinizing hormone-releasing hormone (LHRH) agonists. LHRH agonists suppress testosterone by decreasing the number of pituitary LHRH receptors and testicular receptors, thereby desensitizing the testes to luteinizing hormone (LH). As a result of their depleting effects, levels of circulating testosterone and dihydrotestosterone decrease to prepubertal levels. LHRH agonists more completely suppress androgen than MPA or CPA. Leuprolide and triptoreline are given intramuscularly in doses of 3.75 or 7.5 mg monthly. They can cause a surge in gonadotropin secretion in the first 2–4 weeks of treatment. Because of this effect, patients receiving treatment with LHRH agonists should temporarily be prescribed an androgen receptor blocker, such as flutamide. The typical flutamide oral dosage is 250 mg three times a day. It can be discontinued after 2–4 weeks. Side effects of LHRH agonists are related to hypoestrogenic states and consist of erectile failure, hot flashes, and decreased bone mineral density.

Antidepressants

SSRIs have been proposed for alleviating paraphilic symptoms because of their adverse side effects of diminished sexual desire and arousability. A study comparing the effectiveness of ▶ fluvoxamine, ▶ fluoxetine, and ▶ sertraline in paraphilics found all three effective in reducing the severity of fantasies and no significant differences in overall efficacy. It is unclear whether the SSRIs are selectively useful in individuals with a clear obsessive-compulsive disorder component, comorbid anxiety, or depressive disorder underlying the paraphilia or, rather, whether they have a more generalized usefulness for the paraphilias. The SSRIs and other antidepressants are highly variable in the degree to which they cause the sexual side effects that might be beneficial in managing paraphilias.

Neuroleptics and Other Agents

▶ Neuroleptic agents have been reported to diminish paraphilic behavior and fantasies. ▶ Lithium and ▶ anticonvulsants have been reported to be useful in treating sexual impulsivity. However, the successful use of neuroleptics and mood stabilizers in treating paraphilias may reflect their efficacy for the comorbid ▶ mania or other psychotic states that are often associated with paraphilia.

Cross-References

- ▶ Antipsychotics
- ▶ Benzodiazepine
- ▶ Fluoxetine
- ▶ Lorazepam
- ▶ Monoamine Oxidase Inhibitors
- ▶ Mood Stabilizers
- ▶ Paroxetine
- ▶ PDE-5 Inhibitors
- ▶ Phenothiazines Neuroleptics
- ▶ Phosphordiesterase-5 Inhibitors
- ▶ Selective Serotonin Inhibitors
- ▶ Sertraline
- ▶ SSRIs
- ▶ Tricyclic Antidepressant

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Sharp Microelectrode Recording

Definition

Sharp microelectrode recording denotes the implementation of intracellular recording techniques using fine microelectrodes that access the interior of the cell by penetrating through the membrane.

Cross-References

► Intracellular Recording

Short Interfering RNA

► Antisense Oligonucleotides
► siRNA

Short-Term and Working Memory in Animals

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Definition

Short-term memory refers to a storage mechanism that retains information for a limited period of time. In animals, working memory (WM) is conceptualized as a form of short-term memory that encompasses both storage and processing functions. In WM, information is not only held transiently in mind but also actively manipulated; items may be monitored, compared and/or associated to other items and incoming information as they are recalled. Information in WM is active on the time scale of several seconds, and is sensitive to attentional distraction. The main role of WM is to keep track of relevant information, continuously update it, and use it to shape behavior in the present. In animals, the prefrontal cortex plays a central role in WM, and disruption to its intrinsic circuitry or its connectivity with other brain regions leads to several cognitive deficits. In animals, a wide range of psychoactive agents affect WM.

Impact of Psychoactive Drugs

Recently, much attention has been focused on the psychopharmacology of WM. Two main developments have converged to create this interest. First, there have been significant advances in our understanding of the anatomy and organization of the neurotransmitter pathways in the mammalian brain. These pathways include the major monoaminergic (dopamine, serotonin and norepinephrine) and cholinergic projections, which innervate diverse forebrain regions that have discrete psychological functions. This has refined our understanding of the neurochemical basis of pathophysiological conditions such as ► Parkinson's disease, ► Alzheimer's disease, and ► schizophrenia, which are characterized by memory loss and cognitive disorganization. Second, research has linked poor psychosocial functioning to persistent cognitive deficits, including WM, which fail to improve with current pharmacotherapies. Consequently, there has been an important need to identify pharmacological compounds intended to improve cognitive deficits in psychiatric illness and dementia (see ► cognitive enhancers), and WM impairments have become important targets for treatment.

In animals, WM is assessed using the spatial delayed response task, which evaluates the animal's capacity to act on the basis of stored information rather than information available in the environment. Typically, a monkey is shown the location of a food morsel. The food morsel is then hidden from view. After a delay of several seconds, the monkey is required to choose one of the two locations. To be rewarded, the animal must remember where the food was located prior to the delay period. In a variation of the task, ► spatial delayed alternation, the monkey is required to alternate between left and right food wells in successive trials that are separated by delay periods. In this latter version, the monkey is not permitted to observe the experimenter baiting the food well. Therefore, to be correct on any given trial the monkey must remember which response was made last. In rats, spatial delayed alternation is a commonly used ► rodent test of cognition which exploits the ease with which rats can remember different locations and hence, have used spatial stimuli as in the

T-Maze and ▶ radial arm maze (Dudchenko 2004). The ▶ delayed (non)-match to sample is another test of WM, but it is used more commonly in monkeys than rats (see ▶ primate models of cognition). Lesions of the dorsolateral prefrontal cortex in monkeys and medial prefrontal cortex in rats profoundly impair WM performance in these tasks (Dalley et al. 2004; Goldman-Rakic 1987). This finding has proven to be extremely useful in the study of the psychopharmacology of WM; the prefrontal cortex is highly sensitive to its neurochemical environment and small changes in the degree of prefrontal monoamine and acetylcholine neurotransmission contributes significantly to prefrontal WM function.

Dopaminergic Drugs

The work of Brozoski et al. (1979) was the first to demonstrate that ▶ catecholamines played a critical role in the modulation of spatial WM function in the prefrontal cortex. Large catecholamine depletions of the prefrontal cortex using ▶ 6-hydroxydopamine (6-OHDA) in monkeys, impairs performance in spatial WM tasks to the same degree as large prefrontal lesions, and can be pharmacologically reversed with dopamine (DA) agonists such as levadopa (▶ L-DOPA) and ▶ apomorphine. Spatial WM deficits can be mimicked in rats and monkeys by acute, local infusions of DA D_1 receptor antagonists into the ▶ prefrontal cortex, and similar cognitive impairments can be observed following systemic administration of ▶ haloperidol.

In addition to the detrimental effects of reducing DA transmission in the prefrontal cortex, increased DA turnover in the prefrontal cortex impairs spatial WM as well. This is because WM relies on an optimal level of mesocortical DA, which functions according to an inverted 'U-shaped' relationship between DA and cognitive performance (Arnsten 1998). This means that "too much or too little DA" is associated with impaired WM performance. For example, in animals, mild stressors such as ▶ conditioned fear or a weak footshock preferentially increase DA turnover in the prefrontal cortex compared with other DA terminal fields. Mild stress exposure to monkeys or rats produce WM deficits that can be blocked with low pre-treatment doses of DA D_1 receptor antagonists such as SCH 23390, typical ▶ antipsychotics such as haloperidol, or atypical ones such as ▶ clozapine. This stress-induced WM deficit can be mimicked in rats by infusing DA D_1 agonists (e.g., SKF 81297) directly into the prefrontal cortex which can be blocked with a pretreatment dose of a DA D_1 receptor antagonist. Relative to the pretreatment effects of DA antagonists, however, the β adrenergic antagonist ▶ propanolol, or the ▶ SSRI fluoxetine, are not effective in reversing stress-induced WM deficits, illustrating the importance of dopaminergic mechanisms of WM in the prefrontal cortex.

Research has now established the importance of the DA D_1 receptor family in the regulation of prefrontal WM function. Selective antagonists that work on the D_2 receptor in the prefrontal cortex are mostly ineffective. Overall selective D_1/D_5, but not D_2/D_3 receptor antagonist infusion in the prefrontal cortex impairs WM in rats and monkeys. However, although D_2/D_3 antagonists have little effect on WM when infused in the prefrontal cortex, systemic treatment of these drugs improves WM in monkeys and humans (see ▶ short-term and working memory in humans). More research is needed to establish where in the brain the actions of these drugs are taking place.

Disruptions in delayed response tasks are not necessarily indicative of a specific impairment in WM. WM relies not just on holding information online but also overlapping mechanisms of attention which enable the active maintenance of information within a WM system. Recent research indicates that different levels of prefrontal DA activity may be required for different cognitive processes so that DA D_1 receptor stimulation sufficient to improve one cognitive function may serve to impair another. Thus, although treatments with ▶ psychostimulants such as ▶ amphetamine facilitate mechanisms of arousal (or attention), they disrupt WM, and enhance ▶ long-term memory. This has led to the idea that arousing conditions in animals such as white noise or highly emotional contexts can impair short-term recall (i.e., WM) but benefit long-term retention, and suggest the existence of independent memory systems in animals, including rats.

Adrenergic Drugs

While antipsychotic medications exert their benefits primarily by modulating the DA neurotransmitter, they also affect ▶ norepinephrine (NE) receptors. Recent studies in animals have shown that NE has just as powerful an influence on the prefrontal cortex as DA. In the prefrontal cortex, NE has opposing actions at α_2- and α_1- adrenoreceptors (AR) with respect to WM function. Thus, while NE enhances WM via α_2-AR stimulation, it impairs WM via α_1-AR stimulation. For example, α_2-AR agonists such as clonidine guanfacine, or medetomidine administered systemically improve WM in rats and monkeys (including aged monkeys), which can be blocked with α_2-AR antagonists such as ▶ yohimbine. Yohimbine alone is sufficient to impair WM performance. The improved WM effect of α_2-AR agonists is pronounced in monkeys with large catecholamine depletions and under conditions of high interference or distraction, conditions that require

prefrontal function. Performance of tasks that do not depend on the prefrontal cortex is not improved by treatment with α_2-AR agonists (Arnsten 1998).

NE has a lower affinity for α_1-AR than α_2-AR, which means a high level of NE release is necessary to engage α_1-AR in the prefrontal cortex. In addition to increasing DA, exposure to ▶ stress preferentially increase NE in the prefrontal cortex. Hence, α_1-AR antagonists infused into the prefrontal cortex have little effect on WM under nonstressed conditions. By contrast, rats and monkeys exposed to uncontrollable stress, which causes NE activation at α_1-AR markedly impairs WM function. Infusing phenylephrine, a highly selective α_1-AR agonist, directly into the prefrontal cortex, mimics the detrimental effect of stress on WM. This impairment can be reversed by coinfusion of the α_1-AR antagonists, urapidil. Together, these findings suggest not only that the therapeutic effects of antipsychotic medication may be due in part to α_1-AR blockade, but also that α_2-AR agonists such as clonidine may serve to protect prefrontal function, and therefore WM from the detrimental effects of stress.

Cholinergic Drugs

▶ Atypical antipsychotics such as ▶ clozapine and ▶ risperidone, in addition to increasing DA release in the prefrontal cortex, also increase ▶ acetylcholine (ACh) release in the prefrontal cortex. It is thought, therefore, that ACh release in the prefrontal cortex may also contribute to the ability of atypical antipsychotics to improve cognitive symptoms of WM. In rats, for example, local prefrontal infusions of the cholinergic muscarinic receptor antagonist ▶ scopolamine produce spatial WM deficits in delayed match to sample tasks. These deficits can be ameliorated with cholinergic treatments such as ▶ physostigmine, an acetylcholinesterase inhibitor. However, it is now apparent that cortically projecting cholinergic neurons play a crucial role in attentional processing, and failures in ▶ attention may contribute to an overall WM deficit (McGaughy et al. 2000). Thus, ▶ delay-independent deficits in delayed match to sample tasks following prefrontal cholinergic manipulations are thought to reflect impairments in attention, rather than mnemonic processing *per se*. Nevertheless, more research is needed to fully appreciate the role of prefrontal ACh in cognitive function, especially WM. Recent observations suggest that the function of prefrontal ACh is to distribute attentional capacity in tasks that require effortful processing such as holding a stimulus online in WM.

Unlike the muscarinic ACh receptor, nicotinic cholinergic receptors have received much less attention. Recently however, the effects of ▶ nicotine as a ▶ cognitive enhancer have made it particularly attractive for clinical use. Both acute and chronic ▶ nicotine treatments significantly improve WM performance in rats using the radial arm maze. Chronic treatment with nicotine agonists has been shown to improve memory performance in other tasks such as ▶ passive avoidance, and in other species including monkeys, mice, and zebrafish (Levin et al. 2006). In addition to enhancing WM performance, nicotine also improves ▶ attention. Chronic nicotine infusion diminishes the impairing effects of antipsychotics such as ▶ haloperidol, risperidone, and clozapine on attention, whereas ▶ mecamylamine, a nicotinic antagonist used sometimes as an anti-addictive drug, decreases attentional performance, and WM. The cognitive impairing effects of mecamylamine have reduced its clinical utility for smoking cessation.

The temporal lobe structures such as the ▶ hippocampus and perirhinal cortex, also receive a dense cholinergic input from the medial septal (MS) nucleus and the vertical limb of the diagonal band of Broca (VDB). Although the hippocampus and related structures are known to be critical for certain memory functions (see ▶ short-term memory and ▶ long-term memory), robust WM impairments following manipulations to the cholinergic septo-hippocampal pathways have been difficult to demonstrate.

Serotonergic Drugs

One characteristic feature of atypical antipsychotic drugs is their high affinity for various serotonin 5-HT receptors, especially 5-HT_{1A} and 5-HT_{2A}, which are densely localized within the limbic cortex of humans and animals. These 5-HT receptors received much attention because they are involved in the action of ▶ hallucinogens such as lysergic acid diethylamide (LSD) and psilocybin, but there is growing evidence from animal experiments indicating a role for serotonin in modulating cognitive functions. While there is considerable evidence connecting the serotonergic system to cognitive functions of ▶ behavioral inhibition, its modulatory role in WM has not been well characterized. Much of the earlier work on the role of 5-HT in WM used nonselective global strategies in which the entire 5-HT system was manipulated by increasing or reducing central 5-HT transmission. Thus, in rats, global 5-HT depletion using 5, 7-dihyroxytrptamine (5, 7-DHT) or *p*-chlorophenylalanine (PCPA) had little effect on delayed nonmatch to position tests of WM. By contrast, 5-HT ligands with varying degrees of receptor specificity have been shown to disrupt WM performance, and in some cases improve it. Importantly, although the prefrontal cortex is substantially innervated by serotonergic fibres

from the raphe nuclei in monkeys and rats, 5-HT depletions in the prefrontal cortex does not impair WM performance. In addition, although the 5-HT_{2A} receptor is abundant on the dendrites of prefrontal pyramidal cells implicating a role for it in WM function, there is no direct evidence linking 5-HT_{2A} receptor activation (or deactivation) with changes in spatial WM. Furthermore, the physiological evidence for the apparent deleterious effects of prefrontal 5-HT_{2A} blockade on WM stands in contrast to the proposed benefit of 5-HT_{2A} properties of atypical antipsychotics such as clozapine, olanzapine, and risperidone; these drugs share potent 5-HT_{2A} and relatively weaker DA D_2 receptor antagonism. While it is thought that the clinical efficacy of atypical antipsychotics might be due to increased prefrontal DA release, further experiments are needed to evaluate the impact of pharmacological treatments targeted to alter both DA and 5HT signalling on WM performance (Meltzer et al. 2003).

Other Neurotransmitters and Psychoactive Drugs

► GABA receptors are the major targets for ► benzodiazepines and related ► anxiolytics. ► Alcohol and benzodiazepine such as ► diazepam, both potentiate actions at $GABA_A$ receptors, and both impair WM performance in rats. In monkeys, WM performance depends on appropriate GABA transmission in the dorsolateral prefrontal cortex.

► Dissociative anesthetics such as ► phencyclidine (PCP) and ► ketamine work primarily as ► NMDA receptor antagonists and produce WM deficits in rats performing spatial delayed alternation or delayed match to position tasks. Low doses of AMPA/kainate antagonists produce delay-dependent WM impairments. In addition, potential ► anxiolytics such as LY-354740, which act as $mGLU_{2/3}$ receptor agonists, autoregulate ► glutamate release in the prefrontal cortex and reverse WM deficits caused by NMDA antagonist treatment.

Conclusion

The prefrontal cortex is critical for guiding behavior using WM. In WM tasks, animals can code and recall constantly changing locations or stimuli as in delayed response and delayed alternation tasks. Animals can also track in WM their recent choices from a set of stimuli, and update relevant information in order to respond on a moment-to-moment basis. As in humans, a disruption to WM in animals prevents the execution of effective organized behavior, a behavioral deficit that is evident in patients with dementia and psychiatric illnesses. While improvements in WM predict favorable behavioral outcomes, the neurochemical basis of WM is not yet fully understood. Animal studies have demonstrated convincingly, that catecholamines (DA and NE) are involved in WM function but there is also evidence that pro-cholinergic drugs can ameliorate WM deficits. Although there is little evidence for a direct role for serotonin in WM, serotonin receptors are used as targets for antipsychotic drug development. That existing antipsychotic drugs possess many pharmacological profiles, it is likely that any therapeutic action on WM will involve interacting receptor mechanisms.

Cross-References

► Acetylcholine
► Amphetamine
► Anxiolytics
► Attention
► Atypical Antipsychotics
► Behavioral Inhibition
► Benzodiazepine
► Cognitive Enhancers
► Hallucinogens
► Haloperidol
► 6-Hydroxydopamine
► Long-Term Memory
► Nicotine
► NMDA Receptor
► Norepinephrine
► Primate Models of Cognition
► Psychostimulants
► Radial Arm Maze
► Rodent Tests of Cognition
► Scopolamine
► Short-Term and Working Memory in Humans
► Short-Term Memory
► Spatial Delayed Alternation
► SSRI

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Short-Term and Working Memory in Humans

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Definition

The term short-term memory is considered to refer to just one component of working memory and is generally used only to describe a range of tasks that focus explicitly on short-term storage, e.g., digit span tests. Working memory refers to a broader set of processes that facilitate the ability to encode, maintain, store, hold on-line and retrieve representations of information for further processing or recall (Baddeley 2007). Working memory processes are active temporarily for a short period of time, on the order of seconds. These processes include short-term storage of information, but also executive processes that operate on the stored material. Working memory is mediated by a widely distributed neural system in the human brain, including (not exclusively) the prefrontal cortex (PFC), the striatum, the posterior parietal cortex and the inferotemporal cortex.

Impact of Psychoactive Drugs

Evidence indicates that the major ascending neuromodulators, in particular dopamine, but also noradrenaline, acetylcholine and serotonin can influence working memory performance in humans. However, the effects of drugs that affect these neuromodulators depend on (1) the particular task demands under study, i.e., the stage (encoding, delay, probe) and type (e.g., spatial vs. non-spatial) of working memory, (2) the neural region that is targeted by the drug (e.g., the striatum or the ▶ prefrontal cortex), (3) the baseline neurochemical state of the system and (4) the receptor-specificity of the drug. Accordingly, drugs that are known as ▶ cognitive enhancers can induce impairments on some tasks and in some individuals. Similarly drugs that are known as cognitive inhibitors can induce improvements on some tasks and in some individuals.

A variety of paradigms are used to study working memory in humans. Examples of tasks in behavioral psychopharmacological studies include the self-ordered spatial working memory task from the Cambridge neuropsychological test automated battery (▶ CANTAB), which requires self-ordered searching through a set of boxes to locate hidden tokens, tests of digit span and *the* ▶ *delayed match-to-sample* (DMTS) *test*. Although the ▶ *Wisconsin Card Sorting Test* (WCST) and related tests were not designed to test working memory (▶ behavioral flexibility), adequate performance also critically relies on intact working memory, in particular its executive components. Neuroimaging studies which employ positron emission tomography (▶ PET imaging) or functional magnetic resonance imaging (▶ magnetic resonance imaging (functional)) have often employed blocked versions of *the* ▶ *n-back task*, which do not directly allow the disentangling of its different components (e.g., maintenance during delay vs. flexible updating during encoding). Other neuroimaging studies have used variants of the DMTS paradigm, or adaptations, which do allow such decomposition.

Dopaminergic Drugs

Best studied are the effects of dopaminergic drugs on working memory. Acute administration of single low doses of dopamine receptor agonists, such as ▶ bromocriptine or ▶ pergolide, affects working memory performance on DMTS tests as well as tests measuring the executive components of working memory (n-back, WCST). Low doses seem more beneficial than high doses, which might induce sedative side effects. Beneficial effects of bromocriptine and other dopamine-enhancing drugs like levodopa have been observed in patients with ▶ Parkinson's disease and traumatic brain injury. These effects are most pronounced on tests measuring the executive, flexible updating components of working memory (e.g., n-back, self-ordered searching, WCST, DMTS with stimulus-reordering requirements), but not on tests measuring only the maintenance component of working memory (e.g., DMTS). Non-specific catecholamine enhancers like ▶ amphetamine and methylphenidate, which affect both dopamine and noradrenaline (▶ methylphenidate and related compounds), can also improve working memory performance on the more executive working memory tasks (i.e., n-back, self-ordered searching, WCST) in healthy volunteers, as can the COMT

inhibitor tolcapone. Improvements after methylphenidate, amphetamine and ▶ tolcapone in young healthy volunteers and after levodopa in Parkinson's disease are accompanied by, and correlated with reductions in activity in fronto-parietal brain regions, possibly reflecting enhanced processing efficiency and higher signal to noise ratio. Conversely agents that block dopamine D2 receptors, like ▶ sulpiride, can impair working memory. However paradoxical improvements have also been observed following sulpiride administration in some individuals, perhaps reflecting predominant action at self-regulating autoreceptors. Effects of acute tyrosine depletion are less consistent, questioning the reliability of tyrosine depletion as a modulator of dopamine function.

Some data have suggested that spatial variants of the DMTS and self-ordered search tests are more sensitive to manipulations of dopamine than are tests of non-spatial working memory. However, a number of prominent caveats have been highlighted (Mehta and Riedel 2006). For example, the spatial variants of the DMTS test often loaded on movement preparation to a greater extent than did the non-spatial variants, thus confounding modality-dependency with dependency on movement preparation.

The direction of the effects of dopaminergic drugs depends on baseline working memory capacity, as measured for example, with the *listening span test*: Dopamine D2 receptor agonists like bromocriptine and ▶ cabergoline, as well as D2 receptor antagonists like ▶ haloperidol have opposite effects in subjects with high and low working memory capacity. Similar dependency on baseline working memory capacity has been observed for the non-specific catecholamine enhancers methylphenidate and amphetamine. For example, low-span subjects with low working memory capacity benefit from bromocriptine in terms of set-shifting performance on the WCST, while high-span subjects with high working memory capacity are impaired by bromocriptine. The direction of drug effects, however, cannot be predicted from working memory capacity alone; rather the type of working memory test must also be taken into account. Thus while benefiting in terms of flexible set-shifting on the WCST, low-span subjects are actually impaired by bromocriptine on the DMTS test, which loads more highly on the robust maintenance rather than on the flexible updating of current representations.

The dependency of these dopaminergic drug effects on baseline working memory capacity has been hypothesized to reflect dependency on baseline levels of dopamine. Evidence for this hypothesis comes from neurochemical PET studies showing that working memory capacity, as measured with the listening span, correlates positively with baseline dopamine synthesis capacity in the striatum. Higher working memory capacity is associated with higher dopamine synthesis capacity (Cools and D'Esposito 2009). The implication of these data is that subjects with low baseline levels of dopamine benefit from dopamine-enhancing drugs, at least in terms of the flexible updating component of working memory, while subjects with already optimized levels of dopamine are impaired by the same dopamine-enhancing drugs. This is consistent with the existence of an "Inverted U" shaped relationship between dopamine and cognitive performance (▶ short-term and working memory in animals).

Individual variability in baseline dopamine levels might reflect individual variation in genetic predisposition. Opposite effects of amphetamine, which increases both dopamine and noradrenaline transmission, as well as tolcapone are seen on PFC activity during n-back performance as a function of genetic variation in COMT (catechol-*O*-methyltransferase). Amphetamine and tolcapone increase the efficiency of PFC processing during n-back performance in subjects homozygous for the val allele of the COMT gene polymorphism, who have hypothetically reduced PFC dopamine function. By contrast, amphetamine and tolcapone reduce efficiency of PFC processing in subjects homozygous for the met allele, who have hypothetically enhanced PFC dopamine function (e.g., Mattay et al. 2003).

Theoretical models and preliminary results suggest that the effects of dopaminergic drugs on working memory will depend also on the neural locus of drug action. For example, bromocriptine, which stimulates dopamine receptors, modulated the flexible updating of information during encoding of a DMTS test and these effects are accompanied by modulation of neural activity in the striatum. Conversely, bromocriptine modulated activity in the PFC during (the resistance to distraction in) the delay period of a DMTS test (Cools and D'Esposito 2009). Further study is necessary to identify the neural loci of dopaminergic drug action during component processes of working memory.

Research with experimental animals and computational modeling work has suggested a particularly important role for D1 receptor stimulation in the on-line maintenance of information in working memory (short-term and working memory in animals). However, agonists used in human research so far (i.e., bromocriptine, pergolide) have affinity for both D1 and D2 receptors. The lack of selective D1 receptor agents available for human research has limited the ability to investigate the supposed D1 receptor selectivity of dopaminergic drug effects on working memory. Future study should address this issue,

for example, by making use of receptor-selective ▶ genetic polymorphisms or neurochemical PET imaging with receptor-selective ligands.

Similar lack of methods available for human research prevents the study, in human volunteers, of another current hypothesis, which states that effects of dopamine depend on the mode of transmission affected. Specifically, phasic and tonic modes of dopamine transmission might influence different (updating vs. maintenance) component processes of working memory.

Noradrenergic Drugs

Although much work with experimental animals has focused on a role of ▶ noradrenaline (in particular the alpha-adrenergic system) in (the maintenance components of) working memory (▶ short-term and working memory in animals), work with humans has concentrated more often on long-term and emotional memory. Nevertheless, empirical studies using selective noradrenergic manipulations in human volunteers have revealed a role for, in particular, the beta-adrenergic system in modulating (executive components of) working memory, perhaps via their well-accepted modulation of (selective and sustained) attentional processes (▶ attention). Specifically working memory performance is consistently impaired by the beta-blocker ▶ propranolol, which penetrates the blood-brain barrier easily, but generally not by ▶ oxprenolol and atenolol, which have more limited central activity. The α_2 adrenoceptor agonist clonidine also generally impairs working memory, possibly via a presynaptic mechanism of action. However, dose-dependent effects of clonidine as well as effects of other α_2 adrenoceptor agonists (like guanfacine), α_2 adrenoceptor antagonists (like ▶ yohimbine) and acute noradrenaline potentiation with ▶ reboxetine are less consistent (Barch 2003; Chamberlain et al. 2006; Ellis and Nathan 2001).

Cholinergic Drugs

Cholinergic drugs are known to affect working memory performance. Specifically, working memory performance benefits from agents that enhance cholinergic function, such as ▶ physostigmine, while being impaired by agents that block cholinergic function, such as ▶ scopolamine (Barch 2003; Ellis and Nathan 2001). The effects might be receptor-specific, with muscarinic and nicotinic receptors mediating distinct (spatial and non-spatial) types of working memory. Cholinergic effects are particularly pronounced in the presence of distraction.

Consistent with the well-known link between acetylcholine and stimulus detection (or vigilance), cholinergic effects in working memory are hypothesized to reflect changes in the selectivity of attentional processing during encoding, thus simplifying demands during maintenance and retrieval. In keeping with this hypothesis are findings that cholinergic antagonists, like scopolamine which is sometimes referred to as a "memory-inhibitor," impair the encoding but not the maintenance or the retrieval of new information. Furthermore, the anticholinesterase inhibitor physostigmine, sometimes referred to as a "memory-enhancer" improved accuracy on a task that maximized demands for ▶ attention, while leaving unaffected accuracy on a matched working memory task. Neuroimaging results from studies with physostigmine have substantiated hypotheses from work with experimental animals that acetylcholine promotes stimulus-driven shifts in attention by enhancing encoding- and attention-related activity in the posterior sensory cortex (Bentley et al. 2004).

Serotoninergic Drugs

Although manipulations of the indolamine ▶ serotonin (5-HT, 5-hydroxytryptamine) have been shown to alter performance on tasks involving long-term (verbal) memory ▶ consolidation and affective components of impulse control processing, it remains unclear whether serotonin is involved in working memory. Effects on memory of the most common procedure to manipulate central serotonin in humans, the dietary ▶ acute tryptophan depletion (ATD) procedure are generally restricted to delayed recall, not extending to immediate recall. ATD also does not affect spatial working memory, consistent with a lack of effect of PFC 5-HT loss on spatial working memory performance in monkeys (▶ short-term and working memory in animals). Furthermore, ATD administered an hour after word learning left delayed recall unaffected. These data suggested that ATD affects memory consolidation rather than the encoding or retrieval of information. Few studies have examined effects of selective serotonin receptor agents on working memory. One study revealed that ▶ fenfluramine impaired performance on a spatial working memory task in a delay-dependent manner. Effects of ketanserin, a $5HT_{2A}$ receptor blocker, on spatial working memory tasks are inconsistent. It is not unlikely that any effects of $5HT_2$ receptor stimulation or blockade reflect indirect effects on dopamine transmission. Further work is required to investigate interactions between 5-HT and dopamine as well as acetylcholine, and the possible receptor selectivity of any effects (there are at least 17 serotonin receptors which may serve different functions).

Other Psychoactive Drugs

The ▶ benzodiazepine sleeping pills and tranquillizers (e.g., ▶ triazolam, ▶ diazepam [trade name Valium],

►lorazepam) are some of the best known drugs to cause memory impairment and facilitate the transmission of the major inhibitory neurotransmitter ►GABA (γ-aminobutyric acid). However, like the so-called memory-enhancing (anti-dementia) drugs, which enhance cholinergic transmission, these benzodiazepines are thought to act primarily on processes other than those affecting qualitative aspects of working memory. These processes include episodic memory (►long-term memory humans) and/or processing speed (Curran and Weingartner 2002).

The NMDA receptor antagonist ►ketamine, which affects the transmission of the major excitatory neurotransmitter ►glutamate, produces impairments on manipulation in working memory as well as other so-called frontal tests, known to rely on the executive components of working memory (Curran and Weingartner 2002).

The wake-promoting agent ►modafinil, which affects the catecholamine, glutamatergic, GABAergic, orexin and histamine systems in the brain, while having little abuse potential, has been shown to improve working memory in a number of studies in healthy volunteers (with or without sleep-deprivation), with some evidence for dependency on baseline performance. Improved working memory following modafinil has also been observed in patients with ADHD, schizophrenia and depression and might reflect primary modulation of the catecholamines (Minzenberg and Carter 2008).

Notes of Caution

Psychoactive drugs modulate the effects of neurotransmitter systems that are diffuse and widespread, innervating large undifferentiated parts of cortex (and subcortical structures). Receptors of the different neurotransmitters are often co-localized on the same cells. Therefore, despite clear evidence for distinct functions, the different systems must interact to determine optimal working memory. Further, drugs with preferential effects on one system (e.g., serotonin, glutamate) might exert secondary effects on other systems (e.g., dopamine). In addition, most drugs are not selective for one particular system. For example, propranolol also exhibits affinity for serotonin receptors.

Conclusion

Working memory is disturbed in a range of neurological and psychiatric disorders, including schizophrenia, Parkinson's disease, attention deficit hyperactivity disorder and traumatic brain injury. The treatment of these cognitive deficits will benefit from a better understanding of the psychopharmacology of human working memory. Consistent with the observation that all these disorders implicate abnormal dopamine neurotransmission is the conclusion that human working is most sensitive to drugs that affect dopamine neurotransmission. Particularly pronounced are effects of dopaminergic drugs on tests measuring executive and flexible updating components of working memory. This might reflect the fact that compounds used for human research all act at D2 receptors.

The direction and extent of these drug effects vary greatly between different tasks and between different individuals. Factors that contribute to this variability include task demands and baseline dopamine levels in underlying brain regions. Further work is required to establish the regional selectivity of working memory processes and dopaminergic drug effects. Drugs affecting acetylcholine also modulate performance on working memory tests, probably via altering attentional processes. Working memory is less consistently sensitive to drugs affecting serotonin neurotransmission. Further research is necessary to elucidate the role of noradrenaline, glutamate and GABA in human working memory.

Cross-References

►Attention
►Behavioral Flexibility: Attentional Shifting, Rule Switching, and Response Reversal
►Cognitive Enhancers
►Methylphenidate and Related Compounds
►Modafinil
►Short-Term and Working Memory in Animals
►Tryptophan Depletion

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Short-Term Memory

Definition

A protein synthesis-independent type of memory in charge of maintaining recently acquired information behaviorally available while long-term memory is being consolidated.

Short-Term Plasticity

► Synaptic Plasticity

Shyness

► Social Anxiety Disorder

Sibutramine

Definition

Sibutramine is an amphetamine derivative that is used as an appetite suppressant. It is a serotonin and norepinephrine reuptake blocker. It is indicated as an antiobesity agent as an adjunctive therapy within a weight management program for those that do not respond to diet alone.

Cross-References

► Appetite Suppressant

Side Effects

► Drug Toxicity

Signal Detection Theory

Definition

A quantitative method of analyzing behavioral data that discriminates between independent indices of overall discriminability (e.g., of discriminative stimuli or of memory traces) and response bias, which might reflect motivational factors or a particular response (e.g., spatial) bias. Useful, for example, in separating pain measures into their sensory and emotional concomitants.

Signal Transduction Pathways

► Signaling Cascades

Signaling Cascades

Synonyms

Signal transduction pathways

Definition

The molecular events that link extracellular stimuli to intracellular responses by means of a multistep sequence of events, generally integrating and amplifying.

Signals

► Discriminative Stimulus
► Drug Cues

Sildenafil

Definition

Sildenafil is a PDE5 inhibitor that is sold under the name Viagra for the treatment of erectile dysfunction. Its primary competitors on the market are vardenafil (Levitra) and tadalafil (Cialis). It is also on the market under the name Revatio to treat arterial pulmonary hypertension. Of note, sildenafil is currently being tested as a possible treatment for stroke.

Cross-References

► Erectile Dysfunction
► PDE5 Inhibitors
► Phosphodiesterase Inhibitors
► Pulmonary Hypertension

Silencing RNA

► siRNA

Simulation Models

Synonyms
Animal model with construct validity

Definition
An animal model intended to model a specific human disorder as closely as possible. It typically involves mimicking the etiology or the pathology of the disease and subsequently assessing whether the resulting changes in brain and/or behavior are similar to those found in humans with the disease.

Cross-References
► Schizophrenia: Animal Models

Simulations of Psychopathology

► Animal Models for Psychiatric States

Sinemet

► Anti-Parkinson Drugs

Single Barrel Micropipette

Definition
A single micropipette, filled with saline solution, usually employed for the recording of neuronal activity.

Single Nucleotide

► Single-Nucleotide Polymorphism

Single-Nucleotide Polymorphism

Synonyms
Polymorphism; SNP

Definition
DNA sequence variations that occur when a single nucleotide (adenine, thymine, cytosine, or guanine) in the genome sequence is altered; usually present in at least 1% of the population. For example, two sequenced DNA fragments from different individuals, AAGCCTA to AAGCTTA, contain a difference in a single nucleotide.

Cross-References
► Gene Expression and Transcription
► Haplotype
► Pharmacogenetics
► Pharmacogenomics

Single Photon Emission Computed Tomography

► SPECT Imaging

Single Photon Emission Tomography (SPET)

► SPECT Imaging

Siphonodontaceae

► Celastraceae

siRNA

Synonyms
Short interfering RNA; Silencing RNA; Small interfering RNA

Definition
siRNA stands for small interfering RNA, also known as silencing or short interfering RNA. In contrast to classical antisense oligonucleotides, siRNA is a class of double-stranded RNA molecules, 19–25 nucleotides in length,

with 2-nucleotides 3′ overhangs on either end and a phosphate group at each 5′ end (Fig. 1A). siRNA can efficiently knock down expression of target genes via the RNA interference (RNAi) pathway, which was first described in the nematode worm *Caenorhabditis elegans* in 1998 by Andrew Z. Fire and Craig C. Mello. Any gene of interest with known sequence can be targeted by siRNA that match the mRNA sequence. siRNA may also recruit RNAi-related pathways, including activation of cellular antiviral mechanisms (e.g., the interferon response) or interference with the chromatin structure of the genome.

Cross-References

- ▶ Antisense Oligonucleotides
- ▶ RNA Interference
- ▶ RNAi

Sirolimus

- ▶ Rapamycin

Site-Specific Knockout

- ▶ Conditional Knockout

Skilled Performance

- ▶ Psychomotor Performance in Humans

Sleep

Definition

Sleep is a recurring state of inactivity accompanied by loss of awareness and a decreased reaction to the environment. It is accompanied by characteristic, complex patterns of physiological activity and behavior and is found in all mammalian species. Its function is unclear but may involve restoration of brain and bodily functioning.

Cross-References

- ▶ Insomnia

Sleep Apnea

Definition

Sleep disorder involving temporary cessation of breathing during sleep.

Sleep Bruxism

Definition

A stereotyped movement disorder characterized by grinding or clenching of the teeth during sleep. The disorder has also been identified as *nocturnal bruxism*, *nocturnal teeth grinding*, and *nocturnal teeth clenching*. Among the symptoms of sleep bruxism are abnormal wear on the teeth, the grinding sounds associated with bruxism, and jaw muscle discomfort.

Cross-References

- ▶ Arousal Disorders
- ▶ Confusional Arousals
- ▶ Night Terrors
- ▶ Parasomnias
- ▶ Sleepwalking

Sleep Enuresis

- ▶ Parasomnias

Sleep Paralysis

- ▶ Parasomnias

Sleep Related Dissociative Disorder

- ▶ Parasomnias

Sleep Related Eating

- ▶ Parasomnias

Sleep Terrors

► Parasomnias

Sleeplessness

► Insomnias

Sleepwalking

► Parasomnias

Slow-Release Morphines

Synonyms
SROMs

Definition
SROMs are a group of pure opiate agonists that are products of ► morphine with retarded release galenics and are only registered in some European countries for the indication of opioid maintenance treatment. SROMs are suitable for patients who do not tolerate other agents such as ► methadone because of side effects or show an inadequate suppression of withdrawal symptoms.

Slow Waves

► Function of Delta Waves

Small Interfering RNA

► siRNA

Smart Drugs

► Cognitive Enhancers: Neuroscience and Society

Smooth Pursuit

► Eye Movement Tasks

Smooth Pursuit Task

Definition
A simple eye movement task in which participants follow a target with their eyes as it moves smoothly backward and forward on the horizontal plane. Important measurements include velocity gain (the ratio of eye velocity to target velocity) and the number of saccades that occur during pursuit.

SMS201-995

► Octreotide

SNP

► Single-Nucleotide Polymorphism

SNRI Antidepressants

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Synonyms
Serotonin-norepinephrine reuptake inhibitors

Definition
The serotonin-norepinephrine reuptake inhibitors (SNRIs) are a class of ► antidepressants that simultaneously inhibit the reuptake of both ► serotonin and ► norepinephrine. SNRIs are primarily used to treat ► major depressive disorder (MDD).

Following the development of the tricyclic antidepressants (TCAs), the monoamine oxidase inhibitors (MAOIs), the selective serotonin reuptake inhibitors (SSRIs), and the norepinephrine-dopamine reuptake inhibitors (NDRIs), SNRIs are one of the most recent classes of antidepressants

approved for the treatment of MDD. Many TCAs, such as ▶ clomipramine, ▶ imipramine, and ▶ amitriptyline, also inhibit the reuptake of serotonin and norepinephrine. However, the SNRIs differ from the TCAs in two major ways: (1) they do not possess a tricyclic-like structure and (2) they do not have a clinically-relevant affinity for any monoaminergic, histaminergic, or cholinergic receptors or for the sodium channel. As a result, they are safer (i.e., have a lower risk of arrhythmia and seizures) and better-tolerated (i.e., have a lower risk of sedation, somnolence, and weight gain).

Pharmacological Properties

Four SNRIs have been developed and marketed to date: ▶ venlafaxine, ▶ desvenlafaxine, ▶ duloxetine, and ▶ milnacipran. First introduced in the early 1990s, venlafaxine is the prototypical agent of this class. Milnacipran was introduced as an antidepressant in the late 1990s in Europe, and received approval in 2009 for the treatment of fibromyalgia in the United States. Duloxetine was first marketed in 2004 in the United States. Desvenlafaxine, the newest SNRI, is an active metabolite of venlafaxine.

The efficacy of all four SNRIs in the treatment of MDD in adults has been well established in multiple randomized, double-blind, placebo-controlled trials (Montgomery and Anderson 2006; Papakostas and Fava 2007; Perahia et al. 2006; Ricknes et al. 2004). In addition to their use as antidepressants, some SNRIs have been approved by the United States Food and Drug Administration (FDA) for the treatment of other Axis I disorders in adults, including ▶ generalized anxiety disorder (venlafaxine, duloxetine), ▶ panic disorder (venlafaxine), ▶ social anxiety disorder (venlafaxine), and fibromyalgia (duloxetine, milnacipran).

It has been proposed that SNRIs may be more effective in the treatment of MDD than the SSRIs, perhaps due to their simultaneous action on both serotonin and norepinephrine transporters (Papakostas et al. 2007). However, whether this difference is clinically relevant (Papakostas et al. 2007), and whether it applies to all SSRIs remains unclear (Montgomery and Anderson 2006; Lam et al. 2008).

The efficacy and safety of the SNRIs have not been established for children, adolescents, or the elderly. The United States FDA placed a "▶ black box warning" (signifying the possibility of severe adverse events) on the labeling for all four SNRIs based on pooled analysis of data for nine antidepressants (SSRIs and others) describing an increased risk of suicidal ideation and/or suicide gestures in a pediatric population. Therefore, close monitoring is required when prescribing SNRIs or other antidepressants for MDD, especially in vulnerable populations.

Pharmacokinetics

All four SNRIs are well absorbed after oral ingestion and show modest to excellent bioavailability; they are primarily metabolized in the liver and eliminated by the kidney.

The ▶ bioavailability of venlafaxine extended-release capsule formulation is about 45%, while for the immediate release tablet it is 100% (relative to an oral solution). Approximately 27% is protein-bound. Venlafaxine is metabolized extensively by the hepatic ▶ cytochrome P450 (CYP) isozyme 2D6; O-desmethylvenlafaxine is its active metabolite. Approximately 87% of a dose of venlafaxine is excreted by the kidneys, 82% as metabolites and 5% remaining unchanged. The ▶ elimination half-life for venlafaxine and O-desmethylvenlafaxine are about 5 h and 11 h respectively, but they are prolonged in patients with hepatic and/or renal impairment.

After oral administration, desvenlafaxine has a bioavailability of approximately 80%, and 30% is protein-bound. It is metabolized primarily by the liver via conjugation, and to a lesser extent via the hepatic cytochrome P450 CYP 3A4. Forty-five percent of desvenlafaxine is excreted via the kidneys in an unchanged form. The elimination half-life of desvenlafaxine is 10 to 11 h, but it is prolonged in patients with impaired liver function.

Duloxetine is well absorbed after oral administration; its bioavailability ranges between 50% and 80% (decreased among smokers). It is more than 90% protein-bound. Duloxetine is metabolized by the hepatic cytochromes P450 CYP 2D6 and 1A2, and it is ultimately eliminated in the urine (70%) and feces (20%). Its half-life is approximately 12 h.

Milnacipran is well absorbed after oral use. Its bioavailability is about 85%. Protein-binding is low (approximately 13%), and it is nonsaturable. The drug is metabolized by the liver to an unknown extent, primarily via glucuronidation, and it does not appear to be metabolized via the hepatic cytochrome P450 system, suggesting that it might have some pharmacokinetic advantages (including a low drug-drug interaction potential). Milnacipran has no active metabolites. The excretion of milnacipran is mainly (90%) through the kidneys, and its half-life is 8 h (Puozzo et al. 2002).

Cross-References

▶ Antidepressant
▶ Desvenlafaxine
▶ Duloxetine
▶ Generalized Anxiety Disorder
▶ Major Depressive Disorder
▶ Milnacipran
▶ Monoamine Oxidase Inhibitors (MAOIs)
▶ Panic Disorder

- ▶ Selective Serotonin Reuptake Inhibitors (SSRIs)
- ▶ Serotonin Syndrome
- ▶ Social Anxiety Disorder
- ▶ Tricyclic Antidepressants (TCAs)
- ▶ Venlafaxine

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Social Anxiety Disorder

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Synonyms

Avoidant personality disorder; Social phobia

Definition

Social anxiety disorder (SAD) is recognized as a highly prevalent (up to 13.3% lifetime prevalence rate) as well as a chronic disorder with onset during the teenage years (Kasper 1998). Although the disorder is associated with significant disability, which includes educational and occupational capabilities that has a negative impact on the ▶ quality of life, it is highly underdiagnosed and undertreated. SAD is recognized as a serious medical condition that is accompanied by significant disability since it starts in early life and therefore impairs the otherwise occurring socialization including the development of coping skills. This view has been strengthened by data showing that SAD cannot simply be equated with shyness or with avoidant personality traits, and by evidence that this disorder is a discrete entity associated with distinct psychobiological dysfunctions (Lanzenberger et al. 2007) and responsive to specific pharmacotherapeutic interventions (Kasper et al. 2003).

Within SAD, patients have been divided into those with generalized and non-generalized (discrete, specific, circumscribed, and performance anxiety) symptoms. Whereas generalized SAD affects the individual in more than one social situation, non-generalized SAD is specific and circumscribed and may be for instance performance anxiety with pure speaking fears. Pharmacotherapeutic dissection of different SAD subtypes may be possible and it emerged that clear ▶ placebo differences can only be achieved with generalized SAD. For performance anxiety beta-blockers are useful but demonstrated to be ineffective in generalized SAD.

Role of Pharmacotherapy

Most pharmacotherapeutic studies, specifically the systematic ones with ▶ selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (▶ SNRIs) have been carried out in patients suffering from generalized SAD. The most commonly used primary efficacy scale in medication studies of SAD is the Liebowitz social anxiety scale (LSAS) (Liebowitz 1987), which enables also the comparativeness of the studies.

Early work demonstrated that irreversible ▶ monoamine oxidase inhibitors (MAOIs; e.g., ▶ phenelzine) are effective in the treatment of SAD, but these agents are limited by their side effect profile, the need for dietary precautions, and drug interactions (Versiani 2000). Studies with the reversible MAOI ▶ moclobemide indicated effectiveness in earlier but not later development program studies and have therefore not been granted indication status by health regulatory authorities (Brunello et al. 2000). More recent work has established the efficacy of several SSRIs (Montgomery et al. 2004), and these agents have been recommended as first-line pharmacotherapy agents.

The available ▶ placebo-controlled studies have been carried out for acute as well as long-term efficacy, including relapse prevention (see Table 1). Interestingly, the question if psychological treatment is able to enhance the pharmacotherapy has only been addressed in one study and there are no placebo-controlled studies to

Social Anxiety Disorder. Table 1. Social anxiety disorder.

	SSRIs	TCAs	Benzodiazepines	Others
Acute efficacy	Escitalopram, Fluoxetine, Fluvoxamine, Paroxetine, Sertraline	–	Alprazolam, Bromazepam, Clonazepam	CBT, Phenelzine, Moclobemide, Brofaromine, Venlafaxine, Gabapentin, Pregabalin, Olanzapine
Long-term efficacy	Escitalopram, Fluvoxamine, Paroxetine, Sertraline	–	–	CBT, Phenelzine, Moclobemide, Venlafaxine
Relapse prevention	Escitalopram, Paroxetine, Sertraline	–	Clonazepam	CBT
Enhanced efficacy of psychological treatment	Sertraline	–	–	–
After nonresponse	–	–	–	–

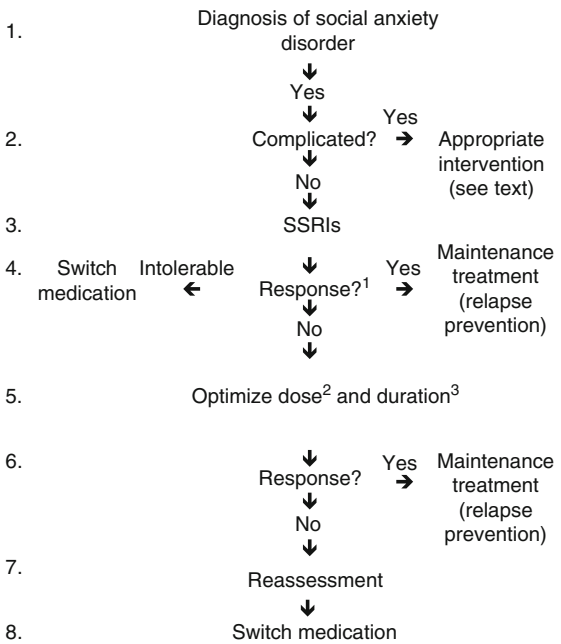
Placebo-controlled studies (*SSRIs* selective serotonin reuptake inhibitors; *TCAs* tricyclic antidepressants; *CBT* cognitive behavioral therapy) (Baldwin et al. 2005)

guide the clinicians which treatment to administer after treatment-nonresponse, an approach which is available for the indication of depression. The main group of medications which has been studied is SSRIs and interestingly there are no studies with ▶ tricyclic antidepressants (TCA) which indicates that pharmacotherapy of SAD was developed after the introduction of SSRIs for the indication of depression. A few studies with ▶ benzodiazepines and SNRIS as well as ▶ pregabaline have been conducted. Pregabaline is not a benzodiazepine as may be suggested by the name. It differs insofar from the other available medications used since it binds with high specificity to the α_2-δ subunit of P/Q-type voltage-gated Ca^{++} channels, thereby reducing the influx of Ca^{++} at nerve endings and attenuating the release of excitatory neurotransmitters such as norepinephrine, glutamate, aspartate, substance P, and calcitonin gene-related peptide.

In addition to pharmacotherapeutic approaches, cognitive behavioral psychotherapy has been studied in a placebo-controlled design indicating superior efficacy to placebo, however, no medication control group has been assigned in these treatment trials.

Cross-Reference

There is a high rate of ▶ comorbidity (up to 60%) between depression and anxiety disorders as well as between anxiety disorders themselves and antidepressants have been used and granted indication by health authorities for both depression and anxiety disorders. It is apparent, that both SSRIs and SNRIs work in depression as well as in different forms of anxiety disorders, including SAD, and for SAD additionally benzodiazepines (▶ clonazepam) as well as to a lower extent pregabaline have been studied (Zohar et al. 2002).



SSRIs: Selective serotonin reautake inhibitors

[1]Response indicates 50% symptom reduction, remission may take 2–3 months

[2]Most likely increase, same dosages as in depression

[3]6–8 weeks

Social Anxiety Disorder. Fig. 1. Algorithm for the pharmacotherapy of social anxiety disorder in primary practice (After: Stein et al. 2001).

An algorithm for the pharmacotherapy of SAD in primary practice has been developed by Stein et al. (2001) and divided into different steps as outlined in Fig. 1. Firstly, this algorithm indicates the necessity to establish

a diagnosis and to clarify if certain complications may have an impact on the choice of medication to be used, like comorbid severe depression or suicidality which requires specific therapeutic regimens. If this can be ruled out SSRIs could be initiated and if patients are responsive a maintenance therapy can be continued with the same dosage of medication with which remission has been achieved. Interestingly, the same dosages are used for SAD as for depression. Whereas in depression a clear response might be observed already after 2–3 weeks' time this usually takes at least 6–8 weeks in SAD, since patients need to experience the social situation in which the symptoms appeared before. If intolerable side effects are emerging, the switch to another SSRI or SNRI can be considered, although there are no placebo controlled studies to justify this approach. Thereafter an optimization of the dosage (most likely an increase) as well as the duration of treatment (over 8 weeks) needs to be taken into account before a treatment response can be expected. If this regime does not lead to remission a reassessment as well as a switch to another type of medication, like pregabaline, can be considered. However, it needs to be noted that pregabaline does not have the indication for SAD, and that this approach is also not substantiated by placebo-controlled switch studies.

Conclusion

SAD is not a mild form of mental disorder but a clinical meaningful medical illness with an established pathophysiology which deserves early diagnosis and distinct treatment. Since SAD starts early in life and may result in a disabling disorder, the treatment of selected pharmacotherapeutic and psychotherapeutic interventions need to be initiated early in the course of the illness. Our continued progress in understanding and managing SAD will result in a progress in delineating the subtypes and treatment responses to this condition.

Declarations of Interest

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Social Behavior

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Definition

Social behavior is behavior between members of the same species. However, depending upon the context, it may more specifically signify nonaggressive, nonterritorial, nonsexual behavioral interactions between members of the same species.

Impact of Psychoactive Drugs

Social Behavior

Social behavior is in its broadest sense behavior taking place between members of the same species. It can therefore include territorial, parental and sexual behavior

as well. However, individuals living in groups have a special need to communicate because they have to share resources, coordinate activities such as hunting or foraging, defend the territory against intruders and protect the group against predators. Social species such as humans, monkeys and rats have therefore developed communication systems and internal organizational structures that allow them to live in proximity without having to engage in frequent fights over resources. Fighting may cause injury and can jeopardize the welfare of the individual and of the group, and it is therefore something that must be avoided if possible.

Drug effects in animals are typically studied to predict how the drugs may affect human behavior and the relevance of studying drug effects on social behavior in animals such as rats, mice, and monkeys may seem rather distant to the complexity of human social behavior and structure. However, humans are also a social species that has a highly hierarchical organization and are very territorial, and while the exact details will differ between species, the more general responses can be comparable. We often view human behavior to be fundamentally different from animals, but a very obvious example of human territorial behavior is how we define countries and borders and the vigor with which we defend our territory. Another more mundane example is how we feel if someone sits in "our chair" in a classroom. The social hierarchy is similarly very obvious in many work situations and when observing an interaction between two individuals with different status in an organization: from body posture and movements it can easily be understood, which of the individuals has the higher status. The military is an example of an organization where this hierarchy has been practiced to its fullest extent.

In this essay, social behavior will be used to indicate nonaggressive, nonterritorial and nonsexual social behaviors between members of a species that live in social structures. It is therefore the normal behavior we express when interacting with other people in a daily-life situation. This type of social behavior is disturbed in many diseases such as ► depression, ► anxiety, social phobias, ► schizophrenia, and ► autism; it may be affected by drug side effects, e.g., corticosterone, and it may be changed as a result of another condition, e.g., chronic pain.

In relation to psychopharmacology, social behavior represents a very interesting group of behaviors. They are important aspect of human behavior with a clear biological function, they are disrupted in many diseases, they are complex behaviors that must be normalized by a treatment, and because it is a set of complex active behaviors it is relatively easy to dissociate the nonspecific, e.g., sedation from specific drug effects.

Social species usually have a rich repertoire of communication signals, but typically for other species than our own we are only able to observe and record a fraction of these. For example, rats and mice rely to a great extent on olfactory signals and ► ultrasound in their communications and presumably also use very discrete facial and body postures that we do not recognize, and the level of information that we are able to extract from an encounter between two individuals is therefore very limited. This therefore does not mean that their communication systems and social organization are simple and primitive, but rather that we are not able to record and interpret the true level of complexity. For example, most studies on social behavior between pairs of rats record time spent investigating, following, and grooming the other individual as an index of the level of social behavior. These measures are very crude and probably disregard 95% of the true communication that exist between the rats. However, for the purpose of studying drugs that interfere with the social structure, this may be sufficient – it should just be realized that it does not represent the true level of communication.

A number of factors need to be considered, when studying social behavior. One factor is, as mentioned above, that each species will use different routes of communication, e.g., visual, auditory, olfactory, and postures and movements. Humans have, compared to most animals, a rather inferior olfactory sense and we will rarely be able to monitor communication using this channel. Similarly, we will rarely be sensitive to small discrete postures and movements in a different species than our own, and for auditory signals, we cannot perceive signals above 15 kHz unless we use special equipment. A second factor is strain differences in the chosen species. There are considerable differences between different lines of rats and mice in terms of their level of ► aggression and anxiety, and this will affect the study. A third factor is the influence of other behavioral categories on the observed social behavior. ► Sex differences and estrus cycle will affect the level of sexual behaviors in an experimental situation and repeated exposure to a particular arena may prompt the appearance of strong territorial behaviors, thus increasing the level of aggressive behaviors. A fourth factor is that diseases, just as for humans, will affect the behavior of an animal and particularly for transgenic animals or aged animals, this can be a concern. It has for example been reported that some of the transgenic lines of mice carrying an Alzheimer's disease mutation have inferior vision and reduced level of hearing. Also, in case a drug

causes pain or induces, e.g., nausea, this will affect behavior as well.

A final factor is that experimental conditions and handling will affect the outcome of an experiment. A stressed animal or an animal placed in an aversive experimental situation will necessarily exhibit a different behavior compared to a nonstressed or a nonanxious animal. These factors need to be controlled and what may constitute an aversive stimulus for that particular species needs to be considered. However, it is also possible to use aversive stimuli to control the types of behavior that the animals express and that are studied. For example, the light level in an arena will have considerable impact upon the behavior of a rat. High-light conditions will produce an anxiogenic state in the rat, which will reduce the level of active behaviors, whereas a low-light condition will increase the level of natural behaviors, e.g., explorative and social behaviors (Whishaw and Kolb 2005). The olfactory level in the arena and the number of repeated visits to the arena will affect the speed with which the animal begins to perceive the arena as a part of its territory and thereby the level of aggressive behaviors it expresses in order to defend its territory, if confronted with a conspecific. The level of aggressive behavior is also affected by the housing condition of the animals, e.g., in rats single housing will increase the aggression level. Light/dark cycle will affect the sensitivity of the animals to drugs. If animals are tested during their normally active period, i.e., during the night for a rat, it will be more sensitive to drug effects compared to testing conducted in the day time, i.e., the rats inactive period. Finally, handling can have unexpectedly strong effects on behavior, e.g., handling a rat by the tail can stress it so much that it becomes impossible to study social interations, and the presence of a computer in the experimental room can affect behavior because the rats may be able to hear it.

Standard Test Paradigms

Social behavior can in principle be studied in any situation that involves two or more members of the same species. Complex situations involving many members living in a stable structure is likely to provide more detailed information on the effects of drugs on normal behavior or on behavioral abnormalities in animals carrying a disease, but it can be very difficult to standardize a test of this type to allow comparison of different drugs and the amount of time required to study drug effects may become so demanding that it in practice becomes impossible to compare drug series. For these reasons a number of simplified, standardized behavioral tests have been developed that allow the experimental observation of some aspects of social behavior thought to be relevant to human behaviors.

One of the most routinely used tests for social behavior is the ▶ social interaction test where two rats or mice are placed simultaneously into an arena and where their level of social behavior is recorded for 7–10 min (File and Seth 2003). The animals may be familiar with the arena and to each other. The test is usually performed in a high-light and a low-light configuration. For the high-light configuration, the arena is brightly illuminated and this will create an aversive environment since rats and mice in general avoid open, brightly lit areas. Their natural tendency will be to avoid the center of the arena and to stay in the periphery of the arena, where they usually remain inactive. Using this design, it has been shown by many researchers that anxiolytic drugs such as the ▶ benzodiazepines, ▶ diazepam and ▶ chlordiazepoxide, will increase the level of social interaction, indicating a reduced level of anxiety in the animals, whereas drugs that lack ▶ anxiolytic effects are inactive. However, it should be noted that the avoidance of open spaces is a biologically appropriate response for a rat and a mouse, and the test therefore studies drug effects on natural behaviors and not on pathological anxiety, which is the type we seek to treat in human patients.

