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Walter R. Hess (1881-1973)

RICHARD JUNG *

Am 12. August 1973 starb Walter Rudolf *Hess* im 93. Lebensjahr in Ascona nach einer über sechs Jahrzehnte währenden Tätigkeit als Physiologe. Mit dem Zürcher Physiologischen Institut war *Hess* 1912–1917 als Assistent und Privatdozent, 1917–1951 als Professor und Direktor und 1951–1960 als Emeritus eng verbunden. Dort hat er seine berühmten Arbeiten über das vegetative System, den Schlaf und die Motorik durchgeführt und war Lehrer vieler Generationen von Physiologen und Ärzten. Sein Lebensweg ist kurz zu schildern, seine Forschungsleistungen bedürfen einer ausführlicheren Darstellung.

Biographie und Persönlichkeit

Der Lebensweg. *Hess* wurde am 17. März 1881 in Frauenfeld (Kanton Thurgau) als Sohn eines Gymnasialprofessors der Physik geboren, dem er die frühesten Anregungen zur naturwissenschaftlichen Forschung verdankt [40]. Er studierte 1899–1905 in Lausanne, Berlin, Kiel und Zürich Medizin. Nach ophthalmologischer Ausbildung und früher Heirat mit Luise *Sandmeyer* 1909 wurde er 1912 nach dreijähriger augenärztlicher Tätigkeit wieder Physiologe. An der Zürcher Universität, die ihm über 60 Jahre geistige Heimat blieb, wurde *Hess* 1913 Privatdozent und 1917 ordentlicher Professor der Physiologie und Direktor des Physiologischen Instituts. Von 1912–1951 hat er das Zürcher Institut nur kurz verlassen: für wenige Vortragsreisen, für die Ferien in Ascona, wo er seine Bücher schrieb, und nur einmal für ein Jahr Forschungsarbeit in Bonn als Gastassitent bei *Verworn* 1915/16. Für seine Entdeckung der Hirnstammreizeffekte auf das Verhalten der wachen Katze, die er 1927–1947 in systematischen Experimenten ausbaute, erhielt *Hess* 1949 den *Nobelpreis für Physiologie und Medizin.* Außer zahlreichen Ehrenmitgliedschaften Wissenschaftlicher Gesellschaften und Akademien erhielt er die Carl-Ludwig-Medaille und die Johannes-Müller-Medaille. 1951 wurde er emeritiert, arbeitete aber an der Auswertung seiner Experimente weiter, bis er sich im 85. Lebensjahr ganz in sein Ferienhaus in Ascona zurückzog.

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Der Physiologe. Sein langes Forscherleben in der Physiologie führte *Hess* vom Kreislauf [4, 5, 12] zu den vegetativen Hirnfunktionen [7, 14, 20], zur Atmung [13, 17, 18, 21], zum Schlaf [9–11, 16, 28], im dritten und sechsten Lebensjahrzehnt zur Motorik [3, 22–27] und schließlich zur Psychophysiologie [39].

Hess begann seine wissenschaftliche Arbeit 1903 als 22jähriger Student mit der eigenwilligen Beobachtung und Erklärung einer Gefäßanomalie, von der er mechanische Gesetzmäßigkeiten des Blutgefäßverlaufs mit ihrer Bedeutung für den Kreislauf ableitete [1]. Er erregte damit die Aufmerksamkeit W. *Rouxs*, des Begründers der Entwicklungsmechanik. Seitdem beschäftigten ihn die Kreislaufphysiologie und Neurophysiologie als Forschungsgebiet über fünf Jahrzehnte. Dennoch unterbrach er die geplante experimentelle Arbeit für fast sieben Jahre: 1905 begann er unter Einfluß des Ophthalmologen *Haab* eine klinisch-augenärztliche Fachausbildung an der Zürcher Augenklinik und arbeitete dort über Augenmuskellähmungen und ihre Doppelbildmessung [3]. Nach seiner Heirat eröffnete er eine Praxis als Augenarzt in Rapperswil am Zürcher See. Er wollte zunächst durch ärztliche Tätigkeit ein sicheres Familieneinkommen haben. Doch sein wissenschaftlicher Impetus und seine Liebe zur Physiologie setzten sich bald wieder durch: 1912 ging er an die Universität Zürich zurück, wo er sich im Physiologischen Institut bei *Gaule* schon im nächsten Jahre mit einer Arbeit über die Hämodynamik habilitierte [47]. 1915/16, während des ersten Weltkriegs, arbeitete er ein Jahr in Bonn bei Max *Verworn*, dem damals führenden deutschen Neurophysiologen. *Verworns* allgemeine Physiologie und sein weiter biologischer Aspekt, der von den Einzellern bis zum menschlichen Gehirn reichte, waren für *Hess* prägende Eindrücke. Doch die Erkrankung *Verworns*, der in *Hess'* Gegenwart seinen ersten cerebralen Schlaganfall erlitt, und die Kriegsverhältnisse beeinträchtigten die gemeinsame Arbeit.

Die Rückkehr nach Zürich brachte durch die Erkrankung *Gaules* für *Hess* eine schwere Zeit, die er mit Energie und Zähigkeit meisterte. Er mußte sich von 1916 bis 1919 fast ganz dem Unterricht und der Institutsorganisation widmen, mehrfach unterbrochen durch kurze Einberufungen zum Militärdienst. *Hess* konnte damals nur wenige Experimente über die Organdurchblutung fortführen, und die Forschung blieb bis zum Kriegsende liegen. Sein meist 15stündiger Arbeitstag reichte von morgens 7 bis abends 22 Uhr mit Vorlesungen, Kursen, Institutsordnung und Anleitung seiner Assistenten. Zwei tüchtige Mitarbeiter, die sich 1920/21 bei ihm habilitierten, der vorwiegend biophysikalisch ausgerichtete Alfred *Fleisch* und der mehr biochemisch-pharmakologisch interessierte Ernst *Rothlin*, halfen ihm, das Zürcher physiologische Institut trotz der ungünstigen Zeitverhältnisse zu neuer Aktivität zu führen. Nach *Gaules* vorzeitiger Emeritierung wurde der 36jährige *Hess* gegen manche Widerstände zum Professor

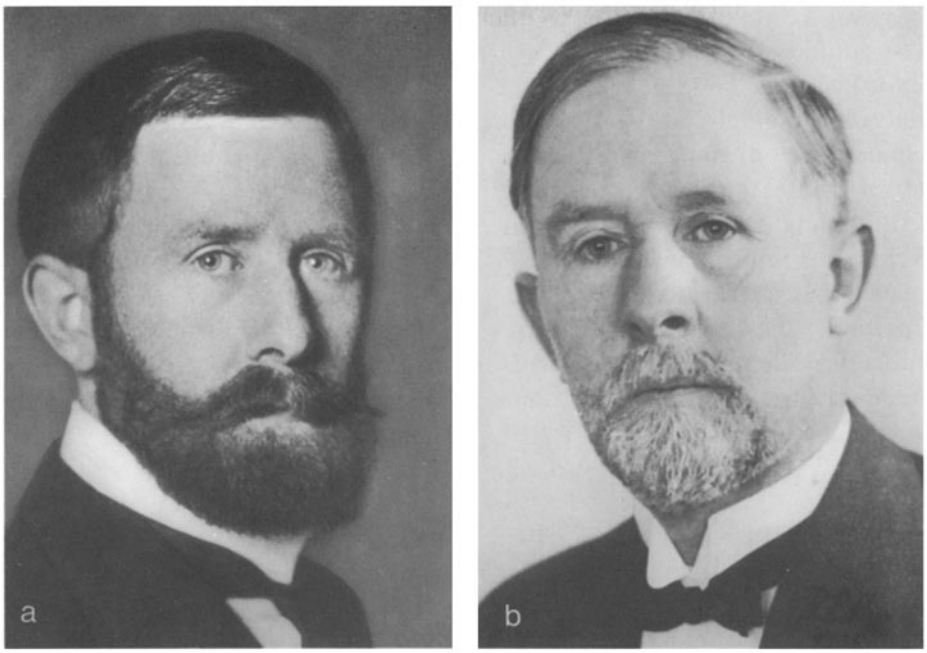
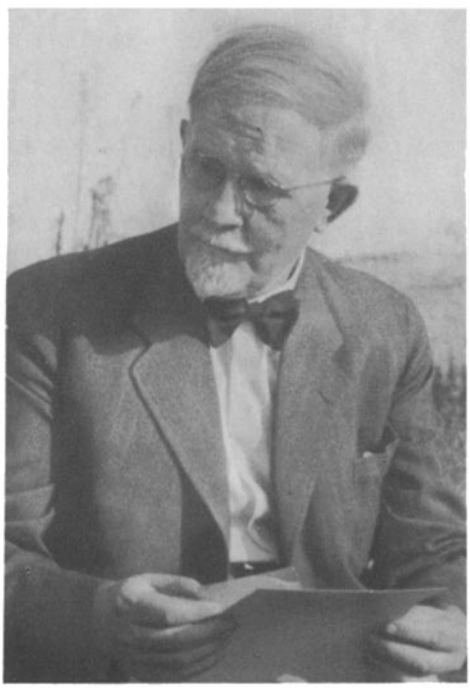