In the low-light configuration, the arena is only illuminated by dim red light to simulate a night-time situation, which is non-aversive to rats and mice, and they will typically explore the entire arena and engage in frequent social interactions, e.g., rats will typically investigate the novel area together. Under these conditions it is possible to evaluate manipulations that disrupt social behavior, e.g. to model a disease condition, or to determine if a drug causes side effects that affect normal behavior. An example of a disease model is phencyclidine-induced social isolation (Ellenbroek and Cools 2000). ▶ Phencyclidine (PCP) is an NMDA-antagonist that often is abused by humans and it has frequently been observed that PCP will induce a type of symptomatology, which resemble the negative symptoms of ▶ schizophrenia, i.e., the inability to engage in normal social relations. PCP will potently disrupt social behavior in rats, and this disruption can be reversed by ▶ antipsychotic drugs that in patients have an effect on the negative symptoms, e.g., ▶ clozapine and ▶ risperidone, whereas drugs that only affect the positive symptoms, e.g., ▶ haloperidol or that are not effective in the treatment of schizophrenia, e.g., ▶ citalopram and diazepam, are ineffective.

A different test paradigm is the ▶ social recognition test, which typically is performed in rats, where the level

of social behavior or social interest is used as a measure of recognition. In this test, an adult rat is allowed, e.g., 5 min, to investigate a juvenile rat. The juvenile is removed and after a certain time period, e.g., 30 min, 2 h or 24 h, either the same juvenile or a different juvenile is presented to the adult rat. If the adult rat recognizes the juvenile it will spend less time investigating it compared to the situation where it is a novel juvenile. Drug studies have shown that ► nicotine, which is known to improve memory in humans, can prolong the time period in which the adult rat recognizes the juvenile, whereas ► scopolamine, which interferes with memory, reduces the time period. The social recognition test is typically used in two configurations with either a long delay or a short delay until the re-introduction of the juvenile. The purpose of using a long delay is to identify drugs that can enhance memory, e.g., for symptomatic treatment of memory deficits in ► Alzheimer's disease, by demonstrating that a drug extends the time period in which the adult animal recognizes the juvenile. The purpose of using a short delay at which normal animals will recognize the juvenile is to determine whether a drug inhibits normal memory processes, e.g., caused by side effects, or to determine if animals display memory deficits, e.g., in connection with disease models, and whether drugs are able to reverse these deficits. Examples of the latter are scopolamine-induced memory deficits and cognitive deficits in disease-models of e.g., Alzheimer's disease, schizophrenia, and ► stroke. Finally, it is possible to administer the investigative drug at different time points in the testing sequence to determine which aspects of the memory process it affects, e.g. administering it after the first presentation of the juvenile to determine if it affects the ► consolidation of memory.

Cross-References

► Animal Models for Psychiatric States
► Antidepressants
► Antipsychotic Drugs
► Anxiety: Animal Models
► Autism Spectrum Disorders and Mental Retardation
► Benzodiazepines
► Cognitive Enhancers
► Dementias: Animal Models
► Dementias and Other Amnestic Disorders
► Depression: Animal Models
► Ethopharmacology
► Nicotine
► Schizophrenia
► Schizophrenia: Animal Models

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Social Challenge

► Social Stress

Social defeat

Definition

Social defeat is a procedure in which a smaller "intruder" rodent (rat or mouse) is introduced into the cage of a larger and aggressive "resident" rodent. The resident rat usually attacks the intruder rodent until it manifests a submissive posture. Additionally, the mere presence of the resident rodent (a threat condition) is sufficient to provoke physiological and behavioral stress responses in the intruder rodent that are similar to those obtained after the physical confrontation (Miczek et al., 2008).

Cross-References

► Aggression

Social Impairment

Definition

Individuals with ► pervasive developmental disorders (PDDs) have core social impairments that are persistent and severe. These impairments can be seen through deficits in multiple different behavioral and relationship realms. Core social impairment seen through nonverbal behavior can consist of deficits in eye contact, facial expression, and gestures that are used to help regulate social interaction. Often there is a failure to develop age-appropriate friendships. Core social impairments can consist of a lack of spontaneous seeking to share achievements or interests with other individuals. They are also commonly exhibited by a deficit in social reciprocity with individuals having a decreased awareness of others. They

can be exhibited by a lack of empathy and awareness of the needs of others.

Cross-References

► Autism Spectrum Disorders and Mental Retardation

Social Interaction Test

Definition

Two animals, typically rats or mice, are placed into an arena and their interactions, for example, investigation, following, and grooming, are recorded for a period of time, usually 5 to 10 min. Social behaviors such as following, adjacent lying, and anogenital sniffing are recorded by an observer or via automated image analysis. Many drugs modulate behavior on the social interaction test: benzodiazepines, MDMA, and oxytocin tend to increase social interaction while amphetamines, cannabinoids, NMDA antagonists, and withdrawal from various ► drugs of abuse tend to decrease social interaction. In the high-light version of the then test, the arena is brightly illuminated and this creates an aversive situation for the animals, which results in low levels of social interaction. In this configuration, it is possible to identify drugs or manipulations that reduce the inferred level of anxiety in the animals, that is, they result in an increased level of social interaction. In the low-light version, the arena is only illuminated with low, typically red light in order to minimize aversive cues. In this configuration, the level of interaction will be maximal and it is possible to test drugs or manipulations that reduce the normal level of social interactions. In addition to light level, which is the strongest experimental factor, the animals' familiarity with the arena can be varied, for example, by having been introduced to the arena prior to the testing session, and whether the animals know each other prior to the testing session. Familiarity with the arena will reduce the level of aversive cues, but will also increase the level of territorial behavior, resulting in more fighting between the animals. Familiarity between the animals being tested can reduce the level of aversive cues during the testing situation and the level of fighting, because a hierarchy does not have to be established, but it may also increase variability in the data, because the animals will have a preestablished rank that not will be present if they are unfamiliar to each other.

Cross-References

► Amphetamines
► Anxiety: Animal Models
► Benzodiazepines
► Cannabinoids
► Methylenedioxymethamphetamine (MDMA)
► Oxytocin
► Social Behavior
► Withdrawal

Social Phobia

► Social Anxiety Disorder

Social Recognition Test

Definition

The test uses social memory, that is, remembering having seen another individual before, as a measure of cognitive function. A juvenile is introduced to an adult animal, typically rats are used, for 5–7 min and the level of investigative behavior performed by the adult animal toward the juvenile is recorded. After a delay of typically 30 min, 2 h or 24 h, either the same juvenile or a novel juvenile is introduced to the same adult animal and the level of investigative behavior is recorded. If the adult animal recognizes the juvenile, the level of social investigation will be lower compared to the situation, where the adult male does not recognize the juvenile or it is a novel juvenile. In a variant of this test, an object is used instead of a juvenile animal. When the test is conducted using short delays between the two testing sessions, it is possible to identify drugs or manipulations that interfere with memory and learning, whereas for longtime delays it is possible to identify drugs or manipulations that enhance cognition.

Social Stress

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Synonyms

Social challenge

Definition

In most general terms, social stress refers to the immediate response to a change in the social life of an individual, either in response to separation or confrontation. If the social stress persists, pathological consequences become evident in suppressed reproductive, immune, and metabolic functions and in social intercourse; many cardinal symptoms of psychosis, depression, and drug abuse, such as anhedonia-like responses, dysregulated circadian rhythms, weight, and movements, emerge in vulnerable individuals.

Impact of Psychoactive Drugs

Types of Social Stress

In the definition of social stress and the response to ► stress, pressures, loads, and strains, as characterized in the physical, engineering, and military sciences, serve as metaphors for physiological, cellular, and molecular events. In biological systems, the concepts of homeostasis and allostasis are important in the definition of stress – the former defining a set point surrounded by minimal and maximal limits and the latter referring to constantly changing boundaries. Like many other stressors, maternal separation stress and stress arising from social conflict in adulthood incorporate the rapid sympathetic and slower hypothalamic–pituitary–adrenal (HPA) responses. In addition to these changes in the autonomic nervous system, many physiological and neurobiological features are unique to the specific social stress.

Social Isolation, Crowding, and Instability

Most primate species and other socially cohesive species, such as rats, require social contact, and deprivation of this contact constitutes a type of social stress that eventually results in behavioral, physiological, and neurochemical pathologies (*social isolation*). In contrast, in animal species that disperse after puberty, single housing mimicks the life of males who mark, patrol, and defend their territory and exclude other males. The opposite type of social stress is represented by *crowding*, which in most cases leads to lethargy and eventual increased mortality. High population density profoundly alters the toxicity to drug action as demonstrated earlier by increased amphetamine toxicity in crowded mice. In species with well-defined social hierarchies, the establishment of social stratification by *instability* can be stressful. Experimentally, the constant rearrangement of social groups of laboratory animals has been used to induce constant social instability, although with questionable validity.

Maternal Separation Distress

Two types of *maternal social separation* stress have been identified with behavioral and neurobiological consequences that continue into adulthood and that are particularly relevant to drug abuse and affective disorders. Experimental studies in rodents have identified a critical developmental period in rodents, starting about 3–4 days after birth, during which individuals are hyporesponsive to stress in terms of glucocorticoid activation. Brief separations of pups from the dam (ca. 15 min/day) during this period render the individual more resistant to stress in adulthood, possibly related to anxiety-like responses. In contrast, prolonged separations from the dam (ca. 180 min/day) enhance the hypothalamic–pituitary response to stress in adulthood, possibly relevant to anhedonia, a core symptom of affective disorders.

The amount of play and its intensity during adolescence determine how individuals cope with stress later on as adults. Some adolescents appear to be particularly vulnerable to social defeat stress, and these episodes of stress can impair neural maturation. Of particular concern is the impact of social stress during adolescence on the later acquisition of compulsive drug taking.

Social Defeat Stress

Social stress in adulthood is experienced most often in aggressive confrontations, typically during the formation of dominance hierarchies and during the breeding season. The *socially defeated* animal rapidly learns to display the species-typical defensive and submissive postures, acts, and signals. The physiological and behavioral consequences manifest themselves by impaired social interactions, particularly reproductive activities, reduced exploration, disrupted foraging, less feeding, and drinking. Even a single episode of ► social defeat stress impairs circadian activity, nociception, and motor activity, and activates cellular activity in mesencephalic and corticolimbic nuclei. Repeated episodes of social defeat stress amplify these neurobiological and behavioral consequences over a long term. These enduring neuroadaptive changes lead to sensitized stimulant responses, similar to those after intermittent stimulant drug treatment. Repeated social defeat stress engenders also deficits in memory that relies on intact hippocampal activity.

Social Subordination Stress

When social stress is continuous rather than episodic such as in *subordinate* animals that are continuously exposed to the presence of higher ranking individuals, its behavioral repertoire and physiological functions are severely

compromised, in extreme cases leading to a morbid course. Subordinate animals are characterized by scars and wounds, inactivity, immunosuppression, elevated ACTH and glucocorticoid activity, lower androgens, eventual testicular regression, and adrenal hypertrophy. The persistent behavioral, immunological, and endocrine characteristics of a subordinate animal lead to lowered success in transmitting genes into the next generation and ensuring the survival of its offspring.

Neurobiology and Psychopharmacology of Maternal Separation Stress

GABAergic, glutamatergic, monoaminergic, and opioid peptidergic mechanisms are activated during the separation stress of an infant from the dam. In most myomorph rodents, maternal separation stress is evident behaviorally by the emission of loud and frequent ► ultrasonic vocalizations during the first 2 weeks after birth. Similar distress vocalizations are emitted in avian and primate species. These vocalizations are sensitive to the suppressive effects of agonists at the 5-HT_1 receptor family, positive modulators of the ► $GABA_A$ receptors, and $mGluR_{2/3}$ receptor agonists. Drugs which are clinically effective as ► anxiolytics (e.g., ► benzodiazepines, ► buspirone) and ► antidepressants (e.g., SSRIs, SNRIs) effectively reduce the ultrasonic distress vocalizations by rodent pups that are separated from the dam and litter mates. These vocalizations may be expressions of affective distress and serve primarily the immediate purpose to prompt retrieval by the dam and, during prolonged separations, thermoregulatory functions may become relevant. While the GABAergic, glutamatergic, monoaminergic, and opioid receptor systems continue to undergo significant maturation during the first weeks of life of rodents, the pharmacological manipulations of these targets may result in effects on affective vocal responses that differ from those in the mature adult.

Repeated maternal separation stress in the first 2 weeks after birth results in profound and long-lasting changes in the expression of the message for ► GABA, ► glutamate, and ► neuropeptides such as CRF and opioid peptides and their receptors. A key variable is the duration of the maternal separation; for example, prolonged daily maternal separations resulted in increased mRNA for CRF in hippocampal cells relative to the lower mRNA levels of CRF after short separations (180 vs. 15 min/day). Two types of long-term consequences are significant from a psychopharmacological perspective. First, rodent pups that are repeatedly separated from the dam and littermates can show depressive-like behavioral and neural phenotypes, and antidepressant treatment can prevent some of these changes. Secondly, of particular significance are the large and persistent increases in ► alcohol and stimulant self-administration and in sensitized responses to stimulant challenge in adults that were exposed during the stress hyporesponsive period to repeated long episodes of uncontrollable maternal separation stress, although these increases are limited to specific experimental conditions.

In addition to the hyporesponsiveness to psychomotor stimulants during adolescence, social defeat stress during this developmental period renders adolescents far less sensitive to the psychomotor stimulant effects of amphetamine or cocaine relative to adults in several rodent models. Repeated exposure to social defeat stress or to cocaine activates adolescent neural circuits in a remarkably similar manner suggesting shared mechanisms of emerging resilience and vulnerability.

Neurobiology and Psychopharmacology of Social Defeat and Subordination Stress

In adulthood, even a single episode of social defeat stress may increase the release of DA in mesolimbic, but not striatal structures as assessed by in vivo ► microdialysis and fast-scan voltametry, complementing earlier evidence for noradrenergic activation in both the perpetrator and victim during social confrontations. Stimulant-evoked DA rises in the ► prefrontal cortex, and ► nucleus accumbens are very large after the intruder rat has experienced several episodes of social defeat providing evidence for neural sensitization. This stress-sensitized release of cortical and accumbal DA needs to be integrated with the often reiterated hypothesis of DA's special role in reward processes.

Increased serotonergic impulse flow characterizes socially stressed tree shrews and mice, as is evident in the activity of raphé cells as well as in the terminals in the ► hippocampus. Chronic social subordination stress results also in reduced affinity and message for receptors of the 5-HT_1 family in several animal species. Persistent changes in cellular activity after repeated social defeat stress are evident not only in the raphé cells, but also in the VTA (► ventral tegmental area), prefrontal cortex, and ► amygdala.

The study of brief social defeat stress and of continuous subordination stress represents a promising source of information on account of anxiety- and depressive-like physiological and behavioral profiles in several animal models. Social defeat can engender features indicative of profound emotion, ranging from anhedonia to intense fear. The loss of social initiatives and the lack of

experiencing pleasure ("anhedonia"), most often assessed by the preference for sweet tastes, in animals that were exposed to uncontrollable, unpredictable, and chronic social defeat stress, can be attenuated by ► tricyclic antidepressants and ► SSRIs. In parallel, antidepressants can reverse the social subordination and stress-induced suppression of neurogenesis in the hippocampus. Endogenous ► brain-derived nerve growth factor (BDNF) is profoundly suppressed by continuous social subordination stress, and increased BDNF activity is detected in the VTA in animals exposed to intermittent episodes of brief social defeat stress suggesting an important role of this factor in the contrasting neuroadaptations after brief versus continuous social stress.

In anticipation of an imminent episode of social defeat stress, animals become hyperthermic and start to emit distress calls; these physiological and behavioral indices are interpreted to reflect intense emotional states. In fact, clinically effective ► anxiolytic drugs which act as positive modulators at $GABA_A$ receptors or at 5-HT_{1A} receptors attenuate these anxiety-like responses. These anxiolytic-like effects of benzodiazepines, ► buspirone, and also alcohol of the anticipatory hyperthermia and ► distress vocalizations contrast with the absence of ameliorative effects on defensive responses in reaction to social stress.

In laboratory rodent models, similar to other mild stressors such as tail pinch or foot-shock pulses, intermittent defeat stress induces a persistent, sensitized, psychomotor stimulant response upon challenge with a moderate dose of ► cocaine, ► amphetamine, ► morphine, or ethanol. As little as one defeat experience is sufficient to induce a sensitized locomotor activation to a challenge with D-amphetamine, and this effect grows in magnitude and extends in time after repeated episodes of social defeat stress. Blockade of ► glutamate receptors in the VTA prior to each stress episode can prevent the sensitizing effect of stress, and this protective effect critically depends on BDNF and phosphorylation of ERK and CREB. Behavioral and neural ► sensitization have been hypothesized to contribute to the neuroadaptations that escalate drug seeking and taking.

The long-postulated facilitative effects of social stress on drug abuse are more directly examined under experimental conditions that quantify the rate, amount, and persistence of drug intake as a result of exposure to discrete episodes of social stress. Similar to other types of intermittent stress, brief episodes of social defeat stress in laboratory rats and nonhuman primates can facilitate the acquisition of stimulant and possibly alcohol self-administration, increase the rate of regular daily drug intake, and especially increase the amount and duration of cocaine self-administration under unlimited access conditions ("binging"). Mechanistic studies have begun to delineate the glutamatergic, GABAergic, and peptidergic modulation of DA in the VTA–accumbens–prefrontal cortex–amygdala neural circuit as being critical for social defeat stress to escalate psychomotor stimulant intake.

In contrast to the intense and prolonged cocaine taking after episodic social defeat stress, continuously threatened subordinate rats responded less to a stimulant challenge in terms of locomotor hyperactivity and accumbal DA release, and they ceased self-administering intravenous cocaine sooner when given unlimited access relative to controls. There is indication that BDNF in the VTA, prefrontal cortex, and amygdala is suppressed as a result of chronic subordination stress. The divergent adaptations in BDNF cells after episodic relative to continuous social stress appear, characteristic of escalated versus suppressed cocaine taking that follow different types of stress. To which extent the controllability of stress determines the BDNF activation in the prefrontal cortex remains to be determined.

In sum, considerable evidence points to different kinds of social stress as risk factors for initiating, escalating, and resuming ► drug abuse in vulnerable individuals. The hyperdefensive behavior, weight dysregulation, signs of anhedonia, altered sleep, and activity patterns, and the profile of HPA activity in subordinate animals bear similarities to cardinal signs of depressed patients. Other signs in the physiological and behavioral repertoire of socially stressed animals may reflect anxiety-like responses. Understanding the intracellular cascade of events in mesocorticolimbic circuits for the transition from episodic to continuous, inescapable social stress in infancy and adulthood promises to provide insight into basic reward processes that are relevant for addictive and affective disorders.

Cross-References

► Aggression, Clinical
► Antidepressants
► Antipsychotics
► Anxiolytics
► Depression
► Distress Vocalizations
► Drug Self-administration
► Reinforcement Disorders
► SSRI
► Stress: Influence on Drug Action

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Sodium 4-Hydroxybutyrate

► Oxybate

Sodium 5-Ethyl-5-(1-Methylbutyl) Barbiturate

► Pentobarbital

Sodium Oxybate

Definition

The sodium salt of gamma-hydroxybutyrate (GHB).

Solvent Abuse

► Inhalant and Solvent Abuse

Solvex

► Reboxetine

Somatization

► Somatoform and Body Dysmorphic Disorders

Somatoform and Body Dysmorphic Disorders

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Synonyms

Abridged somatization; Functional somatic syndromes; Health anxiety; Heightened illness concern; Hypochondria; Illness anxiety

Definition

Pharmacologic agents have long been recognized as potentially helpful for patients with somatic symptoms such as insomnia and neuropathic pain. However, there have been very few well-controlled studies on the pharmacologic treatment of specific somatoform disorders as defined by DSM-III-R and ► DSM-IV. This section will summarize what is known, based on well-controlled studies on the pharmacologic treatment of three somatoform disorders – hypochondriasis, somatization disorder, and body dysmorphic disorder (BDD).

Role of Pharmacotherapy

Pharmacotherapy of Hypochondriasis

The advent of the ► selective serotonin reuptake inhibitors (SSRIs) in the early 1990s led to a series of case reports suggesting efficacy for various depressive and anxiety disorders. Of particular relevance was the superior efficacy profile of the SSRIs, compared to primarily noradrenergic agents, in ► obsessive–compulsive disorders. Perhaps because of the favorable side effect profile and the striking efficacy for obsessional disorders proffered by the SSRIs, case reports and small series appeared, suggesting that agents with serotonergic activity might be particularly beneficial in helping patients with hypochondriasis as noted by Fallon and Feinstein (2001), with positive findings reported for clomipramine, fluvoxamine, fluoxetine, citalopram, paroxetine, nefazodone, and imipramine. Responder rates were high in the small (10–18 subjects) uncontrolled series for treatment completers, ranging from 70 to 89%. Clinicians were advised to treat patients for 8–12 weeks for optimal efficacy.

Controlled data on the use of medication in the treatment of hypochondriasis, however, is limited to two ► randomized trials. In 2008, Fallon et al. (2008) conducted a ► placebo-controlled study of ► fluoxetine for

hypochondriasis among 45 randomized patients. At the primary end-point of week 12, the proportion of clinician-rated global improvement responders to fluoxetine compared to placebo was significant for the completer and minimum treatment samples and at the margin of significance ($p = 05$) for the intent-to-treat (ITT) sample. The responder rate for the ITT sample at week 12 was nearly twice as great for those patients randomized to fluoxetine (62.5%) as compared to placebo (33.3%). Because this pattern of improvement was also seen at week 8, it was suggested that a treatment duration of 8 weeks of medication might be sufficient to test efficacy. When a conservative imputation method was used in which all patients not rated were categorized as nonresponders, the ITT responder rate at week 12 was 14/24 (58.3%) for fluoxetine vs. 4/21 (19.0%) for placebo ($p = 007$). The degree of improvement in hypochondriasis at week 12 was moderate on average, but improvement appeared to increase over time. Fluoxetine was generally well-tolerated, as demonstrated by the comparable rates of study withdrawal for the fluoxetine-treated and placebo-treated groups. Although the sample size was small, these results support the conclusions that fluoxetine treatment is effective, durable, and well tolerated.

In 2007, Greeven et al. (2007) conducted a randomized controlled trial among 112 patients comparing the efficacy of cognitive behavior therapy (CBT), ▶ paroxetine, and a ▶ placebo (administered in a ▶ double-blind fashion) in the treatment of hypochondriasis.

Patients were randomly assigned to one of the three treatments for 16 weeks. The main outcome measure was the Whiteley Index. The authors considered subjects who scored at least one standard deviation below the mean pretest score on the Whiteley Index as responders. For the ITT and completer cohorts, pooled CBT and paroxetine were significantly superior to placebo, but did not differ significantly from each other. The responder rates for the ITT and completer cohorts were 45 and 54% for CBT, 30 and 38% for paroxetine, and 14 and 12% for placebo. For the ITT analysis, only CBT differed significantly from placebo. In the completer analysis, both paroxetine and CBT differed significantly from placebo. This study supported the authors' conclusion that paroxetine and CBT are each helpful short-term treatment options for patients with hypochondriasis.

Patients with no insight into the irrationality of their illness concerns are often diagnosed as having ▶ delusional disorder, somatic subtype. Case reports and small series have reported the efficacy of typical and atypical antipsychotics in the treatment of delusional parasitosis in particular, with marked improvement in two-thirds of cases. The antipsychotic ▶ pimozide was reported as effective for delusional parasitosis in two small placebo-controlled trials with ON–OFF–ON designs, but the use of pimozide remains a concern because of the increased risk of torsades de pointes and sudden death resulting from the drug's tendency to prolong the electrocardiographic QT interval. Two meta-analyses of controlled studies of patients with delusional parasitosis, including one by Lepping et al. 2007, have supported the benefits of typical and atypical antipsychotics. Whether SSRIs may play a role in the treatment of psychotic forms of health anxiety has not yet been adequately studied.

Pharmacotherapy of Somatization Disorder

Pharmacologic studies of somatization disorder are few. This reflects the stringency of the diagnostic criteria and the consequent rarity of the full-blown syndrome, which makes clinical trials extremely difficult. To circumvent this problem and to examine therapies for the much larger population of patients who frequent primary care doctor's offices, researchers have conducted studies of patients who meet criteria for a spectrum of somatization conditions, primarily abridged somatization, which requires meeting fewer somatic criteria for diagnosis. There have also been meta-analyses, such as by Kroenke (2007), of studies conducted in patients who would meet the even more encompassing umbrella category of medically unexplained symptoms (MUS). Prior research suggests that roughly half of patients with MUS have a concomitant mood or anxiety disorder and that about one-third would meet criteria for a somatoform disorder.

A meta-analysis by O'Mallay et al. (1999) identified studies of MUS, mainly representing headache, fibromyalgia, functional gastrointestinal disturbances, idiopathic pain, tinnitus, and chronic fatigue. Ninety-four randomized controlled trials (RCTs) were found that compared different ▶ antidepressant medications, including tricyclics and SSRIs; of these, 69% of the studies documented favorable outcome on either a pain score, a global assessment score or a summary symptom index. Of concern is that high withdrawal rates were seen in almost two-thirds of the studies. Of further concern is that only 37% of the studies reported the side-effect profiles from the antidepressant medications.

St. John's wort was reported as efficacious in two 6-week's duration placebo-controlled treatment studies of MUS. The earlier study had 149 subjects, of whom 108 met criteria for either somatization disorder or abridged somatization disorder. More recently, Muller et al. (2004) studied 173 subjects, of whom 67 met criteria for somatization or abridged somatization disorder. Improvement

was reported in both studies for symptoms and psychological status.

► Venlafaxine was studied in 112 patients with "multi-somatoform disorder" in a randomized double-blind controlled trial by Kroenke et al. (2006). Although pain improved, no change was noted in total somatic symptom score.

In the RCT of fluoxetine for hypochondriasis conducted by Fallon et al. (2008), although improvement in hypochondriasis was noted, there was no significant difference between drug and placebo in improvement in total quantity of somatic symptoms.

Opipramol, a tricyclic ► anxiolytic with high affinity for sigma receptors, was studied in a placebo-controlled trial in 200 patients with mixed somatoform disorders (primarily somatization, abridged somatization, and an autonomic dysfunction syndrome). Although a reduction in total somatic symptoms and psychological symptoms was noted, the effect size was small.

Overall, these studies suggest that antidepressants may have a beneficial role in the treatment of some of the MUS disorders known as "functional somatic syndromes" – fibromyalgia, irritable bowel, and headache. Data supporting the benefit of pharmacologic agents for abridged or full somatization disorder is weaker. Although studies suggest a benefit for agents such as St. John's wort, the effect size is not very large. Further study is needed to identify better treatments for this particularly troubled group of patients.

Pharmacotherapy of Body Dysmorphic Disorder

Following the advent of the SRIs, open treatment studies of patients with BDD suggested beneficial effects of clomipramine, fluoxetine, and fluvoxamine, which was further confirmed by a 16-week double-blind crossover-design study of 29 subjects using ► clomipramine vs. desipramine conducted by Hollander et al. (1999). This crossover study showed clomipramine, a tricyclic with potent ► serotonin and ► norepinephrine reuptake inhibition, to be superior to desipramine, a tricyclic with predominant norepinephrine reuptake inhibition, on all primary outcome measures of BDD, including patients' obsessive preoccupation with perceived body defects, repetitive behaviors in response to this preoccupation, and global ratings of symptom severity. Additionally, a placebo-controlled study in 2002 by Phillips and colleagues of fluoxetine ($n = 67$ randomized, 59 completed) showed preferential response to fluoxetine at weeks 8 and 12 for treating the symptoms of BDD and for improving functional outcome.

While different SRIs have not been compared directly in the treatment of BDD, initial studies showed a variety of them to have efficacy and tolerability. Several open-label studies have been done, including two with ► fluvoxamine ($n = 15$ and $n = 30$ and one with ► citalopram ($n = 15$). Additionally, in an open label study of ► escitalopram with 15 subjects with BDD, 73.3% ($n = 11$) reported significant symptom improvement, with 33% much improved and 46% very much improved at 4.7 ± 3.7 weeks. Comparison studies, assessing the degree of response and time to response, are needed. One study, which examined the quality of pharmacotherapy for BDD among 151 individuals in a convenience sample found that, while many had been tried on an SRI (65.6%), only 12.9% of SRI trials were considered optimal and only 21.5% were considered minimally adequate. Optimal treatment is often considered a minimum of 12 weeks in duration, with at least 2–4 weeks at the highest dose tolerated by the patient.

While SRIs are certainly effective for BDD, 25–50% of patients do not respond to current pharmacotherapies and; even among responders, the degree of improvement is often only partial. While the data are limited, augmentation with another psychiatric agent, such as ► buspirone, may be helpful once the SRI has been optimized. Nonpsychiatric medical treatments, including the most commonly topical dermatologic treatments or creams, do not appear effective for the treatment of BDD.

Review by Philips (2004) suggested there is no convincing evidence supporting the use of ► antipsychotic medications in BDD. Although initial case reports suggested that delusional BDD responded to pimozide, a small ($n = 28$) placebo-controlled, double-blind study of pimozide augmentation of fluoxetine in BDD by Phillips in 2005 showed it to be no more effective than placebo (18.3% responding to pimozide and 17.6% responding to placebo), even in more delusional patients. Contrary to expectations, the delusional variant of BDD appears to respond to SRIs alone, with similar findings in adolescents with BDD. In the 1999 study of Hollander et al. (1999), clomipramine was surprisingly more effective for delusional patients than nondelusional patients, whereas the study of Philips et al. 2002 showed an equivalent BDD symptom response to fluoxetine (50 vs. 55%). Of note, in the latter study, delusional BDD patients were significantly less likely to respond to placebo than nondelusional patients.

Cross-References

► Antidepressants
► Generalized Anxiety Disorder
► Obsessive-Compulsive Anxiety Disorders
► SNRI Antidepressants
► SSRIs and Related Compounds

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Somatostatin

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Synonyms

Somatotropin release-inhibiting factor; SRIF

Definition

Somatostatin (somatotropin release-inhibiting factor, SRIF) is a cyclic peptide widely expressed throughout the central nervous system (CNS), in endocrine tissues, and in the gastrointestinal tract (GIT). The 14 amino acid peptide, somatostatin (SRIF-14), was first identified and isolated from ovine hypothalamic extracts by Guillemin and collaborators (Brazeau et al. 1973) during their search of GHRH hormone/growth hormone (GH) releasing hormone, instead they identified SRIF as a potent inhibitor of growth hormone release from the pituitary. Subsequently, a longer N-terminally extended form (SRIF-28) was identified in the periphery, both deriving from the same prepropeptide.

Pharmacological Properties

Introduction

About 20 years later, a rat ▶ neuropeptide with strong homology to SRIF was identified, cloned, and named ▶ cortistatin (CST) due to its supposed brain selective expression; however, CST is also present in the periphery. In rodents, CST is a tetradecapeptide (CST-14), sharing up to 11 amino acids with SRIF, whereas the human homolog is a heptadecapeptide (CST-17). Similar to SRIF, a longer isoform of CST has also been identified, i.e., CST-29. Both peptides (SRIF and CST) are produced as prepropeptides, which are then processed to the final forms by peptide cleavage; it is strongly suggested that SRIF and CST are the products of gene duplication (De Lecea 2008; Hoyer et al. 1995). Finally, neuronostatin, a somatostatin-gene derived peptide isolated from gut, has recently been mentioned to be expressed in some brain regions, but activation of SRIF receptors does not seem to mediate its reported neuroendocrine effects.

SRIF exerts a wide range of biological actions, including inhibition of secretion of growth hormone, insulin, glucagon, and gastrin as well as other hormones secreted by the pituitary and the GIT. SRIF also acts as a neuromodulator in the CNS and, in addition, has marked antiproliferative effects on a wide range of cancer cells (Viollet et al. 2008). Although various physiological parameters, including transitions between sleep phases, ▶ consolidation of short- and long-term memory, and locomotor activity, respond in an apparently peptide-specific manner to SRIF and CST, both peptides in the short and long forms have nanomolar affinity for each known SRIF receptor subtype (sst_1–sst_5). The existence of specific CST receptors has not been demonstrated so far in spite of major efforts (Siehler et al. 2008). Clinically, SRIF receptor modulation is targeted primarily in the endocrine and gastrointestinal sphere, especially in a number of gastroenteropancreatic (GEP) cancers, although preclinical evidence points at a number of other diseases, such as inflammation, pain, migraine, epilepsy, additional cancers,

and neuropsychiatric disorders such as ► depression and ► Alzheimer's disease (Viollet et al. 2008).

SRIF and CST Receptors

SRIF and CST act via a family of ► G-protein-coupled receptors (GPCRs); it was suggested initially that there are two receptors, based on pharmacology and distribution studies; receptors were distinguished by their high affinity or low affinity for ► octreotide (SMS-201–995); however, in the early 1990s, at least five receptors (sst_1–sst_5) have been cloned and characterized from various species. Sequence homology is 39–57% among the five subtypes, each being highly conserved across species. Based on structural and operational features, they are divided into two groups: SRIF-1 (sst_2, sst_3 and sst_5 receptors) and SRIF-2 (sst_1 and sst_4 receptors), distinguished by high affinity for small analogs such as octreotide, seglitide (MK-678), and ► lanreotide (BIM-23014) for the SRIF-1 group. They have nanomolar affinities for SRIF and CST, and will be generically referred to as SRIF receptors here. In humans, SRIF receptors are encoded by five nonallelic genes, located on chromosomes 14, 17, 22, 20, and 16, respectively. Genes coding for sst_1, sst_3, sst_4, and sst_5 are intronless, whereas in rodents the sst_2 gene contains three introns, which result in the generation of two receptor splice variants, sst_{2A}, and sst_{2B} (Hoyer et al. 1995).

Studies utilizing subtype selective SRIF analogs in both in vivo and in vitro experiments, demonstrate that sst_2 receptors are the major player in the SRIF receptor family with broad inhibitory effects on the endocrine secretion e.g., growth hormone, insulin, glucagon, gastrin, ► cholecystokinin, vasoactive intestinal peptide, and secretin, as well as the exocrine secretion, e.g., gastric acid, intestinal fluid, and pancreatic enzymes. sst_2 receptors also seem to play a major role in various forms of GEP cancers, in epilepsy and pain. The sst_1 receptor may function as an autoreceptor in the basal ganglia, the ► hypothalamus, and the eye and possibly in the ► hippocampus. It is also involved in regulating insulin secretion (Thermos et al. 2006). sst_3 receptors are enigmatically localized to neuronal cilia, and sst_3 antagonists have marked behavioral effects (Viollet et al. 2008). sst_4 receptors are highly expressed in the cortex and the hippocampus and in the lung, where their role still remains to be defined; in the mouse they modulate epileptic activity whereas in the rat it seems that this effect is largely assigned to sst_2 receptors (Moneta et al. 2002). Hippocampal sst_4 have been recently shown to be involved in the selection of memory strategies, switching from the use of hippocampus-based multiple associations to the use of simple dorsal striatum-based behavioral responses (Gastambide et al. 2009). sst_5 receptors mediate the inhibition of insulin release from the pancreatic β-cells in addition to regulating growth hormone release (Viollet et al. 2008).

Currently, octreotide and lanreotide are in clinical use for the treatment of acromegaly, diarrhea, and various GEP tumors, whereas [^{111}In] penteotride is used for whole body tumor imaging. Other SRIF receptor agonists are in development for additional indications, such as Cushing's disease.

CST and SRIF appear to produce different effects both in the brain and in the periphery, especially in the immune system. Due to these differences, the existence of CST-specific receptors has been suggested: MgrX2 and GHS-R1a are two unrelated orphan receptors reported to have affinity for CST; however, these reports have not received positive confirmation. On the other hand, there is convincing evidence for CST and SRIF to act with similar high affinity and efficacy at the known sst_1–sst_5 receptors (De Lecea 2008; Siehler et al. 2008). Since the existence of specific CST receptors is still an open question, thus we will generically refer to SRIF receptors here.

SRIF and SRIF Receptors in the Brain

Two types of somatostatinergic neurons exist in the CNS: long-projecting neurons and short GABAergic interneurons. SRIF neurons are primarily located in the hypothalamus, hippocampus, striatum, cerebral cortex, ► amygdala, preoptic area, olfactory bulb, and brainstem. Concerning receptor mapping, data from receptor autoradiography, RT-PCR, in situ hybridization and immunocytochemistry studies and receptor knockout/LacZ knockin use allow to state the following: all five SRIF receptors are present in the brain, sst_2 being the most prominent whereas sst_5 shows the lowest expression levels. sst_2 is often coexpressed with other given subtypes in a tissue-specific way, and the functional meaning of such differential expression repertoires is currently under study. In rodents and humans, the olfactory bulb expresses sst_2, sst_3, and sst_4, when the anterior olfactory nucleus does express primarily sst_2, the neocortex, sst_2 and sst_4; in the hippocampus, DG and CA3 region express sst_2 whereas the CA1 region displays both sst_2 and sst_4; in the amygdala and locus coeruleus, sst_2 expression is largely predominant, whereas the hypothalamus expresses sst_1 and sst_2 receptors. sst_5 receptors are very scarce in the brain. The sst_3 receptor is peculiar, as its mRNA is highly detected in several brain regions; however, the sst_3 protein does not distribute in a somatodendritc fashion, as the other receptors, but is restricted to somatic neuronal cilia, whose function remains elusive (see Viollet et al. 2008).

Somatostatin and its receptors (sst_1, sst_2, and sst_3) are also transiently expressed concomitantly during early sensory and brain development, suggesting that they may participate in ontogenetic processes.

The Somatostatin System in Health and Disease

Beside its neuroendocrine functions, somatostatin and its receptors have neuromodulatory roles, influencing motor activity, sleep, sensory processes, and cognitive functions. SRIF and its receptors are altered in affective and neurological disorders, e.g., depression, migraine, pain, epilepsy, and Alzheimer's disease. SRIF acts as a neuromodulator, e.g., of gamma-aminobutyric acid (► GABA), ► glutamate, and ► acetylcholine, and has both pro- and anticonvulsant activity, that are potentially relevant to the neurobiology of affective disorders. A consistent alteration observed in depression is the state-dependent decrease of CSF SRIF (Roca et al. 1999). However, such a decrease is seen also in other patient populations where cognition is or may be impaired, such as ► schizophrenia, Alzheimer's dementia, drug refractory epilepsy, and multiple sclerosis. The SRIF decrease in affective illness and active multiple sclerosis has been considered state dependent, in that levels normalize with recovery from the acute episode. On the other hand, increased SRIF levels have been reported in psychiatric illness where cognition is accelerated, as in ► mania and ruminative or ► obsessive-compulsive disorder (Viollet et al. 2008). Finally, acromegalic patients treated with somatostatin agonists are largely devoid of migraine attacks.

Which Role for the Various SRIF Receptors?

sst_2 receptors: Somatostatin induces an inwardly rectifying K^+ current in almost all projection neurons of the lateral amygdala: these effects are blocked by an sst_2 antagonist or mimicked by a sst_2 agonist. A role for sst_1, sst_3, or sst_4 receptors was ruled out since selective agonists were ineffective. Preclinical data suggest a role of somatostatin neurons in the central nucleus of the amygdala in rats on fear, since octreotide applied locally on caudal pontine reticular nucleus neurons blocks fear potentiation. These cellular effects support ► anxiolytic as well as ► anticonvulsant and antiepileptogenic actions of somatostatin or analogs in the amygdala (Fendt et al. 1996). Somatostatin also plays a critical role in the acquisition of ► contextual fear memory, but not does not tone fear learning, which supports a role for SRIF in hippocampal synaptic plasticity in processing contextual information. These data are in line with an anxiety phenotype presented by the sst_2 KO mouse, which is also impaired with respect to memory. SRIF modulates ► glutamate release in the striatum, an effect that is abolished in sst_2 receptor KOs. The sst_2 receptor modulates neprilysin, which affects $A\beta_{42}$ metabolism. SRIF KO mice have higher concentrations of the $A\beta_{42}$ peptide, accumulation of which leads to late-onset sporadic Alzheimer's disease. sst_2 and sst_4 receptors also seem to interact positively on the phosphorylation of ► Tau proteins at the Ser 262 site, a site modified in Alzheimer's disease. On the other hand, 3 and 6 h after middle cerebral artery occlusion (MCAO) in the rat, sst_2 receptors were internalized excessively in cerebrocortical neurons adjacent to the infarct and sst_2-deficient mice exhibit a 40% reduction of infarct size after permanent distal MCAO and a 63% reduction after transient proximal MCAO as compared to wild type animals. Thus, the activation of sst_2 receptors by an endogenous ligand after focal ischemia may contribute to increased sst_2 gene expression and postischemic neurodegeneration (see Viollet et al. 2008).

sst_1 receptors: sst_1 receptors are present in the brain, retina, neuroendocrine cells, endothelial cells, and various human tumors. They are involved in the intrahypothalamic regulation of growth hormone (GH) secretion and modulate somatostatin release in basal ganglia. We have proposed an autoreceptor role for sst_1 receptors located on somatostatin neurons in the hypothalamus, basal ganglia, retina, and possibly hippocampus. Thus, sst_1-selective analogs may play a role in various diseases, such as retinal and endocrine dysfunctions, cancer, and neuropsychiatric disorders. We have reported NVP-SRA880, an sst_1 antagonist to promote social interactions, reduce aggressive behavior, and stimulate learning. SRA880 reduced contextual/fear conditioning without affecting cue-elicited freezing in rats (Thermos et al. 2006). Further, sst_1-selective analogs have been shown to mimic the inhibitory effect of SRIF on GH secreting pituitary tumors; in medullary thyroid carcinoma, calcitonin secretion/gene expression is inhibited by sst_1-selective agonists. Finally, sst_1-selective agonists inhibit endothelial activities, suggesting utility for sst_1-selective agonists in angiogenesis.

sst_3 receptors: A potential role for sst_3 has been proposed in hippocampal dependent memory. sst_3 null mutant mice showed a severe impairment in their ability to recall previously learned spatial information. NVP-ACQ090, an orally active somatostatin sst_3 receptor antagonist has marked sociotropic effects in intruder mice, shows sociotropic effects in aggressive resident mice, and increases the social exploration of an intruder toward a non-aggressive resident rat. ACQ090 has anxiolytic-like activity in stress-induced hyperthermia and pronounced antidepressant-like effects in both the modified rat forced swim test and in olfactory bulbectomized rats. Thus, sst_3

receptor blockade has profound central effects in animal models for neurological and psychiatric disorders.

sst_4 receptors: There is evidence in the mouse that the main role in mediating the antiepileptic effects of SRIF is by the sst_4 in conjunction with sst_2 receptor, whereas in the rat only sst_2 is involved. Unprovoked seizures are observed in the sst_4 KO. The sst_4 receptor couples to the K^+ M-current (I_M, Kv7), which is an important regulator of cortical excitability; mutations in these channels cause a seizure disorder in humans. SRIF augments I_M in hippocampal CA1 pyramidal neurons. When seizures were induced by a systemic injection of kainate, only sst_4 knockouts showed an increase in seizure sensitivity. sst_2 and sst_4 appear to mediate the majority of SRIF inhibition of epileptiform activity in CA1. sst_4 receptors could therefore be an important novel target for developing new antiepileptic and antiepileptogenic drugs, but it remains to be seen that this applies to humans. sst_4 and sst_2 receptors can interact in a cooperative or in a competitive manner. Thus, when applied in the hippocampus, L-803087, a selective sst_4 receptor agonist, doubled seizure activity and facilitated AMPA-mediated synaptic responses in wild-type mice on average and this effect was blocked by octreotide. However, the sst_4 agonist was no longer active in sst_2 KO mice.

sst_5 receptors: Little is known about sst_5 receptors in the brain, which seem to express very low sst_5 levels, although the LacZ expression of the sst_5 KO looks very high in the hippocampus. Brain penetrant selective ligands are essentially missing or have not produced any remarkable central effect. Peripherally, sst_5 receptors modulate insulin release and various other endocrine effects appear to be mediated by hypothalamic sst_5 receptors.

Outlook

The involvement of SRIF and its receptors in neurological and psychiatric disorders is still largely circumstantial, primarily since selective and brain penetrating ligands have not reached the market yet. However, preclinical evidence as well as changes in SRIF and receptor levels in various diseases strongly suggest that modulating SRIF receptor activity will have clinical relevance in neuropsychiatric diseases.

Cross-References

► Somatostatin Receptors

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Somatostatin Receptors

Synonyms

sst_1; sst_2; sst_3; sst_4; sst_5

Definition

Five SRIF receptors (sst_1–sst_5) have been cloned from various species. Sequence homology is 39–57% among the five subtypes; each is highly conserved across species. They have nanomolar affinity for SRIF and CST. Human SRIF receptors are encoded by five nonallelic genes, located on chromosomes 14, 17, 22, 20, and 16, respectively. Genes coding for sst_1, sst_3, sst_4, and sst_5 are intronless, whereas in rodents the gene for sst_2 contains three introns, which result in the generation of two receptor splice variants, sst_{2A} and sst_{2B}. SRIF receptors are GPCRs; they couple to G_0/G_i proteins and modulate cyclic AMP production and other transduction pathways.

Somatotropin Release-Inhibiting Factor

► Somatostatin

Somatuline

► Lanreotide

Source Analysis

► Source Localization Techniques

Source Localization Techniques

Synonyms

Source analysis

Definition

Source localization techniques refer to a set of mathematical techniques for identifying the locus or loci of neural activity that give rise to a particular ERP voltage distribution measured on the surface of the scalp. By making assumptions about the physical properties of the skull, brain, and underlying active neural populations, these methods attempt to constrain the number of possible source configurations that can explain the observed scalp distribution. Preexisting knowledge about the brain and further assumptions, for example, about the number of active sources, are needed to arrive at a plausible solution. An important shortcoming of source localization techniques is that there is no means of quantifying the likelihood that a solution is correct.

Cross-References

► Event-Related Potentials
► Inverse Problem

SP

► Substance P

Spatial Delayed Alternation

Definition

Classical paradigm for measuring short-term (often called "working") memory in rodents generally employing a T-maze and basing the measure of memory on the well--known tendency of rats spontaneously to alternate their spatial choices. The memory load can be increased by lengthening the delay between the first and second trials. Analogous but not equivalent to spatial delayed response task in nonhuman primates.

Spatial Learning in Animals

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Synonyms

Place learning; Spatial navigation

Definition

Spatial learning refers to the process through which animals encode information about their environment to facilitate navigation through space and recall the location of motivationally relevant stimuli. This form of learning is critically dependent on the integrity of the ► hippocampus, although surrounding regions of the temporal cortex and certain forebrain structures also play a role in these processes. It is generally believed that spatial learning entails encoding of the locations of cues relative to the position of other cues in a particular environment that leads to the formation of a cognitive map of an individual's surroundings. Thus, during spatial learning, animals use allocentric spatial cues to navigate in space, keeping track of their position relative to other distal stimuli. Support for this notion comes from the finding of place cells in the hippocampus, where different groups of neurons in this region display consistent changes in firing when an animal is oriented in a particular location in space. Moreover, changing the arrangement of distal spatial cues in an arena reorganizes the patterns of activity in these place cells to match the new orientation of stimuli in the environment. In rodents, one of the most common means for assessing spatial learning is with different types of maze tasks, where rats or mice use allocentric cues to guide an escape response (e.g., finding a hidden platform in a ► water maze task) or to locate food (e.g., on a ► radial arm maze). The majority of studies that have investigated the psychopharmacology of spatial learning have used these types of tasks. An important caveat is that drugs that alter performance of these tasks do not appear to exert a selective influence on spatial learning and

memory, as they typically can affect other forms of learning independent of the hippocampus. As such, preclinical tests of spatial learning in rodents, either in intact animals or those subjected to treatments that impair spatial learning, are often used as an initial assay to investigate the effects of potential cognition enhancing drugs.

Impact of Psychoactive Drugs

Excitatory Amino Acids

Drugs with interference from glutamatergic transmission, particularly those which block the n-methyl-D-aspartate ► (NMDA) receptor subtype, severely interfere with spatial learning. The systemic administration of either competitive (e.g., CPP) or noncompetitive (MK-801, ► phencyclidine) NMDA antagonists impair learning of spatially cued escape response in a water maze task (reviewed by McNamara and Skelton 1993). Similarly, administration of these compounds also impairs search behavior guided by spatial memory on appetitively motivated tasks such as the radial arm maze. The effects of these treatments seem largely attributable to the blockade of NMDA receptors in the hippocampus, as local administration of these compounds also impairs spatial learning. However, the administration of NMDA receptor antagonists after training have a substantially blunted effect, suggesting that hippocampal NMDA receptors are required for the acquisition and perhaps the initial ► consolidation of hippocampus-dependent memory, but not for its maintenance. These effects do not appear attributable to disruptions in motor or motivational processes because they do not interfere with the ability of animals to learn the approach at a single proximal cue, when, for example, rats must swim to a visible platform in a water maze. In contrast to the above mentioned findings, blockade of non-NMDA (e.g., ► AMPA) receptors impairs both the acquisition and retrieval of spatial information. In this regard, drugs that potentiate currents mediated by AMPA type ► glutamate receptors (ampakines) have shown efficacy in improving spatial and other forms of learning in animal models (Arai and Kessler 2007). The effects of drugs acting on ► metabotropic glutamate receptors have received less attention, although antagonists at mGlur1 and five sites have been reported to impair the acquisition of a water maze task.

The ability of NMDA antagonists to impair spatial learning has been proposed to be related to disruptions in certain forms of ► synaptic plasticity in the hippocampus, given that compounds that impair spatial learning also impede the induction of ► long-term potentiation (LTP) in this region. Notably, blockade of NMDA receptors does not affect maintenance of LTP. Similarly, systemic blockade of these receptors with competitive antagonists induces a selective disruption of the formation of ► place cell activity in the hippocampus. Place fields that formed *de novo* in the presence of NMDA antagonists are unstable, but these treatments do not affect the maintenance of previously established place fields, although they do disrupt the expansion of place fields that occurs with repeated exposure to an environment. These findings are in keeping with the dissociable effects of NMDA antagonism on learning versus ► retrieval of ► spatial memories (Nakazawa et al. 2004).

Acetylcholine

The hippocampus receives dense cholinergic enervation from the septum that mediates theta frequency oscillatory activity, thought to be important for the exploration of novel environments. The blockade of ► muscarinic cholinergic receptors with nonselective antagonists such as ► scopolamine or atropine severely disrupts both spatial learning and memory in a manner independent of the effects of these compounds on sensorimotor and procedural learning (McNamara and Skelton 1993). The use of these compounds in combination with spatial learning tasks has become a popular preclinical animal model for cognitive dysfunction for which to test the effects of potential ► cognitive enhancers. Perturbations in spatial learning induced by these drugs appear to be due to the blockade of postsynaptic M_1 receptors, as similar effects have been observed following peripheral or central administration of M_1 antagonists such as pirenzepine. Conversely, in some instances, enhancing cholinergic transmission can induce a beneficial effect on spatial learning. For example, blockade of M_2 autoreceptors with drugs such as methoctramine or AFDX 116 increases ► acetylcholine release and improves learning on tests of spatial abilities using different maze paradigms. Likewise, ► cholinesterase inhibitors (► physostigmine, ► tacrine) also can improve spatial learning, particularly in aged animals. Drugs of this nature have been used to offset aging-related cognitive decline occurring in human patients. ► Nicotinic cholinergic receptors have also been implicated in spatial learning. ► Nicotine or receptor subtype selective agonists improve spatial abilities in preclinical animal models. Current drug discovery research aimed at developing novel pro-cognitive compounds has focused on the alpha-7 subunit of the nicotinic receptor as a potential target. ► Genetically modified mice lacking this subunit display impairments in spatial and other forms of learning, whereas compounds, which stimulate receptors that include this

subunit, can enhance spatial learning and memory. The development of these compounds may prove beneficial for treating cognitive deficits observed in a number of disorders, including ► Alzheimer's and ► schizophrenia.

Although it is well established that the blockade of cholinergic transmission can impair spatial learning, it remains unclear where these compounds may be exerting their effects. The local administration of muscarinic antagonists into the hippocampus interferes with place cell firing. However, the deafferentation of cholinergic inputs to the hippocampus via 192 IgG-saporin lesions of the septum do not reliably impair spatial learning using water or radial maze tasks (Baxter 2001). This would suggest that impairments in spatial learning induced by the systemic administration of cholinergic antagonists occur via the blockade of extra-hippocampal cholinergic receptors, possibly in different regions of the cerebral cortex. Notably, cholinergic transmission has been heavily implicated in attentional processing. It has been proposed that acetylcholine serves to enhance the influence of feed-forward afferent input to the cortex while decreasing background activity by suppressing excitatory feedback connections within cortical circuits. By enhancing the response to sensory input, high levels of acetylcholine enhance attention to sensory stimuli in the environment and enhance the encoding of memory for specific stimuli (Hasselmo 2006). Thus, even though manipulations of cholinergic transmissions can influence acquisition and performance of tasks requiring the use of spatial cues to guide behavior, the effects of these compounds may not be due to a specific affect on the encoding or retrieval of spatial memories *per se*.

Monoamines

The systemic administration of dopamine antagonists acting at D_1 (SCH 23390) or D_2 (► haloperidol, ► sulpiride) receptors have been reported to impair spatial learning assessed with water maze tasks. In some instances, these effects were accompanied by motoric deficits as well, whereas other reports have shown that lower doses of these drugs that do not induce motor impairments are effective at impairing spatial learning. The hippocampus receives dopaminergic innervation, and studies combining behavioral and electrophysiological methodologies point to a role for D1 receptors in facilitating hippocampal synaptic plasticity, which may enhance the formation of novel spatial memories. Dopamine has been shown to modulate acetylcholine release, which may contribute to some of the effects of pharmacological manipulation of dopamine transmission on spatial learning and memory. Furthermore, dopamine receptor activity in forebrain regions (ventral striatum, ► prefrontal cortex) also appear to be required for some forms of spatial learning and memory, as the local infusion of dopamine antagonists into these regions can also impede acquisition and recall.

Noradrenergic inputs to the hippocampus stem exclusively from the locus coeruleus, the majority of which terminates in the dentate gyrus. Pharmacological manipulations of noradrenergic receptors, particularly the beta subtype with agonists such as isoproterenol can modulate the formation of long-term potentiation in the hippocampus. Furthermore, increases or decreases in noradrenergic tone via blockade (atipamezole) or stimulation (dexmedetomidine) of alpha-2 adrenergic autoreceptors leads to instability of place fields in the hippocampus. Interestingly, however, the depletion of central ► noradrenaline with selective ► neurotoxins does not impair the learning of spatial tasks. Nevertheless, drugs that enhance central noradrenergic activity can improve performance on spatial memory tasks. Much of this research has focused on the contribution of noradrenergic transmission in the memory modulating effects of stress (Roozendaal et al. 2006). For example, the ability of glucocorticoid stress hormones to disrupt spatial and other forms of memory are blocked by the coadministration of beta-1 receptor adrenergic antagonists such as atenolol either systemically or directly into the hippocampus. Conversely, the post-training activation of adrenergic receptors with adrenaline improves subsequent performance of spatial memory tasks, and these effects are blocked by the coadministration of beta-receptor antagonists. These findings suggest that under some conditions, acute increases of noradrenergic activity facilitate the consolidation of new spatial memories. A particularly interesting aspect of these findings is that post-training infusions of these compounds into the basolateral ► amygdala (a region that normally does not contribute to spatial learning) also enhances the consolidation of spatial memories (as well as other forms of learning; Ferry et al. 1999). Enhancements in learning induced by the activation of amygdala adrenoreceptors are thought to be part of a neural mechanism through which stressful or emotionally charged events augment the encoding of new memories.

The hippocampus receives considerable serotonergic innervation and contains a high density of 5-HT receptors, yet, global depletions of brain ► serotonin typically do not impair spatial learning. Nevertheless, the pharmacological manipulation of different 5-HT receptors has been shown to affect spatial learning processes. In general, the blockade of different 5-HT receptors tends to improve

spatial learning, whereas the administration of relatively selective 5-HT agonists induce detrimental effects. For example, systemic or intra-hippocampal administration agonists active at either 5-HT_{1A} (8-OH-DPAT) or 1B (anpirtoline) receptors generally leads to impairments in spatial learning in the water maze (Ogren et al. 2008). Furthermore, the administration of the 5-HT_{1A} antagonist WAY 100635 ameliorates impairments in spatial memory induced by muscarinic antagonism with scopolamine, indicated that 5-HT1A receptor agents may modify spatial memory through interactions with the cholinergic system. Similar improvements in spatial learning have been observed following intra-hippocampal blockade of $5HT_{2A/2C}$ antagonist with ritanserin, or systemic blockade of 5-HT_6 receptors (SB-271046). Thus, it appears that the blockade of multiple 5-HT receptors may actually exert a beneficial effect on spatial learning. Accordingly, identifying novel 5-HT antagonists may prove to be a fruitful strategy in the development of cognitive enhancing drugs.

Cross-References

- ▶ Beta-Adrenoceptor Antagonists
- ▶ Excitatory Amino Acids and Their Antagonists
- ▶ Long-Term Potentiation and Memory
- ▶ Muscarinic Agonists and Antagonists
- ▶ Nicotinic Agonists and Antagonists
- ▶ Rodent Models of Cognition

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Spatial Memory

Definition

Spatial memory refers to memory for the location of objects and self-orientation within the environment.

Cross-References

- ▶ Spatial Memory in Animals
- ▶ Spatial Memory in Humans

Spatial Memory in Humans

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Synonyms

Spatial memory is often used to describe spatial navigation and encompasses egocentric and allocentric memories

Definition

Spatial memory describes information storage and retrieval required for identification and navigation of proximal or distal space. This is distinct from spatial working memory which refers to active representations stored and manipulated over seconds. Two main frames of reference have been described: egocentric, which is related directly to the observer, and allocentric, which is dependent on the relational position of objects in space. Routes depend more on egocentric frames of reference, whereas maps are more flexible to landmark changes and thus depend more on allocentric frames of reference. Although often discussed separately, an emerging view is that both egocentric and allocentric spatial memories are coded but these may interact and depend on interacting brain regions. Spatial memories can be representations of salient cues for navigation or be more detailed representations, including topography, allowing reexperiencing of the environment (Moscovitch et al. 2005). A useful analogy has been proposed such that schematic representations of topography correspond to ▶ semantic memory and detailed representations correspond to ▶ episodic, autobiographical memory. Classic tasks of spatial memory in experimental animals include the ▶ Morris water maze, Olton maze, and ▶ radial arm maze (although these latter tasks can incorporate a large ▶ working memory component). In humans, both static (route reporting

and drawing) as well as real-world tasks can be used and while being informative, they are severely limited in interpretability and control of motivation and strategy. Emerging use of virtual reality provides a mechanism to integrate realistic representations of space and environment with controlled laboratory assessments, including functional brain imaging, which requires the participant to remain still during the course of an experiment.

Functional Neuroanatomy

The human visual system comprises two processing streams, a dorsal "where" system important for spatial navigation and a ventral "what" system for object recognition. Goodale and Milner (1992) emphasized the transformations that may be required for information in each stream, relabeling the dorsal stream as a "how" system. This system was proposed to be involved in action preparation via transformation of visual information using an egocentric frame of reference, whereas the ventral system processed transformation for long-lasting representations using multiple frames of reference. Functional brain imaging, including studies using virtual reality, largely supports this general distinction. For example, Aguirre and D'Esposito (1997) initially trained subjects on learning the location of 16 objects in a virtual town. ► Functional MRI (fMRI) scanning was performed during two conditions in which they judged (1) if the appearance of a location within the town matched the name of a location – the appearance condition; or (2) the direction of travel from a displayed location in the town to a given new location – the position condition. When contrasted against each other, the appearance condition showed greater activation in the fusiform and parahippocampal gyrus as well as occipital regions, whereas the position condition showed greater activation in more dorsal areas (i.e., superior and inferior parietal lobes). This study was performed in only four volunteers, but in general there is an agreement that the ► hippocampus and medial temporal lobe structures are required for the acquisition of spatial memories in humans (Parslow et al. 2005) and while fewer studies have examined retention and retrieval of spatial memories, the results of the ► fMRI study fit with studies showing that detailed episodic spatial memories cannot survive damage to the hippocampus/medial temporal lobe (Moscovitch et al. 2005) and retrieval of spatial memories of taxi drivers in London activates hippocampus/parahippocampal gyrus (Maguire et al. 1997). An alternate view is that the hippocampus may not have a selective role in allocentric spatial memory. For example, in a group of six patients with hippocampal damage performing an image-location memory task, impairments were dependent on the number of items rather than the degree of rotation between study and test phases (Shrager et al. 2007), although the use of smooth rotation might have favored egocentric mental rotation strategies (Burgess 2008).