Abb. 1a, b. W.R. *Hess* als Privatdozent 1914 und als Professor 1936. **a** Der 33jährige Assistent von *Gaule* war damals seit 1912 am Zürcher Physiologischen Institut und seit 1913 habilititert, bevor er 1915–1916 neurophysiologisch bei *Verworn* in Bonn arbeitete. **b** Der 54jährige war seit 1917 Direktor des Physiologischen Instituts der Universität Zürich. 1936, als ich in sein Institut eintrat, bearbeitete *Hess* die Effekte der Zwischenhirnreizung auf Atmung und Kreislauf [20], nachdem er 1926–28 die intrakranielle Reiztechnik an der freien Katze entwickelt hatte [8, 9, 14]

der Physiologie und Institutsdirektor berufen. Die Chance, als junger Physiologe ein eigenes Institut aufzubauen und die Forschung zu fördern, hat *Hess* in 44 Jahren unermüdlicher Tätigkeit erfolgreich ausgenutzt. 1921 konzentrierte sich *Hess* nach einer orientierenden Reise durch die britischen Institute und den Besuch des Internationalen Physiologen-Kongresses in Edinburgh zunächst auf den Abschluß seiner Arbeiten zur Regulierung von Blutkreislauf und Atmung, die zu zwei Monographien [12, 13] erweitert wurden. 1924 schrieb er eine programmatische Arbeit über die Beziehung von psychischen und vegetativen Funktionen [7], die zur gedanklichen Grundlage seiner über zweieinhalb Jahrzehnte dauernden Experimente am zentral-vegetativen System des Zwischenhirns führte (vgl. S. 9).

1929 beim internationalen Physiologen-Kongreß in Boston lernte *Hess* die amerikanischen Physiologen kennen. Seine Hoffnung, W. *Cannon* für seine Konzeption der vegetativen Funktionen zu gewinnen, wurde enttäuscht. Eine gemeinsame Studienreise mit dem deutschen Physiologen *Wachholder* durch die nordamerikanischen Forschungsinstitute brachte

bessere Kontakte, aber *Hess* blieb gegenüber den angloamerikanischen Physiologen reserviert und hielt die stereotaktischen Reizexperimente am narkotisierten Tier mit faradischer Reizung von *Ransom* und seiner Schule für unphysiologisch. Die deutschsprachige Physiologie war seine geistige Heimat, und er fühlte sich in der von ihm so genannten deutschen „Physiologenfamilie" zu Hause, in guter Freundschaft mit Gleichgesinnten und in kritischem Abstand zu anderen. Auch nach Gründung einer eigenen Schweizer Physiologischen Gesellschaft erschien ihm die Schweiz für wissenschaftliche Diskussion und produktiven Ideenaustausch zu klein. Die *Tagungen der Deutschen Physiologischen Gesellschaft* hat *Hess* über fünf Jahrzehnte regelmäßig besucht. Dort trug er seine experimentellen Ergebnisse vor und demonstrierte zuerst seine neue Methode der Zwischenhirn-



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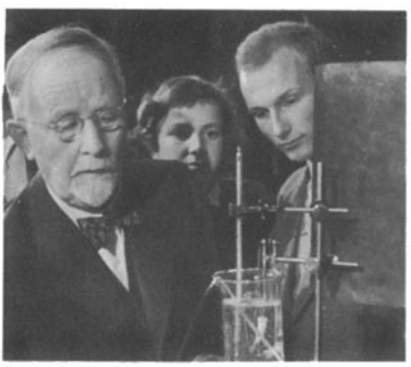


b

c

Abb. 2a–c. *Hess* auf Kongressen, im Institut und zu Hause 1948–1953. a Diskussion mit Fachkollegen auf der deutschen Physiologentagung in Frankfurt 1948. **b** Demonstration eines Experimentes vor Studenten 1949. c Im häuslichen Arbeitszimmer mit dem Papagei auf der Schulter 1953

reizung an der freilaufenden Katze auf der Deutschen Physiologentagung in Bonn 1927 [8]. Er blieb bis in sein hohes Alter ein anregender und kritischer Diskutant auf diesen Tagungen (Abb. 2a). Von 1928–1954 kam er oft nach Baden-Baden zu den Südwestdeutschen Neurologen und Psychiatern, in deren Versammlungen er 1928 und 1929 seine ersten Experimente über Schlafauslösung durch Zwischenhirnreiz bei der Katze im Film demonstrierte [9, 11]. Diese drei Kurzmitteilungen bei Neurologen- und Physiologentagungen [8, 9, 11] waren außer seiner Schlaftheorie [10, 16] über zehn Jahre seine einzigen Publikationen über den Schlaf durch Thalamusreiz. 1932 beschrieb er monographisch seine Methodik der Reizung und Ausschaltung lokalisierter Hirnstrukturen [14] und 1938 die Zwischenhirnbeeinflussung von Atmung und Kreislauf [20].

Hess organisierte Institut und Forschung nach funktionellen Gesichtspunkten. Auch bei Experimenten verwendete er die gleiche Regel, die er als Funktionsprinzip des lebenden Organismus ansah: die Kraft soll dort einsetzen, wo sie ihre *größte Wirkung* entfaltet. Bei der bis 1946 sehr geringen Dauerpersonalbesetzung des Instituts (2 Assistenten, 1 Mechaniker, 1 Sekretärin) hat er Hilfskräfte angelernt und aus eigenen oder aus Forschungsmitteln bezahlt. Eine Kinderschwester, die er im Haus nicht mehr brauchte und deren Interesse für systematische Ordnung er kannte, hat über 20 Jahre die statistische Dokumentation seiner Hirnreizexperimente durchgeführt. Wenn *Hess* beim Experiment einen Reizerfolg sah, fragte er sie, wann und mit welcher Lokalisation der Effekt schon früher vorkam. Wenn Frl. Jaussi (Abb. 3b, links) es nicht auswendig wußte, blätterte sie in der Kartei, und in wenigen Minuten kam die Antwort. So konnte *Hess* Reizpunktkarten der verschiedenen vegetativen und motorischen Symptome aufstellen und dann mit anatomischen Strukturen in Verbindung bringen [31, 36].

Charakter und Arbeitsweise. *Hess* verstand es, systematische Theorie und methodisches Experimentieren in seiner Forschungsarbeit zu vereinen. *Weiter Interessenkreis, gedankliche Klarheit und hartnäckiger Fleiß,* geführt durch *gezielte Theorienbildung* und gezügelt durch *methodische Beschränkung,* das waren die Charakteristika seiner Arbeitsweise und die Grundlagen seiner Erfolge. Daraus entwickelte *Hess* seine Synthese der Physiologie, die mit seinen Forschungsleistungen dargestellt werden muß.

Hess war eine glückliche Mischung eidgenössischer Zähigkeit und Strenge (die er von seinem Schweizer Vater herleitete) mit lebhaftem Forschungsgeist und wachem Interesse für alles Neue (das er als Erbteil seiner sächsischen Mutter ansah [40]). Diese beiden Seiten seines Charakters bestimmten *Hess'* Forschungsimpetus: Die Aufgeschlossenheit für neue Probleme förderte die Vielseitigkeit seiner Physiologie. Zähigkeit und Exaktheit

führten ihn zur systematischen Planung und Ausarbeitung der Ergebnisse über viele Jahre.

Hess war auch ein *Meister experimenteller Methodik* und ihrer kritischen Begrenzung. Obwohl er sich in Gespräch und Diskussion für neue Ideen und Ergebnisse begeistern konnte, begrenzte er seine praktische Forschung auf erreichbare Ziele, die er mit systematischem Denken und kritisch-methodischer Strenge verfolgte. Als ich ihm 1937 in jugendlichem Optimismus vorschlug, seine cerebralen Reiz- und Ausschaltungsexperimente durch die Ableitung von Hirnpotentialen zu erweitern, winkte *Hess* ab. Obwohl er mit O. *Wyss* einen sehr guten Elektrophysiologen als Oberassistenten hatte, meinte er, hirnelektrische Untersuchungen sollten andere Institute machen: er hätte mit der Auswertung der Reizversuche und ihrer ihm immer etwas fremden hirnanatomischen Korrelation schon zu viele ungelöste Aufgaben für das nächste Jahrzehnt.

Hess beschränkte die Hirnstammexperimente auf das Versuchstier *Katze* und begründete dies mit Verhaltensbeobachtungen, der geringen Variation von Hirn- und Körpergröße und der guten Sehorientierung von Katzen im Vergleich zum Hund. Experimente an Affen hielt er bei Hirnstammfunktionen für unnötig kostspielig. Für seine Schlafuntersuchungen war die Katze das ideale Versuchstier, da sie gern und leicht am Tage schläft. Dies erleichterte seine frühen Experimente der Schlafauslösung durch Zwischenhirnreizung [8–11, 28].

Hess erfüllte die doppelte Aufgabe als Lehrer und Forscher, indem er den Unterricht zeitlich genau einteilte und sich für die Experimente bestimmte Stunden und Tage frei hielt. Seine Forschung plante *Hess* kontinuierlich und systematisch. Kein Tag blieb ohne Arbeit. Im Hause am Zürichberg saß er in der Veranda und schrieb, oft mit seinem Papagei auf der Schulter (Abb. 2c). Wenn er aus dem Institut nach Hause kam, und in den Ferien, wenn er seinen Garten in Ascona bestellt hatte, entwarf er seine vielfach umkorrigierten Arbeiten. Im Institut halfen ihm treu ergebene Mitarbeiter, in der Wohnung auf dem Zürichberg und im Sommerhaus in Ascona seine Frau bei der Vollendung seiner wissenschaftlichen Schriften, die alle seine persönliche Prägung trugen. Obwohl ihm, wie er oft sagte, das Schreiben schwer fiel, entstand zwischen 1903 und 1970 in kontinuierlichem Fluß seine erstaunliche Publikationsreihe von 294 Einzelarbeiten und 10 Monographien.