Overall, these studies align with the presence of hippocampus ► place cells in the rodent, monkey, and human brain. In humans, these cells were first described in seven patients with intractable epilepsy undergoing presurgical invasive monitoring, who played the role of a taxi driver in a spatial navigation game (Ekstrom et al. 2003). Cells that responded to specific locations were primarily located in the hippocampus, whereas cells that responded to views of landmarks were primarily located in the parahippocampal region. Indeed, forming memories of places, or landmarks or associating objects with particular locations, appears to require the parahippocampal cortex. Other extrahippocampal regions also important for spatial memory task performance include the posterior parietal cortex and striatum. The former is necessary in the representation of spatial information in terms of egocentric coordinates, allowing reaching and movement plans to be formulated as well as egocentric imagery. The striatum is generally thought to have a role in the learning of the procedural aspects of tasks, and may have dissociable roles in egocentric and allocentric spatial memory consolidation (De Leonibus et al. 2005). Using a task of object exploration with animals entering the same location (egocentric reference frame) or different locations (allocentric reference frame), focal injection of an NMDA receptor antagonist into the dorsal striatum impaired consolidation of the egocentric procedure, whereas intra-accumbens administration impaired both procedures.

Impact of Psychoactive Drugs

In experimental animals, the neurobiology and psychopharmacology of spatial memory have been extensively studied, dominated by the use of the Morris water maze (McNamara and Skelton 1993). The neurotransmitter and molecular mechanisms of medial temporal lobe and cortical structures involved in spatial memory implicate specific drug systems in the accurate acquisition and expression of these memories. Focusing on the hippocampus as the most studied of these regions implicates glutamergic neurotransmittion through ► AMPA and ► NMDA receptors, as well as modulatory influences of the cholinergic and serotonergic inputs. Muscarinic and nicotinic cholinergic receptor blockade as well as serotonin receptor antagonism can all modulate hippocampal glutamatergic and ► GABAergic neurotransmission as well

as the theta rhythm, which is hypothesized to allow rapid transitions between encoding and retrieval.

Glutamate Receptors

The ► NMDA receptor is a major target for glutamate in the brain and its role in ► long-term potentiation is thought to be related to mnemonic encoding. It is no surprise that NMDA blockade using compounds such as AP5, ► ketamine, or MK-801, either intrahippocampal or intracerebral in rats impairs spatial learning using the Morris water maze, without affecting perceptual or motivational processes. For example, a degree of selectivity is suggested by the lack of impairment on a nonspatial discrimination task following AP5 infusion (McNamara and Skelton 1993). ► Metabotropic glutamate receptor agents can also modulate spatial learning. For examples, an mGluR5 allosteric modulator enhances spatial learning in the rat, probably by enhancing LTP and LTD, and an mGluR2 receptor antagonist can impair spatial learning when infused into the nucleus accumbens. Although they are likely to play a role, the function of AMPA and kainate receptors in specific modulation of glutamatergic activity during spatial memory tasks is not well understood; similarly for the influence of NMDA receptor subunits. Aging, at least in mice, is known to be associated with changes in NMDA subunit expression which may contribute to memory decline with aging (Zhao et al. 2009).

Cholinergic Receptors

Studies employing lesions of the cholinergic cell groups in the basal forebrain nucleus basalis magnocellularis or medial septum, pharmacological blockade of acetylcholine receptors, age-related decreases in ► acetylcholine activity, and ► microdialysis to index acetylcholine release provide compelling converging evidence for the important role of the acetylcholine system in spatial memory. However, it is now generally accepted that cholinergic modulation can also influence visual attention, altering cue processing (e.g., Muir et al. 1993), and thus it is important that these additional effects are taken into account. In humans, fMRI and positron emission tomography (► PET) have confirmed the effects of cholinergic enhancement with ► physostigmine on stimulus-driven shifts in ► attention, which can reduce demands on working memory processes in the ► prefrontal cortex.

Within the hippocampus, microdialysis in the rat clearly shows a positive relationship between acetylcholine and spatial learning and memory performance, and in humans it is predicted that patients with cholinergic dysfunction (e.g., ► Alzheimer's disease) or volunteers administered scopolamine will be impaired on tasks of spatial memory via alteration of hippocampal activity based on the proposal that acetylcholine activity dynamics modulates hippocampal-based encoding of new information (Hasselmo 2006). Using a virtual reality-based spatial memory task based on the Morris water maze, deficits in hippocampal activation following scopolamine (0.4 mg s.c.) have been demonstrated in healthy volunteers (Antonova et al. 2009). The task requires the movement (using a trackball) to a platform in a virtual reality arena surrounded by abstract images (see Fig. 1). The memory for place is assessed by removing the platform and asking the volunteer to move to the platform location from the same starting point with different environmental cues (viewpoint-dependent or egocentric condition), or from different starting points with the same environment cues (viewpoint-independent or allocentric condition). Using a different task of spatial navigation (Gron et al. 2006), the ► acetylcholinesterase inhibitor and nicotinic cholinergic receptor agonist, ► galantamine (4 mg b.i.d. for 7 days), has been shown to modulate neural activity in a group of ten patients with ► mild cognitive impairment (these patients have an increased risk for developing clinically defined Alzheimer's disease). Using one-sample *t*-tests galantamine was shown to decrease activity in the supplementary motor area and increase activity in a network of regions known to be associated with this task in young healthy volunteers: occiptotemporal junction, fusiform gyrus, posterior cingulate, parahippocampal gyrus, and hippocampus. While the task depended in part on spatial memory, the use of egocentric or allocentric frames of

Spatial Memory in Humans. Fig. 1. A screenshot of the arena task used by Parslow et al. (2005) reproduced with kind permission from Professor Robin Morris. The goal of the task is to move toward the pole, at first with the pole visible and subsequently after removal of the pole. Changes in the starting position and background environment allow the control of the frames of reference likely to be used in spatial memory recall.

reference was not controlled and the role of motivational and decision-making processes in the completion of such tasks is poorly understood.

Other Neurotransmitters

γ-Aminobutyric acid ► (GABA) receptors control the flow of excitation through the brain. Within the hippocampus, GABA receptors are categorized as ► $GABA_A$ and $GABA_B$, which have differential distribution and control of neuronal activity. Expression of the α_5 subunit of the $GABA_A$ receptor is enriched in pyramidal cells of the hippocampus, thus the knockout mouse can be considered a model of hippocampal $GABA_A$ functionality. Performance is improved in the α_5 subunit knockout mouse after administration of a full ► inverse agonist of the α_5 subunit on the delayed match-to-place Morris water maze task, in which the platform is moved between trials. Dopamine systems have previously been associated with the learning aspects of spatial memory tasks, with degeneration of the nigrostriatal dopamine system associated with learning deficits in the Morris water maze. Long-term effects on the consolidation of aspects of spatial memory, including object displacement tasks impaired after intra-accumbens injection of dopamine D1 and D2 antagonists, as well as improvements with ► levodopa, highlight a role for the striatal dopamine system. However, in terms of normal aging, analysis of impaired performance on the Morris water maze with age, in relation to hippocampal receptor density, showed no associations with dopamine D1 receptors. $Serotonin_{1A}$ receptor binding sites were, however, increased in poor performers in keeping with the proposed role of $5\text{-}HT_{1A}$ receptors in encoding and consolidation of spatial memory rather than retrieval. Interestingly, $5\text{-}HT_{1B}$ knockout mice appear protected against age-related hippocampal memory decline. However, a selective role in spatial memory has been questioned by 5-HT release being associated more closely with motor behavior and feeding behavior during spatial memory tasks rather than task performance. To date, there are no studies in humans that test other agents against spatial memory tasks.

Conclusions

Spatial memory describes a collection of functions associated with spatial information processing including navigation and localizing of objects. Egocentric and allocentric frames of reference have been proposed for spatial processing, but are likely to interact in many situations. Nonetheless, separable functional neuroanatomy appears plausible for egocentric (parietal lobes) and allocentric (hippocampal region/striatum) memory tasks, with the latter emerging recently in functional imaging investigations using virtual reality. In keeping with the research in experimental animals, the hippocampal and proximal medial temporal lobe structures have a central role in spatial memory processing in humans. Predictions from hippocampal neuropharmacology of important neurotransmitters in spatial memory processing imply a degree of opportunity for enhancement in human populations although this remains largely unexplored. A positive association between cholinergic activity and spatial memory in healthy volunteers (using scopolamine) and patients with mild cognitive impairment (using galantamine) is a strong indicator for the scope of behavioral modulation possible with the correct target compounds. Further work with GABAergic agents, particularly α_5 inverse agonists, dopaminergic, and serotonergic compounds is required to validate predictions from experimental animals.

Cross-References

► Human Long-Term Memory
► Human Short-Term and Working Memory
► Short-Term and Working Memory in Humans

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Spatial Navigation

► Spatial Learning in Animals

Spatiotemporal Coincidence

Definition

Signals that arrive at the same time at the same place. A specific example is high-frequency stimulation to induce long-term potentiation by depolarizing postsynaptic synapses at the time when the presynaptic axon is depolarized.

SPC

► Summary of Product Characteristics

Special K

► Ketamine

SPECT Imaging

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Synonyms

Single photon emission computed tomography; Single photon emission tomography (SPET); SPET

Definition

SPECT is a nuclear imaging method that uses a radioactive tracer (radiopharmaceutical) to measure blood flow or to label brain molecules of interest. The radioactive tracers used in SPECT produce a single photon that is detected by a camera sensitive to photon emissions (gamma camera). SPECT can be used in animal and human research and in human clinical diagnosis to non-invasively assay cerebral blood flow (as an indirect marker of neuronal activity) and cell molecular components of interest (targets) such as neurotransmitter receptors, neurotransmitter reuptake transporters, and other proteins of interest. SPECT methods and uses overlap considerably with those of positron emission tomography (► PET), another nuclear imaging method widely used in psychopharmacology.

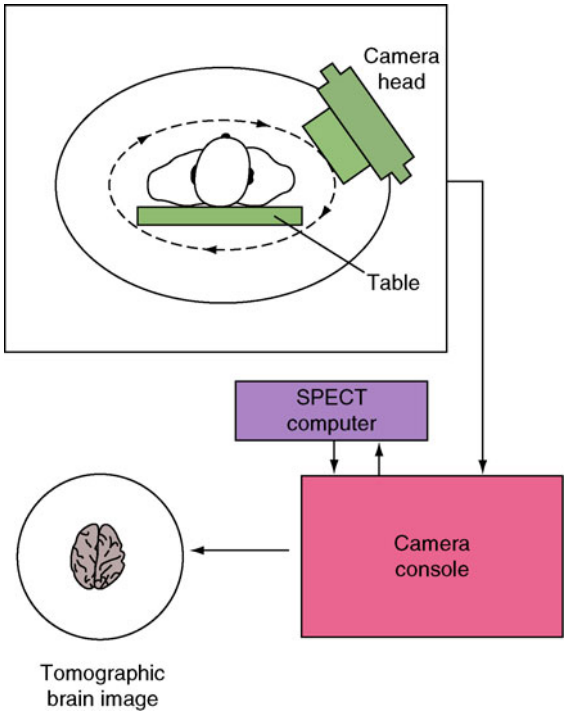
Principles and Role in Psychopharmacology

Basic Method

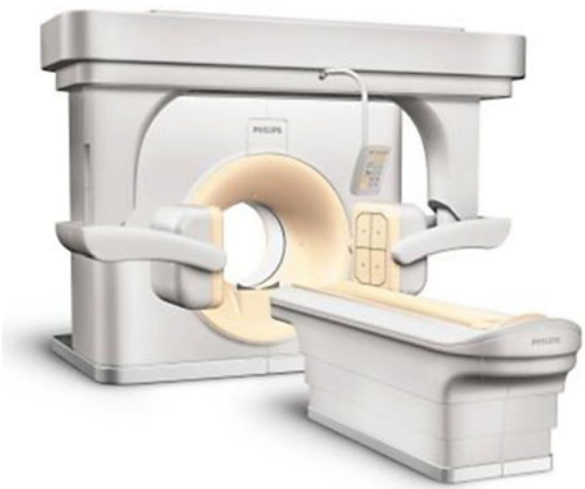
The fundamental principle of SPECT imaging consists of detecting, localizing, and quantifying gamma ray emissions from radiolabeled compounds. Gamma ray emissions are produced when an unstable isotope decays, emitting a photon. The radiolabeled compound is injected intravenously into an animal or human where it circulates throughout the body and to the brain. The photons emitted by the radiolabled compound are then detected with the ► Gamma Camara System. Figure 1 shows a schematic of a SPECT imaging method, and Fig. 2 is an example of a human SPECT imaging system with two gamma cameras that can be positioned to image an area of interest.

SPECT tracers in psychopharmacology are primarily of two types: (1) those that cross the ► blood-brain barrier and distribute nonspecifically in the brain (perfusion radiopharmaceuticals), and (2) those that cross the blood-brain barrier and distribute according to specific molecular targets (target molecule-binding radiopharmaceuticals).

SPECT perfusion ► radiopharmaceuticals (used to measure blood flow) are compounds that cross the blood-brain barrier and then distribute into the extracellular space in proportion to the blood flow to a region (Masdeu and Arbizu 2008). A successful SPECT perfusion tracer must have the correct lipophilicity properties so that it crosses the blood-brain barrier easily, but it must also have no specific binding to brain components. Once



SPECT Imaging. Fig. 1. SPECT imaging system. (Mettler and Guiberteau 2006, p 26).



SPECT Imaging. Fig. 2. Human SPECT Scanner. A two-camera human SPECT scanner. (► http://www.impactscan.org/images/Philips_Precedence_SPECT-CT.jpg. Picture provided courtesy of Philips Healthcare).

the photon counts are detected by the gamma camera system, the relative cerebral blood flow to an area can be determined. Since local neuronal activity is strongly coupled to cerebral blood flow, SPECT tracers can therefore be used as indirect indicators of changes in local neuronal activity.

Unlike SPECT perfusion radiopharmaceuticals, target molecule-binding radiopharmaceuticals must have high ► affinity and specificity for the target molecule. Usually, the affinity for the specific target molecule is at least tenfold greater than the concentration of the target molecule to be imaged. This requires that target molecule-binding radiopharmaceuticals have affinities for their target molecules in the low nanomolar to picomolar range. In addition, these radiotracers must have sufficient lipophilicity to allow penetrance of the blood-brain barrier, but not so high a lipophilicity as to produce high nonspecific binding.

Radiopharmaceutical Synthesis

SPECT radiopharmaceutical synthesis begins with a ► Radionuclide. The two most widely used radionuclides in SPECT imaging are technetium (Tc) as [^{99m}Tc] and iodine (I) as [^{123}I]. SPECT radionuclides are made primarily by irradiating atoms with charged particles (Leslie and Greenberg 2003; Mettler and Guiberteau 2006). A pharmacological molecule of interest, for example a neurotransmitter receptor or reuptake transporter binding ligand, is then chemically attached to the radionuclide to create the ► Radiopharmaceutical. Because ^{123}I, ^{99m}Tc, and other single photon emitting radionuclides are relatively heavy atoms, it is difficult to attach them to small biologically active molecules such as glucose and have such small molecules retain their biological activity. As a result, SPECT radiopharmaceuticals for brain imaging are restricted to molecules with molecular weights of a few hundred, but cannot be too large as they will not pass the blood-brain barrier.

Image Construction

Image construction for SPECT requires the use of a specialized detection system called a gamma camera that uses hardware and software approaches to generate an image that shows the location and intensity of the tracer (Accorsi 2008).

In both SPECT perfusion imaging and SPECT target molecule imaging, mathematical models are used to interpret the results. These models account for the intrinsic properties of the tracer, such as the rate at which the tracer reaches equilibrium in the brain and nonspecific binding of the tracer.

Brain SPECT imaging is often combined with computed ► Tomography (CT) to provide a detailed structural brain image for overlaying SPECT data.

Resolution

The resolution of SPECT imaging is determined largely by the design of the hardware and software for the gamma camera system. Modern SPECT scanners in general clinical use have resolutions of around 1 cm but special small-animal research SPECT scans, using modified hardware and software for image construction, can achieve resolutions of less than 1 mm (Masdeau and Arbizu 2008; Spanoudaki and Ziegler 2008).

Time Course and Availability

SPECT radionuclides have relatively long ► half-lives, for example the half-life for two widely used radionuclides is about 13 h for ^{123}I compounds and about 6 h for ^{99m}Tc compounds. Because of this stability, SPECT ligands can be injected up to several hours before the actual scanning procedure. Some commonly used SPECT radiopharmaceuticals and their indications are shown in Table 1. It is important to note that the availability of these ligands for human research or clinical applications is determined by the rules of each country, so that not all ligands are available in all regions.

Uses

SPECT therefore has broad applicability in basic research and clinical research, diagnosis, and treatment. Based on the principle that increased regional cerebral neuronal activity is associated with increased blood flow, SPECT perfusion studies can provide indirect information related to local neuronal activity and metabolism. SPECT perfusion studies are used to measure baseline blood flow, blood flow changes associated with task-related activity, or blood flow changes associated with drug effects (Malizia 2006).

SPECT imaging with target molecule-binding radiopharmaceuticals can be used to measure the baseline levels of target molecules and can measure the influence of experimental manipulations, genetics, and disease states on target molecules. Two useful examples of SPECT methods as applied to human clinical and research conditions include the study of Parkinson's disease and substance abuse disorders.

In ► Parkinson's disease, a neurodegenerative illness characterized by loss of brainstem dopaminergic innervation of the striatum, SPECT imaging has been used to

SPECT Imaging. Table 1. Sample brain SPECT compounds and applications used in psychopharmacology.

Radionuclide	Half-life	Compound	Acronym	Measurement
^{133}Xe	5.24 days	^{133}Xenon	^{133}Xe	*rCBF*
^{99m}Tc	6.02 h	^{99m}Tc-hexamethylpropyleneamineoxime	^{99m}Tc-HMPAO	*rCBF*
^{99m}Tc	6.02 h	^{99m}Tc-diethylenetriaminepentaacetic acid	^{99m}Tc-DTPA	*CSF*, brain death
^{67}Ga	78.3 h	^{67}Ga-ethylenediaminetetraacetic acid	^{67}Ga-EDTA	Blood-brain barrier permeability
^{123}I	13.2 h	^{123}Iomazenil	^{123}I-IMZ	Central type benzodiazepine-receptor binding
^{123}I	13.2 h	^{123}I-2-((2-((dimethylamino)methyl)phenyl) thio)-5-iodophenylamine	^{123}I-ADAM	Serotonin transporter imaging
^{123}I	13.2 h	^{123}I-β-carbomethoxy-3-β-(4-iodophenyl)-tropane	^{123}I-CIT	Dopamine and serotonin transporters
^{123}I	13.2 h	^{123}I-iodobenzamide	^{123}I-IBZM	Dopamine D_2 receptor ligand
^{99m}Tc	6.02 h	^{99m}Tc-TRODAT	^{99m}Tc-TRODAT	Dopamine transporter sites
^{111}In	2.83 days	[^{111}In-DOTA^0,D-Phe^1,Tyr^3] octreotide	^{111}In-DOTA-TOC	Somatostatin receptor imaging
^{123}I	13.2 h	[^{123}I]5-iodo-3-[2(S)-2-azetidinylmethoxy] pyridine	^{123}I-5IA	Nicotinic acetylcholine receptors
^{123}I	13.2 h	6-iodo-2-(4′-dimethylamino-) phenylimidazo[1,2-a]pyridine	^{123}I-IMPY	β-amyloid plaque imaging

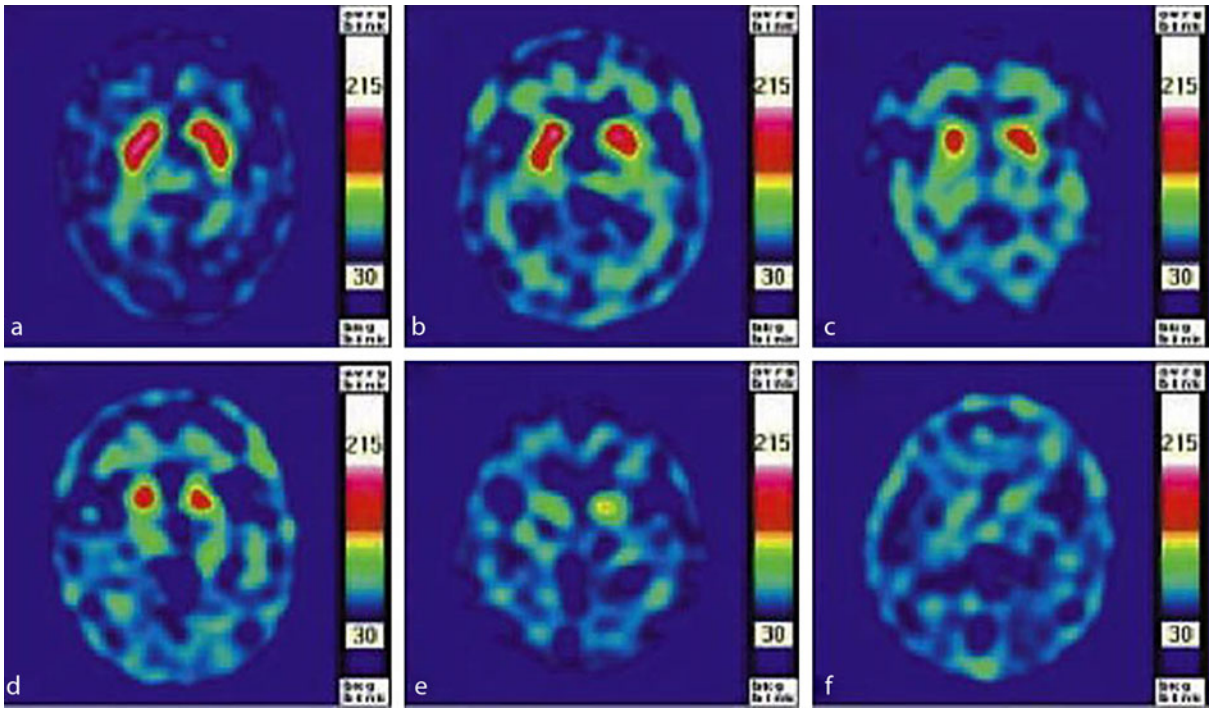
rCBF relative cerebral blood flow; *CSF* cerebrospinal fluid. Modified and adapted from Accorsi 2008. Used with permission

demonstrate reductions in the levels of the presynaptic ► dopamine transporter (DAT) and increased levels of postsynaptic dopamine receptors (D2 subtype). SPECT may also have utility in monitoring Parkinson's disease progression and assessing the success of treatment interventions. In clinical conditions suggestive of early Parkinson's disease, SPECT assays of dopamine status may aid in diagnosis by determining whether early alterations in the DAT or D2 receptors are consistent with this illness (Booij and Knol 2007). Figure 3 illustrates the difference between a healthy control subject and patient's with Parkinson's disease at different levels of severity. As disease severity worsens, there is near complete absence of detectable DAT binding as measured using the DAT ligand [^{99m}Tc] TRODAT-1 (Huang et al. 2004).

As reviewed by Volkow and others (Volkow et al. 2003; Felicio et al. 2009), SPECT (and PET) methods are used widely to study the effects of substance abuse and dependence and have contributed greatly to our understanding of drug effects in humans. For example, SPECT has been used to detect drug-induced changes in the ► serotonin transporter, serotonin receptors, and cerebral blood flow following recreational exposure to 3,4-methylenedioxymethamphetamine (► MDMA; Ecstasy). For multiple drugs of abuse, SPECT imaging has been successful in documenting the effects of drug exposure on receptor and transporter systems (for multiple neurotransmitters, but especially the dopamine system) and on cerebral blood flow. SPECT imaging has also proven critical in documenting the time course of neurotransmitter and blood flow changes associated with acute and chronic drug exposure and following drug withdrawal.

Strengths and Limitations

Strengths of SPECT are considerable. Some SPECT radiopharmaceuticals are less costly, more easily synthesized, and provide a lower radiation dosage than some PET tracers. This enhances the ease of use and acceptability of SPECT for human psychopharmacological research. Limitations of SPECT include the relatively small number



SPECT Imaging. Fig. 3. SPECT imaging in Parkinson's disease. These images show the utility of SPECT, using [^{99m}Tc]TRODAT-1 to measure dopamine transporter (DAT) loss in Parkinson's Disease. The highest signal intensities are shown in red, corresponding to high levels of the DAT. (**a**) Healthy control subject. The bilaterally symmetric bright red regions are the striatum. (**b**–**f**) Represent increasingly severe stages of Parkinson's disease, with progressive loss of striatal DAT binding (From Huang et al. 2004. Used with kind permission of Springer Science+Business Media).

of available radiopharmaceuticals and the resolution of this technique as commonly available for basic and clinical research. Unlike PET, where 18-fluorine-flouro-deoxy-glucose [18FDG] is commonly used to examine cerebral glucose metabolism, there is no comparable SPECT tracer for measuring cerebral glucose metabolism.

Emerging Technology

Emerging technologies include the use of modified gamma camera systems to provide very high spatial resolutions (in the submillimeter range) in animal nuclear imaging research studies. Dual tracer or multi-isotope imaging, in which different tracers are used to image two components simultaneously (e.g., perfusion and receptor binding) hold promise (Accorsi 2008).

Future Directions

With the development of high-resolution gamma cameras and additional radiopharmaceuticals, SPECT imaging can be expected to play an increasingly significant role in psychopharmacological research. In addition to the potential for high resolution pharmacological mapping of neurotransmitter systems in animal models, human applications may increasingly expand to include clinical diagnostic applications such as those detecting early types of degenerative illnesses (such as Alzheimer's Disease or Parkinson's Disease) or neurodevelopmental illnesses (such as ► Autism or ► Schizophrenia).

Cross-References

► Functional Magnetic Resonance Imaging
► Positron Emission Tomography (PET) Imaging

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Spectrograms

Synonyms

Deconvolution; Fourier spectrum; Frequency spectrum; Power spectrum

Definition

Representation of an EEG trace signal by a "virtual" decomposition (by a mathematical operation called ► Fast Fourier Transformation or FFT) of all possible contributing quasi-sinusoidal waves of different carrier frequencies. The result is a descriptor in the frequency domain and allows the distinction, for example, of low, middle fast or high frequencies; these are easily expressed in a magnitude (equal to square root of power) that is a convenient metric of EEG for research purposes.

Cross-References

► Digital EEG Nomenclature
► Electroencephalography

Spectrographic

Definition

A spectrogram is an image that depicts the spectral density of a sound varying with time. Spectrograms are used to analyze *spectographically* the vocalizations of animals yielding quantitative statistics for comparison between a variety of experimental and natural conditions.

SPET

► SPECT Imaging

Spin-Echo EPI

► Echo-Planar Imaging

Spinal Cord Primary Sensory Neurons

Definition

These are neurons with cell bodies located in sensory ganglia with processes terminating in the periphery (skin, viscera, other) and in the spinal cord in the CNS. They convey the first (primary) sensory information to the spinal cord. They vary in cell body size, axon diameter, conduction velocity, and their content of neurotransmitters and neuroactive peptides. These differences and the distribution of central and peripheral ends account for sensory modality content. Small-diameter primary sensory neurons might, in addition, liberate neuropeptides antidromically with pro-inflammatory consequences.

Spindles

► Function of Slow and Fast Alpha Waves

Splice Variant

Definition

Different forms of an expressed protein derived from splicing of different regions of its primary RNA transcript.

Cross-References

► ISOFORM

Spontaneous Activity

► Motor Activity and Stereotypy

SR141716

► Rimonabant

SRIF

► Somatostatin

SRI-Resistance

Definition

It has been suggested that failure to improve Y-BOCS scores by 25% from baseline after treatment with at least two SRIs given at maximally tolerated SPC doses for at least 12 weeks constitutes clinically meaningful SRI-resistance.

Cross-References

► Obsessive-Compulsive Disorder

SROMs

► Slow-Release Morphines

SSRIs

► Selective Serotonin Reuptake Inhibitors

SSRIs and Related Compounds

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Synonyms

Serotonin antidepressants

Definition

Selective serotonin reuptake inhibitors (SSRIs) are a class of drugs primarily developed for the treatment of major depressive disorder (MDD), although most agents now have additional indications, particularly for the treatment of various anxiety disorders. These drugs share a common mechanism of action in that they inhibit the ► serotonin transporter in its reuptake of synaptic serotonin.

Pharmacological Properties

History

First generation ▶ tricyclic antidepressants (▶ TCAs), particularly ▶ clomipramine, are potent inhibitors of the serotonin transporter, but these agents have a wide range of effects on various neurotransmitter receptors, resulting in a substantial side effect burden. Although zimelidine was the first SSRI to receive approval as an antidepressant in Europe, plans to launch it in the United States were abandoned when several cases of Guillain-Barre syndrome were reported. ▶ Fluoxetine became the first SSRI to be licensed in the United States in 1987, and paved the way for an attack on stigma and under-detection of ▶ depression, with an expectation that greater safety and tolerability would be associated with superior treatment outcomes (Kramer 1999). Although this proved not to be the case, it heralded the beginning of a new era in drug development for the treatment of MDD. Over the next decade a whole class of SSRI antidepressants emerged as first line agents for the treatment of MDD, accounting for 60% of prescribed antidepressants in the U.S. Medicaid program (Chen et al. 2008; Healy 1999).

Mechanism of Action

As their name implies, the SSRIs selectively block ▶ serotonin (5HT) reuptake. This occurs through inhibitory actions on the Na^+/K^+ adenosine triphosphatase-dependent carrier on presynaptic neurons. Among the six available SSRIs, ▶ citalopram, ▶ escitalopram and ▶ paroxetine are the most potent blockers of 5HT reuptake. Some SSRIs have additional ▶ antagonist effects on neurotransmitter receptors (Table 1). For example, paroxetine and citalopram have moderate anticholinergic effects and sertraline blocks presynaptic dopamine receptors. Escitalopram is a stereoisomer of citalopram and has been shown to exert actions at both the primary binding sites for the serotonin transporter, and also on secondary ▶ allosteric binding sites, a property not shared by other SSRIs (Sanchez 2006).

There is also evidence from position emission tomography (▶ PET) using a ligand for the serotonin transporter, that 80% or greater occupancy of the transporter occurs with citalopram, paroxetine, and sertraline at standard doses, and no additional binding occurs at higher doses (Meyer 2007). These findings are based on only a small sample of depressed patients, and the SSRIs were not examined across a wide range of doses.

The SSRIs, like their predecessors the TCAs, inhibit neurotransmitter reuptake almost immediately, but often take 2–3 weeks to exert clinically meaningful benefit.

SSRIs and Related Compounds. Table 1. Mechanism of action and indications for six available SSRIs.

Drug	Mechanism of action	Indications
Citalopram	**5HT blockade**; mild NE blockade; Post receptor blockade: ACH; H1, DA and alpha-1 (weak blockade)	MDD; panic disorder
Escitalopram	**5HT blockade**; mild NE blockade	MDD; GAD; panic disorder
Fluoxetine	**5HT blockade**; mild NE blockade; mild post DA receptor blockade	MDD; OCD; bulimia nervosa; panic disorder
Fluvoxamine	**5HT blockade**; mild NE blockade	MDD; OCD
Paroxetine	**5HT blockade**; postsynaptic receptor blockade: ACH	MDD; panic disorder; SAD; GAD; OCD; PTSD; premenstrual dysphoric disorder
Sertraline	**5HT blockade**; mild NE blockade; Post receptor blockade: alpha-1; presynaptic receptor blockade: DA	MDD; OCD; panic disorder; PTSD; SAD; premenstrual dysphoric disorder

NE = norepinephrine; ACH = acetylcholine; H1 = histamine 1; DA = dopamine; MDD = major depressive disorder; GAD = generalized anxiety disorder, OCD = obsessive compulsive disorder; PTSD = post-traumatic stress disorder; SAD = social anxiety disorder

This has been linked to down regulation of the $5HT_{1A}$ terminal autoreceptors. In addition, SSRIs, like other antidepressants, stimulate ▶ neurogenesis, particularly in the CA_3 layer of the ▶ hippocampus after 2–3 weeks of exposure. Animal models of depression using stress paradigms show suppression of neurogenesis which is reversed by antidepressants (Schmidt and Duman 2007).

▶ Pharmacokinetics

The SSRIs are generally well absorbed and not affected by food administration, with the exception of sertraline, where food can increase levels of the drug in plasma. They are metabolized by hepatic microsomal enzymes that are part of the ▶ cytochrome P_{450} system, particularly the CYP_{2D6} isoenzyme, although the $2C_9$, $2C_{19}$ and $3A_4$ isoenzymes are also substrates for several SSRIs (Table 2) (Kennedy et al. 2007).

SSRIs and Related Compounds. Table 2. Pharmacokinetic profile of SSRIs.

Drug	% Bioavailability	Metabolism	Active metabolites	Half life (hours)
Citalopram	80	CYP3A4 CYP219 CYP2D6 Weakly inhibits: CYP2D6	Demethylcitalopram Didmethylcitalopram	35
Escitalopram	80	CYP3A4 CYP219 CYP2D6 Weakly inhibits: CYP2D6	Demethylescitalopram	27–32
Fluoxetine	72	CYP2D6 CYP2C19 Inhibits: CYP2D6, 2C9, 2C19	Norfluoxetine	24–72
Fluvoxamine	53	CYP2D6 CYP2C9 Inhibits: CYP2C19, 2D6, 1A2, 3A4	None	15.6
Paroxetine	50	CYP2D6 Inhibits: CYP2D6	None	21–24
Sertraline	44	CYP3A4 Weakly inhibits: CYP2D6,2C9	Norsertraline	26

It is important to note that certain SSRIs inhibit their own clearance through the inhibition of their metabolizing enzyme, resulting in elevated plasma levels and increased side effects. Both fluoxetine and paroxetine are strong inhibitors of the CYP_{2D6} enzyme, and fluvoxamine is a potent inhibitor of CYP_{1A2}, CYP_{3A4}, and CYP_{2C19}. Therefore, caution should be exercised when combining these drugs with other medications that are metabolized through any of these enzymes, as in the following two examples. ► Codeine requires CYP_{2D6} for its conversion to ► morphine and analgesic effects, and inhibiting this pathway prevents the analgesic effects. In the case of desipramine, a secondary tricyclic antidepressant, combining it with fluoxetine will result in increased plasma levels due to the inhibition of CYP_{2D6}. This can cause cardiotoxicity and, in rare instances, death.

The ► half-life of SSRIs ranges from about 15 h (► fluvoxamine) to over 60 h (fluoxetine), with other agents in the 30 ± 6 h range. This means that in all cases, SSRIs can be prescribed at least once daily and in the case of fluoxetine, the drug remains capable of causing drug-drug interactions 2–3 weeks after the last dose.

Genetic Polymorphisms

There is emerging evidence to support a relationship between ► genetic polymorphisms of the serotonin transporter (5HTT) and response to SSRIs. The 5HTT gene-linked polymorphic region (5HTT-LPR) significantly influences transcription of 5HTT, resulting in differential expression of the serotonin transporter. To date, several reports have linked the 5HTT-LPR "l" allele to superior or faster response to SSRI therapy and the 5HTTLPR "s" allele to greater SSRI-related side effects. However, these findings were not substantiated in a report from the "Sequenced Treatment Alternatives to Relieve Depression" (STAR*D) study, where a search for genetic predictors of treatment outcome with citalopram yielded an association between treatment outcome and a gene that encodes the $5HT_{2A}$ receptor (McMahon et al. 2006).

Efficacy and Effectiveness

The SSRIs have primarily been used to treat patients with MDD, but in nearly all cases, there are additional indications for the treatment of anxiety disorders (Table 1) (Kennedy et al. 2007). While it was initially believed that SSRIs manifested little, if any, variation in ► efficacy for MDD across the class of agents, subsequent meta-analyses have suggested that they do not perform equally. Since most trials were designed with sufficient sample sizes (power) only to detect differences between the novel agent and ► placebo, the inclusion of an active comparator agent to ensure assay sensitivity did not provide sufficient power to compare efficacy between the two active drugs. However, when similar trial design and outcome measures are applied across a series of trials, it is justifiable to pool the data from all subjects and conduct

a ▶ meta-analysis. This methodology provides a large enough sample to detect differences between active agents.

Escitalopram has demonstrated modest but consistent advantages over other SSRIs, but these differences were most significant in the comparisons with citalopram. Using a "multiple-treatments meta-analysis" method, which includes both direct and indirect comparisons of drugs, the efficacy and acceptability of 12 new-generation antidepressants (including the 6 SSRIs) were compared across 117 randomized control trials (Cipriani et al. 2009). Two SSRIs, escitalopram and sertraline, were among the four drugs with significant advantages over the other antidepressants in terms of efficacy. These two agents also had the best tolerability profiles, making them the most favorably ranked overall.

Tolerability

Even though the tolerability and safety profile of SSRIs is superior to the previous generation of TCAs, lack of compliance due to treatment-emergent side-effects remains a significant issue. There are both early transient adverse effects and persistent effects, which frequently result in drug discontinuation. Acute effects most often involve the central nervous system (CNS) and the gastrointestinal (GI) system, while later sustained effects are more likely to influence metabolism and sexual dysfunction (Table 3) (Kennedy et al. 2007).

SSRIs and Related Compounds. Table 3. Common side effect profile of SSRIs across average dose range.

Drug	Averagedose range	10–30%[1]	30%[1]
Citalopram	20–60mg	CNS over arousal	Nausea
Escitalopram	10–20mg	Headaches and nausea	None
Fluoxetine	20–60mg	CNS over arousal	Nausea and headaches
Fluvoxamine	100–300mg	CNS over arousal, dizziness and constipation	Drowsiness, headaches, nausea, nervousness
Paroxetine	20–60mg	CNS over arousal, constipation and dizziness	Drowsiness, nausea, sexual dysfunction
Sertraline	50–200mg	CNS over arousal, dizziness, sexual dysfunction	Headaches and nausea

[1]Drug-placebo differences modified from product monographs
CNS = central nervous system

Central Nervous System

Headache, sleep disturbance, sedation, and paraesethesia are commonly reported in the acute phase of treatment with any SSRI. Although some aspects of sleep are improved with SSRIs, there are reports that SSRIs disrupt sleep continuity and may exacerbate ▶ bruxism and restless leg syndrome. Additionally, while SSRIs generally improve cognitive dysfunction associated with depression, there is evidence, specifically with paroxetine, of drug-related cognitive side effects, likely due to its additional anticholinergic effects.

Gastrointestinal and Metabolic Effects

Nausea is a common gastrointestinal side-effect during the first 2 weeks of treatment with an SSRI, and is most pronounced for fluvoxamine and sertraline. This is generally a transient effect.

Weight gain is a factor that can severely decrease drug compliance. Although initial treatment with SSRIs can result in weight loss, mainly due to nausea and an enhanced feeling of early ▶ satiety, long-term use of SSRIs has been associated with weight gain, particularly with paroxetine (Fava et al. 2000; Kennedy et al. 2007).

Recent studies have suggested that SSRIs may result in the loss of bone mineral density during long-term use. This appears to reflect inhibitory actions of serotonin on osteogenesis. Whether this might contribute to the development of clinical osteopenia or osteoporosis is still unclear.

Sexual Dysfunction

The consensus from a series of well designed comparative studies is that up to 60% of patients receiving SSRIs report some form of treatment emergent sexual dysfunction, with paroxetine and sertraline exerting the greatest burden of sexual side effects (Kennedy and Rizvi 2009). All of the SSRIs have been associated with delayed or absent orgasm/ejaculation and, in some instances, a reduction in libido and arousal. These effects appear to be related to the stimulation of serotonin, particularly its ▶ agonist effects on $5HT_2$ receptors. However, other mechanisms that block cholinergic receptors and inhibit nitric oxide synthase are also likely to be involved as well. This may explain why patients receiving paroxetine compared with

other SSRIs had a significantly greater incidence of erectile dysfunction or reduced vaginal lubrication.

Safety

Suicidality

Depressed patients are at greatest risk for ►suicide attempts during the month before and the first month after starting medication, and the risk progressively declines with treatment. Although most population studies have shown a reduction in rates of completed suicide associated with increased use of modern antidepressants, the issue of suicidality with SSRIs has attracted considerable media attention and appears to be most pronounced in adolescents. The "►black-box" warning for SSRIs in the U.S., Canada and elsewhere, due to findings of increased suicidal ideation, has likely contributed to a decrease in antidepressant prescriptions for children and adolescents. Since the 2003–2004 warning, studies indicate that U.S. and Canadian rates of completed suicide hasve increased for the first time in a decade for adolescents. In adults, meta-analyses of ►randomized controlled trials (RCTs), or analyses of research databases, have found no support for increased suicides with antidepressant use (Möller 2006).

Serotonin syndrome

Excessive serotonin release may result in a clinically significant "►serotonin syndrome", characterized by diarrhea, delirium, tremor, muscle rigidity and hypothermia. This may occur when patients are taking two SSRIs or taking an SSRI with another serotonin-enhancing agent. Therefore, caution must be applied when combining treatments and during dose increases.

Conclusions

Since the launch of fluoxetine, SSRI use has increased to the extent that this is now the most widely prescribed antidepressant class, reflecting a favorable balance between efficacy and tolerability. The ►pharmacokinetic profile of SSRIs allows for easy dosing and long-term use. Future research should be directed to increasing the specificity of agents at the serotonin receptor and transporter sites.

Cross-References

►Aminergic Hypotheses for Depression
►Antidepressants
►Depression: Animal Models
►Depressive Disorders in Children
►History of Psychopharmacology
►Randomized Controlled Trials
►SNRI Antidepressants
►Tryptophan Depletion

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SSRT

►Stop-Signal Task

sst$_1$

►Somatostatin Receptors

sst_2

► Somatostatin Receptors

sst_3

► Somatostatin Receptors

sst_4

► Somatostatin Receptors

sst_5

► Somatostatin Receptors

Stackhousiaceae

► Celastraceae

Standardized Mean Difference

► Effect Size

Startle

Synonyms

Startle response

Definition

The startle response refers to a group of reflexive motor and physiological responses elicited by an intense and sudden stimulus, usually in the auditory or tactile modalities.

Startle Modulation

► Prepulse Inhibition

Startle Response

► Startle

State Dependence of Memory

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Synonyms

Dissociated learning; State-dependent learning

Definition

Traditionally, state dependence is said to occur when an organism remembers better when it is in a state similar to the one in which it learned what is to be remembered than when it is in a different state. While this observation remains essential, progress indicates that the phenomenon of state dependence is not necessarily related or limited to the ability to learn per se in a particular state. Dependence on state occurs with memory processes other than learning as the latter is conventionally understood and may determine what is remembered and when; beyond conscious cognition, it also concerns such functions as emotion, mood, and motor behavior. Thus, the term "state dependence of memory," refers to an attribute of the ability to remember and act upon past experience, which is broader than that implied by "state-dependent learning."

Impact of Psychoactive Drugs

A Word of History

Awareness of state dependence arose in seventeenth century popular and medical culture and concerned states of the internal, physiological, and mental milieu (Siegel 1985). Both that century's most acknowledged accounts and the first experimental investigation of state dependence (Girden and Culler 1937) involved states induced by drugs. Influentially capturing the perception of state dependence at that time, (Overton 1983) attributed state dependence to high, "toxic" doses of drugs; considered state dependence to be genuine only if bidirectional (i.e., if occurring upon both drug-to-placebo and placebo-to-drug changes of state); struggled with the issue as to whether state dependence requires that drug-to-placebo and placebo-to-drug state changes should produce symmetrical failures to remember; and argued on theoretical grounds that state

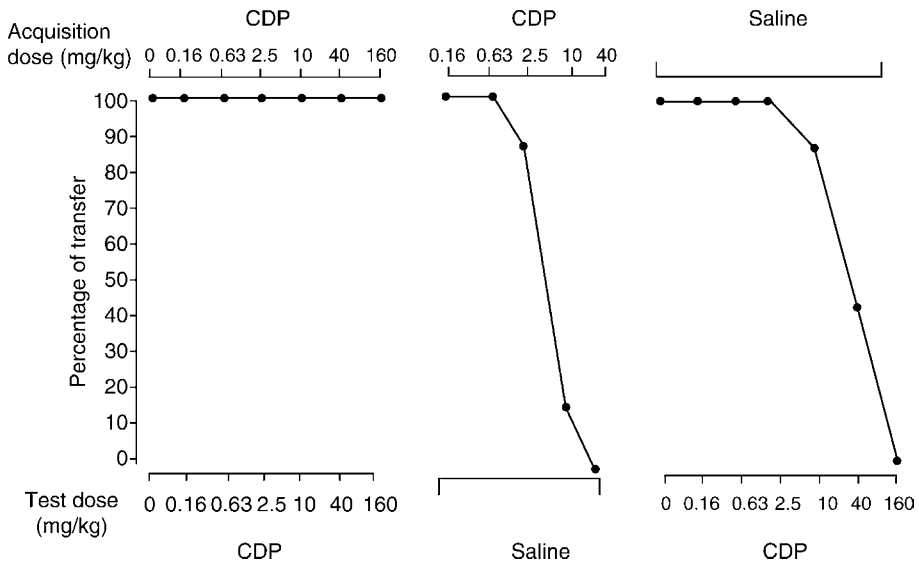
dependence and ► drug discrimination are fundamentally similar. As will be apparent in the following lines, the state dependence concept has much evolved; how and when state dependence occurs has since been studied extensively in humans and animals in well-controlled experimental investigations in laboratory settings.

A Case of State Dependence

Studies of state dependence involve ► learning. The learning assays used may include single trials or multiple-trial learning opportunities, single or multiple-session classical conditioning, or acquisition of an appetitively or aversively motivated instrumental response. As in many ► memory researches, the key dependent variables assess the ability to remember, and recall is often measured operationally by the latency with which a remembered response occurs. The special issue of interest here about the functioning of memory is how memory may vary depending on the similarity or dissimilarity between the state that prevailed at the time of learning and the state that prevails at the time of recall. States thus constitute the independent variable. Failures of "transfer" of the ► engram, or memory trace, are said to occur when recall is hampered by a change of state.

Figure 1 offers an example of state dependence; here, rats are trained in 15 min sessions everyday to press a lever for food reward; every tenth lever press yields access to food (► fixed-ratio: 10, or FR10 schedule). The rat reaches the acquisition criterion when, on a given training session, it completes 10 lever presses within 120 s after the session begins. Two days later, in a test session, recall is measured by determining whether the animal again completes the first FR10 schedule within 120 s. Different groups of rats are trained with (i.e., before the training sessions receive an injection and thus are "under the influence of") either saline or one of different "training" doses of the benzodiazepine, ► chlordiazepoxide (CDP). Later, the rats are tested with (i.e., "under the influence of") either saline or one of different CDP "test" doses.

As shown in the left panel of Fig. 1, recall was perfect by rats that were both trained and tested with saline (points at "0") and by rats that acquired the response while treated with one CDP dose (0.16–40 mg/kg for different rats) and then tested with the same dose. However, as shown in the middle panel, rats trained with 0.16–40 mg/kg doses of CDP and then tested with saline failed to recall in a manner that depended on the training dose, complete failure occurring with 40 mg/kg. Conversely (right panel), rats trained with saline and then tested with 0.16–160 mg/kg doses also failed to recall, now in a manner that varied with the CDP test dose. Thus, state dependence can occur with both drug-to-saline and



State Dependence of Memory. Fig. 1. Results of transfer tests in groups of rats that acquired an operant response in one pharmacological condition (i.e., saline or one of several doses of chlordiazepoxide(CDP) and were tested in either the same or another condition. Upper and lower abscissa: CDP dose at which the animals were trained and tested, respectively; 0 refers to saline. Ordinate: percentage of rats (n=7/group) that in test sessions completed the first FR10 schedule within 120 s. (Redrawn from Colpaert 1990.)

saline-to-drug changes of state, albeit not necessarily at the same dose; here, drug-to-saline transfer failure occurred at doses that were about three-fold lower than those at which saline-to-drug state changes caused transfer to fail (► ED_{50}: 9.8 and 29 mg/kg, respectively).

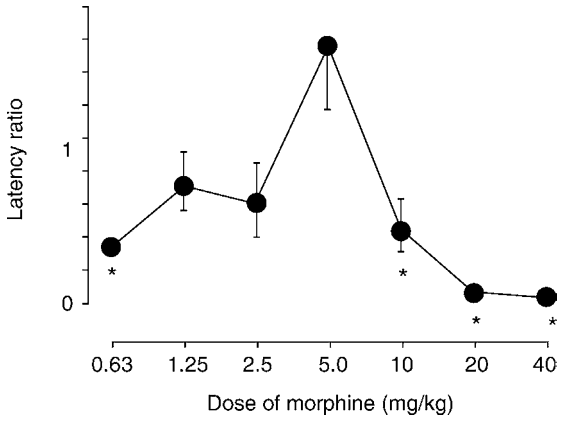
State changes can produce powerful memory failure; under the conditions described above, extreme food deprivation to the point of starvation fails to overcome the inability to remember. Remarkably, studies involving agents such as ► benzodiazepines and ► opiates, to which ► tolerance is considered to readily develop, have so far failed to reveal any evidence that tolerance develops to those agents' ability to induce state dependence; training with drug followed by numerous further drug ("over-") training sessions does not prevent failures of recall when the subjects are later tested with saline.

The state-dependent memory failure is, however, surmountable. Rats trained with saline or CDP 40 mg/kg fail to remember when tested for the first time with CDP 40 mg/kg or saline, respectively; but if later provided the opportunity to learn the same response in the alternative state (i.e., after administration of saline or CDP 40 mg/kg, respectively) rats will eventually learn to recall the response in either state. It is uncertain, though, whether such recall in either state implements only one as opposed to one of two separate ► engrams (Colpaert 1990).

State Specificity

When a response is acquired with saline or with any given agent, the extent to which transfer occurs to other agents may vary widely but it can also be the case that transfer is confined to a narrow class of pharmacologically similar agents. For example, rats trained with ► morphine demonstrate transfer when tested with another μ-opiate receptor agonist, but not with lower-efficacy opiates or any other drug. Recall may be further limited to a particular dose; rats trained with 5 mg/kg morphine remember well when tested with 5 mg/kg, but not with lower or higher doses of morphine (Fig. 2). Thus, ► retrieval can be confined to an exquisitely exclusive, molecularly defined magnitude of activation of a single, particular neurotransmitter receptor (sub)type; these findings highlight memory's state specificity in addition to its state dependence (Bruins Slot and Colpaert 1999).

Specificity can also extend to conditions other than the drug state. For example, a given agent may render state dependent a response that is acquired in a particular set of conditions of arousal and drive for instance, but not the same response in another set of conditions. Equally, with a given agent, a normal-to-drug change of state may impair



State Dependence of Memory. Fig. 2. Results of transfer tests in groups of rats (n=7/group) that acquired an operant response after 5 mg/kg morphine injections and were tested for retrieval with either the same or a lower or higher morphine dose. Retrieval here is measured by the (log-transformed) ratio of the response latency in the last training session to that in the test session (ordinate); data are mean + SEM. (Redrawn from Bruins Slot and Colpaert 1999.)

the retrieval of some but not all items of memory that were acquired in one or another normal set of conditions.

Both these two instances of specificity underlie the ability of states to operate in an often incisive, discrete manner. Partly because of this, state dependence is in many instances overlooked in accounts of CNS function and of CNS drug actions.

State Change: A Mechanism

States and state changes regulate, shape, and direct memory throughout ontogeny; they govern mnemonic normalcy as well as psychiatric and neurological pathogenesis and may constitute the essential neurobiological, or "system," mechanism of different CNS agents.

State Changes in Cognition

Compounds such as ► ketamine and – most prominently – the muscarinic acetylcholine receptor antagonist, ► scopolamine offer drug models of memory disorders, mimicking in unaffected humans the deficiencies that are found in ► Alzheimer's disease. Surprisingly, scopolamine actually may allow fully adequate learning, retrieval ► encoding, ► re-encoding, and ► retention of complex tasks provided that all these memory processes take place in the scopolamine state. However, each of these processes is profoundly impaired when subjects switch from the normal to the drug state (or from the drug to the normal state) as they move from one to the other process. As a

result, the state change that acute scopolamine administration produces in subjects having learned the task in the normal state simulates the regressive, temporally graded retrograde amnesia that is characteristic of Alzheimer's disease. That is, as a function of the scopolamine dose, what can be remembered is limited to what was learned at an increasingly remote point of time in the past while what was learned more recently has become inaccessible (Figs. 3 and 4). Importantly, the state dependence analysis emphasizes the role of state instability, in addition to but more so than that of putative cholinergic hypo-function, in the pathophysiology of such disorders (Colpaert et al. 2001).

Some drug states that are induced after learning or retrieval that occurred in the normal state (i.e., at the time of encoding or re-encoding, respectively) impair subsequent retrieval in the normal state. Drugs may thus pre-empt or erase the normal-state memory of traumatic, pathogenic life events.

State Changes in Anxiety

► Anxiety has long been considered as an acquired drive; i.e., a motivation that is learned in the course of ontogeny. Benzodiazepines exert anxiolytic effects only in as much as they also impair the retrieval of, for example, a food-reinforced ► operant response. In each situation, the benzodiazepines institute a state of memory in which material previously acquired in the normal state cannot be retrieved. Thus, it has been proposed that benzodiazepines impair the retrieval of what in a normal state has previously been acquired what is referred to as anxiety, rather than selectively reducing, or "lysing," anxiety (Colpaert 1990).

State Changes in Pain and Opiate Actions

Pain can be of either physiological (e.g., nociceptive) or pathological (e.g., neuropathic) origin and relates to both its somatosensory and affective/motivational dimensions; the affective/motivational dimension of pathological pain is particularly susceptible to state dependence.

Mammalian newborns learn to synchronize their breathing, which at the prenatal stage is erratic, chaotic, and utterly ineffectual, with the acidity (pH) of arterial blood. This synchrony governs mature breathing, and it has been suggested that rather than merely depress respiration, opiates induce a state in which this learned synchronization cannot be retrieved (Bruins Slot and Colpaert 1999).

State Changes in Affective Disorders

Mood states fluctuate and the memory that prevails at any time is governed by mood congruency, or sameness of mood state. Depressed subjects better memorize new negative-affect than new positive-affect items and remember negative-affect items more effectively in a subsequent depressed episode than in a more elated mood (Blaney 1986; Bower 1981; Colpaert et al. 2000; Eich 2007). While allowing for possible predisposing biological variables, the state dependence of memory uncovers a remarkable pathophysiological mechanism of mood disorders as well as an equally remarkable neurobiological mechanism of antidepressant drug action both of which emphasize the ability to acquire and remember, and disremember, mood.

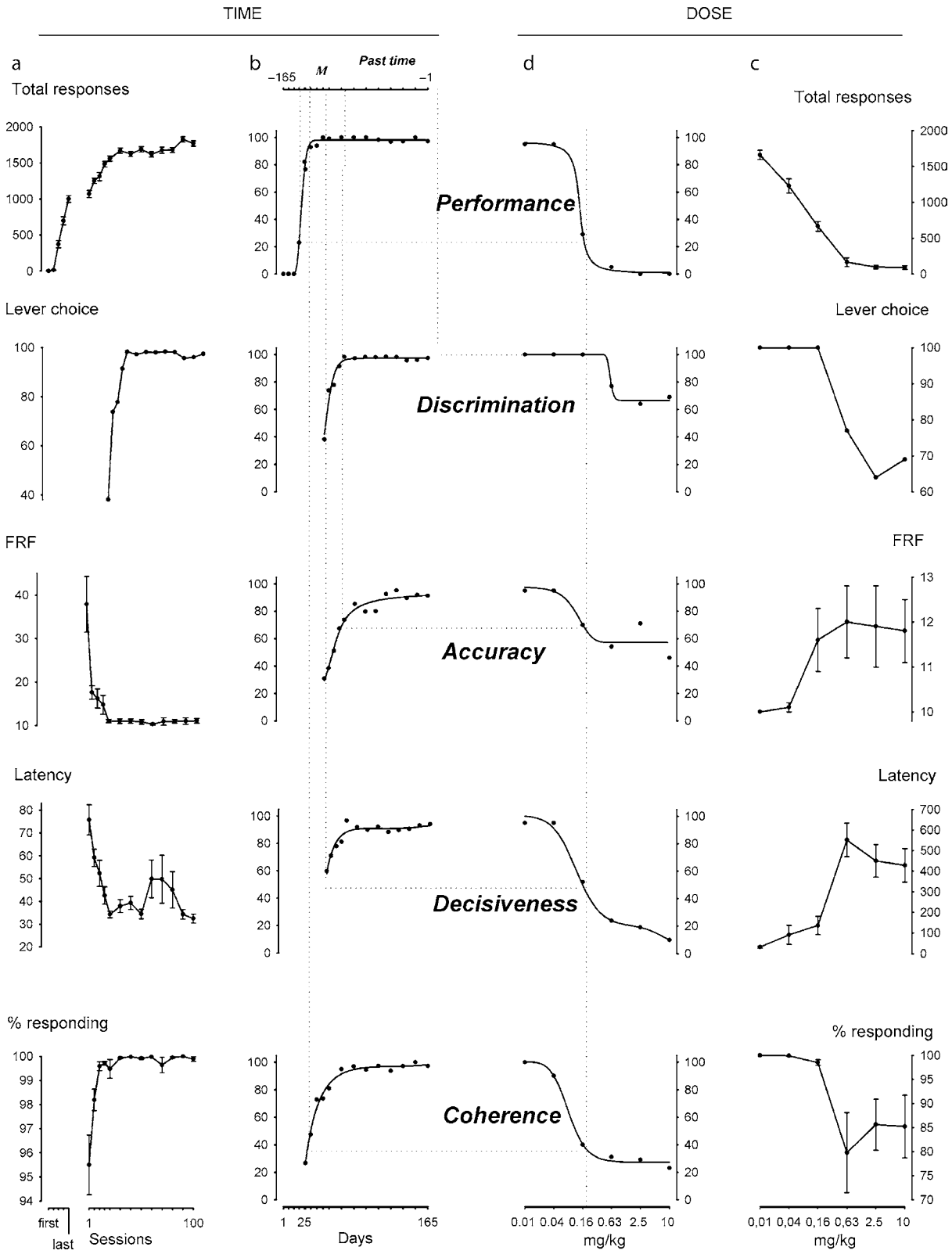
State Changes in Neurological Disorders

Importantly, states and state changes not only govern cognition, but also pervade and affect motor behavior while spanning large swaths of ontogeny. The peculiar features of horizontal locomotion in Parkinson's disease (difficulty with both initiating and arresting locomotion, continuous postural disequilibrium during movement) closely resemble those of 10-month old infants who learn to walk. Under l-DOPA treatment and fluctuating between ON and OFF states, the parkinsonian patient when in an ON state may walk adequately while not remembering what precisely the difficulty it is that he or she has in the OFF state; when in OFF, the patient fails to remember just how he or she succeeds to walk when in ON. Gilles de la Tourette patients similarly alternate episodes of "remembering" with those of "forgetting" their condition, making no distinction between the memory, the knowledge, the impulse, and the act. The patient may or may not be aware of his current state, but any awareness fails to affect the state's implications.

Dependence

Whether occurring in a normal or pathogenic manner in the course of ontogeny, or drug-induced, states create a dependence: one of memory and of the capabilities that it enables to the very point of survival. As such, state dependence is akin to drug dependence in as much the state is required to maintain the homeostasis of memory. When induced by a drug, state dependence constitutes an instance and learned form of drug dependence.

State-dependent memory may or may not encompass the subject's seeking to modify that state; such action appears to depend on the state's perceived affective valence and on the opportunities that are available to acquire behaviors that are instrumental in overcoming or modifying those consequences. Alzheimer patients may be little able to gauge their cognitive deficit and, available treatments being only marginally effective, to learn how to instrumentally overcome the deficit. But, state dependent, compulsive seeking to restore the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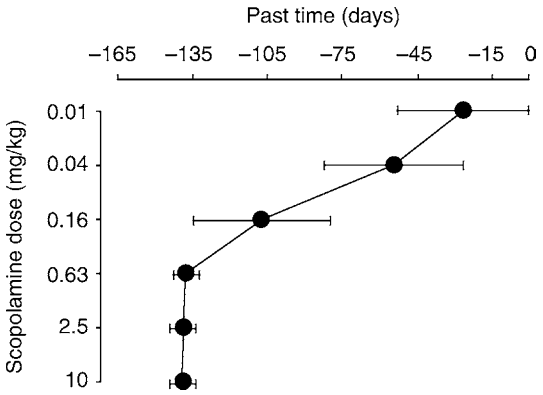
mg/kg
0.01 0.04 0.16 0.63 2.5 10
0,01 0,04 0,16 0,63 2.5 10

original state does appear to underlie opiate addiction, in effect constituting its very "system" mechanism. This implies that the signal transductions that are involved in pain processing and opiate actions thereon are currently thought to proceed in a bidirectional manner; any input to such systems induces not a single but two dual effects that are opposite in sign. Thus, morphine causes not only analgesia as a "first-order" effect, but also a "second-order" hyperalgesia or frank pain that outlasts the analgesia for some time. With chronic opiate exposure, the second-order pain grows and masks the first-order analgesia, resulting in analgesic tolerance. In a parallel manner, opiates also induce two distinct memory states that coincide temporally with their first and second-order effects on pain processing. The first-order opiate memory state is one in which analgesia is encoded, but the second-order state is one in which the individual experiences a possibly excruciating, opiate-induced pain and is enabled to learn and remember that the next opiate administration powerfully relieves that pain, however temporarily. Thus emerges the view that opiate addiction represents the self-medication of compelling opiate pain, with both that pain and the pain-relieving instrumental behavior being encoded in the second-order (withdrawal) state of memory (Colpaert et al. 2006).



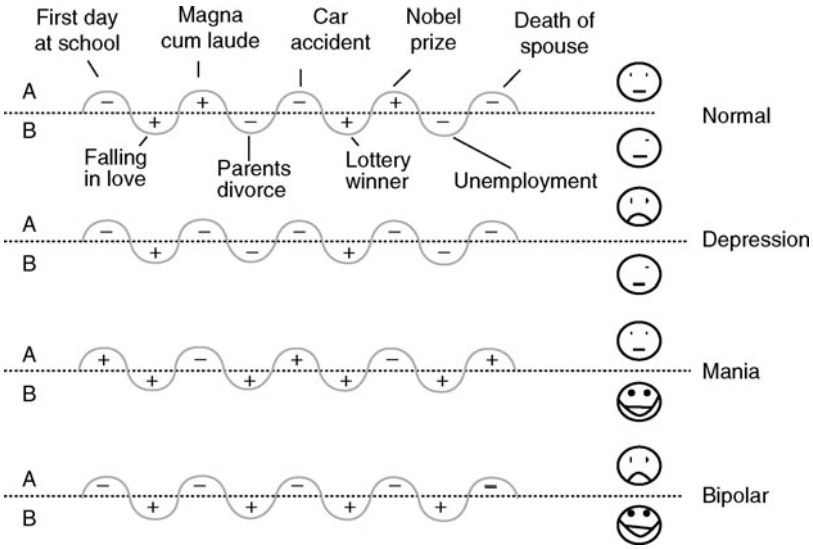
State Dependence of Memory. Fig. 4. Regressive, temporally graded retrograde amnesia induced by a normal-to-scopolamine state changes. Rats were in the normal state trained in a complex task in which learning was assessed from five parameters that characterize the newly acquired behavior (Fig. 3). The acute injection of different doses (ordinate) of scopolamine caused the parameters to assume values that resembled those observed at one or another point in the course of training. The abscissa indicates the remoteness in time (relative to day 0, the last day of training) of such corresponding points (mean ± SEM of the five parameters; day – 165 corresponds to the beginning of training). Increasing doses resulted in a behavior similar to that observed at increasingly remote stages of the acquisition that preceded the drug test. (Redrawn from Colpaert et al. 2001.)

States

Clearly, an organism's memory can operate in any one of a decidedly large number of different states in which engrams can be specifically stored. Such state dependence of memory challenges the common view that an individual possesses a single, unified memory that integrates all past experience and can be acted upon at any time. Rather, at any point of time, memory appears to be locked into, limited to, but also enabled with the unique capabilities of one particular state. As time moves from one to another point, so memory comprises another, equally unique set of retrievable capabilities based on current state.

The state dependence of memory invites the question as to whether ► forgetting occurs at all; it is unclear

State Dependence of Memory. Fig. 3. Studies examining the effects of saline-to-scopolamine changes of mnemonic state on the recall of five aspects of learned behavior. (**a**) Rats were trained for in all 165 days in a complex task in which the different independent measures (e.g., total responding) reflect different aspects (e.g., performance) of what was learned. (**b**) The acquisition data in panel A are here plotted as the % of animals satisfying the learning criterion that was applied to each of the five measures. These % data were fit by best-fitting functions to generate the five learning curves shown in panel B. (**c**) Over the 8-month period that followed training, rats were tested for retrieval after injection of different doses of scopolamine; data from these tests are shown here and expressed as in panel A. (**d**) The scopolamine test data in panel C are here plotted as the % of animals satisfying the criteria used to generate panel B and expressed as in the same manner. These % data were fit with the dose–response functions shown. At 0.01 mg/kg scopolamine, the outcome for each of the parameters was similar (i.e., about 100%) to that at the end of acquisition. Higher doses decreased each parameter value, such that the outcomes resembled those observed earlier in training. Projections are plotted (dashed lines) to identify the point in time-since-the-end-of-acquisition ("past time") with which the test data corresponded. These retrograde projections yielded outcomes that differed among the five parameters, the mean (M along past time) being – 136 days for the 0.16 mg/kg dose. In this manner, the mean was found for all doses, generating the function relating scopolamine dose to past time shown in Fig. 4. (Redrawn from Colpaert et al. 2001.)



State Dependence of Memory. Fig. 5. The shaping of mood states in ontogenesis. Though multiple states can exist, it is sufficient to assume here that memory operates in one of just two cyclically recurrent states (A or B) that are induced by some biological rhythm and are mutually exclusive. Throughout ontogeny (horizontal dotted line), the individual experiences and memorizes life events that have an affective valence that is positive (+) or negative (−). There is no a priori relationship between a state on the one hand and the (valence of) the events that are encountered in a state on the other. In this manner is most likely established in both states A and B, a cumulative memory that retains both positive and negative items (panel I); the overall affective valence of memory is rather neutral in either state and does not greatly differ, or swing, between A and B. This outcome being most probable, panel I represents what because of this greatest likelihood is perceived as a normal individual. However, chance may have it that the events experienced in A or B happen to predominantly be negative or positive (panels II and III, respectively); thus is established in one state a memory that retains items of polarized valence and that differs from the alternative, normal-affect state. These outcomes are less likely and result in recurring episodes of monopolar, depressed or manic, mood. An even smaller chance may result in large-amplitude bipolar mood swings (panel IV) (Colpaert et al. 2000).

whether such failure to remember results from a time-dependent dissipation of the engram or from the non-restoration of the state that prevailed in ontogeny at the time that the memory was established. State dependence definitely does not require forgetting to account for profound retrieval deficits, and state changes constitute a mechanism whereby an engram can be erased; when in an initial state the subject has learned and remembers and when then an alternative state is instituted shortly after retrieval (i.e., at the time of re-encoding), it may be the case that the engram in question is no longer available in the initial state. Further, such a state change may establish, in the alternative state, a memory that is then false (► false memory).

A weakness of state-dependence research resides with a certain vagueness as to what defines a state. Awareness of state dependence historically arose from observations of humans who were "under the influence" of exogenous agents, and the use of drugs in studying state dependence has allowed that in this case states can at least operationally be defined in a highly precise, accurate, and reproducible manner. However, states also arise endogenously and current neurobiology and medicine invoke the existence of a varied array of states that operate at levels of integration ranging from the whole organism to cell assemblies, single cells, or molecular signal transduction (Lydic and Baghdoyan 1999). Fascinating examples include hormone-controlled phases, pacemaker assemblies and circadian and seasonal rhythms, as well as the rise and fall of entire neurotransmitter and other signaling systems in the course of ontogeny. Such states are usually investigated with regard to the particular stimulus–response relationships that they demonstrate, but a wide realm of knowledge remains to be gained in terms of whether and how those states regulate memory.

Learning and memory are also investigated from such perspectives as context-dependence and coincidence detection; how these perspectives shed light on and interlock with state dependence remains to be explored.

Acknowledgment
I thank Drs. V. Curran, I. Kiss, A. Newman-Tancredi, and A. Young for comments and discussions. This essay is dedicated to the memory of Dr. Liesbeth Bruins Slot.

Cross-References
- ▶ Addictive Disorder: Animal Models
- ▶ Analgesics
- ▶ Animal Models of Psychiatric States
- ▶ Antidepressants
- ▶ Behavioral Tolerance
- ▶ Benzodiazepine Agonists
- ▶ Benzodiazepines
- ▶ Bipolar Disorder
- ▶ Declarative and Non-Declarative Memory
- ▶ Dementias and Other Amnestic Disorders
- ▶ Dissociative Anesthetics
- ▶ Drug Discrimination
- ▶ Dysthymic Mood Disorder
- ▶ Emotion and Mood
- ▶ Generalized Anxiety Disorder
- ▶ Inhibition of Memory
- ▶ Mood Stabilizers
- ▶ Opioids
- ▶ Opioid Dependence and Its Treatment
- ▶ Reference Memory and Consolidation

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State-Dependent Learning

▶ State Dependence of Memory

State-Dependent Retrieval

Definition
The notion that information studied in one state is better remembered when retrieved in the same rather than a different state.

Stationary Phase

Definition
The packing material in a column. In RP-HPLC, the most common stationary phases comprise beads of silica (glass-like material), covered by a layer of organic molecules (the bonded phase), comprising alkyl chains, chemically bonded to the silica. These are normally of eight (C8: octylsilane) or eighteen (C18: octadecylsilane: ODS) carbon molecules, tightly packed into the pores in the silica bead. The silica beads are normally 5 or 3μm diameter.

Cross-References
▶ High Pressure Liquid Chromatography

Stavzor

▶ Valproic Acid

Stereoisomers

Synonyms
Enantiomers; Enantiomorphs; Optical isomers

Definition
These usually refer to pairs of drugs, which have identical physiochemical properties but rotate polarized light in different directions (left or right, designated as levo or dextro, "l-" or "d-" and "−" or "+," respectively). They are important as they often have different biological

activities. Thus, an atom found on the drug molecule has bonds that do not permit the attached functional groups to assume different positions relative to one another. For example, ► morphine derived from opium has one important carbon atom with functional groups in positions that rotate polarized light to the left (termed levorotatory). The configuration of this carbon atom also allows the morphine molecule to fit precisely into the pockets and contours of the opioid receptor and to activate it. In other words, the receptor has a structure that matches the levorotatory form. One can also construct morphine synthetically with the functional groups on the same carbon atom in different relative positions. The arrangement of the bonds is such that they precisely mirror those in the levorotatory form and the molecules of this morphine rotate polarized light to the right (show dextrorotatory activity). This synthesized substance is also morphine in a chemical sense, because it has all of the physicochemical properties of morphine made from opium. However, the dextrorotatory form of morphine evokes only the effects of normal morphine that have low chemical structure requirements (e.g., membrane stabilization, convulsions, taste aversion produced by systemic application of opioid); it does not activate the typical pharmacological effects attributed to activity on the opioid receptor. The use of opioid stereoisomers has been recommended in order to exclude so-called "nonspecific" pharmacological effects that are not due to interaction with the opioid receptor.

Cross-References

► Conditioned Taste Aversions
► Receptor: Ligand-Binding Assays and Their Interpretation

Stereotypical and Repetitive Behavior

Definition

Stereotypical and repetitive behavior is commonly seen in individuals with autism spectrum disorders (ASDs) and mental retardation (MR). In lower functioning individuals with ASDs or MR, this usually consists of self-stimulatory, nonfunctional, motor behaviors. However, in mild MR or higher functioning individuals with ASDs, this can consist of verbal and motor rituals, obsessive questioning, rigidly held routines, preoccupation with details, and desire for sameness and completeness.

Cross-References

► Antidepressants
► Antipsychotic Drugs
► Autism Spectrum Disorders and Mental Retardation
► Psychostimulants

Stereotypy

► Motor Activity and Stereotypy
► Stereotypical and Repetitive Behavior

Stimulants

► Psychostimulants

Stimulation

► Stimulation Paradigm

Stimulation Paradigm

Synonyms

Stimulation

Definition

In fMRI experiments, stimulation paradigms are applied to evoke brain activity and accordingly, increased or decreased cerebral perfusion. The variety of stimulation paradigms ranges from no stimulation (resting-state fMRI) over sensory (thermal, visual, or auditory), motor, language, or memory task to pharmacological stimuli. Aside from resting-state fMRI performed while no stimulation is applied, fMRI images are recorded during two states, a resting state (no stimulation) and the activated state during which the specific stimulation is applied. The applied stimulation paradigm is often incorporated as prior knowledge in the subsequent MR image analysis.

Cross-References

► Cerebral Perfusion
► Functional Magnetic Resonance Imaging
► MR Image Analysis
► Pharmacological fMRI

Stimulation Strength

Definition
The objective variables that determine the intensity of Brain Stimulation Reward. These include the current, pulse duration, pulse frequency, and train duration.

Stimulus Control

Definition
A behavioural process wherein different behavior occurs in the presence of different stimuli. It is usually established by arranging different contingencies of reinforcement in the presence of different stimuli.

Stimulus Enrichment

► Environmental Enrichment and Drug Action

Stimulus Generalization

Synonyms
Cue (in psychology); Discriminative cue

Definition
Stimulus generalization occurs when a behavioral response conditioned to one stimulus is elicited by other novel stimuli that were not used during conditioning. For example, animals are conditioned to use a particular stimulus as a discriminative cue and are then tested with a novel stimulus that may resemble the training stimulus in one or more respects. If the animal responds to a test stimulus to the same extent that it does to the training stimulus, then stimulus generalization is said to have occurred. Generalization may be either complete or partial and can reflect both qualitative and quantitative differences between stimuli (e.g., color and brightness of visual stimuli).

Cross-References
► Drug Discrimination

Stimulus Pre-Exposure Effect

► Latent Inhibition

Stimulus Trafficking

► Functional Selectivity

Stop-Signal Task

Synonyms
Response inhibition task; SSRT

Definition
A neurocognitive task designed to provide a sensitive measure of the time taken by the brain to inhibit or suppress inappropriate motor responses. The stop-signal paradigm was originally developed by Gordon Logan in the 1980s, based on a cognitive task first used by Lappin and Erikson in 1966. Versions of the task have been developed both for humans and rats. The stop-signal reaction time (SSRT) task not only provides measures of reaction times and accuracy, but importantly also the latency to inhibit a prepotent response (SSRT). The stopping process is not directly observable and has to be estimated from a stochastic model, the so-called "race model." The model derives the SSRT from the distribution of "go" reaction times and the observed probability of responding on "stop" trials for a given stop-signal delay. The estimated SSRT gives a measure of the duration of the inhibitory process, which starts from the presentation of stop signal. In the version of the task for humans, participants are instructed to respond as fast as possible to a simple stimulus on a computer screen. On some trials, a stop signal is presented after the stimulus but before the response, and participants are instructed to try and stop or inhibit their response. Using this task, impairments in response inhibition have consistently been observed in neuropsychiatric disorders such as attention deficit hyperactivity disorder. In the version of the task for animals, differential presentations of reinforcers are used to train appropriate responding to "go" and "stop" signals. A network in the brain mediating the suppression of a motor response has been detected, involving numerous cortical and subcortical areas including the ► prefrontal cortex and subthalamic nucleus.

Cross-References
► Attention Deficit Hyperactivity Disorders: Animal Models
► Impulse Control Disorders
► Impulsivity
► Rodent Models of Cognition
► Translational Research

Strattera™

► Atomoxetine

Stress

Definition

Stress is a complex psychological construct, which despite many years of research, has yet to be defined operationally in a satisfactory way. In the context of animal models of psychiatric disorders, stress can be defined broadly as forced exposure to events or conditions that are normally avoided. In humans, the definition is extended to incorporate cognitive and emotional responses – for example, "stress is a condition in which the environmental demands exceed the coping abilities of the individual." In laboratory animals, the precipitating events or conditions can be divided into two categories. The first category includes environmental events such as restraint, footshock, tail pinch, and defeat, as well as pharmacological events such as administration of a normally avoided drug (e.g., ► yohimbine). The second category includes food deprivation, social isolation, and ► maternal deprivation; each of these entails the removal of an environmental condition that is important for maintaining the animal's normal physiological and psychological steady-state conditions, a state that the subject will attempt to ameliorate by seeking food, conspecific partners, or the dam.

Cross-References

► Social Stress

Stress-Induced Antinociception

Definition

Decreased pain transmission in response to stressful stimuli. Stress-induced antinociception results in attenuated perception of pain. Both opioid and non-opioid endogenous mechanisms have been implicated in stress-induced antinociception.

Cross-References

► Antinociception Test Methods
► Opioids

Stress: Influence on Drug Action

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Synonyms

Stressful stimuli; Stressors

Definition

In humans, stress often refers to a condition in which environmental demands exceed an individual's coping abilities. In animal models of psychiatric disorders, stress can be defined broadly as a forced exposure to aversive events or conditions that are normally avoided. The term stress includes three related elements: stressors, stress responses, and genetic and environmental factors that modulate the effect of stressors on the organism. Stressors are events, physical or psychological, that profoundly interfere with the organism's normal steady state. These disruptions generate a stress response manifested at the physiological (e.g., activation of the sympathetic nervous system), psychological (e.g., ► anxiety, ► depression), and behavioral (e.g., performance deficits) levels. Factors that modulate the stress response include, among others, genetic predisposition to stress reactivity, and predictability and controllability of the stressors. These factors influence the relationship between the stressors and the stress response, leading to large individual differences in response to a given stressor.

Current Concepts and State of Knowledge

Background

Anecdotal reports that drug use is more likely to occur in individuals exposed to environmental stressors are supported by results from epidemiological studies indicating a high rate of ► comorbidity between stress-related psychiatric disorders such as ► post-traumatic stress disorder (PTSD), anxiety, and depression, and drug addiction. There is also evidence from laboratory studies in humans that exposure to stressors increases cigarette smoking and subjective measures of cocaine, opiate, and alcohol ► craving. The influence of stress on abused drugs appears to occur through all phases of the addiction process: stress facilitates the initiation of illicit drug use,

increases the frequency and amount of ongoing drug use, and precipitates relapse to drug use during periods of abstinence. Stress can also emerge as a consequence of drug addiction, because illicit drug use is associated with problems with the law, the workplace, and the family. The stress caused by the lifestyle of illicit drug users in turn promotes more severe forms of drug addiction. Finally, chronic use of addictive drugs can sensitize physiological and psychological responses to stress.

However, methodological and ethical considerations limit the scope of research that can be conducted in humans addicted to ► drugs of abuse. Consequently, it has been difficult to demonstrate a cause–effect relationship between stress and drug addiction in humans. Cause–effect relationships between stress and drug-taking behavior can be established in laboratory models of drug addiction. These models can be used to identify behavioral and neuronal mechanisms that mediate the effect of stress on drug-taking behavior. Below, we summarize results obtained from preclinical studies in laboratory rats on the mechanisms underlying the effect of environmental stressors on drug-taking behavior, as assessed using the intravenous ► drug self-administration procedure and the ► reinstatement procedure. The drug self-administration procedure is the gold-standard animal model used to assess the rewarding effects of drugs and their abuse liability. The reinstatement procedure is a widely used animal model of relapse to drug-taking behavior during periods of abstinence.

Before reviewing the empirical data on biological mechanisms of the effects of stress on drug-taking behavior, we would like to point out that we will not cover in this short chapter several research topics that are relevant to the relationship between stress and drug addiction. These include (1) the extant and conflicting literature on the effects of stress on oral opiate and ► alcohol self-administration; (2) the conflicting literature on the effects of adverse early life experience (maternal deprivation, social isolation) on drug self-administration in adulthood; (3) the literature on the role of stress systems in the mediation of physiological and psychological withdrawal symptoms of abused drugs; and (4) the literature on the role of the stress hormone corticosterone in the mediation of psychostimulant self-administration in the absence of stress.

Mechanisms of Stress Effects on Drug Self-administration

Investigators have used the drug self-administration procedure to assess the effects of stressors on the acquisition and maintenance of intravenous drug self-administration. When evaluating the findings on the effects of stressors on drug self-administration, it is important to remember that these effects are highly dependent on several variables, including stressor controllability, duration of stress exposure, the time interval between stress exposure and drug availability, the reinforcement schedule, and the dose of the self-administered drug. Additionally, there are large individual variations in the effects of stressors on drug self-administration. In studies on the mechanisms of stressor-induced increases in drug self-administration in rats, investigators have used several stressors including intermittent unpredictable footshock, food deprivation, and ► social defeat.

The stress hormone corticosterone (or cortisol in humans) is released from the adrenals when stressors activate the ► hypothalamic–pituitary–adrenal (HPA) axis. There is evidence that stressor-induced corticosterone secretion is required for the ability of intermittent footshock and food deprivation stressors to facilitate the initiation of ► cocaine self-administration. Additionally, corticosterone may contribute to footshock stress-induced escalation of cocaine self-administration once the self-administration behavior has been established. The mechanisms through which corticosterone promotes the self-administration of ► psychostimulant drugs may involve modulation of dopaminergic neurotransmission in both the ► ventral tegmental area (VTA), the cell body region of the ► mesolimbic dopamine system, and one of its projection areas, the ► nucleus accumbens. The mesolimbic dopamine system is known to mediate the rewarding effects of psychostimulant drugs.

In most previous studies on the effects of stress on intravenous self-administration of psychostimulant drugs, investigators limited access to the drugs for a few hours per day; under these conditions, rats typically maintain stable drug intake over time. Human addicts, however, self-administer psychostimulant drugs such as cocaine in a binge-like pattern that is characterized by extended periods of intense and escalated drug intake over many hours and even days. This binge-like pattern of drug self-administration is also observed in rats that are given unlimited access to cocaine. Thus, after about 20–24 h of continuous cocaine self-administration, rats shift from regulated drug intake, characterized by stable inter-infusion intervals, to dysregulated "out-of-control" drug intake, characterized by unstable inter-infusion intervals and higher hourly drug intake. The emergence of this binge-like pattern of cocaine intake is facilitated by prior exposure to social defeat stress. There is evidence that this

effect of social defeat stress on binge-like cocaine self-administration is due to sensitization of dopamine neurons in the VTA. This sensitization is likely mediated by stressor-induced activation of glutamatergic projections to the VTA. As the neuronal and hormonal responses to stressors are typically stressor-specific, a question for future research is whether the neurobiological mechanism identified for the effect of social defeat stress on binge-like cocaine self-administration generalizes to other stressors.

Stress and Reinstatement of Drug Seeking

The phenomenon of stress-induced ► reinstatement of drug seeking has been demonstrated using several stressors, including intermittent footshock and acute food deprivation. Stress-induced reinstatement is critically dependent on the stress neuropeptide corticotrophin-releasing factor (CRF). This neuropeptide acts in the paraventricular nucleus of the ► hypothalamus to activate the HPA–endocrine stress axis. Additionally, many physiological and behavioral responses to stress are mediated by CRF's effects on extrahypothalamic sites within the central nervous system (CNS).

CRF receptor antagonists decrease both footshock- and food-deprivation-induced reinstatement of drug seeking, while ventricular injections of CRF reinstate drug seeking. Results from studies using pharmacological and endocrine methods indicate that the reinstating effects of stressors are independent of their ability to activate the HPA axis. The critical extrahypothalamic brain sites and projections for CRF's role in footshock-induced reinstatement include the bed nucleus of the stria terminalis (BNST), VTA, and a projection from the central amygdala to the BNST. Within the VTA, footshock causes local CRF release, which leads to increased ► glutamate transmission. This enhanced glutamatergic neurotransmission is critical for stressor-induced reinstatement, presumably due to activation of the mesocorticolimbic dopamine system. This possibility is supported by the findings that injections of D1-family dopamine receptor antagonists into the dorsal, medial ► prefrontal cortex (mPFC) or the orbitofrontal cortex, or of a preferential D3 dopamine receptor antagonist into the nucleus accumbens, decrease stressor-induced reinstatement.

Footshock stress-induced reinstatement is also dependent on noradrenaline transmission: systemic injections of alpha-2 adrenoceptor agonists (which decrease central noradrenaline release) decrease footshock-induced reinstatement, while systemic injections of the alpha-2 adrenoceptor antagonist ► yohimbine (which increases central ► noradrenaline release) cause reinstatement of drug seeking. The critical brain sites and projections for noradrenaline's role in footshock-induced reinstatement include the central amygdala and BNST, and the noradrenergic projection from the lateral tegmental nuclei to these brain sites.

Results from studies in which discrete brain areas were reversibly inactivated confirm the previous findings discussed above on the role of the dorsal mPFC, BNST, central amygdala, accumbens, and VTA in stress-induced reinstatement, and further suggest that the ventral pallidum plays a role in this reinstatement. Results from these studies also indicate that the glutamatergic projection from the mPFC to the accumbens plays an important role in stress-induced reinstatement. This glutamatergic projection is also involved in reinstatement of drug seeking induced by acute reexposure to the self-administered drug.

Recent evidence suggests that the magnitude of footshock- and CRF-induced reinstatement of cocaine seeking depends on the history of prior drug exposure: these effects were significantly stronger in rats that were previously given extended access to cocaine for 6 h/day during training than in rats given drug access for 2 h/day. These and related findings indicate that prior exposure to high doses of cocaine over many days sensitizes brain CRF stress systems, leading to increased vulnerability to stress-induced reinstatement of cocaine seeking. These findings parallel results from human studies demonstrating more pronounced stress-induced craving, anxiety, and physiological responses in abstinent, previously high-frequency drug users than in individuals with a history of less frequent drug use.

Finally, there is evidence from studies in which pharmacological agents were used for a role for several other neurotransmitter systems in stress-induced reinstatement. These include the neurotransmitter ► serotonin, and the neuropeptides ► dynorphin, ► hypocretin (orexin), and nociceptin/orphanin FQ.

Implications for Treatment

The recognition that stress is a key contributor to drug-taking behavior highlights the need for the development and implementation of therapeutic strategies aimed at minimizing the contribution of stress to drug addiction. This is especially important in subpopulations of addicts whose drug use is stress-driven. Identifying which addicts will benefit most from such approaches poses a challenge to drug-addiction treatment providers and will likely require the establishment of new assessment tools for identifying the role of stress in an individual's drug use. The development and approval of new drugs that block CRF receptors and other receptors implicated in stress-induced

drug seeking will hopefully provide important tools for the management of drug addiction.

Acknowledgments
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Cross-References
► Conditioned Place Preference
► Drug Discrimination
► Extinction
► Reinstatement of Drug Self-Administration
► Self-Administration
► Stress

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Stress-Related Mood Disorders
► Adjustment Disorders

Stress-Response
Definition
The spectrum of physiological and behavioral adaptations coordinated by stress system mediators that defend homeostasis and/or promote allostasis.

Stressful Stimuli
► Stress: Influence on Drug Action

Stressors
Definition
Any perceived threat to the individuals' integrity.

Cross-References
► Stress: Influence on Drug Action

Stretched-Attend Posture
► Risk Assessment

Striatum
Synonyms
Neostriatum

Definition
The striatum is a subcortical brain structure. The *corpus striatum*, which includes the putamen rostrally and the caudate nucleus caudally, is a component of the ventral cerebral hemisphere, receiving strong projections from the cerebral cortex and projecting back to it via the thalamus. In addition, the striatum receives a robust dopaminergic innervation from the *substantia nigra* and the ventral tegmental area. It is fundamental for the selection of motor programs in response to external signals, which is triggered by dopaminergic signaling. Its ventral component, the ventral striatum or nucleus accumbens, is a key element in the response to salient stimuli predicting reward, hence inducing intensely motivated states.

Cross-References
► Psychomotor Stimulants

Stroke

Synonyms
Cerebrovascular accident

Definition
Stroke results from the occlusion or bursting of a cerebral blood vessel so that the cerebral tissue is starved of both oxygen and nutrients and this tissue then dies. The large majority of strokes (around 85%) are caused by an occlusion of a major cerebral artery either by a thrombus or embolism. The other strokes are the result of a hemorrhage where a blood vessel bursts in the brain or on the surface of the brain. Stroke is the third major cause of death in major industrialized countries and its incidence is predicted to increase over the next decade.

Subjective Value

Synonyms
Reinforcer efficacy

Definition
Worth of a commodity for an individual. Subjective value is a weighted function of the benefits associated with the commodity (magnitude, quality, ability to fulfill individual's needs) and the costs of obtaining the commodity (price).

Cross-References
► Behavioral Economics

Substance Abuse

Definition
Substance abuse describes when any substance is misused, that is, taken in a way that is actually or potentially harmful to the person concerned. This covers illicit and prescribed drugs, alcohol, tobacco, and inhalants such as cleaning fluid or glue.

Cross-References
► Agoraphobia

Substance Abuse Disorder

► Opioid Dependence and Its Treatment

Substance Dependence

Definition
An unhealthy or addictive pattern of repeated substance use most typically indicated by tolerance to the effects of the substance and symptoms of withdrawal when the substance is terminated for a period of time.

Substance K

► Neurokinin A
► Tachykinins

Substance P

Synonyms
Neurokinin 1; SP

Definition
Substance P (SP) is an 11 amino acids neuropeptide, the first to be discovered from the tachykinin family.

It is generated by alternative splicing of the preprotachykinin gene RNA and mostly expressed in smooth muscles and the central nervous system. SP has been mainly associated in the regulation of pain, emotional processes, and emesis by activation of NK1 receptors.

Substitutes

Synonyms
Surrogate

Definition
Substitutes have an inverse relationship between the substitute and the alternative – as the price of the alternative increases the demand for the substitute increases.

Cross-References
► Behavioral Economics

Substitution

► Cross-Dependence

Subthreshold Diagnoses

► Adjustment Disorders

Subtraction Method

► Cognitive Subtraction

Subtype

Definition

The term subtype, when discussing CRF receptors, refers to the separate genes that give rise to the two CRF receptors, CRF_1 and CRF_2.

Cross-References

► Gene Expression and Transcription

Suicide

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Synonyms

Self-destructive behavior; Self-immolation; Suicide completion

Definition

Suicide is an act of taking one's own life voluntarily, usually intentionally. Suicidal behavior is a general term used to refer to suicide and suicide attempts. Under the latter, we refer to the actions taken to end one's life, irrespective of the degree of intentionality, which does not result in death. While suicidal ideation is not a behavior, it is often considered under the category of suicidal behaviors. It refers to the wish to die, including thoughts of actively ending one's life.

Current Concepts and State of Knowledge

Suicide is one of the leading causes of death worldwide, among the top ten causes of death in most of the world and one of the three leading causes of death for people between the ages of 15–34 (WHO 2000). As such, it has been referred to as the 'leading cause of unnecessary and premature death.' Over the last 45 years, suicide rates have been increasing dramatically, by as much as 60% in some countries. In the USA, this rate is approximately 11 per 100,000, while much of Asia sees a rate exceeding 13 per 100,000. With the notable exception of rural China, suicide is significantly more common among males than females. Western countries, and particularly those from Northern Europe and the ex-Soviet Union, present larger gender effects on suicide rates, while Asian countries tend to have sex ratios closer to one. Age is another important demographic factor that seems to have a large impact on suicide risk. Accordingly, the distribution of suicide risk through the lifespan displays marked age effects, with peaks among youth and elderly age groups.

Suicide methods vary considerably among different countries and world regions and relate to the availability of means to suicide, as well as popular concepts and imagery associated with suicide. As such, in North America, suicide by firearms and hanging are the most common methods, whereas in Asia, suicide by pesticides is the most prevalent. Suicidal behavior has been classified as violent and nonviolent, depending exclusively on the method used. In general, the term nonviolent refers to suicidal behavior by substance intoxication (typically medication overdose) or superficial cuts, which are generally associated with low suicide intent and are frequently of low lethality. All other methods are considered violent.

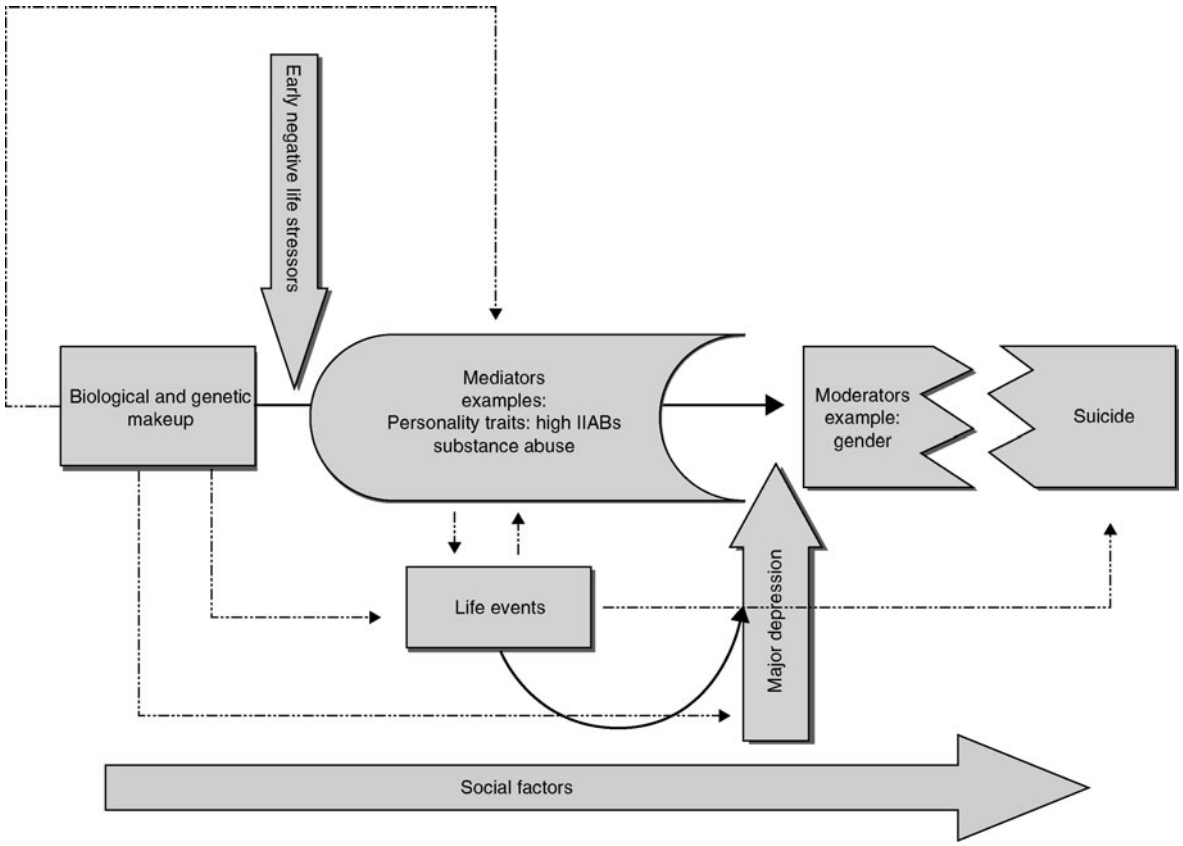
Suicide is strongly associated with psychopathology (Arsenault-Lapierre et al. 2004). While there is significant regional variability in the percentages found, all studies have consistently shown that most individuals who have died by suicide were affected by mental disorders in the last months of their life. Meta-analyses of studies investigating rates of mental disorders among individuals who died by suicide suggest that up to 90% of suicides had a history of mental illness. Table 1 lists the most common mental disorders found among suicide completers, according to different world regions. Mood disorders, and ► major depressive disorder, in particular, are the most common diagnoses among individuals who died by suicide.

Predictors of Suicide

Suicide is a complex behavior, likely the result of several interacting factors. Figure 1 conceptualizes the relationships among key factors believed to play an important role in suicide. While, as mentioned earlier, psychopathology is strongly associated with suicide risk, it is neither sufficient nor specific, as only a fraction of people affected by mental illness will die by suicide.

Suicide. Table 1. Distribution (%) of major diagnostic categories found among suicide completers by psychological autopsy studies according to regions of the world (Adapted from Arsenault-Lapierre et al. 2004).

	European	North American	Australian	Asian
Mood disorders	48.5%	33.6%	32.7%	51.3%
Substance-related disorders	18.6%	40.1%	24.1%	26.7%
Schizophrenia and other psychotic disorders	7.5%	4.2%	24.3%	8.4%
Personality disorders	16.8%	13.4%	17.7%	17.7%



Suicide. Fig. 1.

A positive history of suicide attempts, a history of childhood adversity, certain demographic variables, and issues related to social and medical support have been found to be stronger predictors of suicidal behaviors among psychiatric patients. The risk of suicide completion among clinical populations varies as a function of diagnosis and clinical features. For instance, among patients with major depressive disorder, the risk is conditional on the population of depressed patients, i.e., suicide risk is higher among depressed inpatients, lower among depressed patients from the general population and somewhere in between for depressed outpatients. For the latter group, the percentage of individuals who die by suicide is estimated to be between 2% and 5%. Clinical predictors of suicide among patients with major depression include symptom severity (as measured by a requirement of hospitalization), comorbidity with substance-related disorders, high levels of hopelessness, and a history of a past suicide attempt.

Over the last decades, it has become increasingly clear that individuals who die by suicide also have constitutional risk factors. However, the relationship

between these predisposing factors, which to a certain extent are conferred by the individual's biological make-up, and suicide is not direct, but seems to be mediated and moderated by a number of different factors. Among these factors are clinical and demographic risk factors, such as those listed earlier, history of early life sexual and physical abuse, personality variants such as behavioral traits, and triggering factors such as recent life events and interpersonal stressors.

Epidemiological and clinical studies have consistently suggested that a positive family history of suicide acts as an important risk factor for suicide. As psychopathology also runs in families, a major question has been to what extent suicide aggregates in families independently of psychopathology. Studies have suggested that first-degree relatives of suicide probands have a 4–10 times higher risk of suicidal behavior than relatives of psychiatrically normal controls, and this is once other risk factors and psychopathology are accounted for. Genetic-epidemiological studies suggest that at least part of this familial aggregation is attributable to genetic effects (Turecki 2001).

Several lines of evidence point to the fact that familial transmission of suicidal behavior may be mediated through the transmission of personality traits such as impulsive–aggressive behaviors. Personality traits represent emotional, behavioral, motivational, interpersonal, experiential, and cognitive styles that help us relate to and cope with the world. Clinical and community research suggest links between suicidality and extreme personality profiles. For instance, children who score high on a measure of disruptive behavior, a composite of aggressive, impulsive, and hyperactive behaviors, were found to be more likely to attempt suicide as young adults (Brezo et al. 2008). In general, most clinical and psychological autopsy studies (which use proxy-based interviews to investigate individuals who died by suicide) report elevated measures of ▶ impulsivity and ▶ aggressive behaviors among suicide attempters and completers as compared to controls, particularly among younger individuals. There is also direct and indirect evidence suggesting that relatives of suicide completers and suicide attempters have higher scores on these personality traits than controls.

Impulsivity may be conceptualized as the inability to resist impulses, which, from the strict phenomenological point of view, refer to explosive and instantaneous, automatic or semiautomatic psychomotor actions that are characterized by their sudden and incoercible nature. A more behavioral definition considers impulsivity as a drive, stimulus, or behavior that occurs without reflection or consideration for the consequences of such behavior. However, studies suggest that it is not the exclusive presence of impulsivity that appears to account for its observed association with suicide. Rather, impulsivity is frequently comorbid with other personality traits, particularly aggressive behaviors. As such, suicides tend to have high levels of aggressive–destructive impulsive traits, generally referred to as impulsive–aggressive behaviors. These have been operationally defined in suicide studies as a tendency to react with animosity or overt hostility, without consideration of possible consequences, when piqued or under stress.

Neurobiology of Suicide

The last decades have seen a growing interest in the understanding of the biological processes underlying suicide. Suicidal behavior has been associated with several neurobiological alterations, particularly in neurotransmission. For close to four decades, molecular studies have considered ▶ monoamines as prime suspects in suicidal behavior. ▶ Serotonin, in particular, has been the most investigated monoaminergic neurotransmitter system, and several lines of evidence suggest its involvement in the vulnerability to, and process of, suicide (Turecki and Lalovic 2005). Overall, while not always consistent, studies suggest that suicidal behavior is associated with reduced serotonergic neurotransmission. The evidence supporting serotonergic changes associated with suicide comes from studies using different and complementary approaches, including, but not limited to, investigations of cerebrospinal fluid levels of the serotonin metabolite 5-hydroxyindole acetic acid (5-HIAA), neuroendocrine challenges, postmortem receptor binding and imaging studies with receptor ligands. The serotonergic alterations seem to be more pronounced in the prefrontal cortex, where there is evidence of a decrease in presynaptic ▶ serotonin transporter binding and an upregulation of postsynaptic serotonin receptors. Together, these results imply reduced serotonergic input to this brain region. Among other functions, the ▶ prefrontal cortex is involved in the ▶ behavioral inhibition and expression of emotions. Reduced serotonergic input to this brain region could result in the impaired inhibition of behaviors such as impulsive aggression, which in turn could increase suicide risk.

Although the most extensively investigated neurotransmitter alterations associated with suicide have been those related to serotonergic changes, other neurotransmitters have also been investigated. Among these neurotransmitters are the noradrenergic, dopaminergic, opioid, glutamatergic, and GABAergic neurotransmitter systems. More recently, promising and consistent results have pointed to the implication of the polyamine system, which is involved in the stress response, depression, and suicide.

Alterations have also been reported in several components of different signal transduction systems, as well as in neurotrophic factors, particularly ► brain-derived neurotrophic factor (BDNF) and ► TrkB. These studies suggest that the suicide process may be associated with an altered neuroplastic capacity.

Another interesting avenue investigated in suicide is a possible relationship with lipid metabolism, and more specifically with low cholesterol levels. This intriguing association is supported by evidence from studies that have used different designs, including large cohort studies, observational studies in suicidal, impulsive or violent populations, and experimental studies in animals, as well as postmortem brain studies (Golomb 1998). The use of different study designs and the replication of the findings across different populations have added validity to this still polemical association. A number of hypotheses have been advanced in an attempt to understand the possible relationship between cholesterol and suicide, but only a few of these hypotheses have been the subject of experimental testing. Whether this association proves to be true or not, one possible way to understand it is through an evolutionary point of view. It is not unreasonable to think that dietary needs, hence cholesterol levels, should be associated with certain behaviors, such as ► aggression. Aggressive behaviors may have conferred advantages on early humans who were hunting for food. Such an evolutionary link between cholesterol and aggression, preserved in the link between impulsive aggression and suicide, could underlie the observed relationship between cholesterol and suicide risk. If this is the case, there should also be molecular mechanisms connecting cholesterol levels to molecular correlates of aggression/suicide.

Treatment

There is no specific pharmacological treatment for suicidal behavior. There is evidence, however, that certain pharmacological interventions used for the treatment of the underlying mental disorder are more effective than other ones in reducing suicidal behavior in these patients. Two examples of such treatments are lithium and clozapine. ► Lithium is a salt used primarily in the maintenance treatment of ► bipolar disorder. There is substantial evidence indicating that lithium is effective in reducing the risk of suicidal behavior among bipolar patients (Baldessarini et al. 2006). While some preliminary evidence suggests that the antisuicidal effect of lithium may be independent of its mood-stabilizing properties, this issue requires further investigation. Similarly, ► clozapine, an atypical ► antipsychotic drug, is believed to have antisuicidal properties (Meltzer 2005). As for lithium, it is unclear if the antisuicidal properties are independent of its neuroleptic effects.

Two psychotherapeutic interventions have provided evidence of efficacy in reducing suicidal behavior. Cognitive-behavioral therapy applied in 10 sessions designed specifically to prevent suicide attempts has been shown to be effective in primarily depressed adults with recent histories of suicide attempts (Brown et al. 2005). Dialectic behavioral therapy, which is a variant of cognitive behavioral therapy developed specifically to treat patients with borderline personality disorder, has also shown evidence that it reduces suicidal behavior in this population (Linehan et al. 1991).

Cross-References

► Aggressive Behavior
► Bipolar Disorder
► Depression
► Impulsivity
► Lithium
► Major Depressive Disorder

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Suicide Completion

► Suicide

Sulpiride

Definition

Sulpiride is a ► typical antipsychotic based on antagonism of postsynaptic D_2 dopamine receptors. Agonism at the gamma-hydroxybutyrate receptor may contribute to its antipsychotic properties. Sulpiride has fewer ► extrapyramidal side effects, but also reduced antipsychotic potency, as compared with many other typical antipsychotics. At lower doses than used for antipsychotic treatment, its prominent action is presynaptic dopamine autoreceptor antagonism, giving rise to antidepressant and stimulating effects. Secondary clinical uses are thus treatment of depression and vertigo. Sulpiride is currently not approved in the USA and Canada. Together with the atypical antipsychotic ► sultopride, sulpiride falls under the chemical class of benzamides.

Cross-References

► Antipsychotics
► First-Generation Antipsychotics

Sultopride

Definition

Sultopride is an ► atypical antipsychotic of the same chemical class as sulpiride (benzamides). Sultopride's action at antipsychotic doses exceeds D_2 dopamine receptor blockade to include antagonism of D_3 and 5-HT_7 receptors. Agonism of the GHB receptor may contribute to its properties. Like sulpiride, low doses of sultopride predominantly block dopaminergic autoreceptors, facilitating dopamine release. This action, as well as its 5-HT_7 receptor antagonism, likely explains it efficacy at low doses for treating depression. Sultopride is not currently approved in the USA.

Cross-References

► Antipsychotics
► First-Generation Antipsychotics
► Second and Third Generation Antipsychotics

Summary of Product Characteristics

Synonyms

Product information; SPC

Definition

The SPC is the basis of information for healthcare professionals on how to use a medicinal product safely and effectively. The package leaflet (PL) is drawn up in accordance with the SPC. The SPC sets out the agreed position of the medicinal product as distilled during the course of the assessment process. The content cannot be changed except with the approval of the originating competent authority.

Summation Test

Definition

The summation test is one of two widely accepted tests for whether a stimulus functions as a ► conditioned inhibitor (► retardation of acquisition test is the other). In the summation test, a putative conditioned inhibitor is presented in compound with a separately trained excitatory conditioned stimulus (CS) – that is, one that evokes a conditioned response. If the stimulus functions as a conditioned inhibitor, it should decrease conditioned responding evoked by the separately trained excitor relative to controls that receive the excitatory CS alone, and the excitor in compound with an alternative stimulus that was not a signal for non-reinforcement. Because alternative accounts for response inhibition remain with just the summation test, the strongest case for a stimulus functioning as a conditioned inhibitor also requires the use of the retardation test.

Cross-References

► Blocking, Overshadowing, and Related Concepts
► Classical (Pavlovian) Conditioning
► Occasion Setting With Drugs
► Pavlovian Fear Conditioning

Supervisory Attentional System

► Executive Functions

Suppressed Behavior

► Punishment Procedures

Suppressibility

Definition

Many patients with tic disorders describe a capacity to limit tic expression, at least temporarily. Patients will describe that suppression requires concentration and that it is ultimately time-limited (► tics).

Surface (or Deep) Field Potentials

► Electroencephalography

Surrogate

► Substitutes

Sustained Attention

Synonyms

Vigilance

Definition

Sustained attention is the capacity to maintain attention over time on repetitive tasks. It is the need for continuous allocation of processing resources that distinguishes vigilance from other forms of attention, such as divided or selective attention. In humans and other animals, under normal conditions, deficits in sustained attention emerge during "boring" and/or routine activities, especially in situations of low event rate.

Cross-References

► Attention
► Attention Deficit and Disruptive Behavior Disorders

Switch in Preference

► Preference Reversal

Sympathectomy

Definition

Lesion of the sympathetic (noradrenergic) branch of the peripheral autonomic nervous system. Experimental sympathectomy is achieved by administration of a systemic toxin, affecting all branches of the system or by extirpation of individual spinal or cervical ganglia to deafferent specific branches.

Sympathetic Neurons

Definition

These are neurons located in prevertebral and paravertebral ganglia. They are a main component of the so-called autonomic nervous system. These neurons are controlled by preganglionar terminations originating in the spinal cord and their axons are distributed throughout the skin, blood vessels, glands, the heart, and viscera. Upon stimulation, they release the neurotransmitter ► noradrenaline (norepinephrine) with the exception of some neurons innervating the sweat glands that release ► acetylcholine. The main functions are maintaining the peripheral vascular tone, accelerating the heart frequency, and inhibiting gastrointestinal motility.

Synaptic Consolidation

Definition

Synaptic consolidation is defined as the stabilization of new memories over time, typically on the timescale of 4–8 h.

Synaptic Plasticity

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Synonyms

Neuronal plasticity; Short-term plasticity

Definition

In general terms, synaptic plasticity describes a change, persistent or transient, of morphology, composition, or signal transduction efficiency at a neuronal synapse in response to intrinsic or extrinsic signals. ► Long-term potentiation (LTP) and ► long-term depression (LTD) likely represent the most extensively studied forms of synaptic

plasticity, which itself is the best characterized form of neuronal plasticity, the cellular substrate for learning and memory.

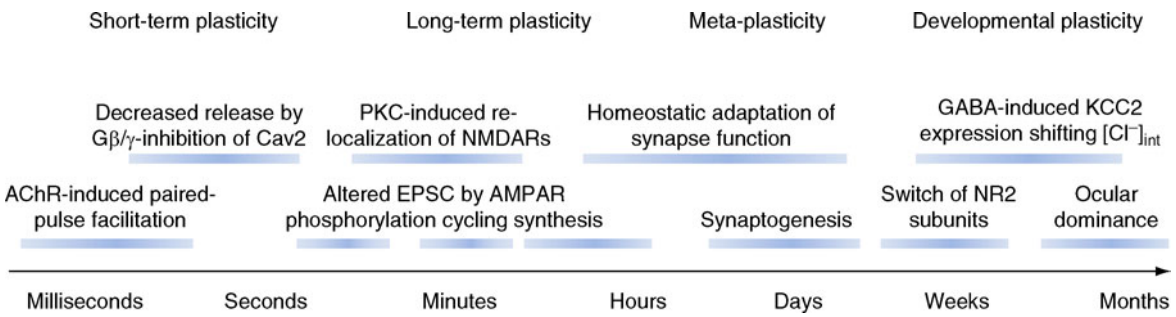
Physiology and psychopharmacological modulation of LTP and LTD are described in detail elsewhere (see Cross-References). Like these special cases, most other forms of synaptic plasticity are induced by an associative coincidence of signals in space and time, in line with the theory of the so-called "Hebbian plasticity": A convergence of different second messenger pathways or pre- and postsynaptic activity at the synapse itself. Of note, the term "synaptic" could either point to the origin or the affected target of such signals. However, for many phenomena related to drug effects, this distinction cannot be conclusively drawn because a differentiation of cause and effect in neuronal networks is inherently difficult for drugs acting at multiple sites and over a relatively long period of time.

Forms of synaptic plasticity beyond LTP and LTD comprise short-term plasticity (STP) based on presynaptic transmitter release probability, postsynaptic spine motility, translocation of proteins between extrasynapticand synaptic sites, epigenetic, post-transcriptional or post-translational modifications of synaptic proteins, and changes of intra- and extracellular ion concentrations. Some of those changes are described as "► meta-plasticity" because they have been shown to change the ability of synapses to undergo classical forms of plasticity like LTP or LTD (Abraham 2008). Common to all those changes is their link to an altered function of synaptic transmission. This could be experimentally shown for some but not all of the above-mentioned examples, and there are certainly more mechanisms to be uncovered by improved and refined approaches and technologies.

The concept of synaptic plasticity was already introduced more than 100 years ago, with W. James, E. Tanzi, E. Lugaro, and D.O. Hebb making milestone contributions in the development of this principle, long before T. Lomo and T.V. Bliss in P. Andersens laboratory could experimentally show in 1973 that specific electric stimuli induce persistent changes in synaptic transmission efficiency, both in vitro and in vivo (see Berlucchi and Buchtel 2009 for a recent review of historical aspects of synaptic plasticity).

For a long time, electrophysiological techniques like extra- or intracellular recordings remained the gold standard to observe synaptic physiology. It is only recently, that optical imaging complemented the functional information with structural data at the level of single synapses in living tissue.

Models of synapses usually show synaptic signal transmission between neurons as a "static element" that can be described by a fixed input–output relation: for a single event of chemical signal transmission between neurons, a presynaptic stimulus leads to a defined postsynaptic response. In the most classical case of synaptic transmission, a presynaptic action potential depolarizes the ► presynaptic bouton, which contains the machinery for vesicular release. A rise of intracellular calcium ($[Ca^{2+}]_{int}$) induces the release of vesicle-stored neurotransmitters into the synaptic cleft. The transmitter activates postsynaptic receptors that trigger electric or second messenger signals in the postsynaptic cell. When one or several of the contributing synaptic components change their function, the synapse undergoes plastic changes that can last from milliseconds to days or years. More special cases of synaptic signal transmission, like electrical synapses formed by gap junctions, are not described further, as there are to date still very few studies on their structural or functional plasticity. Figure 1



Synaptic Plasticity. Fig. 1. Types of synaptic plasticity across a timescale spanning several orders of magnitude. Depicted is a nonexhaustive selection of mechanisms underlying synaptic plasticity sorted by their approximate time of expression. A common type of classical LTP and LTD is reflected by altered AMPA receptor mediated EPSCs. *Cav2* presynaptic, high-voltage activated calcium channels of the Cav2 family; *PKC* protein kinase type C; *NR2* subunit family 2 of the NMDA receptors; *AChR* acetylcholine receptor; *KCC2*, potassium-chloride cotransporter type 2; $[Cl^-]_{int}$ intracellular chloride ion concentration; *Gβ/γ* β/γ subunit of trimeric G-protein; *EPSC* excitatory postsynaptic currents.

shows some examples of synaptic plasticity across a large temporal spectrum. In vivo optical imaging of postsynaptic compartments in glutamatergic neurons, so-called ▶ dendritic spines, suggests that synaptic plasticity is the rule rather than the exception in the lifetime of a synapse.

Impact of Psychoactive Drugs

The diversity of synaptic plasticity implicates that there are numerous potential pharmacological mechanisms that affect synapses and their function. The below-given examples only reflect a selection of the better studied links between psychopharmaceuticals and synaptic plasticity. As for many other aspects of psychoactive drugs, we have to acknowledge that there are still many gaps in our understanding of their molecular mechanism of action and link to synaptic function. As a general rule – taking into consideration the prerequisite for ▶ spatio-temporal coincidence – it is helpful for deciphering such links to focus on ▶ second messenger systems triggered by targets of psychopharmacological drugs and study their effect on synaptic proteins that are involved in the above-described plasticity process.

Linking Dopamine Receptors with NMDA Receptors via DARPP-32

A prominent example of this approach is the link between ▶ dopamine and *N*-methyl-D-aspartate ▶ (NMDA) receptors that are key mediators of many forms of LTP. This connection may even provide a molecular basis for the clinical manifestation of both positive and negative symptoms in schizophrenia via the mutual interaction between dopaminergic and glutamatergic signaling networks (Stone et al. 2007). Phosphorylation of the dopamine and cAMP-regulated phosphoprotein (▶ DARPP-32) by either dopamine receptor-induced protein kinase A (PKA) or by NMDA receptor-triggered calcineurin reciprocally affects either receptor system via protein phosphatase 1 (PP1), and modulates the late phase of LTP by influencing the extracellular signal-regulated kinase (ERK) pathway. With its multiple phosphorylation sites, DARPP-32 is an excellent coincidence detector and signal integrator, as many more protein kinases and phosphatases regulate the signaling properties of DARPP-32. Stimulants like ▶ amphetamines, ▶ nicotine, and ▶ caffeine all show impaired efficacy in transgenic mice with ablation or genetically diminished phosphorylation capacity of DARPP-32. Antipsychotics like ▶ haloperidol that block dopamine receptors were also shown to affect DARPP-32 phosphorylation in the same direction as the above-described stimulants. The differential behavioral consequences induced by both classes of drugs may arise from cell-specificity in DARPP-32 phosphorylation as found in striatonigral versus striatopallidal neurons (Bateup et al. 2008). Several alternative explanations exist. The activation of the immediate early gene necessary for LTP maintenance, Arc/Arg3.1, for example, needs simultaneous signaling of Gαs-coupled receptors like dopamine D_1 receptors, and calcium influx through NMDA receptors. It will need further studies to fully understand the interaction between dopaminergic and glutamatergic systems at the synaptic level.

Proteins involved in DARPP-32 signaling, especially PP1 and calcineurin, provide an interesting additional link between receptor function and synaptic plasticity via their modulation of the actin cytoskeleton in postsynaptic compartments.

Antidepressants, Mood Stabilizers, and Antidementia Drugs Modulate the Number of Dendritic Spines in the Hippocampus

The plasticity of synaptic morphology received much attention in recent years because of the technological revolution in genetic labeling and optical imaging. With two-photon, confocal, or evanescent wave imaging, it became possible to investigate single synapses at submicron resolution in unstained tissue. This development significantly accelerated studies on synaptic morphology that formerly required fixation and often electron microscopy. It was also the basis to identify a new downstream effector system of ▶ antidepressant drugs and the mood-stabilizer ▶ lithium in relation to synaptic plasticity: dendritic and postsynaptic morphology. This was first shown in a rodent model for depression, the bulbectomized rat. One of the anatomical consequences of bulbectomy is a decreased hippocampal volume. It could be shown that the ablation of the olfactory bulb, over a period of several weeks, induced a significant reduction in dendritic spines at glutamatergic neurons in the hippocampus. Loss of dendritic spines is thought to be equivalent to a loss of synaptic function. The antidepressant tianeptin was effectively protecting against spine loss in this animal model. Corroborating this finding, electron microscopy studies in ovariectomized rats found a similar increase in synapse number after short-term ▶ fluoxetine treatment, and subchronic treatment of ▶ imipramine was found to significantly modify synaptic morphology and increase dendritic spine density in hippocampal subregions of healthy adult rats. Increased expression of neurotrophic factors like BDNF may provide a mechanistic link between the monoaminergic system modulated by antidepressants

and synaptic morphogens like filamentous actin. Tyrosine phosphorylation of β-catenin by BDNF is known to promote dissociation from cadherin, a major structural component of many synapses. Notably, β-catenin is also downstream of glycogen synthase kinase GSK-3β, the molecular target of mood stabilizers like lithium. Lithium treatment of stressed rats increased dendritic arborization of hippocampal pyramidal cells, also affecting the number of dendritic spines in this brain region (see also Pittenger and Duman 2008).

Dendritic spines can grow and collapse within minutes, and the NMDA receptor was shown to be a necessary trigger for such major though reversible changes in synaptic morphology. ► Memantine, one of the few available drugs for the treatment of ► Alzheimer's Disease (AD), acts as a partial NMDA receptor antagonist. In primary hippocampal cultures, memantine was shown to prevent dendritic spine loss and shape changes induced by oligomers of amyloid β (Calabrese et al. 2007), providing a potential mechanism for its therapeutic efficacy in AD patients. Beyond AD, the ► Fragile X Syndrome, the most common inherited cause of mental impairment and the most common known cause of autism, was linked to defects in synaptic plasticity. Lack of the Fragile X Mental Retardation Protein (FMRP) induces dysregulation of spine morphogenesis and exaggerated metabotropic glutamate receptor-dependent LTD. FMRP is a synaptic protein regulating dendritic RNA delivery and translational repression. Based on pharmacological and genetic experiments, current theories see FMRP and the metabotropic glutamate receptor 5 (mGluR5) as counterparts in dendritic protein synthesis. There is pre-clinical evidence that genetic suppression of mGluR5 or the mGluR5 antagonists MPEP and fenobam can re-balance the system at the physiological level and improve cognitive performance of mice lacking FMRP. This was corroborated by a pilot clinical trial with the mGluR5 antagonist fenobam (Berry-Kravis et al. 2009) and will followed up by further clinical studies using improved drugs from this new evolving class of psychoactive drugs.