Hess' Konzeptionen und Forschungsleistungen

Forschungsergebnisse. Die wichtigsten physiologischen Leistungen von *Hess* seien im Folgenden mit ihrem Zeitgang kurz charakterisiert:

1) *Systemkonzeptionen des Blutkreislaufs und der Atmung* als Kombination hämodynamischer Faktoren mit peripheren und zentralen Regulationen (1913–1931 [4, 5, 12]).
2) *Funktionsordnung des vegetativen Systems* mit zentraler Organisation von zwei reziprok koordinierten Untersystemen, die er *ergotrop* und *trophotrop* nannte (1924–1938 [7, 16, 30]).
3) Methodische Entwicklung der *subkortikalen Hirnreizung beim freibeweglichen Tier* (1927–1931 [8, 14]).
4) Erforschung der *Zwischenhirnfunktionen* für vegetative und Verhaltensregulationen (1929–1949 [20, 22, 31, 37]).
5) Begründung der experimentellen *Schlafforschung* mit Entdeckung der Schlafauslösung durch elektrische Thalamusreizung (1929–1944 [9, 16, 28]).
6) *Entdeckung richtungsbestimmter motorischer Regulationszentren* im Zwischenhirn und Mittelhirn (1941–1943 [22–24]).
7) Koordination der *Zielbewegung und Stützmotorik* beim Menschen (1941–1965 [24, 27, 42]).
8) Synthese physiologischer Verhaltenskoordinationen mit psychischen und vegetativen Funktionen (1943–1962 [26, 39]).

Integrative Physiologie. *Hess* interessierte sich immer für die *ganze* Physiologie, und seine Arbeiten reichten in einem breiten Spektrum von den Kreislauf- und Atmungsfunktionen bis zur Hirnphysiologie. Reines Spezialistentum war ihm fremd. Er war, wie *Verworn*, ein *synthetischer Denker*. Physiologische Mechanismen sah er immer im Zusammenhang mit ihrem biologischen Zweck innerhalb des Organismus und mit dem Ziel des Tieres im triebgesteuerten Verhalten. Kreislauf, Atmung, vegetative Funktionen und Hirntätigkeit studierte er experimentell als Teilfunktionen des ganzen Organismus. *Hess* wurde nicht müde, seine Schüler mit vielfach variierten Beispielen dynamisch-integrierter Körperregulationen zum funktionell-physiologischen Denken zu erziehen, das er dem statischen „anatomischen" Denken entgegensetzte. Seine Physiologie war eine Synthese von Theorie und Experiment zur Erforschung integrativer zielgesteuerter Leistungen, die eine lebendige Ordnung im Organismus erkennen läßt. Einen ähnlichen Gegensatz sah er zwischen seiner integrativen System-Physiologie und der mehr auf "facts" und Einzelanalyse eingestellten Haltung angelsächsicher Physiologen, denen oft die Tatsache alles und die Theorie nichts galt. Für *Hess* dagegen brachten Einzeltatsachen nur Hinweise für Funktionsgesetze. Nur ihre gesetzmäßige Wiederholung oder Zusammenhänge mit anderen Tatsachen waren als physiologische Funktionen zu werten, in die er auch psychische Leistungen einschloß [7]. Seine Betonung von *Ziel und Funktionsordnung* ist oft als „teleologisch" mißverstanden worden, war aber

immer *biologisch* gemeint. Daher suchte er auch Beziehungen zur Verhaltensforschung von *Lorenz* und seiner Schule und zu v. *Holsts* Regelungsprinzipien. Für *Hess* war das Gehirn eine Struktur- und Funktionsordnung, die als „dynamisches Kräftespiel" nie zur Ruhe kommt, nur bei relativem Gleichgewicht Ruhe vortäuscht und in einem dauernden Wechsel von Erregung und Hemmung verschiedener Systeme biologisch-zielstrebig arbeitet [39].