Synaptic plasticity is not a phenomenon restricted to the postsynaptic part of neuronal synapses. In the example of amyloid β-induced spine collapse, presynaptic boutons have been also affected and spontaneous synaptic transmission impaired. Morphological changes of presynaptic structures currently are targets of numerous studies. Functional plasticity of presynaptic proteins is particularly important for LTP at GABAergic synapses and most forms of STP. This short-lasting form of plasticity is dependent on the vesicular release machinery and modulated by a number of mechanisms regulating presynaptic calcium (Zucker and Regehr 2002).

Nicotine Receptors Affect Short-term Plasticity by Regulation of Vesicular Transmitter release

Presynaptic nicotinic acetylcholine receptors (nAChR) are an important trigger for increased presynaptic calcium and have been shown to regulate STP in a number of brain areas. Particularly, the α7 nAChR channel is a target for a number of drug candidates currently in clinical development for the treatment of negative symptoms in ► schizophrenia or ► mild cognitive impairment. Those receptors are expressed in many neurons at presynaptic sites while they control as postsynaptic receptors on GABAergic neurons the inhibitory tone in the hippocampus. Presynaptically, there is strong evidence that nAChR control release probability of several neurotransmitters, notably also of ► dopamine. Earlier studies using tonic application of subtype selective nAChR agonists showed a role for non-α7 AChRs in the regulation of dopamine release. More recently, phasic and short-term activation pattern of synaptosomes revealed a significant role of α7 receptors in the control of the readily releasable pool of dopamine (Turner 2004). The increase in dopamine release upon phasic AChR stimulation was dependent on the calcium-binding protein calmodulin but not on presynaptic high-voltage-activated calcium channels, as was the case for the non-α7 receptor mediated dopamine release. An increase in the number of vesicles ready to release their neurotransmitter upon stimulation facilitates neurotransmission for the next few synaptic events, and thus represents a form of STP. Nicotinic α7 receptors show an agonist-dependent rapid and strong desensitization after activation, and this desensitization likely turns strongly desensitizing agonists such as nicotine into functional antagonists when they are constantly present. Partial α7 receptor agonists like MEM3454 from Memory Pharmaceuticals may well have a different effect due to their increased activation of α7 receptor mediated steady-state current. Still, a continuous presence of the drug may impair phasic cholinergic signaling via those receptors. In this respect, allosteric positive α7 receptor modulators are likely to keep ► phasic signal transmission intact and thus may show a stronger impact on synaptic facilitation at dopaminergic synapses and therapeutic efficacy.

In summary, there is good evidence that psychotherapeutics influence forms of synaptic plasticity beyond LTP and LTD. Whether changes of synaptic structure or function upon treatment with psychoactive drugs are purely coincidental or causally correlated with their therapeutic

effect remains to be determined for most cases. Given the relevance of synaptic plasticity for cognitive and emotional processes, this form of neuronal plasticity is no doubt a major contributor to the behavioral effects induced by psychopharmacological drugs.

Cross-References

- ► Extracellular Recording
- ► Intracellular Recording
- ► Long Term Depression
- ► Long Term Potentiation
- ► Nicotinic Agonists and Antagonists
- ► Tonic Signals

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Synaptic Pruning

Definition

A process by which synaptic contacts between neurons, across which neurotransmitters and other chemical messengers are released in support of information processing, are normally reduced or eliminated in postnatal development. The overabundance of metabolically expensive synaptic contacts present in many brain regions in early life is thought to set the stage for processes of competitive elimination, in which those neural connections that carry the most functionally relevant forms of information survive and grow, while those carrying the least are removed. In many brain regions, this process may be particularly robust or entering its finishing stages during adolescent neurodevelopment.

Synaptic Reconsolidation

Definition

Synaptic reconsolidation is defined as the return of a consolidated memory to an unstable state, from which it must restabilize in order to persist. Typically, restabilization, or reconsolidation, takes several hours. Reactivating, for example, recalling or retrieving, existing memory can induce reconsolidation.

Synesthesia

Definition

Synesthesia is the crossing of senses, a phenomenon whereby stimulation of one sensory modality leads to automatic and involuntary experience of stimulation in a second sensory modality. Examples: to smell colors and to visualize sounds as colors.

Syntocinon

- ► Oxytocin

T

Tachykinins

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Definition

Tachykinins are short-chain amino acid neuromodulators found from invertebrates to mammals sharing the common C-terminal amino-acid sequence: Gly-Leu-Met-NH2. The name Tachykinin suggests the ability of these molecules to induce rapidly (tachys, swift) a contraction of smooth muscles (kineo, to move).

Pharmacological Properties

History

In 1931, Euler and Gaddum characterized an unidentified substance able to induce rapidly contraction of intestinal tissue. They named it ► substance P (SP) because it was stable in a dry powder form. Substance P remained the unique mammalian member of the tachykinin family until identification of ► neurokinin A (NKA) in 1983. Other mammalian tachykinins have been isolated since: neuropeptide K (NPK), neuropeptide γ (NP γ), ► neurokinin B (NKB), endokinins, and hemokinins. Studies of the distribution pattern of tachykinins showed a widespread expression in peripheral tissues where they have various effects such as inducing vasodilatation, hypotension, or contraction of smooth muscle. In the central nervous system, the three prominent mammalian tachykinins SP, NKA, and NKB are widely distributed with different distribution patterns. Maximal NKB concentrations are found in the cortex, whereas SP and NKA share a more similar distribution with a strong expression in the spinal cord and in the nuclei implicated in emotional process (e.g., nucleus accumbens, septum, amygdala). At a cellular level, SP and NKA are mostly co-localized in neurons and interneurons with glutamate, GABA, monoamines or acetylcholine. One or several tachykinins can be expressed within the same neurons and be co-released with classical neurotransmitters or neuromodulators (Beaujouan et al. 2004). The co-expression of SP and NKA is not surprising since there are three genes that encode for all known mammalian tachykinins. SP, NKA, NPK and NP γ mRNA are generated by alternative splicing of a unique preprotachykinin-A (PPT-A) gene. NKB is derived from a second gene, the preprotachykinin-B (PPT-B) gene. A third gene, the more recently cloned preprotachykinin-C, is coding for hemokinins and endokinins that are primarily expressed in non-neuronal cells.

In parallel with the discovery of new peptides from the mammalian tachykinin family, three types of receptors have been identified. They belong to the ► G-protein coupled receptors (GPCR) superfamily containing seven transmembrane domains. The activation of tachykinin receptors leads to a transduction cascade, which in turn activates, among others, phospholipase C, the release of intracellular Ca^{2+} and the stimulation of neurotransmitter release (Chahl 2006). However, tachykinins are neuromodulators, preferentially released when neurons are strongly activated (or under pathological conditions). Consequently, blockade of their receptors by ► antagonists may result in effects only when the system is stimulated (Hökfelt et al. 2000). This is of great relevance as it may provide pharmacological targets for therapeutic applications with potentially less pronounced side effects than drugs acting on tonically active modulators such as ► monoamines. Tachykinin receptors termed NK1, NK2 and NK3 bind with a high affinity respectively, SP, NKA, and NKB. Antagonists for these receptors have been suggested to have therapeutic value in a variety of areas, including inflammation, emesis, ► anxiety and ► depression However, the development of highly selective antagonists was hampered by findings from pharmacological and molecular studies that showed the existence of NK1 receptor isoforms with different affinities for tachykinins and a tissue specific expression. Furthermore, it was observed that several NK1 receptor antagonists have a greater affinity for the guinea-pig and human receptor than for the rat and mouse receptor (Beaujouan et al. 2004). This species heterogeneity, evidenced for NK1 and NK3, but not for NK2 receptors, had a major impact in the development of specific antagonists for these receptors as it

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required the development of suitable behavioral models in atypical species such as guinea pigs and gerbils to characterize their psychopharmacological properties.

NK1 Receptor Antagonists

The development of highly selective NK1 receptor antagonists was initiated after the discovery of the role of substance P as a key mediator of pain processes. NK1 antagonists were used as tools to specify the topological and functional features of NK1 receptors leading to the idea that SP could be used for the treatment of other pathologies such as emesis, ► Parkinson's disease, anxiety or depression. Thus, the use of these antagonists in experimental research on depression and anxiety was based, for instance, on findings showing (1) an expression of SP and NK1 receptor in fear and depression-associated pathways; (2) fear-related behaviors after intracerebroventricular injection of SP and reduced fear following the peripheral administration of NK1 receptor antagonists; (3) that binding sites for SP are co-localized with those of monoamine transmitters in the human brain.

The antidepressant- and anxiolytic-like effects of MK-0869 (aprepitant), the first NK1 receptor antagonist tested in human, were initially demonstrated in a range of animal models. The further development of NK1 and SP receptor knock-out mice confirmed these results as mutant animals displayed an anxiolytic- and antidepressant-like phenotype.

Several randomized, ► placebo-controlled, ► double-blind, clinical studies were carried out to measure the safety and efficacy of aprepitant. In an initial clinical phase II trial, aprepitant was shown to display significant antidepressant activity. It was well tolerated, and had fewer side effects than the selective serotonin reuptake inhibitor, ► paroxetine, which was used as a positive control in this study. Unfortunately, this result was never replicated in phase III clinical trials, thereby questioning the idea that NK1 receptor antagonists may be effective antidepressants (Rost et al. 2006).

NK2 Receptor Antagonists

The identification of NK2 receptors in a number of peripheral tissues such as the smooth muscles of the gastrointestinal tract, the respiratory and the urinary tracts, along with studies using selective NK2 receptor antagonists has led to the idea that this receptor may represent a potential therapeutic target for a wide-range of disorders, including irritable bowel syndrome, pulmonary and urinary tract disorders. The demonstration of the existence of NK2 receptors in the brain has been made much later. Data obtained from adult brain were not convincing due to non-specific binding and poor selectivity of ligands, and weak expression of the NK2 receptor. In 2001, the demonstration of the existence of central NK2 receptors was made using radiolabelled endogenous NKA in the presence of NK1 and NK3 receptor antagonists to avoid labeling of other tachykinin binding sites. These results were strengthened by detection of NK2 receptor mRNA in human and rat in brain structures affected in mood disorders, such as the ► prefrontal cortex and the ► hippocampus. Moreover neurochemical studies have identified a central regulatory role of NK2 receptors on monoaminergic and cholinergic neurotransmission. For instance, in anesthetized rats, the peripheral administration of the NK2 receptor antagonist, saredutant, has no effects on basal ► norepinephrine levels in the prefrontal cortex but reduces its release elicited by tail pinch. In addition, in non-anesthetized rats, local infusion of saredutant in the septum blocks stress-induced increase of hippocampal acetylcholine release but has no effect on basal conditions (Desvignes et al. 2003). These results underline the ability of NK2 receptor antagonists to regulate neurotransmission only when systems are activated (Steinberg et al. 2001).

Furthermore, recent data suggest an interaction between the tachykinin system and ► corticotropin-releasing factor (CRF). CRF is a neurohormone known to be involved in the regulation of the stress axis and in the etiology of mood disorders. The injection of saredutant was found to block CRF-induced increase in acetylcholine and norepinephrine release, suggesting that NK2 receptor antagonists counteract, at least in part, the effects of stress on neurotransmission.

At a behavioral level, the activation of central NK2 receptors by intracerebroventricular administration of NKA produces ► anxiogenic-like effects. Moreover several NK2 receptor antagonists have been shown to produce ► anxiolytic-like activity in animal studies. For example, GR159897 and saredutant exhibited anxiolytic-like effects in exploration-based procedures such as the light/dark and the ► elevated plus-maze tests. It is noteworthy that the anxiolytic-like properties of saredutant were observed across species as evidenced in the mouse defense test battery, the marmoset human intruder test and the social interaction test in gerbils and rats. In addition, saredutant also exhibited antidepressant-like properties in the rat forced swim test. Moreover, the drug attenuated physical degradation in the mouse ► chronic mild stress test (Griebel et al. 2001; Louis et al. 2008). In addition to the neurochemical and behavioral effects of NK2 receptor antagonists, molecular and cellular studies showed that

chronic treatment with saredutant upregulates cAMP response element binding protein (CREB) and promotes ► neurogenesis in ► hippocampus after chronic stress exposure in mice. Similar effects are observed with classical antidepressant treatment such as ► fluoxetine. Together, these results suggested that selective NK2 receptor antagonists could have therapeutic utility for the pharmacological treatment of ► mood disorders and anxiety. Unfortunately, the low efficacy and poor brain penetration of the NK2 receptor antagonist tested in recent clinical trials did not allow a definitive conclusion on the pertinence of the target.

NK3 Receptor Antagonists

The NK3 receptor has been the least studied of the NK receptor family. The first paper on a selective NK3 receptor antagonist, published in 1995, was the starting point of numerous studies which explored the pharmacology of the NK3 receptor (Edmond-Alt et al. 1995).

In peripheral tissues, similar to other tachykinin receptors, it was found that the NK3 receptor plays a role in smooth muscle contraction. However, NK3 receptors are mostly expressed in the central nervous system with a wide distribution throughout the spinal cord and brain, in particular in limbic areas, well known to play a crucial role in psychiatric disorders. Importantly, the activation of NK3 receptors expressed on dopaminergic neurons by the highly selective agonist senktide leads to an increased dopamine release in the striatum and the prefrontal cortex. This excitatory activity, as well as the stimulation of serotoninergic and noradrenergic systems, is blocked by the selective NK3 receptor antagonist osanetant, but not by NK1 or NK2 antagonists (Spooren et al. 2005). Decreasing the dopaminergic activity may be of interest for the treatment of the positive symptoms of ► schizophrenia since all currently approved antipsychotics share this feature.

Cross-References

► Chronic Mild Stress
► Distress Vocalizations
► Elevated Plus Maze
► G-Protein Coupled Receptors
► Isoforms
► Selective Serotonin Reuptake Inhibitors
► Social Interaction Test

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Tachyphylaxis

Definition

Tacyphylaxis is the rapid development of tolerance to the effect of a drug. That is, the response to a drug rapidly decreases after a few initial doses. In the case of hallucinogens, the process is thought to be a result of rapid desensitization and internalization of serotonin 5-HT_{2A} receptor.

Tacrine

► Acetylcholinesterase and Cognitive Enhancement

Tail Suspension Test

► Behavioral Despair

Tandospirone

Definition

Tandospirone displays anxiolytic and antidepressant properties with a short ► half-life. Its main pharmacological mode of action is as a potent 5-HT_{1A} receptor ► partial agonist. Its active metabolite displays antagonistic action at α_2-adrenergic receptors. Tandospirone is a member of the piperazine and azapirone chemical classes. It is prescribed mainly in Japan and China. A Western equivalent of the same pharmacological class is buspirone, which is prescribed for ► generalized anxiety disorder, ► panic attacks, and as augmentation of treatment with serotonin reuptake inhibitors.

Cross-References

► Buspirone

Tardive Dyskinesia

Definition

Tardive dyskinesia (TD) is a chronic neuromotor side effect of dopamine-blocking medications, characterized by abnormal involuntary movements of voluntary musculature that are generally slow and that can be irreversible. It can include abnormal rotatory or sinuous movements of the mouth, lips, neck, trunk, hands, arms, and legs. It is identified as a side effect of long-term antipsychotic use; risk factors have been identified (e.g., age, duration of exposure), but there is no specific means of precisely predicting who will develop TD. With the ► first-generation antipsychotics, prevalence rates in chronically treated patients approximated to 25%. Evidence for the newer, ► "atypical" antipsychotics indicates that none of these agents are without risk of TD, although prevalence rates appear notably lower. The precise pathophysiologic mechanisms underlying TD have not been elucidated, although high and sustained levels of dopamine D_2 occupancy have been implicated. Many putative pharmacologic treatments have been investigated, although only a few (e.g., ► tetrabenazine in Canada) have gained an indication for treatment of TD. TD has proven inconsistent in its response to all treatments, variable over the course of the illness, and is frequently irreversible. Other tardive movements (e.g., tardive dystonia) are also linked to chronic antipsychotic exposure.

Cross-References

► Antipsychotics
► First-Generation Antipsychotics
► Schizophrenia
► Second-Generation Antipsychotics

Taste Aversion Learning

► Conditioned Taste Aversions
► Long-Delay Learning

Taste Reactivity Test

Definition

This is a method that can be used to determine in the rat the motivational valence of a taste without having the test subject actually ingest the fluid. Ralph Norgren and Harvey Grill discovered that rats show distinct orofacial (movement of the mouth and tongue and opening of the mouth, gaping and face washing and wiping) reactions to the intraoral application of sapid solutions. The reactions observed can be characterized as appetitive or aversive, depending on whether the fluid evokes an ingestive or rejective reaction. This test can be used as a method to assess tastes paired with drugs that produce conditioned taste preferences or taste aversions.

Cross-References

► Conditioned Taste Aversions
► Conditioned Taste Preferences

Tastes as Conditioned Stimuli for Drugs

► Conditioned Taste Aversions
► Conditioned Taste Preferences

TCAs

► Secondary Amine Tricyclic Antidepressants
► Tertiary Amine Tricyclic Antidepressants
► Tricyclic Antidepressants

TCE

► Trichloroethane

TDM

► Therapeutic Drug Monitoring

Temazepam

Definition

Temazepam is an intermediate-acting (half-life 8–20 h) benzodiazepine used to treat insomnia. Side effects include a hangover effect (residual drowsiness) the next morning, dizziness, nausea, and vomiting. Prolonged use of this drug is not recommended because of risks for dependence. Temazepam is also used recreationally usually to dampen the effects of withdrawal associated with other drugs, for example, cocaine and MDMA. The gel capsule form of temazepam (called "jellys") was withdrawn after being associated with intra-arterial injection for the purposes of getting high, which caused severe vascular injury and limb ischemia leading to amputations.

Cross-References

► Benzodiazepines
► Sedative, Hypnotic, and Anxiolytic Dependence

Temporal Conditioning

► Timing Behavior

Temporal Discounting

Synonyms

Delay discounting; Time discounting

Definition

Temporal discounting is the change in the subjective value of an outcome as the temporal duration for obtaining that outcome changes.

Cross-References

► Behavioral Economics
► Impulsivity

Temporal Knockout

► Inducible Knockout

Temporal Myopia

Definition

Temporal myopia is the inability to consider the long-term outcomes of an action when making a choice.

Cross-References

► Behavioral Economics

Temporal Processing

► Timing Behavior

Teratogenetic

► Teratogenic

Teratogenic

Synonyms

Teratogenetic

Definition

Agents or conditions that are able to interfere with the normal development and growth of an embryo or fetus. Teratogens include radiation, maternal infections, chemicals, and drugs; they can either halt the pregnancy or produce a congenital malformation.

Cross-References

► Foetal Alcohol Syndrome

Terminal Half-Life

► Elimination Half-Life

Territorial Aggression

Definition

Territorial aggression is defined as the display of aggressive acts and postures for the purpose of excluding other males from the patrolled and marked locale. This type of aggression may vary with the season.

Tertiary Amine Tricyclic Antidepressants

Definition

Tertiary amine TCAs are molecules composed of a three-ring structure that has two methyl groups on the nitrogen atom of the side chain. This group of TCAs includes ► amitriptyline, ► imipramine, ► clomipramine, ► trimipramine, and ► doxepin.

Tests

► Rating Scales and Diagnostic Schemata

Tetrabenazine

Definition

Tetrabenazine is a reversible inhibitor of vesicular monoamine transporters. It reduces uptake of monoamines such as dopamine into synaptic vesicles causing depletion of monoamine stores. It is approved for the treatment of chorea (abnormal involuntary movements) associated with ► Huntington's disease. ► Extrapyramidal side effects are much less common with tetrabenazine than with typical ► neuroleptics. However, it can amplify the risk of depression, and suicidal thoughts and behavior already seen in Huntington's disease patients. Other common side effects of tetrabenazine include drowsiness, insomnia, and ► akathisia. Tetrabenazine has also been clinically evaluated in the treatment of other hyperkinetic disorders including Gilles de la Tourette's syndrome (Tourette's syndrome). It was also used in experimental psychopharmacology as an amine depletor, enabling the role of endogenous amines in responses to other drugs to be investigated. In this application, it has fallen out of use due to the nonspecific nature of the depletions that it produces.

Cross-References

► Amine Depletors
► Antipsychotic Drugs
► Tic Disorders with Childhood Onset

Tetracyclic Antidepressants

► NARI Antidepressants

Tetraethylthiuram Disulphide

► Disulfiram

Tetrazepam

► Benzodiazepines

Thalamocortical 10 Hz Rhythm

► Function of Slow and Fast Alpha

Thalidomide

Synonyms

Thalomid

Definition

Thalidomide is a sedative agent with anti-inflammatory and anxiolytic effects. The drug was prescribed during the late 1950s and early 1960s to pregnant women, as an antiemetic to overcome morning sickness and to improve sleep. Approximately 10,000 children prenatally exposed to thalidomide were born with severe malformations, including the hands and feet attached to abbreviated arms and legs (phocomelia). Thalidomide is now approved by the FDA for the treatment of conditions associated with leprosy, multiple myeloma, and actinic prurigo. Side effects of thalidomide include: severe birth defects, sleepiness, drowsiness, constipation, skin rash, severe headaches, stomach aches, peripheral neuropathy, dizziness and nausea, mood-swings, and a general sense of

illness. The use of thalidomide is forbidden before conception and during pregnancy.

Cross-References

► Autism: Animal Models

Thalomid

► Thalidomide

Therapeutic Benefit

► Efficacy

Therapeutic Drug Monitoring

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Synonyms

Drug plasma level determination for therapy optimization; TDM; Therapeutic drug plasma level monitoring

Definition

The rationale of therapeutic drug monitoring is based on the hypothesis that drug plasma concentrations in the patient reflect better than drug dose the brain concentrations of the active components. For specific drugs, a «therapeutic window» (therapeutic range) can be defined: it represents a drug plasma concentration range defined by a lower threshold below which there is a high probability for an insufficient clinical response. In contrast, drug plasma concentrations higher than the upper threshold result in an increased risk for adverse effects. Drug plasma concentrations within the "therapeutic window" should therefore be synonymous with optimal clinical response. Hence, TDM is the measurement of drug concentrations in the blood of patients in order to facilitate dose adaptation for optimizing treatment. Recently, a consensus guideline was published by a group of experts (AGNP-TDM group (Arbeitsgemeinschaft für Neuropsychopharmacologie und Pharmacopsychiatrie), which should help the clinician to take optimal clinical benefit of TDM in psychiatry (Baumann et al. 2004).

Current Concepts and State of Knowledge

► Pharmacokinetics and Metabolism

The majority of psychiatric patients are treated with psychotropic drugs including antidepressants, mood stabilizers, antipsychotic or anxiolytic/hypnotic drugs, but complications such as non-response, poor tolerance, non-compliance or drug interactions are frequent. Besides pharmacodynamic, pharmacokinetic factors may also be responsible for unsuccessful treatments, in that, in the body and particularly in the brain, inadequate drug concentrations are reached for different reasons, as both environmental and genetic factors control the fate of the drug in the organism.

In order to reach the target organ, the brain, psychotropic drugs are submitted to several steps: ► absorption, ► distribution, ► metabolism, and elimination (ADME). The ► bioavailability of these drugs is 100% when intravenously administered. However, after oral administration it generally varies between 20% and 80%, depending on the drug but also on environmental and genetic factors, due to a limited absorption from the intestine and to metabolism in the liver ("first pass-effect").

Most psychotropic drugs are submitted to metabolism in the liver, in the intestine and in other organs, by phase I (e.g., ► cytochrome P-450) and phase II (e.g., UTP-glucuronyltransferase) reactions. An important consequence is the possible formation of active metabolites, mainly after formation by phase I and rarely by phase II enzymes. These products may differ in their pharmacological and pharmacokinetic properties from their parent compound, but they contribute to the overall clinical profile of the drug.

► Pharmacogenetics

Cytochrome P-450 is the most important enzymatic system implicated in the biotransformation of psychotropic compounds, which are metabolized by one or several isozymes, mainly CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and/or CYP3A/5/7. Some of them are inducible (CYP1A2, CYP2C9, CYP2C19, and CYP3A) and most of them display a ► genetic polymorphism. This can be defined as the presence of at least two genetically determined variants (e.g., alleles) in a population, and such a variant allele has to occur in at least 1% of the population. As a consequence, a high, genetically determined variability may exist in the expression of an active enzyme protein, and patients can be categorized according to

their phenotype: poor (PM), intermediate (IM), extensive (EM), and ultrarapid (UM) metabolizers can be observed. In some UM, gene multiplication is observed, and therefore, the presence of at least three active alleles. These patients are at risk for poor clinical response, as drug levels may never reach concentrations needed for clinical efficacy. In contrast, due to the absence of active alleles, drug plasma concentrations in PM may be within a range leading to adverse effects, already at usual drug doses. IM and EM are characterized by the presence of one or two "normally" active alleles, respectively, but the distinction between these groups is sometimes difficult (Ingelman-Sundberg 2004; Kirchheiner et al. 2004). This has to be considered as a somewhat simplified presentation of the relationship between the genotype and phenotype. Patients may be genotyped, or phenotyped using probes which are specific substrates of the isozyme to be examined (Fuhr et al. 2007). Generally, a single dose of these probes is administered to the patients, and urine or blood is then collected during or after a well-defined period of time for the analysis of the parent compound and its metabolite formed by the enzyme. The metabolic ratio (metabolite/parent compound) informs on the metabolic status, i.e., phenotype, of the patient. Typically, debrisoquin or dextromethorphan are used as probes for phenotyping patients with regard to CYP2D6 activity.

Numerous psychotropic drugs are substrates, inhibitors, and/or inducers of the transporter molecule P-glycoprotein, which extrudes drugs and other xenobiotics from the intracellular to the extracellular space (Thuerauf and Fromm 2006). This transmembrane efflux transporter is expressed in many tissues such as the intestine, liver, and at the ►blood brain barrier and it is encoded by the multidrug resistance 1 gene (*ABCB1*) and belongs to the adenosine triphosphate-binding cassette (ABC) family. It presents a genetic polymorphism and depending on the genotype of the patients, this may have consequences on the transport of drugs in the organism. Therefore, the contribution of this transporter molecule in the regulation of drug distribution in the organism is increasingly recognized; however, the clinical relevance of genotyping patients for P-glycoprotein needs to be further investigated.

On the pharmacodynamic level, most receptor and transporter molecules which are binding neurotransmitters such as norepinephrine and serotonin also present genetic polymorphisms. Numerous studies suggest that there may be a relationship between the pharmacogenetic-pharmacodynamic status of the patients and their response to psychotropic drugs, but these tests are not yet sufficiently validated for their routine use in clinical practice (Arranz and de Leon 2007).

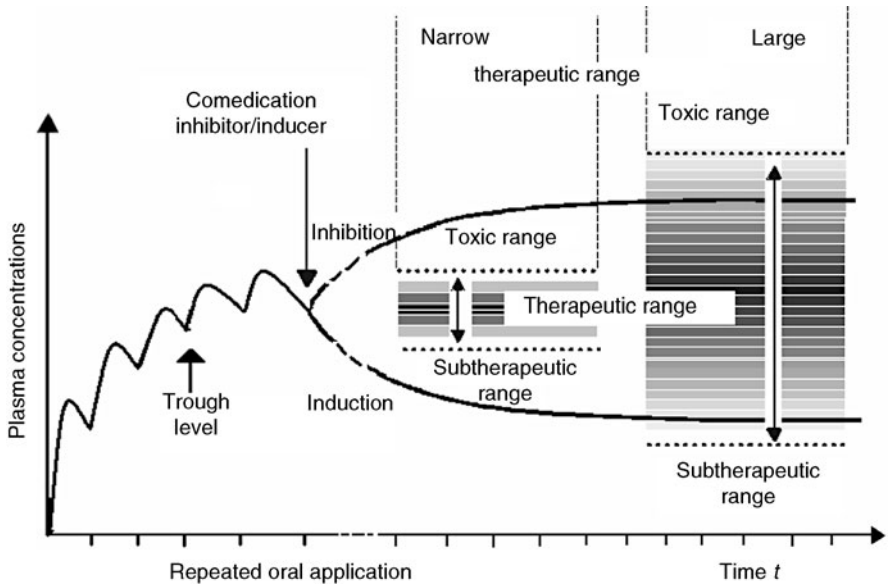
In conclusion, TDM may be advantageously combined with pharmacogenetic tests especially regarding cytochrome P-450, as these tests may provide a useful help for diagnosing pharmacokinetic particularities (Gardiner and Begg 2006).

Indications for TDM

This presentation of the consequences of a pharmacogenetic variability in drug metabolism already demonstrates an indication for TDM. Table 1 summarizes important indications for TDM, which is however absolutely mandatory only for a few psychotropic drugs such as ►lithium, but the clinical usefulness of TDM of antidepressants (Wille et al. 2008) and antipsychotics (Mauri et al. 2007) is widely recognized (Baumann et al. 2004). Indeed, drugs such as lithium, ►tricyclic antidepressants, and the antipsychotic drug ►clozapine display a relatively narrow therapeutic range, while it is wide for some ►antidepressants including SSRI (Fig. 1). One of the main problems in pharmacotherapy is the lack of compliance in patients, as it leads to nonresponse and enhances the risk for hospitalization and rehospitalization. However, there may also be other reasons for insufficient response or adverse effects which lead to interruption of the treatment despite the prescription of doses considered as adequate. This may be a consequence of pharmacokinetic interactions leading to an inhibition or induction of the metabolism of the administered drug. Combination treatments are frequent, as many patients suffering from comorbidities need comedications, or in situations of poor response, they are comedicated with augmenting but pharmacokinetically interacting agents. TDM is also recommended in pharmacovigilance programs as it represents an interesting diagnostic tool. Increasingly, the need for long-term treatments is recognized in order to prevent relapse, but despite apparently good compliance, recurrence of the illness may occur. The pharmacokinetics of psychotropic drugs may be particular in many subjects belonging to the category of "special populations," such as children and adolescents, elderly patients, patients suffering from comorbidities which may result in an impaired absorption, distribution, metabolism, or elimination of the drug. Similarly, problems may occur at the level absorption when galenic forms of drugs are changed, e.g., switching from an original preparation to a generic brand, and vice versa. Depending on the indication, either the availability of "therapeutic ranges" or the knowledge of plasma drug concentrations at defined doses may primarily be helpful for the clinician (Table 1). Table 2 presents a list of recommended plasma concentrations of antidepressants and antipsychotics as defined by the already mentioned group of experts (Baumann et al. 2004).

Therapeutic Drug Monitoring. Table 1. General indications for TDM of psychotropic drugs (after Baumann et al. 2004). Primary clinical relevance of defined therapeutic ranges and dose related drug concentrations.

General indications	Therapeutic range	Dose-related drug plasma concentrations
Suspected noncompliance		x
Drugs, for which TDM is mandatory for safety reasons (e.g., lithium)	x	
Lack of clinical response, or insufficient response even at doses considered as adequate	x	
Adverse effects despite the use of generally recommended doses	x	
Suspected drug interactions		x
TDM in pharmacovigilance programs	x	x
Combination treatment with a drug known for its interaction potential, in situations of comorbidities, "augmentation"	x	x
Relapse prevention in long term treatments, prophylactic treatments	x	x
Recurrence despite good compliance and adequate doses	x	x
Presence of a genetic particularity concerning the metabolism or transport of the drug (genetic deficiency, gene multiplication)		x
Children and adolescents		x
Elderly patients (>65 years)		x
Patients with pharmacokinetically relevant comorbidities (hepatic or renal insufficiency, cardiovascular disease)		x
Forensic psychiatry		x
Problems occurring after switching from an original preparation to a generic form (and vice versa)		x



Therapeutic Drug Monitoring. Fig. 1. Pharmacokinetic behaviour of drugs after their repeated administration, before and after addition of comedications differing by their interaction potential.

Therapeutic Drug Monitoring. Table 2. Recommended target plasma concentration ranges for psychoactive drugs and levels of recommendation for routine monitoring. (From Baumann et al. 2004.)

Drug and active metabolite	Recommended therapeutic range (consensus)[a]	Level of recommendation[b]
▶ Antidepressants		
▶ Amitriptyline plus nortriptyline	80–200 ng/ml	1
▶ Citalopram	30–130 ng/ml	3
▶ Clomipramine plus norclomipramine	175–450 ng/ml	1
Desipramine	100–300 ng/ml	2
▶ Doxepin plus nordoxepin	50–150 ng/ml	3
▶ Escitalopram	15–80 ng/ml	4
▶ Fluoxetine plus norfluoxetine	120–300 ng/ml	3
▶ Fluvoxamine	150–300 ng/ml	4
▶ Imipramine plus desipramine	175–300 ng/ml	1
Maprotiline	125–200 ng/ml	3
▶ Mianserin	15–70 ng/ml	3
▶ Mirtazapine	40–80 ng/ml	3
▶ Moclobemide	300–1000 ng/ml	4
▶ Nortriptyline	70–170 ng/ml	1
▶ Paroxetine	70–120 ng/ml	3
▶ Reboxetine	10–100 ng/ml	4
▶ Sertraline	10–50 ng/ml	3
▶ Tranylcypromine	0–50 ng/ml	5
▶ Trazodone	650–1500 ng/ml	3
▶ Trimipramine	150–350 ng/ml	3
▶ Venlafaxine plus O-desmethylvenlafaxine	195–400 ng/ml	2
Viloxazine	20–500 ng/ml	3
Antipsychotics		
▶ Amisulpride	100–400 ng/ml	3
▶ Benperidol	2–10 ng/ml	3
▶ Chlorpromazine	30–300 ng/ml	2
Chlorprothixen	20–200 ng/ml	3
▶ Clozapine	350–600 ng/ml	1
▶ Fluphenazine	0.5–2 ng/ml	1
▶ Flupentixol	>2 ng/ml	2
▶ Haloperidol	5–17 ng/ml	1
Melperone	50 ng/ml	4
▶ Levomepromazine	15–60 ng/ml	3
▶ Olanzapine	20–80 ng/ml	1
Perazine	100–230 ng/ml	2
▶ Perphenazine	0.6–2.4 ng/ml	2
▶ Pimozide	15–20 ng/ml	4
▶ Quetiapine	70–170 ng/ml	3
▶ Risperidone plus 9-hydroxyrisperidone	20–60 ng/ml	2
▶ Sulpiride	200–1000 ng/ml	3
▶ Thioridazine	200–2000 ng/ml	2

Therapeutic Drug Monitoring. Table 2. (continued)

Drug and active metabolite	Recommended therapeutic range (consensus)[a]	Level of recommendation[b]
▶ Zotepine	12–120 ng/ml	3
▶ Ziprasidone	50–120 ng/ml	4
▶ Zuclopentixol	4–50 ng/ml	3
▶ Mood stabilizers		
▶ Carbamazepine	6–12 g/ml	2
▶ Lithium	0.5–1.2 mmol/l	1
▶ Valproate	50–100 g/ml	2
Anxiolytics/ hypnotics		
▶ Alprazolam	20–40 ng/ml	3
▶ Buspirone	3 ng/ml	4
▶ Clonazepam	20–40 ng/ml	3
▶ Diazepam plus metabolites	300–400 ng/ml	3
▶ Lorazepam	10–15 ng/ml	4
▶ Midazolam	6–15 ng/ml	4
▶ Zolpidem	90–325 ng/ml	5
▶ Zopiclone	60–75 ng/ml	5
Antidementia drugs		
▶ Donepezil	30–75 ng/ml	2
▶ Galantamine	30–100 ng/ml	3
▶ Memantine	7–159 ng/ml	4
▶ Tacrine	7–30 ng/ml	2
Drugs for addiction		
▶ Acamprosate	30–75 ng/ml	3
▶ Bupropion	<100 g/ml	4
▶ Clomethiazole	100–5000 ng/ml	5
▶ Disulfiram	2400 ng/ml	5
▶ Methadone	400–800 ng/ml	2
Methadone	R-meth. >250 ng/ml	2
▶ Naltrexone	<9 ng/ml	4

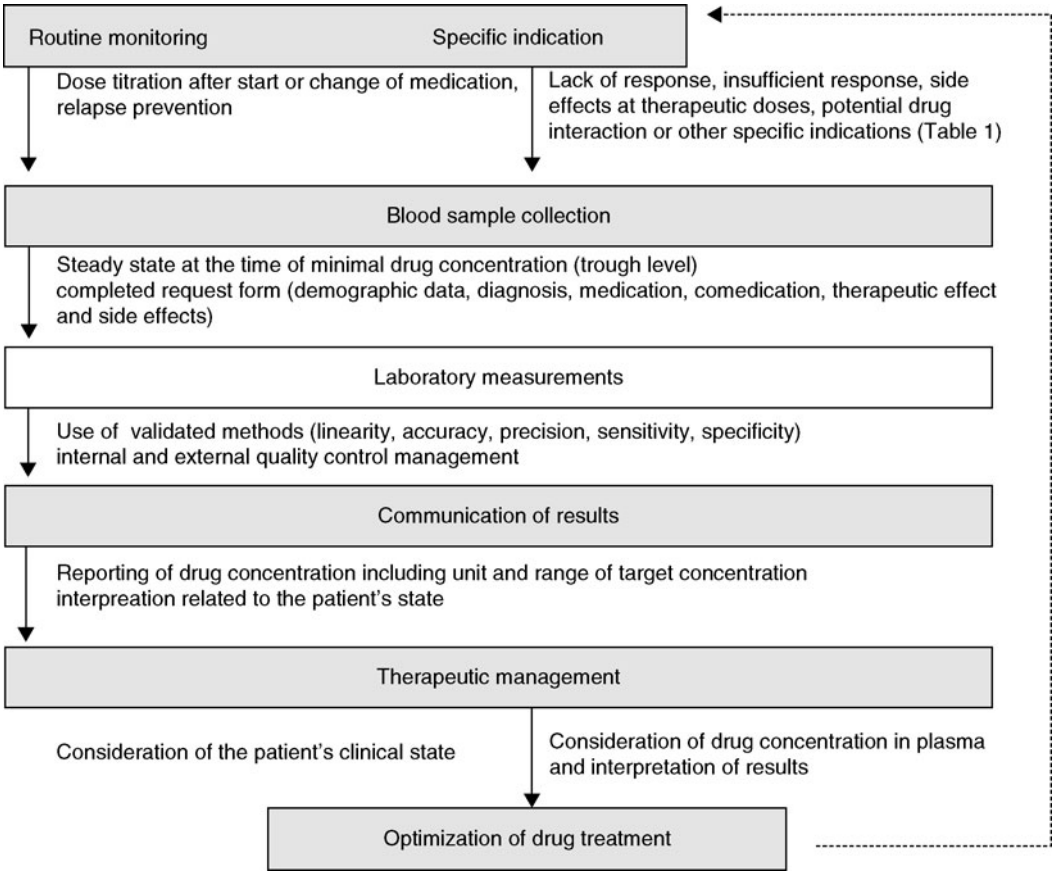
[a]*Therapeutic ranges* indicate trough concentrations of drugs in serum or plasma of patients under steady state medication
[b]*Level of recommendation*

In addition, the levels of recommendation are indicated for each drug, as defined according to the present evidence from studies reported in the literature and to the conclusion from the expert group.

1. *Strongly recommended (for lithium TDM should be a standard of care)*: Established therapeutic range
2. *Recommended*: Suggested therapeutic ranges obtained from plasma concentrations at therapeutically effective doses (fixed dose studies)
3. *Useful*: Suggested therapeutic ranges are plasma concentrations at therapeutically effective doses obtained from steady-state pharmacokinetic studies
4. *Probably useful*: Suggested therapeutic ranges from steady-state pharmacokinetic studies at therapeutically effective doses
5. Not recommended

Practical issues

Figure 2 summarizes the steps which should be considered when TDM is envisaged in a patient. Successful TDM is the result of a fruitful collaboration between the treating physician, laboratory specialists, and, in special circumstances, the clinical pharmacologist. From a pharmacokinetic point of view, TDM should be carried out in



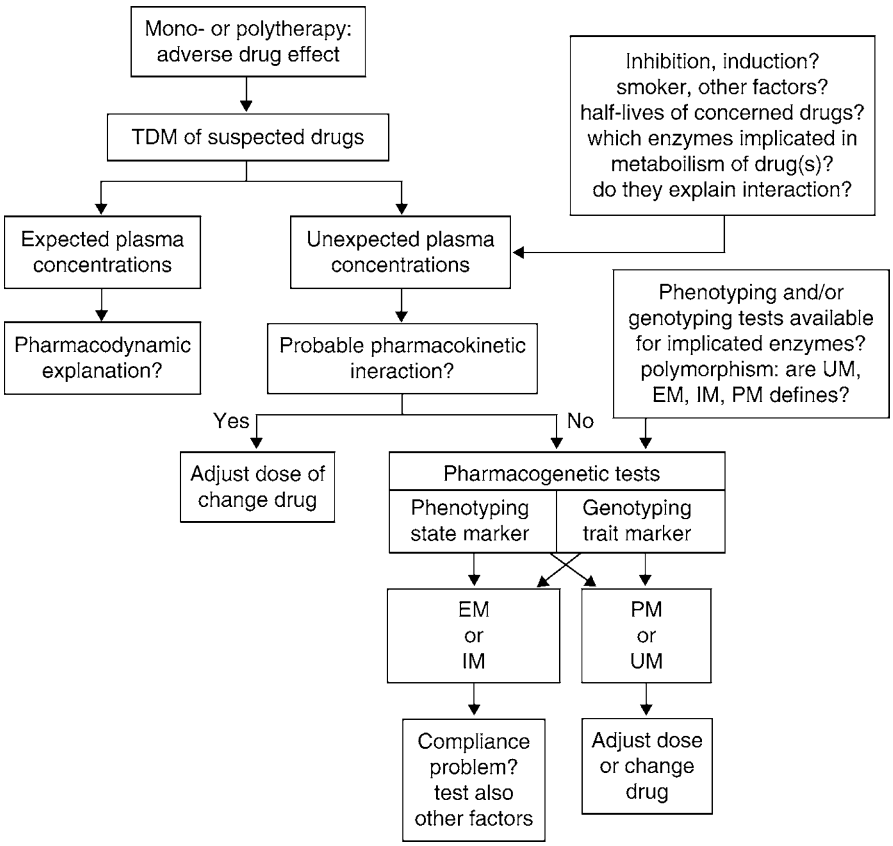
Therapeutic Drug Monitoring. Fig. 2. Schematic presentation of the TDM process for optimization of psychopharmacotherapy (Baumann et al. 2004).

steady-state conditions of both the parent compound and its active metabolite to be co-monitored (Fig. 1). This situation is generally reached within a time period of 4–5 half-lives of the active constituents after treatment is initiated or after adaptation of the dose. Moreover, trough levels (Fig. 1) should be measured, i.e., generally 12–16 h after the last intake of the drug, or in the morning before the first dose of the day is administered. In situations of pharmacokinetic interactions, two situations have to be considered separately. In the case an inhibitor of the metabolism of the drug to be monitored is administered, its new steady-state concentrations are only reached after the inhibitor has reached steady-state conditions, when it exerts a maximal inhibiting effect. After comedication with a metabolism inducing drug, maximal induction is only reached after the inhibitor itself reached steady state and after maximal inducing effect, i.e., stimulation of protein synthesis, is obtained (Fig. 1). This takes generally 1–2 weeks. Practically, it is difficult to be compliant with all these recommendations, as many drugs are administered several times per day, and others display very short (e.g., quetiapine: 2–4 h) or very long elimination half-lives, respectively (e.g., fluoxetine (and its active metabolite norfluoxetine): 3–4 days).

Finally, an example of a frequent but complicated situation is presented in Fig. 3, when adverse effects are observed in a patient during a drug treatment. It presents a decision tree about the optimal combination of TDM with pharmacogenetic tests, as useful tools for the diagnosis of the cause of an unexpected pharmacokinetic behavior of the drug leading to a pharmacovigilance problem (Jaquenoud Sirot et al. 2006).

Cross-References

► Antidepressants
► Antipsychotic Drugs
► Blood–Brain Barrier
► Drug Interactions



Therapeutic Drug Monitoring. Fig. 3. Decision tree for the sue of TDM and pharmacogenetic tests of drug metabolising enzymes in situations of pharmacovigilance problems. **EM** = extensive metaboliser; **IM** = intermediate metaboliser; **PM** = poor metaboliser; **UM** = ultra-rapid metaboliser.

- ► Lithium
- ► Mood Stabilizers
- ► Pharmacogenetics
- ► Pharmacokinetics
- ► SSRI

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Therapeutic Drug Plasma Level Monitoring

► Therapeutic Drug Monitoring

Theta Rhythm

► RSA

Thioridazine

Definition

Thioridazine, like other compounds of its chemical class (► phenothiazines), is classified as a typical antipsychotic, although its pharmacological profile exceeds dopamine D_2 receptor blockade to include antagonism at dopamine D1, alpha-1 adrenergic, and muscarinic cholinergic receptors, and it produces a relatively low incidence of ► extrapyramidal side effects. Cardiotoxicity, retinopathy, and other serious side effects have reduced its use to patients who do not respond to other commonly used antipsychotic compounds.

Cross-References

► Antipsychotic Drugs
► First-Generation Antipsychotics

Thiothixene

Definition

Thiothixene acts at multiple receptors but mainly by dopamine D2 blockade. It is a first generation antipsychotic with an elimination half-life of 34 h, and is mainly metabolized by 1A2 CYP450 isoenzymes.

Cross-References

► First-Generation Antipsychotics

Thioxanthenes

Definition

A group of drugs that includes key members of the first generation of antipsychotic substances that brought about major changes in treatment of schizophrenia. Among the widely used drugs in this category are chlorprothixene, ► flupenthixol, and ► zuclopenthixol.

Cross-References

► Antipsychotic Drugs
► First-Generation Antipsychotics

Third-Generation Antipsychotics

Definition

All first- and second-generation antipsychotics exert their clinical actions by, among other pharmacologic properties, blocking the dopamine D2 receptor. Aripiprazole, a partial D2 agonist, is the first drug with a different mechanism of action. It is therefore considered to be a third-generation antipsychotic.

Cross-References

► Antipsychotic Drugs
► Aripiprazole

Threshold

Definition

The theoretical point at which a sensory stimulus is perceived correctly on at least 50% of occasions.

Thrill Seeking

► Risk Taking

Thrombocytes

► Platelets

Thymoleptics

► Antidepressants

Tiagabine

Definition

Tiagabine is an anticonvulsant drug that is used as a third-line adjunct medication for the treatment of partial seizures in adults and children. It acts by selectively inhibiting the GABA transporter 1 reuptake inhibitor. Thus, it enhances inhibitory ► GABAergic neurotransmission and prevents propagation of neuronal impulses and seizures. Tiagabine reduces seizure frequency but does not produce freedom from seizures and has a low tolerability, for example, low anticonvulsant efficacy compared to other third-line antiepileptic drugs. It also has a high rate of side effects including dizziness, lack of energy, nausea, and nonconvulsive status epilepticus. Open-label investigations have suggested that tiagabine may be used as an add-on medication in anxiety disorders, for example, ► generalized anxiety disorder, and for the treatment of alcohol dependence. It is thought that tiagabine may reduce both ► anxiety and alcohol ► craving in withdrawal, possibly via indirect GABA inhibition of the ► mesolimbic dopamine system. However, its efficacy for these indications has not yet been confirmed in double-blind placebo-controlled studies.

Cross-References

► Alcohol Abuse and Dependence
► Anticonvulsants
► Generalized Anxiety Disorder
► Placebo Effect
► Randomized Controlled Trials

Tic Disorders with Childhood Onset

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Synonyms

Tourette syndrome

Definition

Tic disorders of childhood are a group of probably related conditions characterized by the presence of motor tics and/or vocalizations. Motor ► tics tend to be rapid, jerky movements of the head and neck regions, though other muscle groups may also be involved. Common vocal tics include repetitive throatclearing, grunting, snorting, or shouts. Tic disorders are described as transient or chronic according to the duration. The differential diagnosis is also based on whether both motor and vocal tics are present. The diagnosis of a tic disorder also requires that the tics are not due to the effects of a substance (e.g., stimulants) or another medical condition (e.g., Huntington's chorea).

Role of Pharmacotherapy

Tics are common in children, affecting as many as 20% of the school-age population. In most of these children, the tics are transient and require no intervention. An estimated 1% of children show a pattern of chronic tics that endure over time. Tourette syndrome, defined by the presence of both motor and vocal tics persisting for at least a year, affects 3–8/1,000 children (Scahill et al. 2005). Even among children with chronic tics, many cases are mild, and medication is not warranted. Children with tic disorders appear to be at higher risk for co-occurring conditions such as ► attention deficit hyperactivity disorder (ADHD) and ► obsessive–compulsive disorder (OCD). Thus, the first step in selecting medication for the treatment of children with tic disorders is to identify the most important source of impairment: tics, ADHD, or OCD. The use of pharmacotherapy in children with tic disorders should always be combined with education for the child and the family about the medication, as well as the natural history of tic disorders.

Diagnostic Categories

The following are the three main diagnostic categories of childhood onset of tic disorders:

1. Transient tic disorder (motor and/or vocal tics lasting for at least two weeks but less than 1 year)
2. Chronic tic disorder (motor or vocal tics lasting for more than a year)
3. Tourette syndrome (multiple motor tics and at least one vocal tic lasting for more than a year) (American Psychiatric Association 2000)

All three tic disorders require the onset of tics before the age of 18 years. In addition to the duration criterion, the diagnosis of a chronic tic disorder also requires that there should not have been any significant tic-free period following the onset of tics. Although not specified for the diagnosis, parents often report a fluctuating course for the tics (tendency to rise and fall in frequency and intensity over time). By age 10 years, most patients will report a capacity to suppress tics at least for brief periods and the presence of a warning or ► premonitory urge before the occurrence of some or all of their tics.

There are no diagnostic tests for tic disorders. Except for the tics, the physical and neurologic examinations are usually normal. Neuroimaging procedures (e.g., magnetic resonance imaging) or electroencephalography is rarely indicated. Thus, the assessment of a child referred for a tic disorder includes tracing the onset and course of symptoms, documenting the current severity of motor and phonic tics, inquiring about the presence of premonitory sensations and capacity for tic suppression, establishing the overall impairment caused by the tics, and surveying the treatment approaches implemented to date. Due to their common co-occurrence, ADHD and OCD warrant particular attention in the assessment. The presence of other psychiatric disorders, such as anxiety and depression, also deserves consideration. Because stereotypic movements in children with ► pervasive developmental disorders can resemble tics, overall development as well as social and language competence should also be part of the assessment (Scahill et al. 2006).

Medications Used in the Treatment of Children with Tic Disorders

Drugs Used to Treat Tics. The most widely prescribed drugs for the treatment of tics include ► antipsychotic medications and the alpha 2-adrenergic agonists (see Table 1). Other medications such as tiapride (available in Europe), ► pergolide, botulinum toxin injections, ► topiramate, and ► tetrabenazine have also been used for the treatment of tics. Empirical support for these medications varies. For example, botulinum toxin, topiramate and tiapride have each been shown superior to placebo, tetrabenazine has not. Pergolide, which is a dopamine ► partial agonist, appears to be effective in reducing tics, but has fallen out of use due to concern about adverse effects. The other dopamine partial agonists have not been rigorously evaluated.

Efficacy. To date, most pharmacological trials for the treatment of tics have been relatively small (ranging from 30 to 60 subjects). The magnitude of effect ranges from 30–50% reduction in tics, suggesting that even effective medications are not associated with a large reduction in tics.

Tolerability. The antipsychotics are predictably the most effective medications, but are also associated with a large range of ► adverse effects. The newer ► atypical antipsychotics offered the promise of decreased risk of motor adverse effects. However, the issue of weight gain and the liabilities associated with obesity have emerged as important concerns.

Clinical Use. Given the fluctuating course of tics, medication for tics should be considered only when there clear evidence that the tics are causing persistent interference in everyday life. Frequent and forceful tics may cause direct interference with motor activities or speech. In other cases, the child may be distracted by the bombardment of premonitory sensations and efforts to suppress tics. Still other children may suffer social consequences from noticeable tics. Families need education about the fluctuating course of tics. For example, even

Tic Disorders with Childhood Onset. Table 1. Drugs used for the treatment of tics.

Drug	Usual starting dose (mg/day)	Usual dose range (mg/day)	Adverse effects
Typical antipsychotics			
► Haloperidol[a]	0.25–0.5	1.5–3.0	Sedation, dyskinesia, dystonia, cognitive dulling weight gain, social phobia
► Pimozide[a]	0.5–1.0	2.0–6.0	
► Fluphenazine	1.0–1.5	3.0–6.0	
Atypical antipsychotics			
► Risperidone[a]	0.25–0.50	1.5–2.5	Weight gain, sedation, cognitive dulling, social phobia, drooling, dyskinesia, dystonia
► Ziprasidone[a]	20	40–60	
► Aripiprazole	1.0–2.5	5–10	
► Olanzapine	25–50	200–400	
Alpha 2 agonists			
Clonidine[a]	0.025–0.05	0.15–0.3	Sedation, mid-sleep awakening, irritability
Guanfacine	0.5–1.0	1.5–3.0	
Other topiramate[a]	12.5–25	50–125	Sedation, short term memory problems, headache

[a]Shown to be effective in at least one placebo-controlled trial for tics

after achieving satisfactory results with a tic-suppressing medication, tic exacerbations will occur. The impulse to increase the medication dose with the inevitable exacerbations of tics should be tempered by the increased risk of adverse effects. Finally, there is the matter of how long to maintain children on a tic-suppressing medication. To date, no clinical trials that have adequately addressed this important clinical question. Follow-up studies have shown that many children will have fewer tics at age 18 years compared to 12 years of age. This replicated finding suggests that it is reasonable to consider a decrease or even discontinuation of a tic-suppressing medication in the mid to late teenage years. Understandably, adolescents and their parents may be reluctant to undertake such a course of action. Based primarily on clinical consensus, medication withdrawal should be done gradually. In the case of the antipsychotics (even atypicals), abrupt cessation may result in withdrawal ► dyskinesias and rebound increase in tics. Gradual withdrawal spread over months may also be more acceptable to adolescents and parents.

Drugs used to treat ADHD in Children with Tic Disorders. Based on several case reports of tic worsening upon exposure to stimulant medication, the stimulants have been contraindicated for children with ADHD and a tic disorder. However, accumulated evidence over the past 15 years disputes this as an ironclad contraindication. As in children with ADHD, who do not have tics, the stimulants may fail. Thus, if stimulant medication is not successful either due to tic worsening, other adverse effects, or lack of efficacy, non-stimulant alternatives warrant consideration. Table 2 presents a summary of information on medications that are commonly used and have been studied in children with a tic disorder and ADHD.

Drugs used to treat OCD in Children with Tic Disorders. Children with tic disorders ascertained from clinical settings also have an increased likelihood of OCD compared to general population samples. It has been noted that the obsessive–compulsive symptoms in children with tic disorders differ from those with OCD in the absence of tics. Indeed, a recurring challenge in the assessment of children with tic disorders can be differentiating between tics and compulsive behaviors. For example, some children with OCD express the anxious worry (obsession) that "something bad will happen" if a specific ritual (compulsion) to prevent harm is not completed. By contrast, children with the tic-related form of OCD are more likely to report a feeling or urge to carry out the repetitive behavior and a need to achieve a sense of completion rather than a need to prevent harm. The repetitive behavior in children with Tourette syndrome may be stereotypic in form, such as arranging objects to achieve symmetry or repeatedly picking up and setting down an object on a table.

The first-line treatments for OCD in children are the ► serotonin reuptake inhibitors (SSRIs). Based on available evidence, there is no compelling evidence to support the selection of any one SSRI over another. Clomipramine, fluoxetine, sertraline, and fluvoxamine have demonstrated efficacy in children with OCD in placebo-controlled trials. Citalopram, escitalopram, and paroxetine are also used in clinical settings. In general, the approach to treating a child with a tic disorder and OCD is similar to treating children with OCD who do not have a tic disorder. However, several points warrant consideration when selecting a medication for the treatment of children with OCD. First, 30–40% of children with OCD who are treated with an anti-obsessional medication do not achieve a positive response. In addition, the magnitude of benefit is not large, even for those showing a positive response. Therefore, the benefits of an SRI should not be over stated to children and parents. Second, although compulsive behaviors are common in children with tic disorders, these behaviors may be mild and

Tic Disorders with Childhood Onset. Table 2. Drugs used to treat ADHD in children with tics.

Drug[a]	Usual starting dose (mg/day)	Usual dose range (mg/day)	Adverse effects
► Methylphenidate	12.5–15[b]	25–35[b]	Loss of appetite, insomnia, irritability, mild growth retardation, increase in tics
Clonidine	0.025–0.05	0.15–0.3	Sedation, mid-sleep awakening, irritability
Guanfacine	0.5–1.0	1.5–3.0	Sedation, mid-sleep awakening
► Atomoxetine	18–36	36–80	Vomiting, loss of appetite, insomnia

[a]Each of these medications has been shown to be effective in at least one placebo-controlled trial in children with tic disorders and ADHD
[b]Assuming an immediate release product and TID schedule, third dose about half of the morning dose

medication may not be indicated. Third, and a closely related point, there is evidence in adults with OCD that subjects with co-occurring tics are less likely to show a positive response to monotherapy with an anti-obsessional medication. Fourth, although the magnitude of effect appears similar for clomipramine and the more selective SRIs, clomipramine requires periodic electrocardiograms and blood levels, and it is more vulnerable to drug–drug interactions. Thus, clomipramine is generally regarded as a second-line drug for OCD. Fifth, the combination of anti-obsessional medication plus exposure and response prevention therapy appears more effective than medication alone.

Conclusion

Tic disorders of childhood may be chronic, but they are not usually progressive. The severity of tics range from mild to severe and tics show a fluctuating course. A substantial percentage of children with tics will show a decline by the end of the second decade of life. In addition to tics, children with tic disorders are at higher risk for ADHD and OCD. The aim of assessment and treatment is to identify and remediate the most important source of impairment in order to promote the child's overall development. Pharmacotherapy has an important role to play in the management of children with tic disorders. In addition to medication, children and families are likely to need education about tics and related problems. Behavioral interventions may be used to augment medication or as an alternative to medication in some cases (Woods et al. 2007). Advocacy and education of school teachers and administrators is often critical in securing appropriate school placement and minimizing the social fallout due to tics.

Cross-References

- ► Antipsychotic Medication
- ► Attention Deficit Hyperactivity Disorder
- ► Habit Reversal Training
- ► Obsessive–Compulsive Disorder
- ► Suppressibility
- ► Tics, Motor
- ► Tics, Vocal

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Tics

Definition

Tics are usually stereotyped rapid, jerky movements or brief vocalizations.

Cross-References

► Tic Disorders with Childhood Onset

Tics, Motor

Definition

These may be simple or complex. For example, simple tics may involve single or related muscle groups such as blinking, facial grimacing, or shrugging. Complex tics may include tics occurring in a sequence, such as an arm thrust with near simultaneous head-jerking, or movement such as bending or twirling.

Tics, Vocal

Definition

Vocal tics may be simple or complex. Simple vocal tics may include throat-clearing, grunting, coughing, or snorting. Complex vocal tics may include loud shrieks or blurting out words or parts of words. Verbal tics may involve cursing or other socially inappropriate references, but these tics are not common among patients with Tourette syndrome.

Tight Seal Recording

► Patch-Clamp Recording

Time Discounting

► Temporal Discounting

Time Series

Synonyms
Time series plot

Definition
A time series is a series of data points or observations measured at successive time intervals. With respect to functional magnetic resonance imaging (fMRI) techniques, it refers to a large number of images (e.g., echo-planar images) acquired in sequence and at regular time intervals over the duration of an experiment.

Cross-References
► Magnetic Resonance Imaging (Functional)

Time Series Plot

► Time Series

Time-Specific Knockout

► Inducible Knockout

Timing

► Timing Behavior

Timing Accuracy

Definition
Timing accuracy refers to the estimated duration. Timing accuracy is estimated by the mean or peak time of the response distribution (see Gibbon et al., 1997).

Timing Behavior

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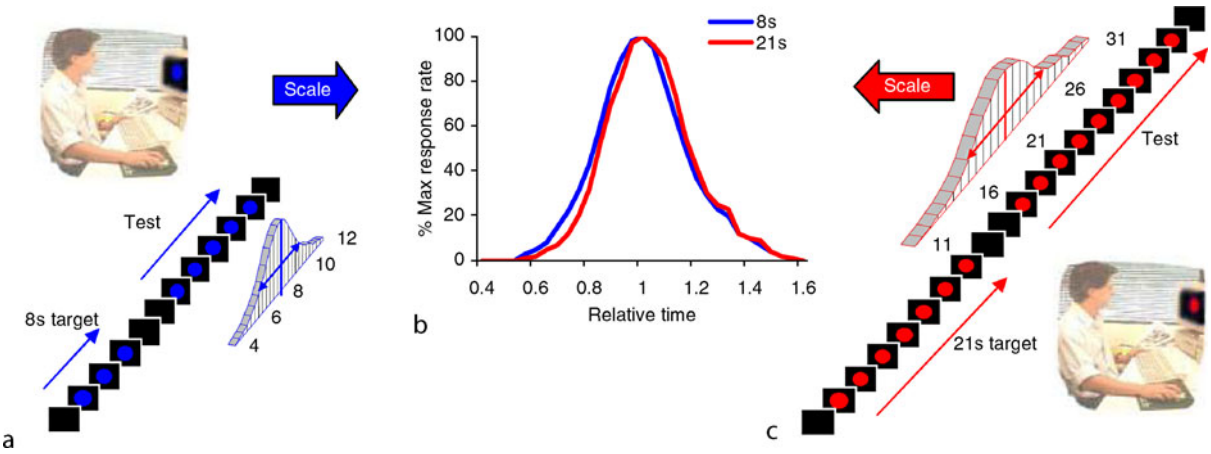
Synonyms
Interval timing; Temporal conditioning; Temporal processing; Timing

Definition
Timing behavior refers to the capacity of subjects to perceive, estimate, and discriminate time intervals (e.g., durations of and between events), to emit (or avoid emitting) behavioral responses at appropriate time intervals, and more generally, to modulate their behavior in time (Buhusi and Meck 2005; Gibbon et al. 1997). Timing behavior includes millisecond timing, ► interval timing, and circadian timing. Millisecond timing refers to the perception, estimation, and discrimination of durations in the subsecond range, crucial for motor control, speech generation and recognition, and music production and perception. Disorders of millisecond timing may result in disorders of motor control (see ► motor activity and stereotypy). Circadian timing (see ► circadian rhythms) refers to repetition of certain phenomena at about the same time each day as a function of the light/dark cycle. The most studied circadian rhythm is sleep, but other examples include body temperature, blood pressure, production of hormones, and digestive secretions. Here, we discuss the effect of psychoactive drugs on timing behavior in the seconds-to-minutes range (interval timing) which is considered crucial to learning and cognition (Gallistel and Gibbon 2000; Williamson et al. 2008).

Impact of Psychoactive Drugs

Protocols Used to Investigate the Neuropharmacology of Interval Timing
The most reliable approach to investigate the neuropharmacology of interval timing in humans and animals is to use a ► reproduction protocol, such as the ► peak-interval (PI) procedure (Matell et al. 2006) although a variety of different timing procedures can be used (see Paule et al. 1999). Idealized data from a PI procedure in two groups of subjects trained to time different durations are shown in Fig. 1. The subject's responses distribute normally around the criterion duration, and the width of this distribution is proportional to the criterion. The way in which the mean and standard deviation of the response distribution covary is typically referred to as the ► scalar property (Gibbon et al. 1997), a strong form of Weber's Law, which is obeyed by most sensory dimensions. The scalar property applies not only to behavioral responses, but also to neural activity as measured by electrophysiological recordings as well as the hemodynamic response



Timing Behavior. Fig. 1. The scalar property is a hallmark of interval timing at both the behavioral and neural levels. In a typical duration reproduction procedure called the PI procedure, subjects receive training trials, during which they are presented with target stimuli of specific durations (here, panel A: 8 s, panel C: 21 s), and test trials, in which the subjects are asked to reproduce the criterion duration. Typically, in peak trials the responses distribute normally around the criterion duration with a width that is proportional to the criterion. When the response distributions are scaled both in amplitude and duration they superimpose, thus demonstrating the scalar property at the behavioral level. (Redrawn from Buhusi and Meck 2005.)

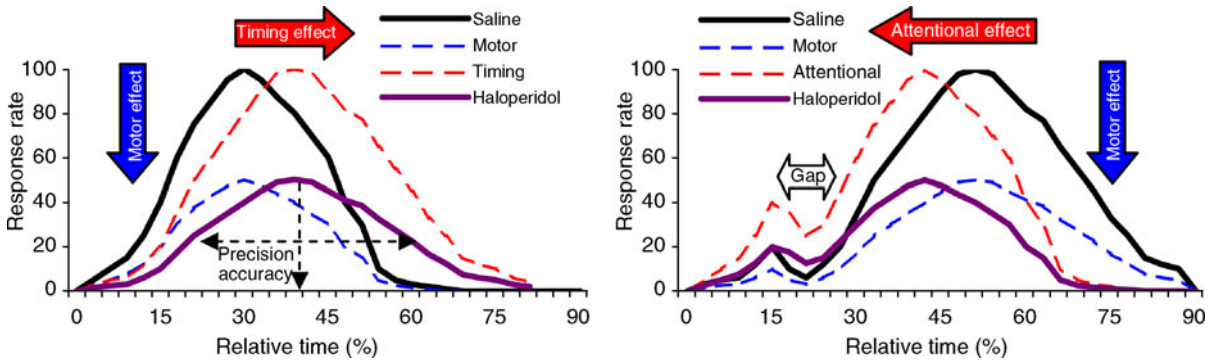
associated with a subject's active reproduction of a timed interval, but not for passive responses triggered at the untimed interval (Buhusi and Meck 2005).

Estimating the Effect of Psychoactive Drugs

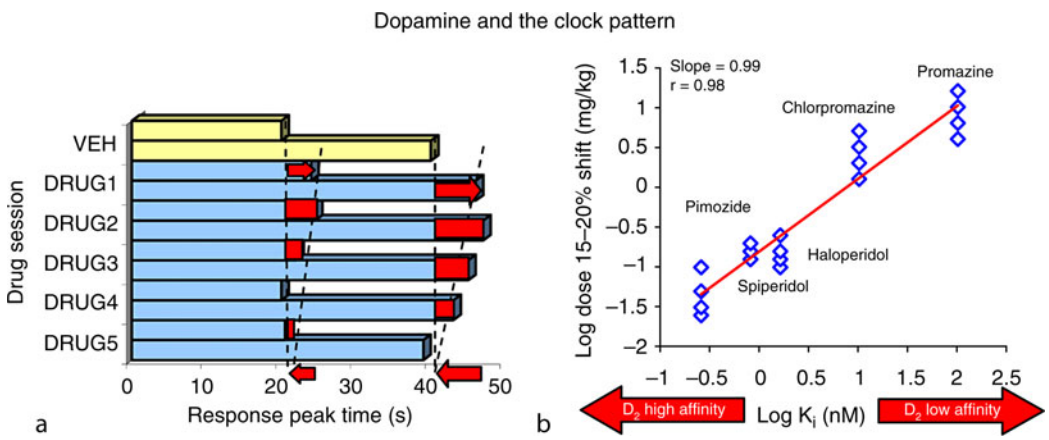
The PI procedure with gaps allows the independent assessment of the effect of psychoactive drugs on timing (► timing accuracy and ► timing precision), as well as their ► attentional effect, and allows the dissociation of these effects from motor/motivational effects as illustrated in Fig. 2. Generally speaking motor/motivational effects of drugs are observed as shifts in the amplitude of the response functions along the vertical axis, while effects on timing are observed as leftward or rightward shifts in the response function along the horizontal axis. Timing accuracy is estimated by the peak of the response function in ► peak trials (Fig. 2 – *left panel*). Timing precision is estimated by the width of the response function in peak trials (Fig. 2 – *left panel*). ► Attentional effects are estimated by inserting gaps (e.g., retention intervals) in a subset of peak trials (Fig. 2 – *right panel*). For illustrative purposes, Fig. 2 shows the effect of systemic administration of the dopamine D_2 antagonist ► haloperidol in the PI procedure with gaps. Haloperidol has both motor/motivational and timing effects: It not only reduces the amplitude of the response function (Fig. 2 – *left and right panels*), but also produces an immediate proportional rightward shift in the peak function (e.g., slows down the speed of the clock as shown in Fig. 2 – *left panel*). When retention intervals are inserted in the to-be-timed duration, haloperidol also increases the attention to time (attentional effect): It diminishes the resetting effect of the retention intervals as shown in Fig. 2 (*right panel*) (Buhusi 2003).

Dopaminergic Drugs: The Clock-Speed Effect

Dopaminergic drugs selectively affect the subjective speed of an internal clock in a variety of animals (Buhusi and Meck 2005; Meck 1996) (Fig. 3). More specifically, when timing is evaluated in the PI procedure, dopamine agonists produce an immediate leftward shift of response function in proportion to the to-be-timed criterion, indicative of an increase of the speed of an internal clock. In contrast, dopamine antagonists produce an immediate rightward shift of response function in proportion to the to-be-timed criterion, indicative of a decrease in the speed of an internal clock (Fig. 3a) (Meck 1996). Repeated administration of dopaminergic drugs is followed by a characteristic decrease in the effect of the drug (Fig. 3a), which is not interpreted as desensitization but rather as recalibration of the timer. The interruption of the drug regimen results in a rebound in the opposite direction (Meck 1996). Dopamine antagonists were shown to produce a deceleration of the subjective clock speed in proportion to their affinity to dopamine D_2 receptor (Fig. 3b) (Meck 1996). The effects of dopamine drugs on clock speed are diminished as a function of experience with the timing task (habit formation) prior to drug administration which



Timing Behavior. Fig. 2. The PI procedure with gaps allows the independent assessment of the effect of a drug on timing accuracy, timing precision, and attention to timing. Here are data from groups of subjects trained to time a 30-s PI procedure, tested under systemic administration of saline and the dopamine D_2 antagonist haloperidol (0.04–0.06 mg/kg i.p). Timing accuracy is estimated by the peak response rate, timing precision by the width of the response function, and attentional effect by the delay of the response function in trials with gaps (*right*) relative to trials without gaps (*left*). *Left panel (peak trials)*: Motor/motivational effects are observed as changes on the vertical axis, while timing effects are observed as proportional changes on the horizontal axis. Here, haloperidol has both motor/motivational effect as well as effect on timing: It slows down timing (rightward shift relative to saline control). *Right panel (gap trials)*: Attentional effects are evaluated by introducing a gap (retention interval) on a subset of peak trials, which delays the response function. Motor/motivational effects are observed as changes on the vertical axis, while attentional effects are observed as absolute changes on the horizontal axis. Here, haloperidol has both a motor/motivational effect and an attentional effect: It reduces the delay following a retention interval, suggesting that subjects are paying more attention to the task. (Adapted from Buhusi 2003.)



Timing Behavior. Fig. 3. The effects of the dopamine D_2 antagonist haloperidol on interval timing are consistent with the slowing down of time accumulation. *Panel A*: Two groups of subjects were trained to time two durations, using 20-s and 40-s PI procedures. Afterward, in test sessions, subjects received systemic administration of vehicle (VEH), then five consecutive sessions with systemic administration of haloperidol. Acute administration of haloperidol results in a sudden rightward shift that is proportional to the estimated durations, whereas its repeated administration results in a gradual return of the estimated time to the criterion duration. *Panel B*: The rightward shift of the estimated time is proportional to the affinity of the drug for the D_2 dopamine receptor. (Adapted from Buhusi and Meck 2005.)

may reflect a change in the balance between dopamine–glutamate interactions (Williamson et al. 2008).

Cholinergic Drugs: The Memory-Storage Effect

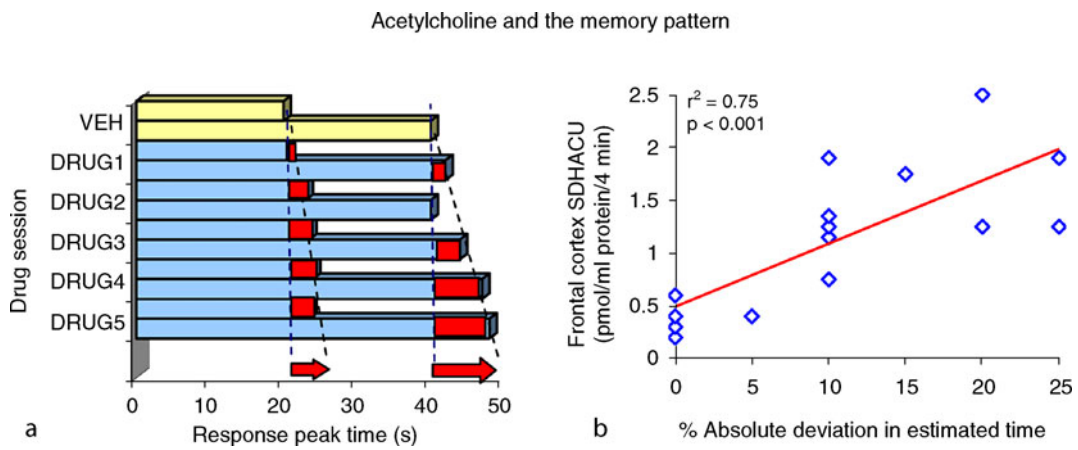
When initially administered, cholinergic drugs have no immediate effects on interval timing. However, repeated administration of cholinergic agonists results in a gradual decrease of the estimated duration, while cholinergic antagonists result in a gradual increase of the estimated duration (Fig. 4a). Discontinuing the drug administration results in a gradual return to the baseline. These results are interpreted as alteration of memory storage of duration. More specifically, reference memory error was found to vary in proportion to cholinergic activity in frontal cortex (Buhusi and Meck 2005; Meck 1996) (Fig. 4b).

Serotonergic Drugs: The Attentional Effect

Time accumulation and attention to the timing task can be dissociated pharmacologically, and they depend on the dopamine and serotonin systems in the cortex and ▶ striatum (Buhusi and Meck 2009; Ho et al. 2002). Administration of the indirect dopamine agonist ▶ methamphetamine shortens estimated durations, and decreases attention to timing (Buhusi 2003). In turn, the dopamine D_2 receptor blocker haloperidol lengthens estimated durations, but facilitates the maintenance in temporal information in working memory (Buhusi 2003). However, the effect of methamphetamine to shorten estimated durations is blocked by depletion of serotonin, suggesting that an intact serotonergic system is required for interval timing. Indeed, specific stimulation of either 5-HT_{1A} or 5-HT_{2A} receptors shortens estimated durations in qualitatively similar ways, an effect antagonized by specific blockade of these receptors. Interestingly, ▶ clozapine – a drug acting on both dopamine and serotonin systems – not only shortens the estimated durations but also facilitates the attention to time (attentional effect) during retention intervals (Buhusi and Meck 2009). Clozapine is reported to have differential effects on dopamine levels in the frontal cortex and striatum: It serves as a dopamine receptor antagonist in the mesolimbic dopaminergic system and as an indirect dopamine agonist in the frontal cortex by its activation of the serotonin 5-HT_{2A} receptors on dopamine neurons. This pattern of pharmacological results is consistent with the hypothesis that the effect of clozapine on time estimation is due to an increase in dopamine neurotransmission in frontal cortex, but not in the dorsal striatum. Together, these data suggest that drug effects on time accumulation and attention to time rely on the interaction between the dopaminergic and serotonergic activation in frontal cortex and striatum (Buhusi and Meck 2009; Ho et al. 2002).

Drugs of Addiction

Acute exposure to ▶ psychostimulants, e.g., ▶ cocaine, ▶ methamphetamine, ▶ nicotine, etc., produces results compatible with the speeding up of an internal clock (Matell et al. 2006; Meck 1996; Paule et al. 1999). These



Timing Behavior. Fig. 4. The effects of cholinergic drugs are consistent with effects on reference memory. *Panel A*: Two groups of subjects were trained to time two durations, using 20-s and 40-s PI procedures. Afterward, in test sessions, subjects received systemic administration of VEH, then five consecutive sessions with systemic administration of the muscarinic cholinergic receptor atropine. Acute administration of atropine results in a gradual scalar (proportional to the timed criterion) rightward shift of the estimated time. *Panel B*: The effect is correlated with the activity of cholinergic neurons in the frontal cortex as measured by sodium-dependent high-affinity choline uptake (SDHACU). (Redrawn from Buhusi and Meck 2005.)

effects are believed to be linked to the addictive and rewarding properties of psychostimulants (see ► self-administration of drugs, ► addictive disorder, animal model), and are susceptible to the effects of overtraining and habit formation. In addition, repetitive, high-dose exposure to psychostimulants such as methamphetamine produces deficits in time perception, possibly due to neurotoxic effects on the dopaminergic system. Of particular interest is the observation that stimulant-dependent individuals exhibit impaired timing and time perception. Taken together, these findings may help to explain why human subjects that abuse methamphetamine or cocaine show more ► impulsivity and less self-control in decision making due to greater discounting of delayed rewards (Williamson et al. 2008).

A Model of Drug Action on Interval Timing

The striatal beat frequency (SBF) model of interval timing ascribes a mechanism for detecting event durations to medium spiny neurons within the dorsal striatum (Buhusi and Meck 2005). These striatal neurons have a set of functional properties that place them in an ideal position to detect behaviorally relevant patterns of afferent cortical input. Briefly, the SBF model posits that medium spiny neurons in the dorsal striatum become entrained to fire in response to oscillating, coincident cortical inputs that become active at a previously trained event duration. In the context of this model, the clock effect of dopaminergic drugs is interpreted as reflecting tonic dopamine levels within the striatum, modulating the oscillatory frequency within the cortex through corticostriato-thalamo-cortical feedback mechanisms. Similarly, the memory effect of cholinergic drugs is interpreted as affecting the synaptic weights of striatal median spiny neurons and tonically active interneurons (Buhusi and Meck 2009; Matell et al. 2006; Williamson et al. 2008).

Cross-References

► Addictive Disorder: Animal Models
► Attention
► Behavioral Economics
► Circadian Rhythms
► Motor Activity and Stereotypy
► Self-Administration of Drugs

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Timing Precision

Definition

Timing precision refers to the trial-by-trial errors in the estimated duration. Timing precision is estimated by the width of the response distribution (see Gibbon et al., 1997).

Timiperone

Definition

Timiperone is a first-generation (typical) antipsychotic drug that belongs to the butyrophenone type approved in Japan for the treatment of schizophrenia. It has general properties similar to those of haloperidol, but it has higher affinity (as an antagonist) for D_2 and 5-HT_{2A} receptors. It also has modest binding affinity for sigma receptors. It can induce ► extrapyramidal motor side effects, drowsiness, and constipation, but it displays low toxicity.

Cross-References

► Butyrophenones
► Extrapyramidal Motor Side Effects
► First-Generation Antipsychotics
► Haloperidol
► Schizophrenia

TMS

► Transcranial Magnetic Stimulation

Tobacco Dependence

► Nicotine Dependence and Its Treatment

Tolcapone

Definition

Tolcapone is a reversible catechol-*O*-methyl-transferase (COMT) inhibitor. Used as an adjunct to l-DOPA or carbidopa therapy for patients with ► Parkinson's disease, tolcapone extends the ► half-life of l-DOPA by inhibiting its breakdown into 3-O-methyldopa and that of dopamine to 3-methoxytyramine. Tolcapone crosses the ► blood–brain barrier and is able to inhibit the breakdown of l-DOPA by COMT both peripherally and centrally. Clinically, it is often used in patients experiencing fluctuations in symptoms and "wearing-off" of l-DOPA effects. Serious adverse effects include liver toxicity with risk of acute fulminant hepatic failure.

Cross-References

► COMT Inhibitor

Tolerance

Synonyms

Acquired tolerance; Resistance

Definition

Tolerance is the diminution of a drug effect after its repeated administration. Tolerance is often identified as a shift to the right in a function that describes the ability of a range of doses of a drug to produce a particular response (dose–response curve). Such tolerance is surmountable in the sense that the original drug effect can be restored increasing the dose at which the substance is administered. Insurmountable tolerance is characterized by a downward shift in the dose–response curve and it is not sensitive to dose adjustment.

Cross-References

► Behavioral Tolerance
► Caffeine
► Pharmacodynamic Tolerance

Toluene

Synonyms

Methyl benzene, toluol

Definition

Toluene is a highly volatile liquid at room temperatures with a distinctive sweet odor. It is one of the most widely abused inhalants. Pure toluene is readily available as a household and industrial product, used primary as a paint thinner and remover. Toluene is also a constituent of many other products such as adhesives, inks, paints, sealants, and disinfectants. It is also a component of gasoline. Toluene is typically abused by sniffing directly from the container or by placing the liquid on a rag or paper bag and breathing the vapors. A particularly dangerous practice is placing a toluene-laden plastic bag over one's head. Overdose death from toluene exposure is possible when users become unconscious while still exposed to the vapor. Toluene metabolites such as hippuric acid can be detected in the blood of users; tests for this can be used to diagnose toluene abuse. Neurological problems are often seen in toluene abusers.

Toluene has been the most widely studied abused inhalant in animal and neuropharmacology studies. When given to animals, it produces abuse-related behavioral effects similar to those produced by ► alcohol and other depressant drugs. Toluene produces very specific cellular effects, primarily on ligand-gated ion channels.

Cross-References

► Inhalant Abuse

Tomography

Definition

Tomography is an imaging method that consists of acquiring information about an object, such as the brain, in two-dimensional slices. These slices can then be integrated to form a three-dimensional image of the object.

Cross-References

► Positron Emission Tomography (PET) Imaging

Tomoxetine

► Atomoxetine

Tonic Signals

Definition

Signals induced by constantly present triggers like neurotransmitters at background level or neuropeptides or hormones present in the cerebrospinal fluid.

Topiramate

Definition

Topiramate is an ► anticonvulsant drug that is used in the treatment of epilepsy in adults and children. Topiramate has several pharmacodynamic actions that contribute to its anticonvulsant properties including inhibitory effects upon voltage-gated NA^+ and Ca^{2+} channels, inhibitory effects at ► AMPA and kainate glutamate receptors, in particular the GluR5 ► glutamate receptor, and positive or negative modulatory actions at certain subtypes of ► $GABA_A$ receptor. Other actions of topiramate that may contribute to its anticonvulsant activity include positive modulation of some voltage-gated K^+ channels, inhibition of carbonic anhydrase, modulation of presynaptic neurotransmitter release, and effects upon intracellular concentrations of GABA in GABAergic neurons. Topiramate is also approved for the prophylaxis of migraine. Its efficacy as an anti-migraine medication is mainly due to inhibitory effects upon AMPA and kainate glutamate receptors and to a lesser extent, inhibitory effects upon voltage-gated Ca^{2+} channels. Topiramate has a wide therapeutic window, that is, the difference between the minimum effective anticonvulsant dose and that causing motor impairment; however, there are several recognized adverse effects of topiramate including paresthesia (unpleasant tingling in the limbs especially the fingers and toes), metabolic acidosis, kidney stones, and acute cognitive impairment. Like other anticonvulsant medications, topiramate has teratogenic effects and should not be administered during pregnancy. Other potential indications for topiramate include weight loss (involving complex pharmacodynamic actions at ► neuropeptide-Y, ► corticotrophin-releasing hormone, and ► glucocorticoid receptors), diabetes (topiramate promotes glucose transporter activation), and binge-eating, drug addiction, and anxiety-related disorders (most likely via effects at AMPA, kainate, and $GABA_A$ receptors).

Cross-References

► Anticonvulsants
► Corticotrophin-Releasing Factor
► Eating and Appetite

Tourette Syndrome

► Tic Disorders with Childhood Onset

Tourette's Syndrome

Definition

Tourette's syndrome is a neuropsychiatric syndrome that typically presents in young children and is characterized by both motor and vocal tics (abrupt, rapid, repetitive, nonrhythmic, stereotyped, temporally suppressible movement/vocalization). Premonitory urges accompany these tics that can range from simple movements/vocalizations, such as blinking, sniffling, or barking, to the more complex squatting, twirling, or coprolalia (obscene utterances). Tic severity and type fluctuate over time, usually becoming less severe or nonexistent into adulthood.

Modified from the Diagnostic and Statistical Manual of the American Psychiatric Association, Fourth edition (► DSM-IV) and the NIH-NLM MedlinePlus Encyclopedia (online).

Cross-References

► Tic Disorders with Childhood Onset

Toxicants

► Neurotoxins

Trace Amines

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Synonyms

Arylalkylamines; Microamines

Definition

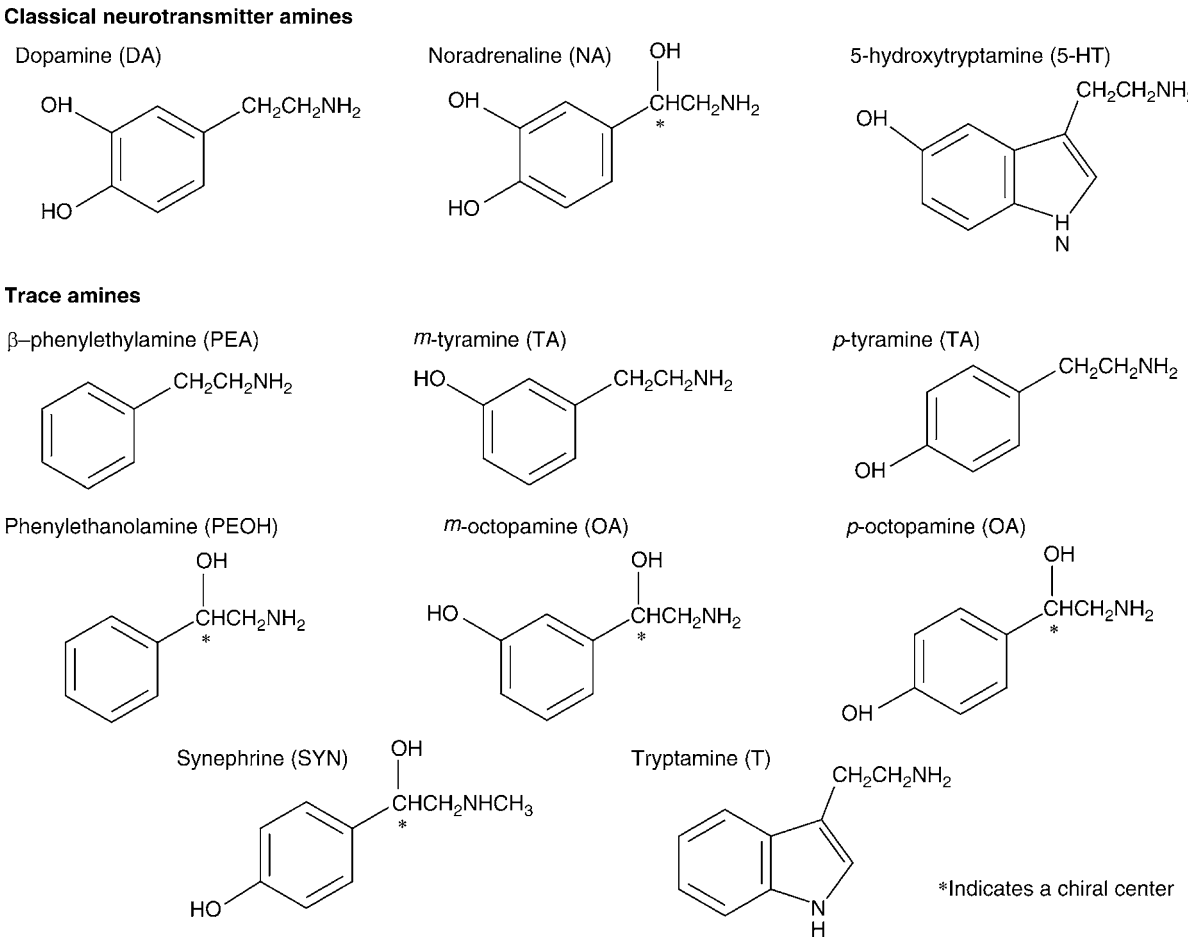
Trace amines, which include β-phenylethylamine (PEA), tryptamine (T), phenylethanolamine (PEOH), the tyramines (TAs), octopamines (OAs), and synephrine (SYN) [some authors include *N*,*N*-dimethyltryptamine (DMT) in this list], are amines related structurally to, but present in the brain at much lower concentrations than, the classical neurotransmitter amines – dopamine (DA), noradrenaline (NA), and 5-hydroxytryptamine (5-HT, serotonin).

Pharmacological Properties

History

The trace amines are so named because of their low absolute concentrations in the brain compared to the classical neurotransmitter amines DA, NA, and 5-HT; they are very similar structurally to these neurotransmitter amines (Fig. 1), but have much higher turnover rates, and PEA and T pass the ▶ blood–brain barrier readily.

In the 1960s through the 1990s, there was a great deal of interest in the trace amines in the central nervous system (CNS) as behavioral and pharmacological studies in animals and neurochemical measurements in body fluids from human subjects suggested their involvement in the etiology and pharmacotherapy of a number of psychiatric and neurological disorders, including depression, ▶ schizophrenia, ▶ phenylketonuria (PKU), ▶ Reye's syndrome, Parkinson's disease, ▶ attention deficit hyperactivity disorder (ADHD), ▶ Tourette's syndrome, epilepsy, and migraine headaches (Baker et al. 1993; Berry 2007). In the 1970s, there was a flurry of activity in trace amine research because of the development of a number of elegant, sensitive analytical techniques which facilitated their measurement in the brain. During the 1980s, there were binding studies done on possible receptors for the trace amines



Trace Amines. Fig. 1. Structures of some classical neurotransmitter amines and trace amines.

and there was also electrophysiological and behavioral research performed which suggested that these amines might act as neuromodulators for DA, NA, or 5-HT. There was a resurgence of interest in the trace amines in 2001, following reports of the discovery of a novel family of ► G protein-coupled receptors, some of which appear to be selectively activated by trace amines.

Synthesis, Catabolism, and Localization

The trace amines PEA, T, and TA are synthesized in neuron terminals by decarboxylation of precursor amino acids (phenylalanine, ► tryptophan, and tyrosine, respectively), catalyzed by the enzyme aromatic L-amino-acid decarboxylase (AADC), the same enzyme involved in the decarboxylation of L-DOPA and 5-hydroxytrytophan (5-HTP) in the synthesis of the ► catecholamines (DA, NA) and 5-HT, respectively. However, tyrosine hydroxylase and tryptophan hydroxylase are the rate-limiting enzymes in the synthesis of the catecholamines and 5-HT, while AADC is the major enzyme involved in the synthesis of PEA, T, and TA. Thus, alterations of AADC activity would be expected to have little effect on brain levels of DA, NA, and 5-HT while possibly markedly affecting the levels of trace amines (Berry 2007).

Tyramine is further metabolized to OA and PEA to PEOH by dopamine β-hydroxylase (DBH). Tyramine and OA have been proposed to function as neurotransmitters rather than neuromodulators in invertebrates. Octopamine can be further metabolized to synephrine by phenylethanolamine *N*-methyltransferase (PMNT) or related methyltransferases. The trace amines are all substrates for monoamine oxidase (MAO), with PEA being a preferred substrate for the MAO-B isoform. Abnormal levels of the resultant acid metabolites of the trace amines have also been reported in several psychiatric and neurological disorders by a number of researchers (Berry 2007; Boulton et al. 1984, 1985).

The trace amines are distributed heterogeneously throughout the brain, with the highest concentrations generally reported in the ► striatum or ► hypothalamus. Burchett and Hicks (2006) have provided a comprehensive review of their regional brain distribution and localization relative to catecholaminergic and serotoninergic neuronal systems in the brain. Although PEA, T, and TA have been shown to be present in synaptosomes, studies with ► reserpine and ► neurotoxins suggest that *m*- and *p*-TA may be stored in vesicles while PEA and T are not (see chapter by Juorio in Boulton et al. 1984). PEA and T appear to cross cell membranes passively, but there is some evidence for activity-dependent veratridine (a neurotoxin causing persistent activation of sodium ion channels) – induced release of *m*- and *p*-TA from striatal slices.

What Is the Function of the Trace Amines in the CNS?

It has long been known that trace amines such as PEA have amphetamine-like effects on the CNS when administered to rats or mice. However, given that the levels required to reach such effects were far beyond normal concentrations in brain, another role was believed to exist under physiological conditions. Researchers found mounting evidence that trace amines may play a neuromodulatory role in the CNS. The trace amines are known to inhibit reuptake of and stimulate release of NA, DA, and/or 5-HT; and in electrophysiological studies, several trace amines have been shown to potentiate the actions of the classical monoamine neurotransmitter amines DA, NA, and/or 5-HT by altering the receptor sensitivity to these neurotransmitter amines, suggesting that the trace amines serve to maintain the activity of the classical monoamine neurotransmitters within defined physiological limits (Berry 2007). PEA has also been reported to stimulate acetylcholine release by activating glutamatergic signaling pathways, and PEA and *p*-TA have been demonstrated to depress $GABA_B$ receptor-mediated responses in dopaminergic neurons. In the 1980s, specific and saturable binding sites for radiolabeled PEA, T and *p*-TA were reported, suggesting that these amines might have a role independent of the classical neurotransmitter amines. Burchett and Hicks (2006) have suggested four kinds of trace amine activity in the CNS: cotransmitters released with the catecholamines or 5-HT; transmitters with their own receptors; false transmitters at catecholamine receptors; and neuromodulators.

Receptors

There has been a resurgence of interest in trace amines in the past few years with the publication of papers in 2001 on the discovery and cloning of a unique family of G protein-coupled receptors, some of which are selectively activated by trace amines (Borowsky et al. 2001; Bunzow et al. 2001), although the mechanisms by which the trace amines activate these receptors are not yet fully defined (Lindemann and Hoener 2005). However, to date only two members of the family have been demonstrated to be responsive to trace amines, and endogenous ligands other than the trace amines which have been proposed include O-methyl metabolites of catecholamines, thyronamine metabolites of thyroid hormones, and imidazoline ligands including β-carbolines (Berry 2007; Bunzow et al. 2001; Grandy 2007).

The trace amine-associated receptor (TAAR) family consists of three subgroups (TAAR1-4, TAAR5, and

TAAR6-9) which are phylogenetically and functionally distinct from other G protein-coupled receptor families and from invertebrate OA and TA receptors (Lindemann and Hoener 2005). Genes for TAARs have been discovered in humans, chimpanzees, rats, and mice. There are marked interspecies differences in the distribution of the TAARs. For example, there are as many as 18 TAARs in the rodent genome and 9 in the human genome. This variability has led some researchers to suggest that these receptors are linked in an intricate way to species-specific functioning (Berry 2007). In humans, all TAAR genes are located in a narrow region in the locus 6q23.1, which has also been linked to schizophrenia and ▶ bipolar disorder. Recent studies on TAAR1 knockout mice suggest that the TAAR1 is a regulator of dopaminergic neurotransmission and that such mice may represent a useful model for development of drugs for treatment of some positive symptoms of schizophrenia. Studies by Sotnikova et al. (2008) in TAAR1-knockout (KO) mice, DA transporter (DAT)-KO/TAAR1-KO mice, and TAAR1-deficient/DA-deficient mice suggested that the TAAR1 is involved in tonic inhibitory actions on locomotor activity, and the authors proposed that blockade of the TAAR1 by antagonists may represent a novel way to enhance the antiparkinsonian effects of L-DOPA.

Several amphetamines [▶ amphetamine, ▶ MDMA (Ecstasy), DOI, 4-hydroxyamphetamine] are relatively potent agonists at the TAAR1 receptor, as are ergometrine, dihydroergotamine, LSD, and the anti-Parkinson agents ▶ bromocriptine and lisuride, and inhibitors of the DA transporter. Interestingly, the trace amine *p*-TA has been demonstrated to be necessary for ▶ sensitization to ▶ cocaine to occur in *Drosophila*. These findings are of interest because it is possible that the TAAR1 may be a mediator of at least some of the effects of drugs of abuse, providing a possible future target for treatment of drug abuse. It is also of interest that several biogenic amine antagonists, including phentolamine, tolazoline, cyproheptadine, dihydroergotamine, ▶ metergoline, and ▶ chlorpromazine, as well as ▶ nomifensine and MPTP, act as agonists at the TAAR1 (Grandy 2007).

Involvement in Psychiatric and Neurologic Disorders: Neurochemical Studies

Several studies looking at the levels of trace amines and/or their acid metabolites in body fluids of patients with psychiatric or neurological disorders found potential links to ▶ depression, ▶ bipolar disorder, ▶ schizophrenia, ▶ Reye's syndrome, ADHD, ▶ Tourette's syndrome, and ▶ phenylketonuria (Baker et al. 1993; Berry 2007; Boulton et al. 1984, 1985), although these studies are not without controversy. Increased PEA levels have been reported in mania while depressed states have been found to be associated with deficits in PEA and the acid metabolites of OA and TA. Links between paranoid schizophrenia and increased PEA excretion have been proposed as well. Decreased body fluid levels of PEA have been reported in Parkinson's disease. Tryptamine levels in urine have also been reported to be increased in schizophrenics and to correlate with disease severity, and plasma levels of the *p*-TA metabolite p-hydroxyphenylacetic acid have been reported to be decreased in schizophrenia. Increased brain levels of PEA have been reported in phenylketonuria. Evidence to date from several research groups suggest decreased urinary PEA in ADHD and Tourette's syndrome; there is also evidence for decreased PEA levels in brain and plasma in ADHD and for decreased urinary levels of *m*- and *p*-TA and indole-3-acetic acid (the major metabolite of T) in Tourette's syndrome. Animal studies and limited data in humans suggest that elevated PEA may be associated with elevated stress and anxiety. Elevations of TA and OA have been reported in hepatic encephalopathy and Reye's syndrome. High doses of PEA can induce seizures in mice, and this effect can be antagonized by, ▶ benzodiazepines, suggesting an interaction with the GABA system. Other studies have suggested that PEA modulates glutamatergic and GABAergic systems. It is of interest that the gene for AADC, the major enzyme involved in the synthesis of the trace amines, is located in the same region of chromosome 7p that has been suggested as a susceptibility locus for ADHD; 7p has also been linked to nicotine dependence.

The effects of drugs used to treat psychiatric illnesses provide further support for the importance of trace amines. It is known that ▶ monoamine oxidase inhibitor ▶ antidepressants such as ▶ phenelzine and ▶ tranylcypromine cause a much greater increase in brain levels of trace amines than classical neurotransmitters such as 5-HT and NA, and increases in the brain levels of PEA have been reported with ▶ tricyclic antidepressants and ECT. l-Deprenyl (▶ selegiline) and rasagiline are used in the treatment of ▶ Parkinson's disease, and because they are selective inhibitors of MAO-B, they cause a marked increase in the brain levels of PEA relative to other amines. The antipsychotics ▶ chlorpromazine, ▶ fluphenazine, and ▶ haloperidol have been shown in studies in rodents to decrease striatal *p*-TA levels acutely; similar studies with PEA have found that antipsychotics increase the rate of PEA accumulation in the striatum (see chapters in Boulton et al. 1984, 1985 for studies on these drug effects).

Summary

Behavioral, pharmacological, and neurochemical studies in animals as well as investigations in body fluids of humans have long suggested that trace amines such as PEA, T, TA, and OA may be involved in the etiology and/or pharmacotherapy of a number of psychiatric and neurologic disorders. There has always been debate about whether the trace amines have a neurotransmitter role. Although there is good evidence that OA may be a neurotransmitter in invertebrates, electrophysiological research has suggested that trace amines act as neuromodulators in the human brain, with their activity related intimately to the classical neurotransmitters amines DA, NA, and 5-HT.

There has been a marked resurgence of interest in the trace amines since reports in 2001 of a unique family of G protein-coupled receptors, some of which are selectively activated by trace amines. These receptors, now termed TAARs, are helping to explain the possible role of the trace amines in the CNS (including their interactions with classical neurotransmitters), the effects of other compounds which may be endogenous ligands at these receptors, and the actions of a number of drugs of abuse and may prove to be very useful in discovering more selective future drugs for the treatment of psychiatric and neurological disorders.

Acknowledgments

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Cross-References

- ► Antidepressants
- ► Anti-Parkinson Drugs
- ► Antipsychotic Drugs
- ► Attention Deficit Hyperactivity Disorder
- ► Bipolar Disorder
- ► Monoamine Oxidase Inhibitors
- ► Schizophrenia

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Tracer

► Radiotracer

Tracer Dose

Definition

A very small concentration at which a radiotracer is administered, such that the presence of the radiotracer itself does not noticeably influence the pharmacology or pharmacokinetics of the process being imaged. For reversibly binding ligands, the usual convention is that the peak binding of the radioligand does not exceed 5% of the available receptor pool. Because the equilibrium bound to free ligand ratio is $B/F = B_{max}/(F + K_D)$ and the free ligand associated with 5% occupancy is approximately 5% of K_D, this restriction insures that binding potential will be measured accurately to within 5%. From the data-fitting perspective, the use of tracer dose also insures that the linearization of the mass action law applied in the compartment model is justified.

Traditional Anticonvulsants

► First-Generation Anticonvulsants

Traditional Antipsychotics

► First-Generation Antipsychotics

Traditional Neuroleptics

► First-Generation Antipsychotics

Traffic Safety and Medicines

► Driving and Flying Under Influence of Drugs

Trait

Synonyms

Characteristic

Definition

Set of behavioral propensities that vary little over time for an individual. Traits may be attributable to genetic make-up of the individual or prior experiences. Classification of individuals based on the traits they exhibit is an aspect of most personality theories.

Trait Independence

Definition

Traits that are independent do not correlate, which indicates that you cannot predict an individual's level on trait A from knowledge of the individual's level on trait B. It is assumed that independent traits have unrelated genetic and neurobiological foundations; however, the phenotypic manifestations of the traits may interact to alter the magnitude of either or both traits.

Tramadol

Definition

Tramadol is a centrally acting analgesic used to treat mild to moderately severe pain. It is an opiate agonist and analog of ► codeine. Notably, tramadol acts quite selectively at the μ-opioid receptor whereas most other opiate analgesics do not share this property. However, it also acts outside the opioid system, enhancing of ► serotonin and ► norepinephrine neurotransmission. ► Serotonin syndrome may occur in patients taking combinations of tramadol and other agents that increase serotonin activity. The relative degree of contribution of each mechanism toward pain control is not fully understood. It is possible that tramadol may have future uses in the treatment of depression, anxiety, and phobias. In contrast to typical opioids, tramadol may enhance immune function. Side effects may include nausea, vomiting, sweating, constipation, and seizure. Tramadol can lead to a physical dependence such that rapid cessation leads to a severe ► withdrawal syndrome that includes tremors, nervousness, insomnia, and flu-like symptoms.

Cross-References

► Analgesics
► Opioid Dependence and Its Treatment
► Opioids
► Pain
► Physical Dependence
► Tolerance

Tranquilizer

► Minor Tranquilizer

Transcranial Magnetic Stimulation

Synonyms

TMS

Definition

A procedure in which brain neurons are activated by means of weak electrical currents induced by an electromagnetic coil applied to the scalp. Treatments are painless and do not require anesthesia. Psychiatric applications have been investigated since the 1990s. TMS is clinically available and appears to be an effective treatment for milder forms of depression. The most common side effects are headache and lightheadedness.

Transcytosis

Definition

A mode of transcellular transport in which a cell entraps extracellular material, mostly macromolecules, in an invagination of the cell membrane to form vesicles, draw them through it, and eject them on the other side. Membrane interaction with the enclosed material can result from nonspecific or adsorptive mechanisms or receptor-mediated processes. Blood–brain barrier capillaries are an active site for transcytosis by which iron via transferrin transcytosis, insulin, and growth factors are delivered to the brain.

Transgenic Animal

► Genetically Modified Animals

Transgenic Organism

Synonyms

Mutant

Definition

Traditionally, an organism with the addition of foreign DNA, whether from the same species or a different one. More recently the term transgenic has been used to refer to any genetically modified organism.

Cross-References

► Ethopharmacology
► Genetically Modified Animals
► Phenotyping of Behavioral Characteristics

Translational Medicine

► Translational Research

Translational Neuroimaging

Definition

Translational neuroimaging refers to the ability to perform imaging methods developed for animals in human subjects. Accordingly, these methods need to fulfill certain criteria such as being noninvasive (MRI) or at least minimal invasive (nuclear imaging techniques) and providing similar readouts taking size, anatomical and functional differences into account. In general, structural and functional MRI are translatable due to their inherent noninvasiveness. Administration of exogenous contrast agents or pharmacological compounds (as performed in fMRI) limit the ability to translate MR methods developed in animals to human subjects. ► Pharmacokinetics, safety, and ethical approval for human applications need to be clarified before administration.

Cross-References

► Functional MRI
► Pharmacological fMRI

Translational Research

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Synonyms

Experimental medicine; Translational medicine; Translational science

Definition

Translational research aims to bring basic preclinical knowledge (from the bench) to clinical practice (to the bedside) by characterizing fundamental mechanisms that play a role in the disease in the laboratory, finding ways to measure this in the human disease state, and developing beneficial healthcare outcomes. It is an iterative process: not only should preclinical findings result in clinical applications, but clinical insights will inform and direct preclinical research. For psychopharmacology, translational research wants to enhance the confidence in a central mechanism that could be of relevance for the treatment of psychiatric or neurological patients by enhancing the predictive value of disease-relevant, preclinical models for the clinic, by refining these models based upon clinical findings (back-translation), and by developing innovative human tests based on preclinical findings (translation). It wants to ensure that the rationale for the progression of a psychoactive compound to man (and proper dose selection) is based on a link between target engagement in the brain and pharmacodynamic (PD) response, by integrating preclinical

neuroscience, experimental medicine (in particular psychiatry and neurology), and pharmacokinetic/pharmacodynamic (PK/PD) modeling expertise. This should result in greater confidence in a molecular target and a compound.

Principles and Role in Psychopharmacology

Over recent years, it has become apparent that the traditional (or classical) approach to develop novel psychoactive drugs to treat patients has not performed well. Many compounds that were identified preclinically failed in the clinic, because they either lacked appropriate efficacy, had poor drug-like PK properties or were hampered by safety issues. This was because many drugs proceeded into the clinic with a leap of faith, because often preclinical data were poor predictors for clinical effects and clinical measures allowing an early and reliable indication of efficacy did not exist, leading to late attrition in large and expensive patient studies only. Translational research should bridge the gap between preclinical research and clinical research, allowing for an early and quantitative indication of pharmacological activity that predicts the efficacy of a therapeutic intervention in patients (McArthur and Borsini 2008; O'Connel and Roblin 2006). It systematically addresses the questions whether a compound shows target tissue exposure, activity on the molecular target, and modulation of the desired biochemical pathways by looking at PK/PD markers, and whether activity in a model system is predictive of clinical outcome, trying to identify suitable surrogate endpoint markers. Besides predicting efficacy, translational research also addresses mechanism-based toxicology to de-risk drug development (of note, idiosyncratic toxicology, unrelated to the mechanism of action of a compound, cannot readily be predicted).

Surrogate Endpoint Markers

A surrogate endpoint marker could be a trait marker, reflecting diagnostic accuracy, or a state marker, being predictive of clinical outcome. In psychopharmacology, surrogate endpoint markers could comprise, for example, genetic or genomic markers, neurochemical markers (e.g., ► cerebrospinal fluid (CSF) measures), neuroendocrine markers (e.g., reflecting activity of the ► hypothalamic-pituitary-adrenal (HPA) axis), electrophysiological markers (e.g., electroencephalographic (► EEG) measures), molecular imaging data (e.g., functional magnetic resonance imaging (► fMRI), measures of brain metabolic activity using ► deoxyglucose imaging or target occupancy positron emission tomography (► PET) imaging to show target engagement), autonomic markers (e.g., measures of heart rate, skin conductance, or body temperature), or types of behavior that can be measured across species. Ideally, analogous or even homologous measures should be used, with the inherent assumption being that they are mediated by the same neural substrates across species. However, a problem inherent to these markers is that often the relationship between changes in marker activity in patients and clinical outcome is not clear. ► Prepulse inhibition (PPI), for example, can be readily measured and seems to be mediated by the same neural systems across species. PPI deficits have been reported in a number of psychiatric disorders, including ► schizophrenia. Antipsychotics have been reported to alleviate PPI deficits in schizophrenic patients, but how exactly this translates into clinical improvements remains elusive. Consequently, these markers are currently not accepted as clinical endpoints by health authorities in clinical trials.

Translation and Back-Translation

A translational approach refers to the development of clinical tests based on learning from preclinical experimentation. Current clinical trial endpoints are largely based on patient assessment using rating scales, although notable exceptions do exist, for example, the urine testing for illicit substances in the area of drug dependency, breath CO measures in tobacco smoking studies, or the measurement of CSF amyloid levels in ► Alzheimer's patients. With the growing emphasis on translational research, ever-increasing efforts are being undertaken to explore alternative, dimensional measures to align clinical research with preclinical findings. A behavioral example in the field of anxiety is ► fear-potentiated startle, a paradigm that was well characterized in animals and has been translated for use in humans (healthy volunteers and patients) (Nordquist et al. 2008).

Conversely, we can learn from the clinic and aim to back-translate to the preclinical setup. Of note, there are only a few signs and symptoms that are specific for a particular psychiatric disorder, while many symptoms cut across diagnoses. Therefore, preclinical behavioral tests most likely will address a certain diagnostic dimension that may be an important feature of multiple psychiatric disorders (Markou et al. 2009).

The degree to which we can back-translate will depend on the species-specificity of the diagnostic dimension under investigation. For example, we can readily measure ► sensorimotor gating in animals (e.g., using PPI), which is impaired in psychiatric disorders such as schizophrenia, and can assess motivational types of behavior

that resemble anhedonic symptoms seen in schizophrenia and depression, but we cannot readily measure animal equivalents of some psychiatric symptoms such as hallucinations, delusions, or suicidal thoughts. Non-behavioral, electrophysiological (e.g., EEG), neurochemical, neuroendocrine, autonomic, or imaging measures also lend themselves well to a (back-)translational approach, for example, the measurement of CSF amyloid levels in animals. Yet, other types of human pathological behavior have not been sufficiently explored in animals to allow conclusions whether preclinical equivalents exist (Markou et al. 2009), especially when going beyond ► face validity, for example, for some of the cognitive symptoms seen in schizophrenia, indicating the emerging nature of this field of research.

PK/PD Markers

PK/PD markers assess the relationship between the desired or undesired effects of a drug and its effect at the molecular target (PKs: what the body does to the drug; PDs: what the drug does to the body). Possibly the most straightforward marker would be the measurement of the plasma concentration of a drug in relation to its efficacy, either in preclinical species or man. Alternatively, one can study the concentration of a drug or its metabolites in CSF. Preclinically, target occupancy can be measured ► ex vivo or ► in vivo in tissue homogenates, brain slices, or other imaging techniques such as ► μPET, which then can be related to occupancy in man, provided a suitable radioactive PET ligand exists, and the degree of occupancy can be related to the desired or undesired effects of the drug under investigation. In principle, surrogate endpoint markers as those mentioned earlier could also be used as PK/PD markers, provided one can link the PD measures to target occupancy/drug levels. Once this relationship is firmly established preclinically, this information can be used to predict the pharmacologically active dose in man (Nordquist et al. 2008). Of note, occupancy only shows target engagement and the occupancy of a target required to induce desired or undesired effects in preclinical species can only be used as a guide since different levels of occupancy may be required in patients for a drug to have clinical effects.

The Model System

While it is possible to measure many markers across species (although several exceptions exist – see above), it is equally important to use an appropriate manipulation of the model organism, be it an animal or a healthy volunteer, leading to a model with high ► construct validity. This seems particularly relevant for the measurement of surrogate endpoint markers.

Psychiatric disorders have traditionally been challenging to model in animals in a manner directly translatable to human research (Markou et al. 2009). First, we lack a good understanding of the pathophysiology of psychiatric disorders, which makes it difficult if not impossible to develop an animal model that incorporates the causative factors leading to disease, that is, our ability to build models based on strong construct validity is limited. This is further complicated by the fact that classification schemes for psychiatric disorders are primarily based on symptom clusters, thereby risking that diseases with different underlying etiologies but related symptoms are grouped within the same category. Consequently, different animal models may be needed to address different etiological factors of a disorder as defined by contemporary classification schemes. Alternatively, different manipulations have to be performed in the same animal to better model the disease. While it seems relatively straight forward to model some psychiatric disorders in animals, for example, ► drug abuse (Kreek et al. 2009), we do not really know what the ideal model for other psychiatric disorders, such as schizophrenia or depression, should be (Markou et al. 2009).

Complicating this approach is the fact that psychiatric classification schemes have changed over time, sometimes rendering models that were established according to the definition of an older classification scheme inappropriate to depict a disorder as defined in the newer classification. For example, many preclinical anxiety tests were developed before anxiety disorders were split into different categories by the third edition Diagnostics and Statistical Manual of Mental Disorders of the American Psychiatric Association (DSM III), published in 1980. Currently, we need models that adhere to the classification scheme of the next edition, ► DSM IV, published in 1994, and in the future DSM V it can be anticipated that classification schemes will change again (Steckler et al. 2008).

In healthy volunteers, challenges are for ethical reasons more limited than those that can be performed preclinically. Such challenges, which are also used in preclinical research, can be pharmacological (e.g., NMDA antagonists to model the glutamatergic hypofunction in schizophrenia) or non-pharmacological (e.g., psychological stress exposure to increase stress-related anxiety). However, it should also be noted that not all challenges that are used in man have been successfully back-translated to animals, often because of species-dependent behavioral differences, and

often questions about the robustness of the healthy volunteer models remain to be addressed.

Predictive Validity – Key Requirement for Translational Research

Often, it is this combination of a model system mimicking (some of) the pathophysiology of a psychiatric disorder and the use of a relevant test that holds potential for a translational model, although notable exceptions do exist (e.g., target engagement often can be measured in healthy animals and humans and is very informative for expected target engagement in patients). A stringent requirement for the translational approach is the ability to link the readout from the model system to clinical outcome. Key for that is the demonstration that efficacious treatments in the clinic, be it a drug or other approach, are active in the model (correct positives), while treatments that fail to therapeutically improve the disorder of interest should be inactive on corresponding preclinical measures (correct negatives), that is, it needs to be demonstrated that the model has a high ▶ predictive validity. In the absence of a clinically used treatment, one may revert to treatments that have shown efficacy in healthy volunteer models following appropriate challenges to gain more confidence in the ▶ predictive validity of an animal model, but this then leaves one with uncertainty about the translational value of the healthy volunteer model for the patient situation, also because the ability to relate such experimental healthy volunteer data to accepted clinical outcome measures is often lacking. Unfortunately, there is a shortage of suitable treatment approaches that can be used for the validation of translational models in psychiatry because suitable treatments for many psychiatric symptoms simply do not exist than can be used as correct positives (Markou et al. 2009).

Advantages and Limitations of the Translational Approach

The major advantages of translational research reside in a more stringent approach to psychopharmacological drug development, trying to bridge more closely between preclinical and clinical measures and using model systems of high construct and predictive validity. It is hoped that this should lead to faster and better informed go/no-go decisions, more efficacious drugs, and consequently reduced attrition rates during late drug development. It is also evident, however, that we still lack good surrogate endpoint markers for certain diagnostic dimensions and also lack clarity on what would constitute the best model systems for certain psychiatric disorders.

Thus, although the approach seems highly credible and promising (Sultana et al. 2007), only time will tell whether translational research will be really advantageous over more classical approaches in drug development to reduce attrition rates (Wehling 2006).

Cross-References

▶ Cerebrospinal Fluid (CSF)
▶ Construct Validity
▶ Deoxyglucose
▶ Drug Dependence
▶ Electroencephalography
▶ Ex Vivo
▶ Face Validity
▶ Fear-Potentiated Startle
▶ fMRI
▶ Hypothalamic-Pituitary-Adrenal (HPA) Axis
▶ In Vivo
▶ μPET
▶ Predictive Validity
▶ Prepulse Inhibition
▶ Sensorimotor Gating

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Translational Science

▶ Translational Research

Transmembrane Helix

Definition

Part of an integral membrane protein that spans the entire cell membrane, with the transmembrane part of the protein coiled as an helix.

Transporter

Definition

A protein whose function is to terminate signaling by a neurotransmitter that has been released into the synaptic cleft. It does so by removing (transporting) the neurotransmitter away from the receptors, and back into the nerve terminal that released it. It can then either be destroyed or repackaged for future use.

Tranxene

► Chlorazepate

Tranylcypromine

Definition

Tranylcypromine is a nonselective, irreversible inhibitor of the enzyme monoamine oxidase. It is a cyclopropyl analogue of ► amphetamine although its effects and mechanism of action are quite different. It was one of the earliest ► antidepressants and was much used prior to the development of more effective and safer medications. Its use is largely limited to cases of depression that have failed to respond to other medications. It increases tissue concentrations of ► catecholamine and ► indoleamine neurotransmitters by slowing their metabolism; it also elevates the effects of biologically active dietary amines by increasing their absorption from the gastrointestinal tract and by impairing their breakdown. Dangerous interactions occur if foodstuffs high in monoamines or their precursors are consumed, a common example being the hypertensive crisis caused by the ingestion of tyramine from mature cheese and red wine. Tranylcypromine also potentiates the effects of later antidepressants such as the tricyclics and may produce toxic reactions if taken together.

Cross-References

► Antidepressants
► Monoamines
► Serotonin Syndrome

Traumatic Stress (Anxiety) Disorder

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Synonyms

Posttraumatic stress disorder

Definition

Introduction

Conservative figures estimate that between one- and two-thirds of the population in Western countries are exposed to a traumatic event of a magnitude that might eventually lead to posttraumatic stress disorder (PTSD). Of those exposed, 10–20% develop PTSD, which is a long-lasting debilitating illness with substantial impact on the individual's work, family, social relations, and quality of life (Yehuda et al. 2005; Zohar et al. 2008). The disorder is characterized by the presence of three distinct, but co-occurring, symptom groups. *Re-experiencing* symptoms are intrusions of the traumatic memory in the form of distressing images, ► flashbacks, nightmares, or dissociative experiences. *Avoidance* symptoms consist of attempts to actively avoid reminders of the traumatic event including persons, places, or things associated with the trauma and/or passive behaviors reflecting ► emotional numbing and constriction. *Hyperarousal* symptoms include insomnia, irritability, impaired concentration, hypervigilance, and increased ► startle responses. In order to fulfill the criteria for PTSD, these symptoms must impair social, occupational, or interpersonal function, and persist for at least a month following the trauma.

What is unique with regard to the pharmacological treatment after an exposure to trauma is that it is heavily influenced by the time elapsed since the trauma and not only by the severity and nature of the symptoms (which are also judged along a time line) (Nutt et al. 2000; Stein et al. 2006, 2009a,b). Six different conditions might surface following trauma exposure and each might require different treatment strategies. These include: acute stress reaction (ASR), acute stress disorder (ASD), acute PTSD

(1–3 months), chronic PTSD (over 3 months), other psychiatric disorders (such as depression, panic disorder, obsessive compulsive disorder (OCD), psychosis, etc), and specific problems including sleep disorders, sexual dysfunction, aggression-impulsivity problems, addiction, etc (Bandelow et al. 2008; Davidson et al. 2005).

Role of Pharmacotherapy

Acute Stress Reaction (ASR)

This initial reaction to trauma includes symptoms of disorientation, autonomic symptoms of panic and anxiety (elevated heart rate, sweating, etc.), and sometimes amnesia of the traumatic event, lasting for a few days only.

This is considered a normal reaction (up to 70% of those exposed to a traumatic event meet the criteria for ASR). There is no recommendation for pharmacological intervention for the vast majority of individuals experiencing ASR, as there is no treatment that has been scientifically supported at this stage. However, in specific cases of extreme agitation, medications may be used. The tradition of frequent use of ▶ benzodiazepines has recently been criticized, as it might interfere with the normal spontaneous remission (which takes place in 80–90% of the cases) (Zohar et al. 2008).

Individuals having experienced such a reaction should be advised of the need for monitoring if symptoms do not subside within a few weeks. However, those with past history of depression, anxiety, and substance abuse, and those with ▶ dissociative reaction, panic-like response, and severe agitation should be followed up more closely, as they are all considered risk factors for developing PTSD (Bandelow et al. 2008; Stein et al. 2006, 2009a; Zohar et al. 2008).