Kreislaufphysiologie. Die Funktionen des Blutkreislaufes haben *Hess* seit seiner Gefäßarbeit [1] als Student besonders interessiert. Erste selbständige Leistungen waren ein Apparat zur Messung der *Blutviskosität* 1907 [2] und die Habilitationsschrift über das *Ökonomieprinzip der Hämodynamik* 1914 [4]. Daraus entwickelte sich im Laufe von zwei Jahrzehnten eine systematische Untersuchung der *Kreislaufregelung,* die 1930 monographisch dargestellt wurde [12]. 20 Jahre bevor die Regelprinzipien mit dem Stichwort „Kybernetik" in der Neurophysiologie aktuell wurden, hat *Hess* alle Regulierungen mit dem später so benannten negativen und positiven "Feedback" an den Leistungen des Blutkreislaufs klar beschrieben. Als einfachste Regelung der Gewebsdurchblutung betrachtete er die *Nutritionsreflexe,* die er auch „Eigenreflexe des Kreislaufs" nannte und mit der Propriozeptivität der Muskulatur in Parallele setzte: Die Gefäßerweiterung durch CO_2 und lokale Stoffwechselprodukte einschließlich der Axonreflexe sorgt für adäquate Blutversorgung entsprechend der Tätigkeit der Organe. Antagonistisch zum Nutritionsreflex wirkt der *Entlastungsreflex,* der in Parallele zur Vaguswirkung am Herzen, den Depressor- und Carotis-Sinus-Reflexen, eine *Schutzfunktion* für das Gewebe hat. Beide reziprok arbeitenden Reflexe zügeln auch mit gleichzeitiger Aktivierung die Durchblutung und den Gewebsstoffwechsel. Auch der meist wenig verstandenen Gefäßerweiterung durch antidrome sensible Impulse gab *Hess* einen funktionellen Sinn zur Regelung der Gewebefunktion: Die Schmerzfasern unterstützen eine schmerzunterschwellige Gewebstrophik. Nur bei stärkeren Reizen entstehen Schmerz oder Entzündung, bei schwächeren nur physiologische Durchblutungssteigerungen. Man erkennt in den antagonistischen Konzeptionen der Durchblutungsregelung unschwer den Ursprung von *Hess'* Schema des trophotropen und ergotropen vegetativen Systems [16, 30].

Wie der Untertitel seiner Kreislauf-Monographie [12] zeigt und *Hess* in der Einleitung betonte, war die Kreislauffunktion für ihn „eine Gelegenheit, in die integrativen Leistungen des vegetativen Nervensystems Einblick zu nehmen". Die Durchblutungsregelung arbeitet ebenso wie die vegetative Innervation als Anpassung an die Leistung des Organs und hat eine „Dynamik höherer Ordnung". Neben der Herztätigkeit und den für das Gewebe entscheidenden Kapillarfunktionen betonte *Hess* auch die Tätig-

keit der Arterien und Venen, die er auf ihre organspezifischen Reaktionen untersuchte. Das Herz wird als Hilfsapparat der eigentlichen kapillaren Austauschvorgänge angesehen, und die Entlastungsreflexe werden im Antagonismus zu den Nutritionsreflexen ähnlich der kardialen Vagus- und Sympathicuswirkung als Erholungs- und Leistungsfunktionen gedeutet. Auf die cerebralen Kreislaufregulationszentren ging *Hess* in dieser Monographie noch nicht genauer ein, tat dies aber später nach systematischer Auswertung seiner zentralen Reiz- und Ausschaltungsversuche im Zwischenhirn 1938 [20].

Ergotrope und trophotrope vegetative Leistungen. Sein Interesse für das vegetative System führte *Hess* zu einer theoretischen Systemkonzeption, die er in einer ersten weitgehend spekulativen Arbeit über „Wechselbeziehungen psychischer und vegetativer Funktionen" 1925 als Programm für experimentelle Untersuchungen veröffentlichte [7]. Im Gegensatz zur anatomischen Zweiteilung sympathischer und parasympathischer Nerven benützte *Hess* das *Leistungskriterium* für seine Einteilung in zwei funktionelle Untersysteme: 1) das *ergotrope* System, das die Leistungsbereitschaft animaler Funktionen fördert; 2) das *trophotrope* System, das für Erhaltung und Erholung der Gewebsleistungen sorgt. Im ersten Entwurf [7] hatte er das zweite auch „histotropes" und später „endophylaktisches" System [30] genannt, und solche terminologischen Eigenwilligkeiten erschwerten manchmal das Verständnis für *Hess'* klare Gedankenwelt in der physiologischen Forschung. Mit *Cannon* konnte sich *Hess* in einem Gespräch nicht über eine gemeinsame Konzeption und Terminologie einigen, und die Entdeckung der cholinergen und adrenergen Transmitterstoffe machten auch die alte pharmakologische Zweiteilung sympathischer und parasympathischer Drogenwirkungen problematisch. Anatomisch werden ergotrope Funktionen in der Peripherie nach *Hess* vorwiegend, aber nicht allein durch sympathische Nerven vermittelt. Beide Systeme gehorchen einer *zentralen Steuerung*, deren Erforschung sich *Hess* zur Lebensaufgabe machte. Im Gehirn sind beide Funktionssysteme anatomisch nicht klar unterscheidbar und offenbar noch enger antagonistisch verkoppelt. Nachdem *Hess* 1925 auch den Schlaf mit seiner Erholungswirkung als trophotrope Funktion bezeichnete [7], hat er die lange vernachlässigte physiologische Schlafforschung entscheidend angeregt. 1933 hat er ein übersichtliches Schema über die Funktionsverknüpfungen beider Systeme in einer Programmschrift über den Schlaf [16] gegeben. Diese Theorien konnten erst experimentell geprüft werden, nachdem seit 1934 hirnelektrische Registrierungen aus dem schlafenden Gehirn gemacht wurden und *Bergers* EEG auch beim Menschen die objektive Erfassung der Schlafveränderungen ermöglichte. Hirnelektirsche Schlafuntersuchungen hat *Hess* nur in wenigen Experimenten mit seinem Sohn an der schlafenden Katze 1950 begonnen.