Acute Stress Disorder

ASD is the severe end of ASR, and is diagnosed (according to ▶ DSM IV) when the prescribed symptoms of PTSD occur, along with dissociative symptoms (detachment, depersonalization, dissociative amnesia, etc.), but within 4 weeks of the trauma, and lasting for a minimum of 2 days. The risk of developing PTSD for those individuals is substantially higher, and might be up to 50%. As is the case for ASR, the "non-pharmacologizing" rule is applicable; however, closer monitoring is recommended (Bandelow et al. 2008; Stein et al. 2006, 2009a; Zohar et al. 2008).

Acute PTSD (up to 3 months)

Although there are no controlled studies for the treatment of acute PTSD, the data derived from treatment of chronic PTSD might be applicable. ▶ Paroxetine, ▶ fluoxetine, and ▶ sertraline are all FDA-approved for the treatment of PTSD. The recommendation for treatment with these medications (which are all ▶ selective serotonin reuptake inhibitors – SSRIs) is to aim for full therapeutic dose (e.g., paroxetine 20–40 mg or sertraline 100–150 mg), gradually titrated. If there is no response within 12 weeks, the condition is considered as chronic PTSD with one failed medication trial.

If the response is an improvement to the extent of complete remission of symptoms, it is advisable to continue the treatment for 6–12 months from attaining remission, and to taper off the medication very gradually. There are currently no studies supporting the efficacy of treatment lasting more than a year, but as in other anxiety disorders, continuing treatment beyond that is recommended. A follow-up visit is recommended within 3 months of stopping pharmacological treatment.

In cases in which ▶ anxiety and unrest symptoms are prominent, adjunctive treatments, including pharmacotherapies, can be used. In any case, it is advisable to monitor progress a month after beginning the extra treatment and, if there is no response or numerous side effects, to stop it. These treatments include: benzodiazepines for treatment of anxiety and unrest that are not responding to SSRI, or until the SSRI takes effect. A short-term use is recommended (but not immediately after the trauma). When using benzodiazepines, a high-potency drug is preferable, with a short half-life, such as ▶ alprazolam of 0.5–1 mg or ▶ lorazepam of 1 mg. If a lengthier (yet still limited) treatment is required, a drug with a long half-life is preferable (▶ clonazepam 10–30 mg, ▶ diazepam 5–10 mg, or ▶ clorazepate 1–2 mg). However, as there is high co-morbidity of addiction in PTSD, it is very important that the treatment be limited in time, and if ▶ tolerance develops to the drug, it should be gradually be tapered down. In any case, before recommending benzodiazepines, past drug, alcohol, or benzodiazepine dependence must be ruled out.

Low doses of second-generation antipsychotics, such as ▶ olanzapine 2.5–7.5 mg, ▶ quetiapine 50–200 mg, ▶ risperidone 1–3 mg, and ▶ amisulpride 50–200 mg have been studied. The efficacy of these medications in treatment of PTSD is yet to be tested in larger, controlled studies (Bandelow et al. 2008; Davidson et al. 2005; Stein et al. 2006, 2009a).

Chronic PTSD (over 3 months)

The first-line treatment here is SSRI, titrated gradually to a full therapeutic dose. Even if remission is achieved, guidelines suggest continuation of treatment for 6–12 months from attaining remission, and then to taper off

the medication very gradually. Although currently there are no studies supporting the efficacy of treatment lasting more than a year, the consensus is to continue treatment beyond that, as in other anxiety disorders. Follow-up visits are recommended at 3, 6, 9, and 12 months after cessation of pharmacological treatment. In cases of partial response (i.e., around 30% improvement), a dose increase and continuation of the same medication for a further 12 weeks is recommended. In the instance of non-response to a treatment trial (less than 50% decrease in symptom severity) after at least 12 weeks, a treatment change is recommended as follows.

In case of no response to SSRIs, switching strategies have been proposed. These include switching to another SSRI, switching to an SNRI at a dose that would enable dual action (e.g., ▶ venlafaxine 225 mg and above), or augmentation with an antidepressant with a different mode of action (e.g., desipramine 150–200 mg, ▶ reboxetine 4–8 mg, ▶ mirtazapine 15–45 mg, ▶ mianserin 30–60 mg) as an add-on to SSRI. However, when administering these drug in conjunction with SSRIs (e.g., ▶ fluoxetine, ▶ fluvoxamine, and ▶ paroxetine), drug–drug interactions should be monitored. It should be noted that none of these methods are supported by controlled trials, and thus, there is no solid evidence to prefer one over another.

Second-line treatment alternatives (after at least two other attempts) include switching to tricyclic drugs (▶ imipramine 150–300 mg), or a ▶ monoamine oxidase inhibitor (MAOI) (e.g., ▶ phenelzine 30–75 mg). Accepted precautions for the use of MAOI should be taken (washout period of at least 2 weeks after previous medication and dietary limitations).

Non-response or "resistant PTSD" is usually defined as occurring after three full treatment attempts as described earlier. In resistant PTSD, treatment combinations such as augmentation with ▶ second-generation antipsychotics may be considered (there are reports regarding the use of risperidone 1–3 mg and olanzapine 2.5–10 mg) as mood stabilizers (e.g., ▶ lamotrigine and ▶ topiramate). However, as these recommendations are largely based on case series and not controlled studies, they should be taken with "a pinch of salt." In any case, multiple medications should be avoided wherever possible, with a rule of thumb aiming at no more than 2–3 concurrent medications (Bandelow et al. 2008; Davidson et al. 2005; Nutt et al. 2000; Stein et al. 2003, 2006, 2009a,b).

Other Psychiatric Conditions

Co-morbidity is very common in chronic PTSD patients. Co-morbid diagnoses should be made according to the accepted criteria in ▶ DSM/▶ ICD. ▶ Major depressive disorder (MDD), ▶ OCD, ▶ panic disorder, alcohol and substance (drug) abuse, ▶ psychosis, and ▶ bipolar disorder are some of the most frequent co-morbidities.

In each of these disorders, the therapeutic approach is to treat both the PTSD and the co-morbid disorder. Consequently, the therapeutic approach is the accepted practice for each specific disorder. Priority of treatment will depend on the severity of each disorder and the subjective suffering of the patient or his or her immediate environment (partner, children, relatives, etc.) (Nutt et al. 2000; Stein et al. 2009a).

Specific Problems

Sleep Disorders

Complaints of sleep disruption are very common in PTSD, although there is sometimes a large discrepancy between the complaints and sleep laboratory data.

Therapeutic options include low doses of ▶ prazosin (5–10 mg) – currently, the only drug to have been tested in a ▶ double-blind study and found effective, particularly in cases of nightmares. Other possibilities (which have not been tested specifically) include ▶ melatonin 5–10 mg, clothiapine 20–60 mg, or levopromazine 12.5–50 mg.

Other treatment options include the following:

Hypnotic drugs. Common ▶ hypnotics, such as ▶ zolpidem 10–20 mg and ▶ zopiclone 7.5–15 mg, have clear benefits, but also disadvantages (e.g., developing tolerance). Therefore, it is not recommended to use these medications for more than 2–3 weeks consecutively. The recommendation is to treat for a defined period wherever possible, and not indefinitely.

Medications that are not considered "sleeping pills" and are not associated with tolerance, are antidepressants that cause drowsiness, such as mirtazapine 14–45 mg, ▶ trazodone 50–200 mg, or ▶ amitriptyline 10–25 mg.

Maintenance treatment for sleep disorders might focus on avoiding tolerance during long-term treatment.

If the patient takes a hypnotic drug, treatment should be discontinued after 2–3 weeks. In patients who take the drug for longer duration, it is advisable to stop as soon as an improvement is observed. In both cases, cessation of treatment should be carried out carefully and gradually.

There are reports of an increased prevalence of ▶ sleep apnea in PTSD. Therefore, patients at increased risk of sleep apnea (middle-aged, overweight men with short necks, and whose bed-partners report snoring) should undergo an appropriate screening, and if needed, a specific treatment tailored for them. Great care should be taken with these patients when prescribing drugs with side

effects such as depression of respiration (such as benzodiazepines, non-benzodiazepine hypnotics, and opioids).

Sexual Dysfunction

It is important to differentiate between problems with libido, arousal, orgasm, or combinations of these. Libido and orgasm problems could be side effects of one of the drug treatments, and if required, an alternative treatment could be tried.

► Erectile dysfunction can also be related to side effects of drug treatment. First, an organic cause should be ruled out (diabetes, dyslipidemia, high blood pressure, hormonal problems, etc.). When treating erectile dysfunction, phosphodiesterase inhibitors (► sildenafil [*Viagra*], vardenafil [*Cialis*]) can be effective.

Aggression and Impulsivity Problems

Available treatments include ► mood stabilizers (including topiramate 50–150 mg, lithium 600–1,500 mg, or ► valproaic acid 60–2,000 mg) whilst monitoring blood levels, β-blockers (e.g., propanolol 20–80 mg, monitoring pulse and blood pressure), and antipsychotic medications. These approaches are yet to be examined in controlled studies.

Addiction

► Alcohol dependence or cannabinoid, heroin, and ► cocaine addictions are prevalent in PTSD. The co-occurrence of addictions and PTSD is associated with poorer prognosis and increased risk for somatic comorbidity, and should therefore be specifically screened for and treated adequately (Bandelow et al. 2008; Davidson et al. 2005; Stein et al. 2009b).

Summary

The pharmacological approach for PTSD (which is mainly related to SSRIs) is only one component in the complex puzzle comprising appropriate treatment for PTSD. Psychoeducation to the patients and their families, including encouragement to resume previous activities as well as refraining from focusing on compensation issues, along with specific psychological intervention (i.e., prolonged exposure) and social and emotional support, might be as important as the current pharmacological interventions.

Cross-References

► Aggressive Behavior
► Alcohol Abuse and Dependence
► Benzodiazepines
► Insomnias
► Major, Minor, and Mixed Anxiety-Depressive Disorders
► Obsessive-Compulsive Anxiety Disorders
► Panic
► Schizophrenia
► SSRIs and Related Compounds

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Trazodone

Definition

Trazodone is a triazolopyridine that was developed in Italy as an antidepressant and was much used for that indication, although its use has declined. It was one of the early atypical antidepressants and was developed according to the mental pain hypothesis, which postulated that major depression is associated with a decreased pain threshold. It inhibits the reuptake of ► serotonin with lower affinity and selectivity than for typical SSRIs such as ► fluoxetine, and also acts as an antagonist 5-HT_{2A} and 5-HT_{2C} receptors and a histamine antagonist. Its efficacy is comparable to that of ► tricyclic antidepressants but it has a superior side-effect profile. It has also been prescribed for insomnia but evidence of efficacy is lacking

and it is uncertain whether it has a favorable risk–benefit ratio. Adverse reactions reported include drowsiness and priapism (painful and prolonged penile erection). It is metabolized by the liver enzyme CYP3A4. Inhibition of the enzyme by other substances may result in high blood concentrations of trazodone. Grapefruit juice has such an inhibitory property and its consumption is discouraged when trazodone is prescribed.

Cross-References

► Antidepressants

TRD

► Treatment-Resistant Depression

Treatment-Resistant Depression

Synonyms

TRD

Definition

Treatment-resistant depression (TRD) is defined as a major depression disorder in patients who fail to achieve remission with standard antidepressant therapies. TRD can be further distinguished from chronic severe depression as some patients with milder depressive symptoms are still treatment resistant. Present treatments for TRD include ECT, vagus nerve stimulation, and ► transcranial magnetic stimulation.

Treatment-Resistant Schizophrenia

Synonyms

Refractory schizophrenia

Definition

Schizophrenia is considered as a heterogeneous illness with various trajectories of response and treatment outcome. A minority of individuals demonstrate complete resolution of symptoms; at the other end of the spectrum, approximately 25–30% of individuals show minimal response to treatment, at least with ► first-generation antipsychotics. It is these individuals who are designated as refractory or treatment resistant and there are now established criteria to make this diagnosis, criteria that take into consideration previous treatments (including drug, dose, and duration) as well as outcome.

It is important to distinguish this subpopulation of individuals from "partial responders." This latter group also manifests a suboptimal response, but it is more substantial than what is observed in the treatment-resistant population.

The distinction of treatment resistant has important clinical implications, as ► clozapine appears superior to all antipsychotics, including other atypicals, in treating this population. It is estimated that a significant response will be seen in approximately 30–50% of clozapine-treated individuals.

Treatment-resistant schizophrenia can be seen from the earliest stages of schizophrenia, although it can also be observed in individuals who initially appeared responsive to treatment. There are no well-established criteria that can be used clinically to predict which individuals will be refractory or responsive to clozapine.

Cross-References

► Second- and Third-Generation Antipsychotics

Treatment Response

Definition

The magnitude of clinical change can be expressed as the mean change in baseline Y-BOCS scores on active drug compared to placebo, or as treatment "responders" versus "nonresponders." Though no universally accepted definition of treatment response exists, a CGI-I rating of "improved" or "very much improved" and a decrease in Y-BOCS of 25 or 35% are widely used and may separate active from inactive treatments. Thus, an accepted definition of "responder" is an individual who exhibits a Y-BOCS reduction of 35% after treatment as compared to pretreatment scores. This conservative level of improvement contrasts with the standard 50% improvement expected for successful treatment for ► major depressive disorder.

Cross-References

► CGI-I
► Obsessive Compulsive Disorder
► SSRI and related compounds
► Y-BOCS

TR-FRET

Definition

TR-FRET unites TRF (time-resolved fluorescence) and FRET (fluorescence resonance energy transfer).

FRET uses two fluorescent molecules, a donor and an acceptor. Excitation of the donor by an energy source (e.g., a flashlamp) triggers an energy transfer to the acceptor, if the donor and the acceptor are within a given proximity to each other. The acceptor, in turn, emits light at a given wavelength. Because of this energy transfer, molecular interactions between molecules (e.g., a ligand and a receptor) can be assessed by coupling each partner with a fluorescent label and detecting the energy transfer. TRF uses long-lived fluorescent labels combined with time-resolved detection; a delay between excitation and emission detection minimizes prompt fluorescent interferences.

Cross-References

► Receptor Binding

Triazolam

Definition

Triazolam is a short-acting (► half-life 1.5–5 h) benzodiazepine that produces sedative effects by potentiating inhibitory GABAergic neurotransmission at ► $GABA_A$ receptors. It was a leading hypnotic prescribed worldwide for the treatment of insomnia during the late 1980s. However, a high rate of reports of adverse effects including memory loss, confusion, anxiety, bizarre behavior, and hallucinations, as well as several legal cases, led to the drug's license being suspended in several countries including the UK. It is currently approved in the USA for use in small doses for the treatment of insomnia.

Cross-References

► Benzodiazepines
► Sedative, Hypnotic, and Anxiolytic Dependence

Trichloroethane

Synonyms

Methyl chloroform; TCE; 1,1,1-trichloroethane

Definition

Trichloroethane (TCE) is a highly volatile liquid whose vapors are often subject to inhalant abuse. It is a widely used industrial solvent and is contained in many household products including adhesives, cleaning solutions, inks, paints, correction fluids, and shoe polish. TCE is a source of environmental chlorine and as such its use was restricted by the Montreal Protocol to protect the ozone layer. Thus, the availability of TCE in products is much diminished. Nonetheless, TCE is an important abused inhalant because many animal and neuropharmacological studies are done with it as a representative halogenated hydrocarbon-abused solvent. Evidence suggests that it produced effects similar to ► alcohol, other depressant drugs, and abused inhalants.

Cross-References

► Inhalant Abuse

1,1,1-Trichloroethane

► Trichloroethane

Trichostatin A

Synonyms

TSA

Definition

TSA is a chemical agent that has the ability to inhibit the enzymatic activity of Class I and II HDACs. Treatment with this compound leads to the opening of chromatin structure due to an increase in histone acetylation. This compound serves as an HDAC inhibitor.

Cross-References

► Epigenetics
► Histone Deacetylase Inhibitors

Trichotillomania

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Synonyms

Chronic hairpulling

Definition

Trichotillomania is classified as an ► impulse-control disorder in ► DSM-IV. Trichotillomania is characterized by recurrent hairpulling that causes noticeable hair loss and significant distress or impairment. Additionally, according to DSM-IV, trichotillomania requires that an individual should sometimes experience urges prior to pulling, and a sense of pleasure, gratification, or relief after the act.

Role of Pharmacotherapy

Trichotillomania has an estimated lifetime prevalence of roughly 0.6%. However, the estimated lifetime prevalence increases to roughly 3% when preceding urges and pleasure/relief afterward are removed from the diagnostic criteria. Trichotillomania patients have a high rate of ► comorbid illnesses, with approximately 82% of adults presenting for treatment experiencing at least one other Axis I psychiatric disorder (Woods et al. 2006a). Common comorbidities include depression, anxiety disorders, obsessive–compulsive disorder, substance use disorders, posttraumatic stress disorder, and other body-focused impulse control disorders. Trichotillomania in adults has a strong female predominance and a chronic, waxing and waning course. Longitudinal studies of adults with trichotillomania have demonstrated little improvement in symptoms over time (Keuthen et al. 2001). Trichotillomania has an average onset age of around 13 years. It should be distinguished from chronic hairpulling in young children. Hairpulling in young children is considered a behavior consistent with developmentally appropriate environmental exploration and is usually self-limited.

A proper assessment in a patient with trichotillomania involves getting a detailed history of their hairpulling. When discussing hair-pulling behaviors it is important to address (1) antecedent cognitions, behaviors, and feelings prior to pulling, (2) the settings in which pulling occurs, (3) body locations from which pulling occurs, and (4) post-pulling behavior. Trichotillomania patients commonly experience emotions such as boredom, tension, and anxiety prior to hair-pulling episodes and/or a physical urge to pull. Commonly experienced cognitions prior to hairpulling include beliefs about the inappropriate appearance of certain hairs (gray, coarse, etc.), that hairlines or lengths of hair need to be symmetrical or that the patient is unattractive or unlovable because of his or her appearance. Common post-pulling behaviors involve biting, rubbing, or eating the hair. Also, discarding of the hairs in fairly stereotyped ways is the norm. In patients who ingest their own hair, trichobezoars (conglomerations of hair and food that form in the gastrointestinal tract) are of particular concern as they can lead to weight loss, iron deficiency anemia, malabsorption, and even gastrointestinal tract obstruction.

Trichotillomania patients also usually have specific places where they engage in the behavior, i.e., the bedroom or the bathroom. The most common sites of hairpulling are the scalp (73%), eyebrows (56%), eyelashes (53%), pubic region (46%), and legs (15%) (Woods et al. 2006a). A physical examination of areas of hairpulling can uncover areas of irritation, follicle damage, and atypical regrowth of hair, all of which are common in patients with trichotillomania. Rating scales, such as the self-report Massachusetts General Hospital Hair-pulling Scale and the clinician-rated National Institute of Mental Health Trichotillomania Severity Scale, are useful in measuring the severity of trichotillomania symptoms and tracking changes in symptom severity over time.

► Selective serotonin reuptake inhibitors (SSRIs) are the most commonly utilized pharmacological intervention to treat trichotillomania (Woods et al. 2006a) (► SSRIs and related compounds). Initial open-label trials showed improvement over time in trichotillomania patients taking SSRIs. However, in four randomized, blinded, ► placebo-controlled trials, SSRIs have failed to show benefit compared to placebo (Christenson et al. 1991; Dougherty et al. 2006; Streichenwein and Thornby 1995; van Minnen et al. 2003). A ► meta-analysis that combined the results of the four previously conducted trials similarly failed to show any evidence of an improvement compared to placebo treatment (Bloch et al. 2007). Although there is substantial evidence that pharmacological treatment with SSRI is no more effective than placebo in the treatment of primary hairpulling in trichotillomania patients, these medications may still be quite effective in treating comorbid illness in these patients. ► Depression, ► anxiety disorders, and ► post traumatic stress disorder are all common comorbidities in trichotillomania patients, and there is substantial evidence demonstrating improvements in these conditions with SSRI pharmacotherapy. When SSRI pharmacotherapy is initiated in a trichotillomania patient, the goal of therapy should be to specifically target comorbid illness that is impairing to the patient, as SSRI pharmacotherapy for primary trichotillomania has little evidence of efficacy.

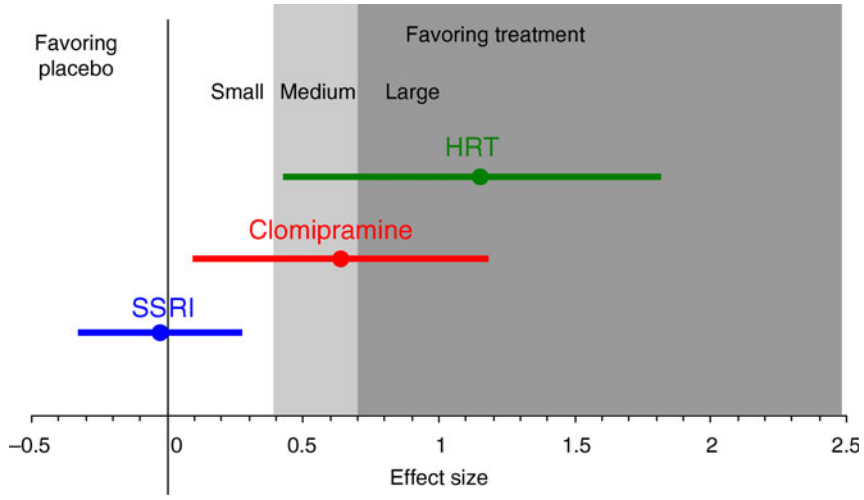
Clomipramine is a ► tricyclic antidepressant (TCA) that has been extensively studied in the treatment of trichotillomania (► antidepressants). Initial results from a 10-week, randomized, double-blind, crossover study of 13 women that compared ► clomipramine, a serotonergically potent TCA, to desipramine, a noradrenergically potent TCA, demonstrated substantial improvement in

trichotillomania patients treated with clomipramine (Swedo et al. 1989). However, most of the patients in this trial experienced a relapse in their symptoms after longer-term treatment with clomipramine. Another small, 9-week, randomized, placebo-controlled parallel-group study showed some increased improvement of trichotillomania symptoms with clomipramine compared to ▶ placebo, but not to the level of statistical significance (Ninan et al. 2000). Clomipramine was very poorly tolerated in this study, with 40% of subjects dropping out early due to side effects. Common side effects associated with clomipramine include weight gain, anticholinergic symptoms, and sedation. The meta-analysis of randomized trials with clomipramine suggests modest short-term benefits when compared to control conditions. However, evidence suggests that benefits from clomipramine are short-lived.

A substantial number of case reports and uncontrolled trials have suggested the possible efficacy of both typical and atypical antipsychotics in trichotillomania (▶ antipsychotic drugs). Additionally, case reports suggest the possible efficacy of glutamate-modulating agents such as riluzole, ▶ *n*-acetylcysteine, and ▶ topiramate. ▶ Naltrexone, a opioid antagonist used to treat urge-related disorders such as alcoholism and ▶ pathological gambling, has shown some evidence of efficacy in uncontrolled trials. Skepticism is warranted when viewing the likely efficacy of any treatment of trichotillomania studied in an unblinded, uncontrolled fashion. Many patients with trichotillomania improve over the short-term regardless of treatment after presenting for initial treatment. Greater familiarity and psychoeducation about the disorder, meeting other individuals with the disorder, supportive clinicians, and engaging in any active intervention against the disorder are all powerful forces toward patient improvement. These aspects of treatment, along with the waxing and waning course of the disorder, make it difficult to assess efficacy in uncontrolled trials.

Role of Non-Pharmacological Therapies

▶ Habit reversal therapy (HRT) is a behavioral therapy designed for the treatment of trichotillomania and tics. HRT is a manualized, behavioral technique that is administered over a period of 2–3 months with a maintenance period for relapse prevention. HRT involves several different components – self-monitoring, awareness training, stimulus control, and competing response training. The self-monitoring component of HRT requires patients to keep records of their hairpulling. Awareness training works to increase patient awareness of hair-pulling behaviors and of high-risk situations that increase the risk of hairpulling. Stimulus control employs interventions designed to decrease the opportunities to pull and to intervene or prevent pulling behaviors. Competing response training involves teaching a patient to engage in a behavior that is physically incompatible with pulling for a set period of time when they feel the urge to pull. In HRT, patients are only permitted to pull after they have engaged in the competing response behaviors.



Trichotillomania. Fig. 1. Relative efficacy of treatments in trichotillomania: effect sizes of habit reversal therapy (HRT), clomipramine, and SSRI. Circles represent the point estimate and lines the 95% confidence intervals for effect sizes for each intervention. (Adapted with permission from Bloch et al. 2007.)

In three randomized, parallel-group studies, HRT demonstrated superior efficacy compared to wait-list or placebo controls (Ninan et al. 2000; van Minnen et al. 2003; Woods et al. 2006b). HRT also demonstrated superiority to pharmacotherapy with fluoxetine and clomipramine in two of these randomized trials (Ninan et al. 2000; van Minnen et al. 2003). A recent meta-analysis demonstrated that, in randomized, controlled trials, HRT shows superior ► effect sizes compared to pharmacological agents for trichotillomania (Bloch et al. 2007). Figure 1 depicts the relative effect sizes of HRT compared to pharmacotherapies for the treatment of trichotillomania. Further trials are needed to demonstrate that HRT will maintain efficacy when compared to control conditions that account for the nonspecific aspects of therapy (i.e., emotional support and psychoeducation).

Support groups (e.g., the Trichotillomania Learning Center in Santa Cruz, California, www.trich.org) can also be very helpful in treating trichotillomania. Such groups can provide treatment referrals and support to individuals experiencing the condition. Often times, hearing other individuals' stories, coping mechanisms and strategies can help the individual develop more effective personal approaches for adjusting to and managing the disorder.

Conclusion

Trichotillomania can cause substantial impairment for individuals who suffer from it. Individuals may have significant dermatological and medical problems as a direct result of hairpulling. Substantial psychosocial impairment may occur due to the resulting hair loss. Effective behavioral treatments for trichotillomania, such as HRT, have been developed over recent years. Access to skilled therapists practicing HRT remains a major challenge for trichotillomania treatment. Currently, expert HRT treatment for trichotillomania is available at only a few academic centers. No pharmacological agents have convincingly demonstrated long-term efficacy in the treatment of trichotillomania. Novel pharmacological treatments are urgently needed given the problem of access to effective behavioral treatments for most patients and given the substantial proportion of patients for whom this behavioral technique is not tolerable or who still do not experience adequate symptom relief.

Cross-References

► Antidepressants
► Antipsychotic Drugs
► DSM-IV
► Impulse Control Disorders
► SSRIs and Related Compounds Selective

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Tricyclic Antidepressants

Synonyms

TCAs

Definition

Class of antidepressants first developed in the 1950's and named after their chemical structure. They are primarily used to treat depression, anxiety disorders, and pain.

Cross-References

► Antidepressants
► Amitriptyline
► Imipramine
► NARI Antidepressants
► Nortriptyline
► Secondary Amine Tricyclic Antidepressants
► Tertiary Amine Tricyclic Antidepressants

Tricyclo[3.3.1.1^{2,7}]Decan-1-Amine

► Amantadine

Trier Social Stress Test

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Synonyms

TSST

Definition

The *Trier Social Stress Test* (Kirschbaum et al. 1993) is a protocol for the induction of moderate to intense psychosocial stress under laboratory conditions. It comprises a 3 min anticipatory period, a 5 min public speaking task, and a 5 min mental arithmetic task in front of an evaluative panel of two adults. The TSST can be employed in adolescents and adults of all ages; a slightly modified version is used when studying children from the age of 7 years and older (TSST-C). Today, the *TSST* is the most widely used psychosocial stress protocol in laboratory studies of human subjects and patient populations.

Principles and Role in Psychopharmacology

Stress and Biological Responses to Threat

Psychosocial stress is a major burden for individual and societies alike. The direct and indirect costs of stress amount to billions of Euros and US dollars in many countries because of the fact that approximately 50% of all days of work absence can be attributed to consequences of stress exposure. While such financial effects burden economies significantly, the individual suffering in response to traumatic or chronic psychosocial stress threatens physical and psychological health. In 2001, the World Health Organization (WHO) therefore listed stress "one of the most significant health problems of the twenty-first century."

In search of mechanisms how stress affects well-being and which measures need to be taken in order to avoid adverse health outcomes, research protocols are required for a reliable induction of stress under laboratory conditions. In animals, different footshock or restraint stress paradigms are widely used. Only relatively few laboratories, however, employ more complex stress protocols that mimic stress exposures in modern human societies.

In human stress research, several paradigms and protocols exist for induction of moderate, acute stress responses. Most of these procedures, such as the *cold pressor test* or the *Stroop test,* evoke sympathetic nervous system responses of small or moderate magnitudes. The other most important bodily system, which conveys the brain´s response to threatening and detrimental stimulation to the organs, remains unaffected by such protocols. The ► hypothalamus-pituitary-adrenal (HPA) axis requires more intense stimulation and threat to the ego before a significant increase in ► corticotropin-releasing hormone (CRH), ► adrenocorticotropin hormone (ACTH), or cortisol occurs.

Deliberate stress activation of the human HPA axis has proven to be difficult under ethically acceptable laboratory conditions. Only variable and inconsistent cortisol responses had been obtained with computerized or several other interactive tasks. As revealed in a meta analysis of 208 laboratory stress studies (Dickerson and Kemeny 2004), a combination of social evaluative threat and uncontrollability is required for a reliable and strong ACTH and cortisol release. Social evaluative threat and uncontrollability are key components of the TSST.

The TSST Protocol

The standard TSST protocol requires at least two different rooms and a total of three lab members as a minimum. Upon arrival at the laboratory, subjects are guided to a standard office room for a first rest period of 30–60 min. Then, the experimenter takes them to a second room for the actual stress task. This room is sparsely equipped with two tables and three chairs, a video camera and a microphone. Behind the larger table, two members of an *evaluation panel* are seated, dressed in white lab coats. The test subject is asked to stand at the microphone facing the seated panel approximately 2 m away. The panel members do not speak at this point yet while the experimenter gives instructions for the TSST to the subject. He or she should imagine having applied for open position at a company or an institution. Out of many other applications, he or she was invited to present him or herself before an evaluation panel to convince them that he or she was the best candidate for the job based on his or her personal characteristics. The first of two tasks therefore is to give an oral presentation about his or her personal strengths and positive aspects. The subjects are told that a video will be recorded for later analysis of nonverbal signs of stress and a voice frequency analysis. Furthermore, the two panel members are described as trained in the detection of verbal

and nonverbal stress signals. In order to prepare this speech, the subjects are given 3 min of preparation time, which they spend sitting at the small desk in the same room. Paper and pencil are provided for sketching the talk; however, the notes cannot be used later in the oral presentation. The experimenter now leaves the subject alone with the two evaluation panel members in the room.

After 3 min, the experimenter asks the test subject to step up to the microphone and to begin with the free speech about him or herself in a clear, loud voice. Most test subjects finish their talk after about 2–3 min of speech time. Then one of the panel members asks them to continue their speech since there was still time left. When the subject halts a second time before the first 5 min are over, the two panel members look at the subject with a neutral facial expression and do not speak for 20 s. Thereafter, they begin to ask personal questions (e.g., "Do you have friends?"). After 5 min exactly, the panel member stop the speech and proceed with a second task. They ask the subjects to perform mental arithmetic, subtracting an odd number from a larger number. Depending on the age of the subject, the difficulty of the problem is adjusted (e.g., for healthy young adults, they have to serially subtract 13, starting at 2011). The subjects are told that upon each error, the panel member would ask them to start anew from the initial number. After 5 min of mental arithmetic, the experimenter enters the room again and takes the subject back to the first room where he or she rests for another 20–120 min depending on the psychological or biological measures taken.

As a mandatory part of every TSST (unless a study on habituation of stress responses is conducted), the subjects have to be fully debriefed after the last psychological or biological measure has been obtained. It has proven helpful to have the two panel members come to the tested subject then (without the white lab coats now) and introduce themselves. They should explicitly explain that the test protocol required them to be nonresponsive and cold in the interaction with him or her.

Small variations of the standard TSST protocol are required when testing retired adults or children and adolescents between ages 7 and16 years. The variations pertain to the topic of the free speech task only. Test subjects of advanced age will be presented with a fabricated advertisement which calls for people willing to donate their time for working in a nonprofit organization (e.g., helping with experiments with elderly subjects in a psychology department). The experimenter asks the subjects to talk to the evaluation panel as a job applicant, presenting his or her personal strengths and positive characteristics. When testing children, the so-called TSST-C (Buske-Kirschbaum et al. 1997) protocol is used. Here, the experimenter reads the beginning of the story to the child and asks him or her to continue and finish the story as interesting and suspenseful as possible. All other aspects of the standard TSST protocol are also used in the elderly and young study populations.

Responses to the TSST

A wide range of psychological and biological response parameters have been studied in the past 15 years of TSST research (Kudielka et al. 2007). The TSST typically induces moderate to large subjective and physiological responses that peak 1–30 min after cessation of the stressful procedure. Approximately 80–85% of all subjects tested show a substantial increase in the respective parameters from the resting (baseline) period to peak values. Self-reported negative mood changes and moderate increases in anxiety ratings are typical. Endocrine, immunological, and cardiovascular parameters increase by 50–300% over baseline. Table 1 provides an incomprehensive list of biological parameters, which are significantly changed in response to the TSST.

Repeated Exposure to the TSST

In many instances, a repeated stress exposure is the ideal study design for the investigation of specific treatment effects. For example, the potency of an ► anxiolytic drug

Trier Social Stress Test. Table 1. Biological parameters responsive to TSST exposure.

Endocrine	Immunological	Other
ACTH	Neutrophils	Coagulation factors
Cortisol	Eosinophils	Hemoconcentration
Epinephrine	Basophils	Heart rate
Norepinephrine	Lymphocytes	Heart rate variability
Prolactin	Tumor-Necrosis factor alpha	Blood pressure
Growth hormone	Interleukin 6	Amylase activity
Testosterone	Interleukin 1 receptor antagonist	MAO-A inhibitory activity
DHEA		NFκB
		Electrodermal activity
		Prefrontal cortex activity
		Amygdala activity

could be tested, or the efficacy of a psychotherapeutic intervention studied using a prepost challenge study design. The TSST can be used for such purposes. Careful attention should be paid, however, whether the crucial TSST response read-out parameter shows habituation effects. When parameters controlled by the sympathetic nervous system are the main read-out variables, the standard TSST protocol can be used repeatedly for the same subjects. ACTH or cortisol responses, however, decline upon the second TSST exposure already (Kirschbaum et al. 1995). HPA axis habituation can be circumvented by changing the test setting (novel rooms/labs, panel members, and experimenters) for each TSST.

Using the TSST as a Group Stress Protocol

Researchers have begun to evaluate a modified TSST protocol for use with groups of 2–6 individuals at the same time (Childs et al. 2006). This allows for investigations of complex interactions between members of a certain peer group, or serves as an economical way of stressing larger numbers of individuals within a brief period of time.

A "Placebo" Version of the TSST

When stressing individuals with the TSST, the researcher might want to differentiate between the specific effects of the social-evaluative stress ("distress") and the effort component involved (orthostatic responses, speech-induced physiological changes etc.). A simple no-intervention control session cannot provide such information. It is therefore required to contrast the TSST induced subjective and biological responses with responses observed under similar setting and effort conditions, however, without a distress component. Such a "► placebo" version of the TSST has been published most recently (Het et al. 2009).

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Trifluoperazine

Definition

Trifluoperazine acts at multiple receptors but mainly as an antagonist at dopamine D2 receptors. It is a ► phenothiazine, a first-generation antipsychotic with a plasma ► half-life of around 13 h. The active 7-hydroxymetabolite has a half-life of 10 h.

Cross-References

► First-Generation Antipsychotics

Triggers

► Drug Cues

Trihexyphenidyl

Definition

Trihexyphenidyl is an anticholinergic agent that binds to M1 ► muscarinic receptors. It blocks the parasympathetic nervous system and causes relaxation of smooth muscle. It is indicated for the treatment of Parkinsonism and drug-induced ► extrapyramidal symptoms. Toxicity and side effect symptoms resemble that of atropine.

Cross-References

► Anticholinergic Side Effects
► Antimuscarinic/Anticholinergic Agent
► Benzatrapine
► Scopolamine

1,3,7-Trimethylpurine-2,6-Dione

► Caffeine

Trimethylxanthine

► Caffeine

1,3,7-Trimethylxanthine

► Caffeine

Trimipramine

Definition

Trimipramine is a ► tricyclic antidepressant with atypical pharmacological properties. Trimipramine produces moderate enhancement of noradrenergic (NA), serotonergic (5-HT), and dopaminergic (DA) transmission by inhibiting reuptake of the neurotransmitters. It is also a potent antagonist of 5-HT_2 and α_1 adrenergic receptors. In addition to its antidepressant properties, trimipramine also has sedative-hypnotic and anxiolytic effects. Furthermore, due to its moderate effectiveness as a D_2 dopamine receptor antagonist, trimipramine has been evaluated as an ► atypical antipsychotic with some limited clinical effectiveness.

Clinically observable antidepressant effects of trimipramine usually become noticeable after 10 days to 4 weeks of treatment. Trimipramine has strong anticholinergic and anti-adrenergic side effects, including dry mouth, sweating, hypotension, and arrhythmias, as well as other effects such as fatigue, dizziness, drowsiness, confusion (especially in the elderly), anxiety, nightmares, increased appetite and, more rarely, hypomania, seizures, delirium, and hematological and hepatic problems.

As with other antidepressants, abrupt termination of therapy triggers withdrawal symptoms, including rebound depression, anxiety, insomnia, or mania.

Tripping

► Hallucinogen Abuse and Dependence

TrkB

Definition

The receptor for ► brain-derived neurotrophic factor (BDNF). It is a receptor protein tyrosine kinase.

Trophic Factors

Definition

The original definition of trophic (from the Greek) is "to nourish." The definition has been expanded to the growth and sustenance of cells and tissues. In biology, the term factor refers to substances (of known or unknown molecular identity) displaying specific actions on specific tissues or cells. The term neurotrophic factor is presently applied to a large number of well-characterized substances with specific actions over cells (neurons and glia) of the peripheral and central nervous system. They are classified in families according to similar molecular characteristics and related biological actions.

Tryptamines

Definition

Tryptamine is the general chemical name for a substance that possesses a bicyclic indole nucleus with an ethylamine moiety attached to the indole 3-position. Within this broad definition, tryptamines may be substituted on the indole ring itself, on the ethylamine side chain, or on the amino group. Molecules with any or all of these types of substitutions would still be generically referred to as tryptamines.

Tryptophan

Definition

Tryptophan is one of eight essential amino acids required by humans; these substances cannot be synthesized by the organism and must therefore be supplied in the diet. Tryptophan is metabolized via the rate-limiting enzyme tryptophan hydroxylase to 5-hydroxytryptophan (5-HTP), which is in turn converted into the major neurotransmitter serotonin (5-hydroxytryptamine; 5-HT). ► Serotonin is broken down to the inactive metabolite 5-hydroxyindoleacetic acid (5-HIAA), but can also be metabolized further to the neurohormone ► melatonin. Tryptophan is sold as a dietary supplement and has been investigated as a mild ► hypnotic and as an adjunctive agent to enhance the efficacy of ► antidepressant drugs; studies of such uses have been inconclusive. In the early 1990s, tryptophan was implicated in the pathogenesis of eosinophilia–myalgia syndrome (EMS), a potentially disabling autoimmune reaction; subsequent investigation suggested that impurities introduced during a flawed manufacturing process

were responsible, although some authorities have held that tryptophan itself is also implicated.

Cross-References

► Melatonin
► Serotonin

Tryptophan Depletion

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Synonyms

Dietary tryptophan depletion; Rapid tryptophan depletion

Definition

Acute tryptophan depletion (ATD) is a technique designed to investigate directly the effects of low serotonin levels in humans. Participants in ATD studies ingest an amino acid mixture that is devoid of tryptophan. This lowers brain tryptophan and, therefore, brain serotonin synthesis.

Principles and Role in Psychopharmacology

Principles of ATD

Ingestion of an amino acid mixture containing all the essential amino acids except for tryptophan induces protein synthesis. As tryptophan is incorporated into protein its level in the blood and tissues declines. Because brain tryptophan hydroxylase, the rate-limiting enzyme on the pathway from tryptophan to ► serotonin (5-hydroxytryptamine, 5-HT), is not normally saturated with tryptophan this results in a decline in serotonin synthesis. ATD was originally developed to investigate the symptoms associated with low brain serotonin levels. It has also been used in conjunction with drugs (and nonpharmacological treatments) to see effects of the drug that are reversed by ATD. Reversal of the effect suggests that normal serotonin function is an important component of the drug effect. The assumption behind the ATD method is that decreased synthesis of serotonin results in decreased release of serotonin from neurons, i.e., decreased serotonin function. This assumption remains untested but presumably the extent to which changes in serotonin synthesis will change release of serotonin depends in part on the firing rate of serotonin neurons, which may vary depending on the exact experimental conditions used. Therefore, the question of whether changes in serotonin synthesis lead to changes in serotonin function is too simplistic. The relevant issue is whether there are circumstances in which it is possible to demonstrate that ATD leads to changes in aspect of brain function that seem to be mediated by serotonin. Furthermore, because the coupling between serotonin synthesis and serotonin function is not necessarily the same in humans and experimental animals, studies on the effect of ATD on extracellular levels of serotonin in rodents may not be relevant to human studies.

Methodology of ATD

The principles, methodology, and results of ATD studies have been discussed in a number of reviews (Hood et al. 2005; Neumeister 2003; Young and Leyton 2002). The most commonly used amino acid mixture is that of Young et al. (1985), which is based on the amino acid content of human milk (and therefore presumably optimized for human consumption) and contains 100 g of amino acids. The control mixture is usually the same except for the addition of 2.3 g L-tryptophan. Both control and active mixtures contain no ► glutamate, glutamine, aspartate, or asparagine to reduce the size of the mixture and to avoid any potential adverse effects of the ingestion of large quantities of these free amino acids. As they are not essential amino acids, this should not alter the ability of the tryptophan deficient mixture to lower tryptophan levels. Some researchers have used mixtures that omit more of the nonessential amino acids, while some have used 50 g of amino acids in the same proportion as in the 100 g mixture. The 102.3 g control amino acid mixture will tend to lower brain tryptophan levels somewhat, like most proteins, because it has lower levels of tryptophan than of the other large neutral amino acids that tend to inhibit tryptophan uptake into brain. While this could be seen as an advantage, as it is a conservative control, some researchers have used control mixture with higher tryptophan levels. There is little evidence from direct comparisons of different methods on the advantages and disadvantages of the various depletion and control mixtures.

Plasma tryptophan reaches its lowest level in about 5 h after amino acid mixture ingestion and experimental measures are usually performed 4–7 h after mixture ingestion. Depletions of plasma tryptophan are normally in the range 70–90%, with even greater lowering of serotonin synthesis as measured by positron emission tomography. Depletion of tryptophan is usually greater in women than in men. How large the depletion needs to induce

changes in mood is not clear, but the decline in plasma tryptophan probably needs to be more than 50% (Booij et al. 2002).

Effects of ATD

The majority of ATD studies have noted effects on mood, behavior, and cognition in drug-free participants. ATD has a wide range of effects on mood, depending on the characteristics of the participant undergoing the procedure. In general, effects are greater in those with a greater susceptibility to ▶ depression. For example, healthy never depressed males usually show no change in mood, but healthy never depressed males with a family history of depression show a modest lowering of mood. In keeping with the greater incidence of depression in women than in men, healthy never depressed women sometimes (but not always) show a modest lowering of mood. Formerly, depressed patients off medication occasionally show a dramatic lowering of mood into the clinical range that resolves quickly at the end of the study once brain serotonin synthesis is normalized. Effects in such patients are more likely to be seen with recurrent depressive episodes, female gender, and previous suicidal ideation or attempts. There is some evidence that supports the idea that the magnitude of the effect on mood after ATD may be a predictor of future depression, but more research is needed on this topic. Overall, studies in drug-free individuals suggest that low serotonin can contribute directly to lowered mood, but that it is not sufficient by itself to lower mood. The other neurochemical factors contributing to a susceptibility to lowered mood after ATD are not known.

Effects of ATD on ▶ anxiety in health individuals, when seen, are smaller than those on mood. ATD has no effect on untreated patients with panic disorder and has minimal effect on the response to panicogenic treatments. In keeping with the large animal literature showing that low serotonin increases ▶ aggression, ATD has been shown in several studies to increase the response in laboratory tests of both aggression and impulsivity. Results of the effect of ATD on cognition have not always been consistent, but there is some consistency in the findings that ATD has adverse effects on aspects of memory, particularly memory ▶ consolidation, while it can improve focussed ▶ attention. Effects on cognition have been seen in the absence of effects on mood.

ATD has been used to investigate the role of serotonin in a variety of ▶ antidepressant treatments. In newly recovered depressed patients who are on serotonin reuptake inhibitors, the majority of patients showed a marked lowering of mood, similar to that when they were depressed, which resolves when their serotonin synthesis is normalized. No such effect is seen in patients on norepinephrine reuptake inhibitors. These results suggest that, in the short-term, maintenance of serotonin function is necessary component of the antidepressant action of serotonin reuptake inhibitors, but not norepinephrine reuptake inhibitors. In a small number of studies ATD also reversed the antidepressant effect of bright light therapy and ▶ monoamine oxidase inhibitors, but not that of ▶ tricyclic antidepressants, lithium, electroconvulsive therapy, and cognitive therapy. While ATD reverses the therapeutic effect of serotonin reuptake inhibitors in patients with depression, results in anxiety disorders are not as clear-cut. ATD can enhance the response to panicogenic agents in patients with panic disorder who are on serotonin reuptake inhibitors, and reverse the therapeutic effect in patients with social anxiety disorder. It does not cause greater obsessive or compulsive symptoms in patients with ▶ obsessive-compulsive disorder (OCD), who have responded to treatment with a serotonin reuptake inhibitor. On the other hand, such patients may show lowered mood or enhanced anxiety, raising the possibility that the therapeutic effect of serotonin reuptake inhibitors in OCD may be due in part to effects on mood and anxiety rather than directly on the core symptoms of OCD.

Other studies have used ATD to look at the role of serotonin in the action of a variety of different drugs. The number of these studies is small and results must be considered tentative. ATD has little effect on symptoms in patients with ▶ schizophrenia treated with ▶ neuroleptics. It decreased the cocaine-induced high and desire for cocaine suggesting that serotonin release has a role in the action of ▶ cocaine. It blocked the analgesic effect of morphine in response to the cold pressor test in participants, who had not taken ▶ morphine previously. However, the relevance of this to a role for serotonin in the clinical analgesic effects of morphine are not clear. Finally, ATD decreases the release of prolactin in response to the serotonin releaser, ▶ fenfluramine, suggesting that fenfluramine releases primarily newly synthesized serotonin.

Ethical aspects of ATD

Given that low serotonin is associated with depression, aggression, and ▶ suicide, participants in ATD studies need to be monitored carefully. At the end of an ATD study, serotonin levels of participants should be restored to normal as quickly as possible. This is best done by administration of tryptophan, but has been done more often by allowing participants to eat high protein foods. In a study of ATD in recovered depressed patients, some of whom re-experienced depressed mood, the participants

had a positive opinion of their participation in the study. Common views were that participation in the study had changed their perception of their illness, that the study had helped them to gain more insight and facilitated acceptance of being vulnerable and had made them realize how much they had improved during treatment (Booij et al. 2005).

Limitations of ATD

From the practical point of view one of the limitations of the ATD method is the unpalatability of the amino acid mixtures, which often results in nausea and sometimes vomiting. Various strategies have been adopted to reduce these symptoms, including adding strong flavors such as chocolate to the amino acid mixtures and putting the more unpalatable amino acids in capsules, but they do not eliminate the problem. From the theoretical point of view, a limitation is that relating any effect of ATD to lowered serotonin function involves two main assumptions. First, the effect seen is due to decreased release of serotonin; and second, other mechanisms do not contribute to the effect. Amino acid imbalance can alter aspects of brain function. However, the effects of ATD are unlikely to be due just to nonspecific effects of amino acid imbalance as (1) ► acute phenylalanine/tyrosine depletion causes somewhat different effects from ATD, and (2) in one study the effects on mood seen with ATD did not occur when a positive control mixture deficient in lysine was used (Klaassen et al. 1999). ATD will tend to lower the levels of tryptophan metabolites in addition to serotonin. These include tryptamine, ► melatonin, kynurenic acid, and quinolinic acid. While a contribution of these compounds to the effect of ATD cannot be ruled out, given that the effects of ATD are consistent with other research on the role of serotonin, effects of the other compounds are unlikely. Finally, an important limitation in extrapolating from ATD studies to the role of low serotonin in psychopathology, or to the role of serotonin in drug effects, is the short duration of the effect of ATD on serotonin. Longer-term depletion of serotonin through repeated administration of amino acid mixtures is not advisable due to the effects such a strategy would have on protein synthesis and amino acid metabolism.

Cross-References

► Aggressive Behavior
► Amine Depletors
► Aminergic Hypotheses for Depression
► Antidepressants
► Emotion and Mood
► Impulsivity
► Obsessive-Compulsive Disorders
► Panic Disorder
► Social Anxiety Disorder
► SSRIs and Related Compounds

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TSA

► Trichostatin A

Tschat

► Khat

TSST

► Trier Social Stress Test

Two-/One-Way Active Avoidance

► Active Avoidance

Two-Dimensional Gel Electrophoresis

Synonyms

2-DE; 2-D Electrophoresis; Gel electrophoresis

Definition

Two-dimensional gel electrophoresis is based on the separation of proteins in two dimensions based on differences in isoelectric point (pI), and size (molecular weight, Mw). The first dimension, isoelectric focusing (IEF), is usually performed using individual drystrips with immobilized pH gradients (IPG). A number of different pH ranges are available from wide range strips to more narrow-range drystrips. The second dimension in 2-DE is a traditional sodium dodecyl sulfate-polyacrylamide electrophoresis (SDS-PAGE) separation. A wide variety of protein detection methods are compatible with 2-DE such as Coomassie Brilliant Blue, silver staining, and fluorescent staining.

Cross-References

- ► Electrospray
- ► Electrospray Ionization (ESI)
- ► Mass Spectrometry (MS)
- ► Matrix-Assisted Laser Desorption Ionization (MALDI)
- ► Post-Translational Modification
- ► Proteomics

Typical Antipsychotics

Synonyms

Classical neuroleptics; Conventional antipsychotics; First-generation antipsychotics

Definition

Typical antipsychotics are a class of antipsychotic drugs first developed in the 1950s to treat schizophrenia. Typical antipsychotics may also be used for the treatment of acute ► mania, agitation, and other conditions.

Cross-References

- ► Antipsychotic Drugs
- ► Bipolar Disorder in Children

Typical Neuroleptics

- ► First-Generation Antipsychotics

U

Ubiquitin-Proteasome System

Synonyms
UPS

Definition
A specialized system in the cell for regulating the protein composition of cells. Degraded, misfolded, or aberrant proteins are tagged by ubiquitylation for removal by digestion at the cytoplasmic 20/26S proteasome enzyme complex.

Ultrasonic

Definition
Refers to sound energies having a frequency above the human hearing range. The highest frequency that the human ear can detect is approximately 20 thousand cycles per second (20,000 Hz).

Attachment bonds have been proposed to underlie a variety of social relationships, for example, parent–infant, filial, and pair (male–female) bond formation. These are all typically characterized by preferential proximity seeking and all involve a response to separation. These forms of attachment appear to be common to many species including humans, suggesting that the neural basis can be investigated in animal models. Emerging evidence suggests that the biology of attachment in its many forms may also be similar across species.

Ultrasonic Vocalizations

Definition
Ultrasound is a sound with a frequency greater than the upper limit of human hearing, which is approximately 20 kHz (20,000 Hz). Adult rats emit two types of ultrasonic calls: alarm (22 kHz) calls, in aversive and dangerous situations, and appetitive (50 kHz) calls, in appetitive or nonaggressive situations. Both mouse and rat pups emit high-frequency separation/distress calls when separated from their mothers. Adult mice produce ultrasonic vocalizations during nonaggressive situations, particularly during mating. These vocalizations can facilitate or inhibit social interactions.

Cross-References
► Autism: Animal Models
► Distress Vocalization

Unblocking

Synonyms
Post-trial surprise

Definition
The liberation of attention for new learning that is seen when an unconditioned stimulus is either more or less than expected. This is an effect seen in classical (Pavlovian) conditioning and a constraint on the general importance of temporal coincidence as the sole determinant of new learning.

Cross-References
► Classical (Pavlovian) Conditioning

Unconditional Response

Synonyms
UR

Definition
A response elicited by a unconditioned stimulus without previous learning.

Ian P. Stolerman (ed.), *Encyclopedia of Psychopharmacology,* DOI 10.1007/978-3-540-68706-1,

Unconditioned Stimulus

Synonyms
US

Definition
An unconditioned stimulus, for example, electrical shock, elicits a characteristic behavioral response without previous learning (i.e., an unconditioned response).

Unipolar Depression

► Major and Minor and Mixed Anxiety-Depressive Disorders

Unit Price

Definition
The *unit price* is the cost per benefit unit of a commodity.

Cross-References
► Behavioral Economics

Unrelated

► Behavioral Economics
► Independents

Unsatisfactory Sleep

► Insomnias

UPS

► Ubiquitin-Proteasome System

Uptake

Definition
Uptake or reuptake consists in the reabsorption of a neurotransmitter by a transporter located on a presynaptic neuron, or another cell, after it has performed its function of transmitting the signal. Reuptake is necessary for normal functioning because it regulates how long a signal lasts, allowing the recycling of neurotransmitters, and regulating its normal levels in the releasing cell. The uptake process can be experimentally assessed as the incorporation of radiolabeled neurotransmitter by the target cell.

UR

► Unconditional Response

Urge

Synonyms
Craving

Definition
Urge is an involuntary impulse promoting engagement in a given activity.

Cross-References
► Impulse Control Disorders

Urge-Driven Behaviors

► Impulse Control Disorders

US

► Unconditioned Stimulus

Usefulness

► Effectiveness

Utilitarianism

Definition
The philosophical doctrine that an action is right if it promotes happiness and the greatest happiness of the greatest number should be its guiding principle.

V

V_3''

► Binding Potential

Vaccination

Synonyms

Active immunization

Definition

Repeated administration of an immunogen (e.g., vaccine) to the subjects being studied in order to stimulate the immune system to produce drug-specific antibodies. Primary advantages of vaccination are that it requires relatively few administrations to achieve high serum antibody concentrations that can persist for several months and it is relatively inexpensive. The main disadvantages are the delay (1–2 months) to reaching effective serum antibody concentrations and the inability to precisely control those concentrations. Marked variability in antibody concentrations is observed between subjects, with some not achieving required levels.

Vaccines and Drug-Specific Antibodies

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Synonyms

Immunotherapy

Definition

In the context of psychopharmacology, vaccines are drug–protein conjugates that stimulate a subject's immune system to produce drug-specific antibodies that can bind a drug of interest and alter its pharmacokinetics.

Pharmacological Properties

Background

Vaccines and drug-specific antibodies are currently being developed for the treatment of ► drug abuse. Most pharmacotherapies for drug abuse target the neuropharmacological processes that mediate a drug's dependence-related behavioral effects by binding to associated receptors in the CNS (► Nicotine dependence and its treatment, ► Opioid Dependence and its treatment). In contrast, vaccines target the drug itself rather than the brain. Vaccines elicit the production of drug-specific antibodies that bind drug in blood and reduce its distribution into the brain. By acting outside the brain, a primary advantage of vaccines is that they lack the CNS side effects associated with CNS receptor-based pharmacotherapies that can alter normal neural function.

Immunologic interventions such as ► vaccination or ► passive immunization were first suggested as a pharmacologic approach to treating drug abuse over 30 years ago, when it was shown that immunization against ► heroin could reduce the self-administration of the drug in monkeys (Bonese et al. 1974). Since then, vaccines and drug-specific antibodies that are effective in modifying the ► pharmacokinetics and behavioral effects of a wide range of drugs of abuse in animals have been developed, and vaccines against ► cocaine and ► nicotine are currently in clinical trials (Kosten and Owens 2005; Orson et al. 2008; Pentel et al. 2007).

Mechanisms of Action

Drugs of abuse act as reinforcers, and the pharmacokinetic properties of drugs are key determinants of their reinforcing effects (► Operant behavior in animals, ► Pharmacokinetics). The concentration of drug in the brain and the rate at which drug enters the brain are directly related to the strength of its subjective and reinforcing effects. In addition, the rate of elimination of drug is inversely related to the duration of its subjective and reinforcing effects. Vaccines and drug-specific antibodies target these key pharmacokinetic processes.

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The antibodies produced by vaccination against a given drug contain binding sites for that drug. In a vaccinated subject, these drug-specific antibodies are present in the bloodstream and extracellular fluid, but excluded from the brain because they are too large to cross the ► blood–brain barrier. When a vaccinated subject receives the drug, a substantial fraction of the drug is bound to antibody, sequestered in blood, and prevented from entering the brain. The binding of drug in serum also attenuates the normally rapid rise in brain concentrations of drug. In addition, the binding of drug by antibody may make it less available for elimination and prolong its elimination half-life (Orson et al. 2008; Pentel et al. 2007). Slower elimination may be a beneficial effect in some circumstances, as it has been associated with reduced cigarette smoking and enhanced smoking cessation rates.

The efficacy of a vaccine depends upon three key variables: the serum concentration, affinity, and specificity of the elicited antibodies. Because higher ratios of antibody to drug result in greater binding of drug in serum, vaccines must elicit high serum concentrations of antibody to be maximally effective. Higher affinity (strength of binding to drug) increases the bound fraction of drug. Specificity refers to the extent to which the antibodies bind the drug in preference to other compounds. Greater specificity reduces competition from other compounds (e.g., metabolites, endogenous compounds) for antibody-binding sites and reduces the likelihood of adverse side effects. However, in cases where the metabolites of a drug contribute to its behavioral effects (e.g., ► methamphetamine, heroin), antibodies that cross-react with those metabolites would be advantageous.

Although vaccines and receptor antagonists can produce similar attenuation of a drug's behavioral effects, they should not be considered analogous. Receptor ► antagonists block the binding of endogenous compounds (e.g., dopamine, acetylcholine) to receptors, while antibodies do not. In addition, drug-specific antibodies can have the additional effect of increasing the ► elimination half-life of drug, while receptor antagonists do not.

Formulation

Because drugs are typically too small to elicit an immune response, they are rendered immunogenic by linking the drug itself or a structurally related compound (i.e., hapten) through a short linker to an immunogenic carrier protein to form the complete immunogen, which is referred to as a conjugate vaccine. To enhance the immune response, these vaccines are typically combined with an adjuvant such as alum. Carrier proteins are foreign (nonhuman) proteins (Kosten and Owens 2005; Orson et al. 2008), but virus-like particles have also been used (Maurer et al. 2005).

Administration

Initial vaccination schedules in both animals and humans typically involve 2–6 injections at 2–4 week intervals. Periodic booster doses are then needed to maintain satisfactory antibody levels since exposure to the drug by itself, which is not the complete immunogen, does not elicit a booster response (Hatsukami et al. 2005; Martell et al. 2005; Maurer et al. 2005; Orson et al. 2008).

Animal Models

Pharmacokinetics: The effects of immunologic interventions on drug pharmacokinetics are generally similar across different drugs (Kosten and Owens 2005; Orson et al. 2008; Pentel et al. 2007). In rodents, vaccines or drug-specific antibodies produce increases in serum drug concentrations due to the binding and retention of drug in serum, and reduce brain concentrations of cocaine, ► phencyclidine, methamphetamine, morphine, and nicotine following an acute administration of clinically relevant doses. Importantly, some studies have shown that the early distribution of an acute dose to the brain continues to be reduced or slowed during chronic drug administration, even when total drug exposure exceeds the binding capacity of the antibodies (Kosten and Owens 2005; Pentel et al. 2007). This finding suggests that the initial subjective and reinforcing effects of a drug could still be suppressed in the context of ongoing drug use. Finally, immunization can markedly prolong the ► elimination half-life of some drugs because antibody binding restricts elimination to the unbound fraction of drug. For example, immunization can produce a twofold to sixfold increase in the half-life of nicotine and morphine in rats and rabbits, respectively (LeSage et al. 2008; Orson et al. 2008).

Behavioral effects: Animal studies have shown that vaccines and drug-specific antibodies can significantly reduce the behavioral effects of the aforementioned drugs in a wide range of behavioral assays, including seizure induction, acute locomotor activation, development of locomotor sensitization, responding under simple operant schedules of food delivery, and ► drug discrimination. Active or passive immunization against cocaine, methamphetamine, nicotine, and heroin have also been shown to attenuate the acquisition, maintenance, and reinstatement of self-administration of these drugs, which are key animal models of drug use and relapse in humans (► Reinstatement of drug self-administration, ► Self-administration of drugs, ► Addictive disorder: animal models, ► Operant behavior

in animals) (Kosten and Owens 2005; LeSage et al. 2008; Orson et al. 2008). Immunization can also decrease the ability of drug to relieve withdrawal symptoms that occur upon the cessation of drug exposure, yet it has not been found to elicit withdrawal signs when initiated during chronic drug administration (► withdrawal syndromes) (LeSage et al. 2008; Lindblom et al. 2005).

Clinical Trials

Immunogenicity and Safety: Clinical trials have been conducted with three nicotine conjugate vaccines (NicVax, NicQb, and TA-NIC) and one cocaine conjugate vaccine (TA-CD) (LeSage et al. 2008; Orson et al. 2008) (► Randomized controlled trials). Phase I/II trials have shown that these vaccines elicit drug-specific antibodies in a dose-dependent fashion, with marked variability between participants. All vaccines have been well tolerated with no serious adverse events. Antibody levels decrease slowly after the last vaccine injection of the initial immunization period (e.g., 50% decline over 6–8 weeks), but increase again when a booster dose is administered.

Potential Efficacy: Although no Phase III trials have been conducted to rigorously assess the efficacy of vaccination for nicotine or cocaine addiction, the Phase I/II trials mentioned earlier included drug use as either a primary or secondary endpoint to provide the preliminary assessment of efficacy. In general, these trials have shown increased abstinence and reduced drug use in participants receiving the highest vaccine dose or exhibiting the highest antibody levels (LeSage et al. 2008; Orson et al. 2008). Importantly, neither withdrawal symptoms nor compensatory increases in drug use to surmount the effect of vaccination have been reported (Hatsukami et al. 2005).

Conclusion

Taken together, both preclinical and clinical studies suggest that vaccines could have utility in the treatment of drug addiction. However, the lack of control over antibody levels and large variability between subjects is the primary limitation of all current vaccines. Because achieving the highest antibody levels possible will be essential to maximizing the efficacy of vaccination, methods of boosting immunogenicity need to be developed in order to address this issue. Toward this end, vaccine formulations that contain novel haptens, different adjuvants and/or carrier proteins, multivalent vaccines (simultaneous administration of two or more distinct drug–protein conjugates), and combinations of vaccination with passive immunization are being explored (Keyler et al. 2008; Kosten and Owens 2005). Although not explicitly tested, vaccines would not be expected to directly reduce drug ► craving or withdrawal, since these occur when drug levels are already low or absent. Combining vaccination with medications that address craving and withdrawal might therefore enhance their efficacy.

Cross-References

► Addictive Disorder: Animal Models
► Drug Discrimination
► Nicotine Dependence and Its Treatment
► Operant Behavior in Animals
► Opioid Dependence and Its Treatment
► Passive Immunization
► Pharmacokinetics
► Randomized Controlled Trials
► Reinstatement of Drug Self-administration
► Self-administration of Drugs
► Vaccination
► Withdrawal Syndromes

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Vagus Nerve Stimulation

Synonyms
VNS

Definition
A technique for activating brain neurons through the stimulation of afferent fibers of the left vagus nerve by electrical impulses from a small generator implanted in the upper chest. Introduced in the 1990s to treat epilepsy, VNS is clinically available and may be beneficial in severe depression that is resistant to pharmacotherapy. In addition to the risks of implantation surgery, the most common side effects are vocal changes and hoarseness.

Valproic Acid

Synonyms
Convulex; Depakene; Depakine; Epival; Stavzor; Valproate

Definition
A simple branched-chain carboxylic acid that possesses antiseizure and mood-stabilizing properties is rapidly absorbed after oral administration, and exhibits 90% binding to plasma proteins, hepatic metabolism, and a half-life of approximately 15 h.

Valproic acid is used for the treatment of convulsions, migraines, and acute manic or mixed episodes associated with psychiatric disorders. Valproate exerts its effects by increasing the concentration of gamma-amino-butyric acid (GABA) through inhibition of enzymes catabolizing GABA: transferase and succinic aldehyde dehydrogenase. Valproic acid is also a histone deacetylase inhibitor, a property that might be responsible for its teratogenic effects. The side effects due to valproic acid include liver injury, pancreatitis, abnormal bleeding, and birth defects, drowsiness, dizziness, nausea, vomiting, indigestion, diarrhea, weight loss, and tremors. If taken during pregnancy there is a risk of harm to the offspring.

Cross-References
► Anticonvulsants
► Autism: Animal Models
► Mood Stabilizers

Values-Based Medicine

Definition
The theory and practice of effective healthcare decision-making for situations in which legitimately different, and hence potentially conflicting, value perspectives are in play.

Varenicline

Definition
Varenicline is a nicotinic partial agonist developed specifically as a smoking cessation agent. As a partial agonist, it reduces ► cravings for and decreases the pleasurable effects of cigarettes and other tobacco products, and also attenuates effects of nicotine obtained by smoking. Through these mechanisms, it can assist some patients to quit smoking, where its efficacy appears greater than that for nicotine replacement therapies. Its primary action as a ► partial agonist is on the $\alpha4\beta2$ subtype of the ► nicotinic acetylcholine receptor. In addition, it acts on $\alpha3\beta4$ and weakly on $\alpha3\beta2$ and $\alpha6$-containing receptors. A full agonist effect has also been shown on $\alpha7$-receptors. Nausea occurs commonly in people taking varenicline. Other less-common side effects include headache, difficulty in sleeping, and abnormal dreams. Rare side effects reported by people taking varenicline compared to placebo include change in taste, vomiting, abdominal pain, flatulence, and constipation. There has been some concern about more serious neuropsychiatric symptoms.

Cross-References
► Nicotine
► Nicotine Dependence and Its Treatment
► Nicotinic Agonists

Vascular Dementia

Synonyms
Multi-infarct dementia

Definition
Vascular dementia is the second most common form of dementia after ► Alzheimer's disease (AD) in older adults. The term refers to a group of syndromes caused by different mechanisms all resulting in vascular lesions in the brain. Early detection and accurate diagnosis are important, as vascular dementia is at least partially preventable.

Vasoflex®

► Prazosin

Vasopressin

► Arginine-Vasopressin

V_D

► Volume of Distribution

VDCC

► Voltage-Gated Calcium Channels

Venlafaxine

Synonyms
Venlafaxine hydrochloride

Definition
Venlafaxine was the first ► SNRI developed and was marketed as Effexor in the USA, the European Union, and elsewhere in the 1990s. Because it has been available longer than other members in its class and in a greater number of countries, more clinical data have accumulated to describe its efficacy, tolerability, and safety. In the USA, it is approved for major depressive disorder in adults as well as for the treatment of certain anxiety disorders including ► generalized anxiety disorder, ► social anxiety disorder, and ► panic disorder. Venlafaxine is available in two different formulations: an immediate release tablet and an extended release capsule.

Venlafaxine Hydrochloride

► Venlafaxine

Venoms

► Neurotoxins

Ventral Tegmental Area

Synonyms
VTA

Definition
The ventral region of the midbrain, where ► dopamine (DA) cell bodies that project to limbic structures and cortical areas are located.

Ventromedial Prefrontal Cortex

Definition
Ventromedial prefrontal cortex is a part of the ventral part of the brain that plays a role in decision-making and the processing of fear and risk-taking.

Cross-References
► Impulse Control Disorders

VEOS

► Pediatric Schizophrenia

Verbal and Non-Verbal Learning in Humans

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Synonyms
Associative learning; Motor learning; Novel word learning

Definition
Learning is the acquisition of a new ability. The most relevant areas are knowledge, behavior, and skills. In this chapter, non-verbal learning mainly focuses on motor functions and how this learning can be influenced by psychoactive drugs in health and disease. Verbal learning explicitly focuses on the use of language and how our ability to learn and recall new words is modified by psychoactive drugs.

Impact of Psychoactive Drugs

One major aspect of learning is the ability to encode and recall new material or a new function. A neurobiological correlate of learning and memory is ►long-term potentiation (LTP). In LTP, ►synaptic plasticity is evoked by repeated and synchronized firing of pre- and postsynaptic neurons. Thus, all substances that induce or enhance LTP might support or augment learning capacities. Several lines of evidence suggest that ►glutamate metabolism and in particular *N*-methyl-D-aspartate (NMDA) agonists facilitate LTP induction.

Animal experiments have also indicated other neurotransmitters that are presumably involved in learning. For example, in rats the acquisition of motor skills is improved by noradrenergic substances. Lesions of dopaminergic neurons can produce cognitive deficits and impair attentional processes which are relevant for learning abilities.

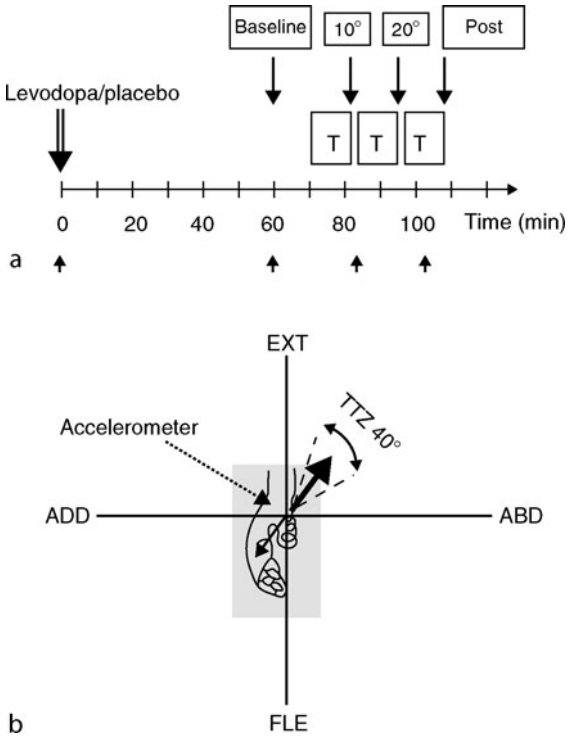
In some learning paradigms, e.g., the serial reaction time task, it is possible to follow the process of learning and to detect the development of implicit and explicit knowledge. In most paradigms, however, it is rather tested whether learning had occurred and whether the application of a psychoactive drug had been able to speed up the learning process or the amount of what had been learnt.

Non-Verbal Learning in Humans

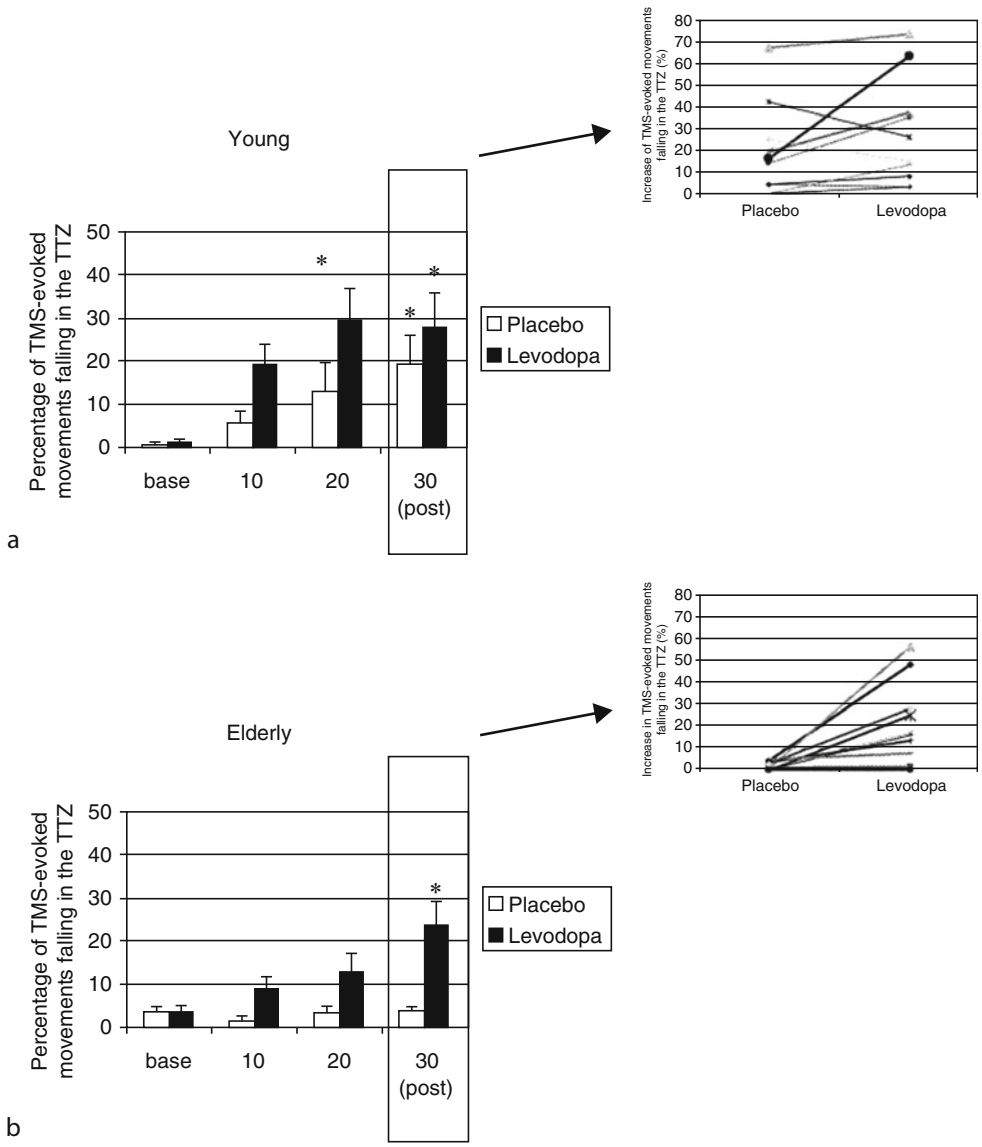
Dopaminergic Drugs

Healthy Subjects The application of a single dose of ►levodopa (100 mg) was able to improve a training-induced motor memory. The task consisted of practising of thumb movements in a different direction than thumb movements evoked by transcranial magnetic stimulation (TMS). After the training period, TMS induced thumb movements in the new, practised direction. In young subjects, the encoding process of this movement was accelerated by levodopa. Elderly subjects performed worse in this task but improved their motor memory encoding by intake of levodopa to levels present in younger subjects (Flöel et al. 2005a; Figs. 1 and 2). Presumably, older subjects have a subclinical dopaminergic deficit per se. Application of 300 mg levodopa induced a small, but significant improvement of motor functions even without training. This effect was only seen in elderly, but not in young subjects. In a study that used a tactile coactivation protocol to induce non-associative learning in the somatosensory system, tactile two-point discrimination was only improved after placebo, but not after levodopa application, suggesting that a potential beneficial effect of levodopa in the motor system is not necessarily generalized to other systems.

Patient Groups In stroke patients, several studies using multiple or single doses of levodopa have been published.



Verbal and Non-Verbal Learning in Humans. Fig. 1. (**a**) Experimental design. L-Dopa/placebo was administered at time 0 in each session, followed by determination of transcranial magnetic stimulation (TMS)-evoked thumb movement directions at baseline (60 min after drug intake) and after 10, 20, and 30 (post) min of training (*downward arrows*). Training consisted of three blocks of brisk thumb movements performed at 1 Hz in the direction opposite to the baseline TMS-evoked thumb movement direction (*T*). Fatigue, attention towards the training task, blood pressure, and heart rate were assessed four times during the experiment (*upward arrows*). (**b**) Diagram showing measurement of thumb movements with an accelerometer positioned on the distal interphalangeal joint (rectangle on the thumb). Baseline TMS-evoked thumb movements in this example fell in a flexion-adduction direction (*thin solid arrow*). Training voluntary thumb motions were performed in the opposite direction (extension-abduction, *thick solid arrow*). At the end of the training period, we measured the percentage of TMS-evoked thumb movements falling in the training target zone (TTZ), the end point measure of the study. (From Flöel et al. 2005a.)



Verbal and Non-Verbal Learning in Humans. Fig. 2. Percentage of ► transcranial magnetic stimulation (TMS)-evoked thumb movements falling in the training target zone (TTZ) in young (**a**) and elderly (**b**) healthy volunteers. In young subjects (**a**), training under placebo led to a progressive increase in TMS-evoked thumb movements falling in the TTZ that became significant after 30 min (A, 30 min [post], *white bar*). L-Dopa + training accelerated the development of this form of plasticity, which became significant after only 10 min of training (A, 10 min, *black bar*). In elderly subjects (**b**), consistent with previous results, training under placebo did not induce changes in TMS-evoked thumb movements falling in the TTZ (B, 30 min [post], *white bar*). L-Dopa + training substantially enhanced the response to motor training, which became significant after 30 min (B, 30 min [post], *black bar*), and that was comparable in magnitude with that identified in younger subjects under placebo and L-dopa (A, 30 min [post], *black* and *white bars*). Note that this effect was evident in five of the seven elderly subjects tested (inset). To illustrate the percentage change in the training + L-dopa versus the training + placebo condition, we summarize the mean change for each subject in each condition in the above insets (A, young; B, elderly). *$p < 0.05$. (From Flöel et al. 2005a.)

Results are inconsistent. In one study with repeated intake of 100 mg levodopa per day for 3 weeks, patients improved in their motor functions significantly stronger than the placebo group. This higher level of performance persisted even after termination of the drug intake period (Scheidtmann et al. 2001). However, a more recent ▶ placebo-controlled study with application of 100 mg levodopa per day for 2 weeks did not demonstrate a superiority of levodopa. Single doses of levodopa were effective in the encoding of a motor memory and in improving procedural motor learning (serial reaction time task) (Flöel et al. 2005b) but did not modulate more clinical aspects of motor functions (dexterity and strength) (Liepert 2008).

Undoubtly, levodopa reduces motor symptoms in patients with ▶ Parkinson's disease (PD). Astonishingly, its effects on cognitive functions and learning abilities are questionable and have even been shown to be detrimental. For example, PD patients treated with levodopa deteriorated in visual memory functions and motor sequence learning. It was suggested that levodopa effects depend on task demands and basal dopamine levels in distinct parts of the striatum.

Methylphenidate produces an increase in dopamine signalling through multiple actions. A trial with 21 subacute stroke patients indicated that the combination of ▶ methylphenidate with physical therapy over a period of 3 weeks improved motor functions and decreased depression. In patients with traumatic brain injury, the drug improved the speed of mental processing and had some effect on tests of ▶ attention and motor performance.

Noradrenergic Drugs

Healthy Subjects The noradrenaline re-uptake inhibitor ▶ reboxetine improved motor skill acquisition in a velocity-depending motor task (Plewnia et al. 2004).

D-amphetamine modulates not only noradrenergic, but also dopaminergic and serotonergic neurotransmission. In a paradigm with training of voluntary thumb movements, ▶ D-amphetamine facilitated use-dependent plasticity. However, in another study, the administration of D-amphetamine did not improve sensory functions in a tactile frequency discrimination training. There is some evidence that D-amphetamine exerts its effects in cognitive rather than motor networks. For example, D-amphetamine improved performance of ▶ selective attention tasks.

Patient Groups In chronic stroke patients, a single dose of reboxetine improved tapping speed and grip strength in the paretic but not in the non-affected hand.

Studies with D-amphetamine in stroke patients are inconclusive. In two studies, drug effects on motor recovery were found. In subsequently performed studies (n = 6), these positive results could not be replicated. A Cochrane review summarized that it is currently impossible to draw any definite conclusions about the potential role of D-amphetamine in motor rehabilitation (Martinsson et al. 2007).

Serotonergic Substances

Healthy Subjects There are no studies with serotonergic drugs for enhancement of learning in healthy subjects available.

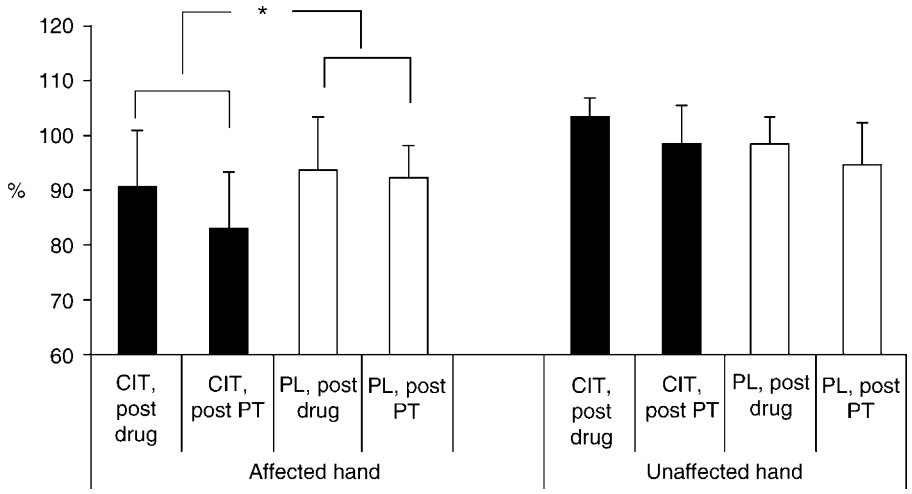
Patient Groups The serotonin re-uptake inhibitor ▶ fluoxetine improved walking and activities of daily living in a group of subacute stroke patients. In eight chronic stroke patients, a single dose of fluoxetine improved motor functions of the affected hand. In another study, the more selective serotonin re-uptake inhibitor ▶ citalopram was used in chronic stroke patients. A single dose of citalopram was able to improve dexterity but not strength in the paretic hand. The effect was pronounced after 1 h of physiotherapy aimed at improving hand function (Zittel et al. 2008; Fig. 3). Taking these three studies together, results seem promising but one has to consider that only a very limited number of subjects have been studied so far.

Cholinergic Substances

This group mainly includes drugs that act as inhibitors of the enzyme acetylcholinesterase. This increases the amount of ▶ acetylcholine. Such drugs have been successfully tested in ▶ dementia and are recommended for patients with mild to moderate Alzheimer's disease.

Healthy Subjects In elderly healthy subjects, ▶ rivastigmine improved motor learning and visuospatial processes. In contrast the ▶ anticholinergic agent biperiden impaired these abilities. In another study ▶ donepezil was applied in elderly subjects and improved their memory performance. In addition, ▶ rapid eye movement (REM) sleep was enhanced, and the positive correlation between memory function and REM sleep duration suggested an interrelationship between these two factors.

Patient Groups There is only limited evidence regarding beneficial effects of ▶ acetylcholinesterase inhibitors in ▶ stroke patients. One case study and one ▶ open-label pilot study suggest that these drugs may enhance the recovery of motor functions, in particular in cognitively



Verbal and Non-Verbal Learning in Humans. Fig. 3. Nine Hole Peg test results, expressed in percentage of the values obtained prior to drug ingestion. CIT, citalopram; PL, placebo; PT, physiotherapy. Error bars indicate standard deviations. *$p < 0.05$. (From Zittel et al. 2008.)

impaired stroke patients. One study combining the application of donepezil with constraint-induced movement therapy only showed a trend towards stronger improvement in the drug-treated group.

Modafinil

This wake-promoting drug is approved for application in patients with abnormal sleepiness, e.g., ▶ narcolepsy and sleep disorders of shift workers. Some studies also suggest that it is helpful in patients with multiple sclerosis suffering from fatigue. A recent study demonstrated that ▶ modafinil blocks ▶ dopamine transporters and increases dopamine in the human brain.

Healthy Subjects Studies in healthy subjects are inconclusive. One study reported a drug-related improvement of several cognitive abilities including digit span, visual pattern recognition memory, spatial planning, and ▶ stop-signal reaction time. Another study suggested an effectiveness in monotonous ▶ working-memory tasks, in a third study modafinil was found to be equal to placebo regarding reaction time, dexterity and the d2 test.

Patient Groups In patients with ▶ Huntington's disease, modafinil increased alertness but did not improve cognitive functions. In contrast, deleterious effects on visual recognition and working memory were observed. In schizophrenic patients, improvements of ▶ executive functions and ▶ attention were found.

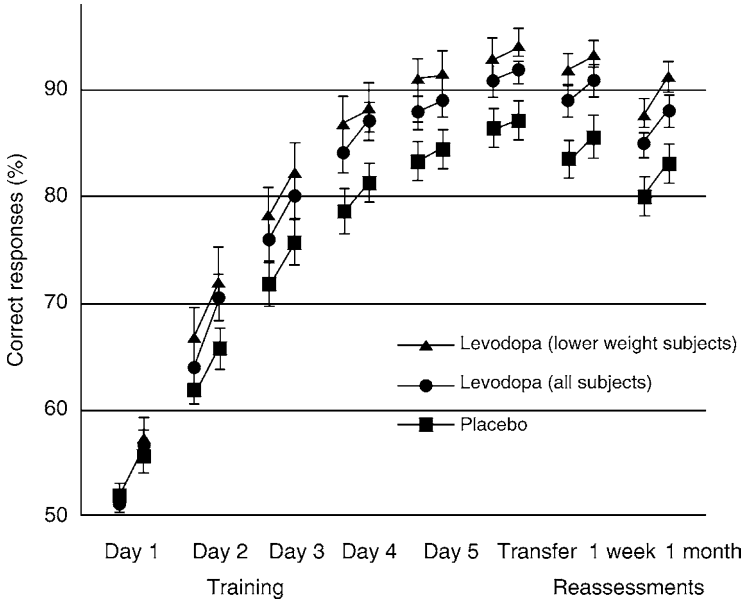
Verbal Learning

Dopaminergic Substances

Healthy Subjects Single doses of 100 mg levodopa improved verbal learning in young healthy subjects. Learning occurred faster and more successful, and the long-term retention of novel word learning was better than in the placebo-treated control group (Knecht et al. 2004; Fig. 4). A comparison between application of levodopa, D-amphetamine and placebo indicated a similar efficacy of levodopa and D-amphetamine and the superiority of both drugs compared to placebo. In contrast to beneficial effects of levodopa, the dopamine-receptor agonist ▶ pergolide impaired novel word learning. The authors suggested that this finding can be explained by the tonic dopaminergic effects produced by pergolide. Due to a much shorter ▶ half-life, levodopa rather exerts a phasic dopaminergic stimulation. Phasic stimulations might be more effective for associative learning.

Patient Groups A very recent ▶ placebo-controlled study in stroke patients indicated that levodopa induced a greater improvement of verbal fluency and repetition than ▶ placebo. This positive effect was particularly obvious in patients with frontal lesions.

▶ Bromocriptine, a dopamine-receptor agonist, has yielded inconclusive results. In one study, reading-comprehension, repetition, dictation and verbal latency



Verbal and Non-Verbal Learning in Humans. Fig. 4. Success in novel word learning in subjects receiving placebo or L-dopa (mean values with standards errors of the means for two daily sessions with 200 trials each). In addition, also shown are results in the subgroup (n = 10) receiving relatively higher doses of L-dopa because their body weights were below the group median. Scores for the reassessments and transfer sessions also are displayed. (From Knecht et al. 2004.)

improved in chronic stroke patients with non-fluent aphasia, However, in another study bromocriptine was not superior to placebo in stroke patients with non-fluent aphasia.

Some preliminary evidence coming from an open-label study with four patients indicated that ► amantadine might be effective in non-fluent speech.

Noradrenergic Substances

Healthy Subjects Several studies have demonstrated that D-amphetamine facilitates verbal memory performance, improves information processing and enhances new word learning. These effects were independent of drug-induced increases of blood pressure and heart rate. It seems that there is an individual optimal D-amphematine dose, since an inverted U-shaped relationship was observed between amount of D-amphetamine and working-memory processing efficiency. This suggests that high doses of D-amphetamine can even impair memory processing. Another factor that influences the results of D-amphetamine application is the cognitive performance at baseline. The drug was effective in individuals with a low working-memory capacity, but deteriorated performance in subjects with high working-memory capacity at baseline.

Patient Groups Two studies performed in stroke patients with aphasia suggested a beneficial effect of D-amphetamine. However, when patients were re-evaluated 6 months later, the effect was gone.

Cholinergic Substances

Healthy Subjects There are no studies that explicitly investigate the effect of cholinergic transmission on verbal learning.

Patient Groups In one study with 26 stroke patients, donepezil reduced the severity of aphasia and improved picture naming to stronger degree than placebo.

Piracetam

The mode of action is unknown, but there is some evidence that ► piracetam enhances glucose utilization and cellular metabolism in the brain.

Healthy Subjects There are no studies available that investigated piracetam effects on verbal learning.

Patient Groups Placebo-controlled trials in subacute stroke patients (n = 203) indicated that application of 4.8 mg piracetam daily reduced aphasic symptoms as

evaluated by the Aachener Aphasie Test (Greener et al. 2001). Treatment duration was at least 6 weeks. A positron emission tomography (▶ PET) study demonstrated increased activity in speech-relevant brain areas as the left transverse temporal gyrus, Wernicke's area and Broca's area in the piracetam group, but not in the placebo group.

Conclusions

Currently, evidence is limited regarding a positive effect of psychoactive drugs that enhance neurotransmission or support cell metabolism. In healthy subjects, the most convincing and most consistent studies were found for the improvement of cognitive function and verbal learning by D-amphetamine and levodopa. Results obtained in elderly healthy subjects might suggest that ageing per se is associated with a subclinical reduction of neurotransmission and that substitution of dopaminergic, cholinergic (and potentially also serotonergic) neurotransmission can be more beneficial than in young subjects.

In patients, acquisition of new abilities or re-acquisition of old abilities is more difficult. We do not know enough about the consequences of brain lesions, e.g., stroke or traumatic brain injury, on neurotransmission. Therefore, it is still unpredictable who might benefit from which type of enhancement of neurotransmission. Hopefully, brain imaging techniques will help to develop hypothesis-driven concepts of specific neuropharmacological interventions. Until then, one can recommend piracetam for treatment of post-stroke aphasia and levodopa for recovery of motor functions.

Cross-References

▶ Acetylcholinesterase and Cognitive Enhancement
▶ Attention
▶ Cognitive Enhancers: Neuroscience and Society
▶ Cognitive Enhancers: Novel Approaches
▶ Cognitive Enhancers: Role of the Glutamate System
▶ Declarative and Nondeclarative Memory
▶ Long-Term Potentiation and Memory
▶ Psychomotor Performance (human)
▶ Psychomotor Stimulants
▶ Short-Term and Working Memory in Humans
▶ Spatial Learning in Humans
▶ Synaptic Plasticity

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Verum

Definition

Literally, "the truth" – a drug with a known and established effect on psychomotor function – which when included as one of the treatment conditions in a study of the effects of an unknown drug serves to demonstrate the sensitivity of the selected psychometric tests to drug-induced changes.

Very Early Onset Schizophrenia (VEOS)

▶ Pediatric Schizophrenia

Vestra

▶ Reboxetine

Vigilance

▶ Attention
▶ Sustained Attention

Violence

Definition
The term "violence" is most frequently applied in reference to pathological forms of aggression in humans. It refers to behavior that exceeds the species-normative levels in terms of intensity, duration, and frequency, typically associated with tissue damage.

Cross-References
► Aggression
► Aggressive Behavior: Clinical Aspects

Visuospatial Process

Definition
Any process in which vision is needed to explore or pay attention to the external space surrounding the subject.

Vitamin R

► Methylphenidate

Vivitrol (Injectable)

► Naltrexone

VNS

► Vagus Nerve Stimulation

Volatile Nitrites

► Nitrites

Volatile Substance Abuse

► Inhalant and Solvent Abuse

Voltage Clamp

Definition
Voltage-clamp recording is an intracellular recording modality where the apparatus controls the voltage across the cell membrane by injecting current as to maintain it at a fixed "command" voltage level. The injected current is the mirror of the ionic current flowing across the membrane at any one time and thus allows for its direct measurement.

Cross-References
► Intracellular Recording

Voltage-Gated Calcium Channels

Synonyms
VDCC; Voltage-dependent calcium channels

Definition
Voltage-gated calcium channels (VDCC) are a group of ion channels that permit the influx of calcium under conditions of changes in voltage (depolarization of the membrane). These channels can be particularly important as the influx of calcium into the presynaptic cell may be required for the release of transmitter substance into the synaptic cleft. Chronic exposure to ► alcohol can cause an increase in the number of these channels (i.e., upregulation). Increasing the number of these channels can lead to an increased or prolonged duration of transmitter release, which may in turn lead to an increased hyperexcitability in the neural circuit.

Voltage-Gated Potassium Channels

Definition
Voltage-gated K_V channels represent large family of membrane ion channels that are selectively permeable to potassium ions. Activation of these channels by changes in membrane voltage produces membrane hyperpolarization to control action potential repolarization, frequency, and firing patterns.

Voltammetry

► Electrochemical Techniques

Volume of Distribution

Synonyms

Apparent volume of distribution; V_D

Definition

The volume of distribution (V_D) is the fictitious (theoretical) volume, expressed in liter or in liter per kilogram, in which a drug would have been distributed by supposing that its concentration is homogeneous, that is, the average tissue concentration is identical to that of the plasma. It is expressed as V_D = dose/C0 (initial concentration). For example, after intravenous injection of 100 mg of a drug whose initial concentration, C0, in plasma is 10 mg/L, the V_D is of 10 L.

Cross-References

- ► Bioavailability
- ► Distribution Phase
- ► Elimination Half-Life or Biological Half-Life
- ► Pharmacokinetics

Volume Transmission

Definition

Volume transmission in the brain usually refers to actions of ► neurotransmitters or ► neuropeptides at a distance well beyond their release sites from cells or synapses. It is established that some peptides such as β-endorphin and ► enkephalins can act on neurons at distances much greater than a synapse but the actual range of influence is still unknown.

Voucher-Based Reinforcement Therapy

► Contingency Management in Drug Dependence

VTA

► Ventral Tegmental Area

W

Wakefulness

Definition

In humans, wakefulness refers to a periodic state during which a person is conscious and aware of the world around him or her. This definition cannot be applied directly to animal subjects, but analysis of its physiological characteristics provides objective measures that can be translated into definitions applicable to rodents and other animals. In the rat, wakefulness is characterized and defined by the presence of low-voltage fast waves in the frontal cortex, a mixed theta rhythm (4–7 Hz) in the occipital cortex, and relatively high electromyographic activity.

Cross-References

► Electroencephalography

Water Maze

Synonyms

Morris water maze

Definition

The water maze task, originally developed by Richard G. Morris is one of the most commonly used paradigms to assess ► spatial learning and memory in rodents. In the typical paradigm, a rat or mouse is placed into a pool of opaque water that contains an escape platform hidden below the water surface. Distal visual cues are placed around the pool that the animal uses to guide its search for the hidden platform. When released, the rat swims around the pool in search of an exit while various parameters are recorded, including the time spent in each quadrant of the pool, the time taken to reach the platform (latency), and total distance travelled. The rat's escape from the water reinforces its desire to quickly find the platform, and on subsequent trials the rat is able to locate the platform more rapidly. Rats and mice typically learn to find the platform in an efficient manner after relatively few trials. In the classic version that assesses long-term ► spatial memory, the location of the platform remains in one location over the duration of testing. A ► short-term memory variation has also been used, whereby the location of the platform changes each training day and animals display substantial reductions in escape latencies and path lengths from the first to subsequent trials. A control version of the task uses a visible platform, so that animals can solve the task without the use of distal spatial cues.

Cross-References

► Rodent Models of Cognition

Weakening of Synaptic Connections

► Long-Term Depression and Memory

Weight Control Drugs

► Appetite Suppressants

Weight Loss

► Appetite Suppressants

Weight Management Drugs

► Appetite Suppressants

Welfare

► Ethical Issues in Animal Psychopharmacology

Ian P. Stolerman (ed.), *Encyclopedia of Psychopharmacology,* DOI 10.1007/978-3-540-68706-1,

Whole-Cell Recording

Definition

Whole-cell recording is a form of patch-clamp recording where the membrane patch covering the tip of the recording electrode after tight seal formation is broken to gain electrical access to the cell's interior. This configuration allows for the recording of membrane currents originating from the entire cell, hence the name.

Cross-References

► Intracellular Recording
► Patch-Clamp Recording

Wisconsin Card Sorting Test

Synonyms

Set-shifting test

Definition

In this test, subjects are presented with a series of multidimensional stimuli, which they have to sort into piles, based on one of the stimulus dimensions, for example, color, number, and shape. After subjects have learned to sort according to one of the dimensions, the rule is changed, so that now subjects have to shift their attention and start sorting according to a different stimulus dimension. Adequate performance depends on accurate working memory representations of the currently relevant dimension as well as recently chosen stimuli.

Cross-References

► Behavioral Flexibility

Wisconsin General Test Apparatus

Definition

A behavioral testing apparatus for monkeys that includes a stimulus tray containing three food wells and a one-way screen for experimenter observation. Objects or plaques can be placed over the food wells and any combination of wells may be baited. The monkey may or may not be given the opportunity to see the food wells being baited. A screen can be placed between the monkey and the food wells if required. A variety of learning and memory tests can be administered in this apparatus.

Withdrawal Syndromes

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Synonyms

Abstinence syndrome; Drug abstinence; Drug discontinuation

Definition

A withdrawal syndrome that can be characterized both at the behavioral and the physiological level occurs when the use of a psychoactive substance that has been taken, usually for a prolonged period of time and/ or in high doses, is either stopped or reduced. The onset and course of the withdrawal syndrome are time-limited and related to the type of substance and dose taken previously. A withdrawal syndrome is one of the indicators of a drug-dependent state, which is very often paralleled by drug ► tolerance, both being due to adaptations within the body and the brain.

Impact of Psychoactive Drugs

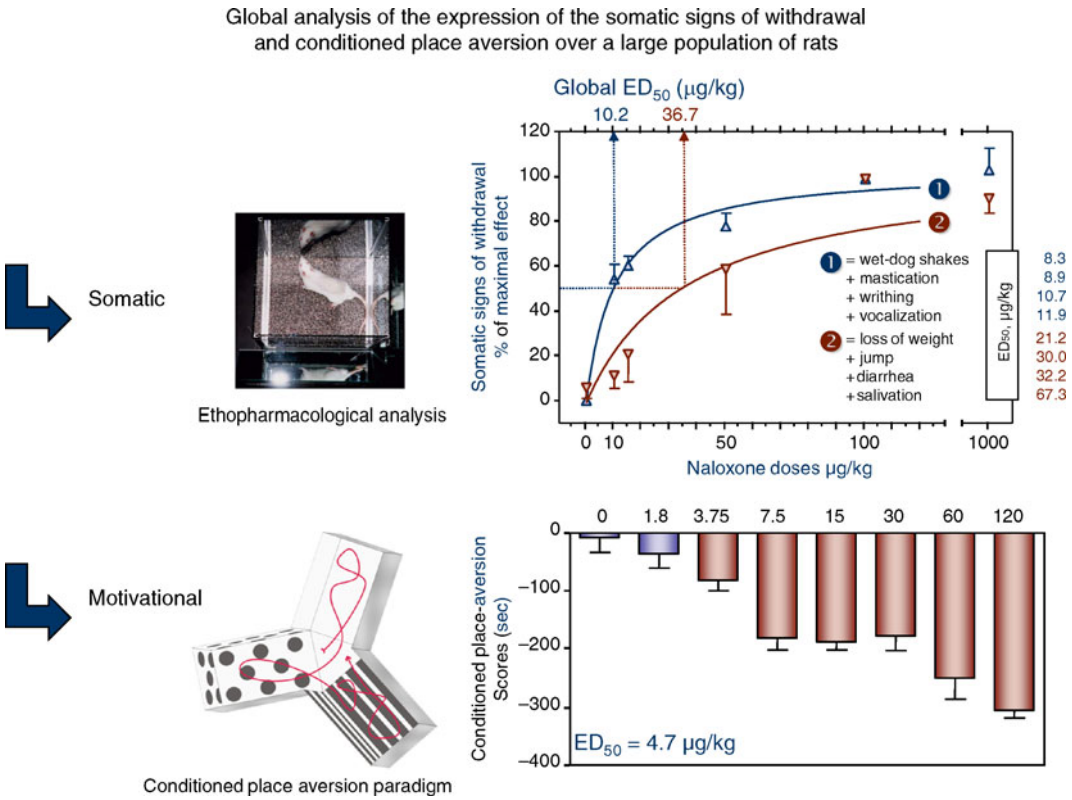
Withdrawal in Drug Addiction

Withdrawal is part of the ► drug addiction process and is a recurring feature of drug addiction because of the aversive state it engenders (► negative reinforcement theory). The symptoms defining withdrawal syndromes are rather well characterized in humans and appear in a time-dependent fashion (Jaffe 1990) depending on the drug being used (► heroin, ► cocaine, ► cannabinoids, ► nicotine, or ► alcohol). During the initial phase following drug discontinuation, a common feature for all drug abuse is that the individual is in a ► dysphoric state. No physical signs are observed at this stage though a strong motivation to use the drug again to relieve this discomfort is experienced. It has been suggested that drug withdrawal induces a motivational state that contributes to the maintenance of drug-taking behavior (Koob et al. 1989). If the drug is not provided, then as a continuum to the affective component of the withdrawal, several somatic symptoms of variable intensity emerge. In humans, the signs range from discomfort, ► anxiety, decreased appetite, sleep disorder, nightmares, irritability, nervousness, restlessness, sweating, aggressiveness, anger, shakiness, stomach pain, diarrhea and weight loss.

Animal models of drug dependence and drug withdrawal have been developed to study both the behavioral and the neurobiological targets of withdrawal. Usually animals are rendered dependent on a drug either through continuous exposure (► osmotic minipumps, ► drug pellets) or repeated exposure (non-contingent systemic administration or self-administered injections) to drugs such as morphine, heroin, cocaine, amphetamine, nicotine, alcohol, tetrahydrocannabinol (THC) or their analogs. A *spontaneous withdrawal* is observed when drug exposure is discontinued and the substance is slowly cleansed from the body. The signs of withdrawal appear quite slowly and become stronger as time passes, progressing from a negative affective state to the expression of somatic signs. A *precipitated withdrawal* is obtained through the administration of an ► antagonist of the receptors on which the drug acts (for instance ► naloxone for opiate dependence, ► mecamylamine for nicotine dependence, and CB1 receptor antagonist for THC dependence) though it should be mentioned that some cross-precipitation of withdrawal may occur (e.g., naloxone is able to induce both THC and nicotine withdrawal symptoms). When precipitated, the signs of withdrawal appear very rapidly and quite intensely due to the abrupt blockade of the receptors. Both affective and somatic components of withdrawal can be reproduced through the use of different doses of the antagonist (low doses induce only a ► negative affective state without somatic signs, whereas high doses induce somatic signs as well) (see Fig. 1 for an example of the different aspects of opiate withdrawal, depending on the dose of naloxone used).

Affective component of drug withdrawal: The negative affective component of withdrawal can be seen in various rodent behavioral models, including conditioned place aversion, conditioned suppression of operant response to food, increased threshold for intracranial self-stimulation, and anxiety measures. In ► the conditioned place aversion model (CPA), the negative affective state of withdrawal is repeatedly paired via ► classical conditioning with a specific environment. Subsequently, rats will avoid this environment and thus display conditioned place aversion, showing that the general negative affective state generated by withdrawal has been transferred to environmental stimuli (Frenois et al. 2005). Such conditioned stimuli have been shown to influence an animal's motivation towards the drug later on. The conditioned suppression model takes advantage of the interruption of an ► operant response (i.e., pressing a lever in order to obtain food). In this model, withdrawal is induced in dependent rats which are engaged in an operant response, and paired with the presentation of a stimulus (sound or odor for instance). The aversive state generated by acute precipitated withdrawal then interrupts the operant response. Thereafter, the simple presentation of this conditioned stimulus will also be able to interfere with the operant response. In the ► intracranial self-stimulation (► ICSS) model, animals learn to electrically self-stimulate a specific brain area – ► the medial forebrain bundle – until they reach a threshold of stable self-stimulation. In dependent rats, the induction of withdrawal produces an increase in *ICSS* thresholds, which is equivalent to a reduction in the ► reward sensitivity to the electrical stimulation of this brain area, indicating a withdrawal-induced ► dysphoric state. When withdrawal is paired with environmental stimuli, such stimuli are then able by themselves to generate an increase in ICSS thresholds. For instance, rats which were allowed to self-administer cocaine intravenously for prolonged periods of time showed elevated ICSS thresholds, the magnitude and duration of which were proportional to the amount of cocaine consumed. ► Anxiety and anhedonia are also components of early withdrawal: a decrease in time spent in the open arms of a ► plus maze or in the periphery of an ► open field has been repeatedly reported, as well as a decrease in the intake of natural rewards such as sucrose.

Physical component of drug withdrawal: The rating of the many physical signs of drug withdrawal in animals is based on the ethological quantification of a broad range of behaviors and somatic symptoms that may be very specific to the drug used. These rated behaviors may vary in intensity and quality depending on the drug used. The major signs in rodents are weight loss, jumping, writhing, body shake, diarrhea, teeth chattering, mastication, swallowing, salivation, chromodacryorrhea, ptosis, chewing, vocalization, eye twitches and rhinorrhea, scratching, facial rubbing, hunched posture, ataxia, irritability, abnormal motor responses, anxiety-like responses, decreased reward sensitivity, and seizures. For instance, opiate withdrawal symptoms are quantified by using the different scales found in the literature. According to the scale of Gellert and Holtzman (1978), some of these indices are quantified in a graded manner whereas others are quantal (either present or absent). Another method, the ethoscore described by Espejo et al. (1994) also makes it possible to obtain a global score for the appearance of somatic withdrawal signs, but is based only on the frequency of chewing and loss of weight. The scale of Gellert–Holtzman presents an asymptotic progression relative to increasing doses of naloxone (ceiling effect, see Fig. 1), whereas the ethoscore progresses linearly. Nicotine withdrawal symptoms are rated



Withdrawal Syndromes. Fig. 1. Global behavioral analysis of naloxone-precipitated opiate withdrawal. The upper panel (curves) shows the expression of two groups of somatic signs of withdrawal (means ± SEM) in response to naloxone injections at the following doses: 0, 10, 15, 50, 100 and 1,000 µg/kg. The first group is represented by the blue curve that fits the means of the signs showing an ED_{50} below 20 µg/kg (body shake, mastication, writhing, and vocalization). The second group is represented by the red curve that fits the means of the signs showing an ED_{50} above 20 µg/kg (weight loss, jumping, diarrhea, and salivation). The global ED_{50} values corresponding to the first and the second group of somatic signs were respectively 10.2 and 36.7 µg/kg. The lower panel (histogram) shows the expression of naloxone-induced conditioned place aversion using the following doses of naloxone during the conditioning phase: 0, 1.8, 3.75, 7.5, 15, 30 and 120 µg/kg. Each bar represents the aversion score (means ± SEM) for one arm of an unbiased Y-maze, which had been previously paired with a naloxone injection during the conditioning phase (brown histograms illustrate significant aversions). Adapted from Frenois et al. (2005).

according to a scale designed by Malin et al. (1992). No scale exists for psychostimulants, as somatic symptoms from psychostimulants have not yet been reported.

Neural Circuits and Neurotransmitters Involved

The expression of a withdrawal syndrome is the consequence of neuroadaptations, which have been engendered by continuous/repeated drug exposure. These neuroadaptations can take place within the brain system on which the drug is acting directly (within system adaptations) and lead, for instance, to decreased or increased sensitivity and/or number of receptors, and increased or decreased release of the neurotransmitter, which activates these receptors endogenously. These neuroadaptations can also take place in systems different from the one on which the drug is acting directly (between system adaptations), which are often counteracting the drug effects. These within- and between-system adaptations might develop with very different kinetics and may follow one after the other. Some of them are directly responsible for the onset of the behavioral manifestations of withdrawal but others can be very long lasting and persist long after the drug is cleared and the overt signs of withdrawal have disappeared (Koob et al. 1989).

Using the different behavioral paradigms mentioned above, the neural substrates of withdrawal syndromes have been studied using different approaches such as brain site-specific injections of drug antagonist, c-fos imaging, and knockout mice (KO) for specific receptors. A brief

synthesis of the findings related to the neurobiological substrates of the withdrawal syndrome is given below.

Brain structures involved: One of the major findings related to drug withdrawal is the dissociation between the neural systems involved in the motivational and somatic components of withdrawal. In terms of brain structures, it has been shown that limbic structures encompassing the nucleus accumbens, amygdala, BNST and prefrontal cortex are involved in the negative affective part of withdrawal from drugs like opiates, cocaine, alcohol, and nicotine, whereas other structures such as the locus coeruleus and the periacqueductal grey (PAG) are involved in the somatic aspect of withdrawal. Using intracerebral injections of either ▶ opiate receptor antagonists (naloxone or methynaloxonium), ▶ nicotinic receptor antagonists (mecamylamine, and dihydro-beta-erythroidine), or ▶ cannabinoid receptor antagonists (SR141716A or AM251), negative affective states are produced and expressed, either by conditioned place aversion, increased anxiety, and increased threshold for ICSS (reviews, Koob et al. 1992 for opiates; Kenny and Markou 2001 for nicotine; Tanda and Goldberg 2003 for cannabinoids). However when the antagonists were injected in other structures such as the locus coeruleus (for opiates), somatic signs emerged even with low doses (Koob et al. 1992). These data were corroborated by c-fos imaging data showing that with low doses of antagonists, limbic structures were activated (among them the central nucleus of the amygdala has been shown to be activated with all drug withdrawal), whereas with higher doses leading to the expression of somatic signs, structures such as the locus coeruleus or PAG are activated (for example, see Frenois et al. 2005 for opiate withdrawal.).

Neurotransmitters and receptors involved: KO mice have been used for different types of receptors, showing that opiate mu-receptor KO mice do not show opiate withdrawal and cannabinoid CB1 receptor KO mice do not show THC withdrawal. Regarding nicotinic receptor KO mice, there is some evidence that some receptor subtypes are involved in the motivational component ($\alpha 4\beta 2$) while others are involved in the physical component ($\alpha 5\beta 4$) of withdrawal. However, available data are conflicting and there is at present no consensus over the role of receptor subtypes in nicotine withdrawal. Among neurotransmitters, ▶ corticotropin-releasing factors (▶ CRF) and ▶ dopamine have been repeatedly involved in the negative affective state associated with withdrawal. Peripheral administration of a CRF antagonist blocks the conditioned place aversion produced by either opiate withdrawal, nicotine withdrawal, or alcohol withdrawal. This effect takes place principally at the level of the central nucleus of the amygdale (CEA) where local CRF receptor antagonist administration (principally CRF1 receptor) diminishes the negative affective state of opiate- nicotine- and alcohol-withdrawal, using CPA, ICSS or anxiety measures (Koob 2008). Thus, intra-amygdala injection of CRF precipitates a negative affective state in opiate-, nicotine-, and alcohol-dependent rats. In rodents, during nicotine-, alcohol-, opiate- and cannabinoid-withdrawal, CRF neurotransmission is increased (review Koob 2008). This CRF neurotransmission involvement which has for long been related to the stress system and the stress response may participate in the anxiogenic aspect of withdrawal.

Dopamine release is decreased in the nucleus accumbens during withdrawal from cocaine, opiate, nicotine, alcohol, and cannabinoid. This reduced release of dopamine may explain the decreased sensitivity to rewards, as demonstrated using ICSS or sweet solution consumption. However, this might be over-simple as, for example, a lesion of dopamine neurons does not modify the affective and somatic aspects of withdrawal (Caillé et al. 2003).

Besides dopamine, other monoamines have also been involved. It has been suggested that noradrenergic functional antagonists can block some aspects of ethanol or nicotine withdrawal (Koob 2008 for alcohol). However, a noradrenergic lesion did not block opiate withdrawal, whereas clonidine (alpha2 agonist) abolished the negative affective state of opiate withdrawal and some (but not all) aspects of somatic withdrawal.

Other neurotransmitters have also been involved, though data are still incomplete. For instance, an increase in glutamatergic neurotransmission has been associated with opiate withdrawal and dynorphin neurotransmission has also been proposed to mediate the negative state of drug withdrawal (Koob 2008).

It is clear that our understanding of the behavioral and neurobiological effects of drug withdrawal is far from complete, though it is progressing rapidly. Using behavioral and neurobiological screening, systematic comparisons among withdrawal from different drugs should bring important information about potential therapeutic targets that can ameliorate withdrawal states and maintain abstinence.

Cross-References

▶ Addiction
▶ Addictive Disorder: Animal Models
▶ Alcohol
▶ Anxiety
▶ Cannabinoids
▶ Classical Conditioning
▶ Cocaine
▶ Conditioned Place Preference and Aversion

- ▶ Dopamine
- ▶ Elevated Plus Maze
- ▶ Liquid diet for Administering Alcohol
- ▶ Morphine
- ▶ Nicotine
- ▶ Noradrenaline
- ▶ Open Field Test
- ▶ Opioids
- ▶ Physical Dependence
- ▶ Serotonin

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Working Memory

Definition

A theoretical construct within cognitive psychology that refers to the structures and processes used for temporarily storing and manipulating information.

Cross-References

- ▶ Short-Term and Working Memory in Animals
- ▶ Short-Term and Working Memory in Humans

X

XTC

► Methylenedioxymethamphetamine (MDMA)

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Y

Y-516

► Mosapramine

Yale–Brown Obsessive–Compulsive Scale

Synonyms

Y-BOCS

Definition

The 10-item Y-BOCS scale, which evaluates the severity of obsessions and compulsions separately, is the standard scale used in treatment outcome studies of ► obsessive compulsive disorder (OCD) (Goodman et al. 1989a, b). The rater measures obsessions and compulsions in terms of the time occupied, how much they interfere with functioning, the patient's degree of distress, and his or her attempts to resist symptoms and the ability to control them successfully. To assess the patient's symptoms, the clinician may wish to use the Y-BOCS symptom checklist, which lists 40 obsessions and 29 compulsions. The 18-item Obsessive–Compulsive Inventory is a shorter alternative. The Y-BOCS scale and checklist along with instructions for their use are available at http://apple.cmu.edu.tw/_u901039/Rating-Scale-YBOCS.pdf. In clinical practice, some clinicians measure symptom change by simply asking the patient to estimate the amount of time taken by symptoms in an average day in the past week.

Cross-References

► Compulsions
► Obsessions

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Y-BOCS

► Yale–Brown Obsessive–Compulsive Scale

Yohimbine

Definition

Yohimbine is a naturally occurring alkaloid. By blocking α_2-adrenoreceptors while sparing a_1-adrenoreceptors, it increases ► noradrenaline release and produces sympathomimetic effects in some organs. It has stimulating properties and is purported to have aphrodisiac qualities.

Cross-References

► Sexual Behavior
► Sexual Disorders
► Short Term and Working Memory in Animals

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Z

Z-Drugs

► Benzodiazepines
► Non-Benzodiazepine Agonists

Zaleplon

Definition

Zaleplon is a non-benzodiazepine sedative-hypnotic that potentiates gamma-amino-butyric acid (► GABA) neurotransmission by binding to the α-subunit of the $GABA_A$ receptor complex, with some selectivity for the α1-subunit. Zaleplon is effective the treatment for insomnia and has an extremely brief duration of action that makes it particularly suitable for treating difficulties in falling asleep (it decreases latency of sleep onset). This drug does not substantially alter the quality of sleep, has little or no residual hangover effects and the recovery from sedation is more rapid than with other ► hypnotics. Zaleplon has a similar side-effect profile to benzodiazepines and other non-benzodiazepine hypnotics although the adverse effects on cognition and psychomotor function are reduced because of the relative selectivity for the ω_1 receptor and the short half-life. Tolerance and dependence may develop with long-term use.

Cross-References

► Benzodiazepines
► Hypnotics
► Non-Benzodiazepine Agonists

Zelapar

► Selegiline

Zero-Order Elimination Kinetics

Definition

Sometimes a drug is absorbed at essentially a constant rate, called zero-order absorption. Zero-order kinetics is described when a constant amount of drug is eliminated per unit time but the rate is independent of the concentration of the drug.

Cross-References

► Bioavailability
► Elimination Half-Life
► Pharmacokinetics

Ziprasidone

Definition

Ziprasidone acts at multiple receptors but mainly as a potent $5HT_{2A}$ receptor antagonist. It is a second-generation antipsychotic with a benzothiazolyl-piperazine structure. The ► half-life is 4–10 h and it is metabolized by various CYP450 isoenzymes, most potently by 3A4. It has to be taken with food. Ziprasidone also inhibits noradrenaline and serotonin reuptake but the clinical relevance of these pharmacological effects has not yet been explored. It is also available as an acute intramuscular preparation. Among the newer antipsychotics, ziprasidone has a lower propensity to induce metabolic side effects.

Cross-References

► Second-Generation Antipsychotics

Zispin

► Mirtazapine

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Zolpidem

Definition

Zolpidem is a non-benzodiazepine sedative-hypnotic belonging to the class of imidazopyridines. It potentiates gamma-amino butyric acid (GABA) transmission by binding to the α-subunit of the $GABA_A$ receptor complex with some selectivity for the α1-subunit. It is commonly prescribed for short-term treatment of insomnia which should not exceed 2 weeks duration as the likelihood of tolerance, dependence, and rebound withdrawal symptoms increases with prolonged use. Like benzodiazepines, it also has anxiolytic, muscle relaxant, and anticonvulsant properties but these are very weak and require higher doses, which increase the severity of side effects. Clinical reports suggest that zolpidem may also be used to dramatically improve the condition of patients with some brain injuries. The side-effect profile of zolpidem is similar to that of other sedative-hypnotics and additionally includes symptoms such as hallucinations and delusions. Additionally, some patients report sleepwalking, migraine, subjective feelings of intoxication, manic reactions, and panic attacks. Tolerance and dependence may develop with long-term use.

Cross-References

► Benzodiazepines
► Hypnotics
► Non-Benzodiazepine Agonists

Zonisamide

Definition

Zonisamide is a sulfonamide ► anticonvulsant. It is a ► GABA agonist that also reduces ► glutamate function and has a ► half-life of 63 h. It has been studied as an adjunctive treatment in various neuropsychiatric disorders ranging from migraine to ► bipolar disorder without leading to conclusive recommendations for its use beyond epilepsy.

Zopiclone

Definition

Zopiclone is a non-benzodiazepine sedative-hypnotic acting as an agonist at the benzodiazepine binding site on gamma-amino-butyric acid (► $GABA_A$) receptors. It is used for short-term treatment of insomnia, to improve both the initiation and maintenance of sleep. Common side effects include bitter metallic taste, disruption of REM sleep, drowsiness, nausea and vomiting, irritability, confusion, depression, and a lack of coordination. More severe side effects including headache, hallucinations, nightmares, and amnesia have also been reported but appear to be rare. Tolerance and dependence may develop with long-term use.

Cross-References

► Benzodiazepines
► Hypnotics
► Non-Benzodiazepine Agonists

Zotepine

Definition

Zotepine is a second-generation antipsychotic that acts as a potent dopamine D2 and $5HT_{2A}$ antagonist. Chemically, it is in the dibenzodiazepine class. It has a plasma half-life of 21 h and is metabolized by 1A2 and 3A4 CYP450 isoenzymes. It also inhibits noradrenaline reuptake but the clinical relevance of this effect has not yet been explored.

Cross-References

► Second-Generation Antipsychotics

Zuclopenthixol

Definition

Zuclopenthixol is a multi-receptor blocking ► thioxanthene ► antipsychotic of the first generation. Its plasma ► half-life amounts to 12–28 h and it is mainly metabolized by 2D6 CYP450 isoenzymes. It is also available in a short-acting intramuscular depot preparation that has an elimination half-life of 48–72 h.

Cross-References

► First-Generation Antipsychotics

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