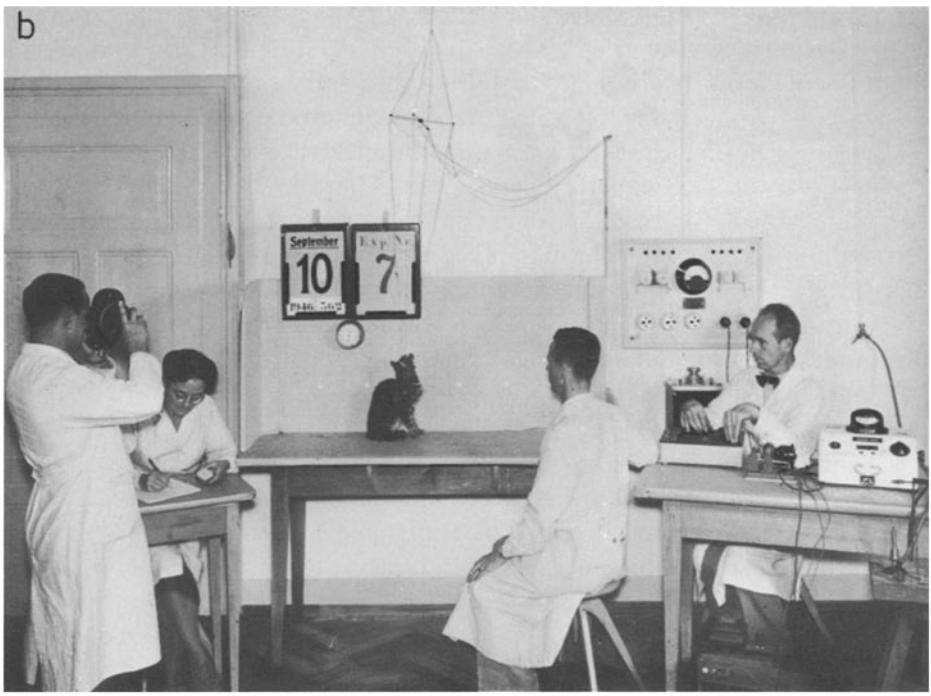
Dann überließ er dieses Feld anderen. Daß im letzten Jahrzehnt die Katecholaminforschung neue Aspekte der neurochemischen Schlafregulationen eröffnete, hat *Hess* zwar interessiert, aber die biochemische Forschung lag ihm fern.

Seine hirnphysiologischen Experimente konzentrierte *Hess* auf das *Zwischenhirn,* in dem er die Integrationszentren der vegetativen Regulationen vermutete, nachdem seit 1909 nur wenige Reiz- und Ausschaltungsexperimente, vor allem der Wiener Physiologen *Karplus* und *Kreidl* auf die Rolle des Hypothalamus für das Vegetativum hingewiesen hatten.

Die Hirnstammreizung an der wachen Katze. Für die Methodik der seit 1925 durchgeführten Zwischenhirnexperimente entwickelte *Hess* eine spezielle elektrische Reizung und Elektrodenlokalisation im Gehirn [14]. Die *Berliner-Blau-Reaktion* nach Eisen-Elektrophorese von den Stahlelektrodenspitzen diente als Makrolokalisation und erste Orientierung auf den horizontal zerlegten Hinrscheiben. Zur histologischen Lokalisation verwendete er auf Rat Oskar *Vogt*s abwechselnde Nissl- und Markscheidenfärbungen der horizontalen Schnittserien. Von diesen ließ er 1926 und 1937 einen fotografischen Atlas der Stammganglien und des Zwischenhirns herstellen [14].

Die von *Hess* entwickelte Hirnreizmethode verwendete *unterbrochenen Gleichstrom,* um auch markarme und marklose vegetative Fasern zu reizen, die durch die üblichen kurzen faradischen Stromstöße nicht erregt werden. Er konstruierte einen kleinen, auf der Schädeldecke verschraubten Standardhalter für sechs Elektroden, so daß die wache Katze mit ihren Zwischenhirnelektroden auf dem Versuchstisch wie in Abb. 3 frei laufen und ohne Fixation und Narkose in ihrem Verhalten untersucht und gefilmt werden konnte [14]. Dagegen erfaßte die etwa gleichzeitig von W. *Ransom* in Chicago systematisierte subkortikale stereotaktische Reizung narkotisierter Katzen mit der alten Horsley-Clarke-Methode lediglich grobe motorische Effekte, aber konnte über Verhaltenskorrelationen wenig oder nichts aussagen. Daher beurteilte *Hess* die Stereotaxie in Narkose sehr zurückhaltend. *Ransom* wiederum kritisierte *Hess'* Schlafexperimente mit ihrer langdauernden Reizung und vermutete elektrolytische Läsionen der Ausschaltung statt Reizung. So kam es nicht zu der wünschenswerten Koordination der beiden Forschergruppen von *Ransom* und *Magoun* in Chicago und von *Hess* in Zürich.

Zur Anatomie hatte *Hess* ein zwiespältiges Verhältnis. Einerseits brauchte er lokalisatorische Kontrollen der Hirnreizungen, andererseits mißtraute er dem statisch-anatomischen Denken. Obwohl seine erste Arbeit 1903 in der Anatomie begann, hat *Hess* schon damals anatomische Strukturen mit ihrer *Funktion* korreliert. Reine Strukturbeschreibung hielt er für ein be-



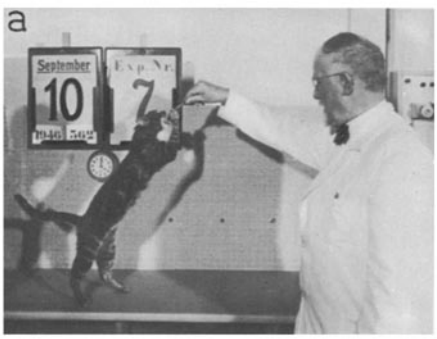


Abb. 3a, b. Reizexperiment an der freien Katze in *Hess'* Laboratorium 1946. a *Hess* gewöhnt die Katze durch Füttern an den Versuchstisch und die experimentelle Situation. **b** Kopf- und Augendeviation der Katze nach oben bei mesencephaler Reizung. – Der Versuchstisch mit Uhr, Datum und Experiment-Nummer für die Filmaufnahme war seit 1928 eine Standardordnung für jedes Experiment. Die Katze trug eine Zuleitung feiner Drähte zum Elektrodenhalter auf dem Schädel, da es noch keine drahtlose Reizung gab. Der Institutstechniker *Jenny* sitzt rechts an der Reizapparatur, zwei Assistenten beobachten und filmen die Katze, und die Sekretärin links protokolliert. Vor 1939 machte *Hess* selbst die Filmaufnahmen der Reizeffekte

schränktes anatomisches Konzept. Er mißachtete Anatomen, die sich aus Freude am morphologischen Detail nur auf Formstudien beschränkten.

Hess sah sich die Elektrodenspitzenpositionen zunächst makroskopisch im Berliner-Blau-Bild an und ließ dann Schnittserien anfertigen [14]. Doch überließ er die eigentliche histologische Auswertung am Zell- und Faserbild anderen. Er pflegte zu sagen, es käme im Gehirn weniger auf die Kerne

an als auf ihre *Verbindungen,* in denen sich die physiologische Ordnung zeige. Darum begrüßte er es sehr, als *Weisschedel* und ich 1936 im Zürcher Institut eine modifizierte Marchi-Methode zur Darstellung degenerierender Fasern von den nach der Reizung durch Koagulation zerstörten Hirnteilen einführten. Die Präparate zeigten nun die efferenten Faserverbindungen der gereizten und koagulierten Strukturen. Allerdings wurden die Grenzen der Marchi-Technik bald deutlich, da sie vorwiegend dicke markhaltige Nervenfasern darstellte, aber die im vegetativen System häufig markarmen, dünnen Fasern nur schlecht erkennbar waren. Die Silbermethoden zur Markierung synaptischer Projektionen wurden damals erst entwickelt und die modernen Enzymdarstellungen anatomischer Projektionen waren unbekannt.

Die Schlafexperimente. *Hess'* Demonstrationen, daß Hirnreizungen Schlaf auslösen, erregten zunächst Erstaunen, entsprachen aber genau seinem Postulat der Erholungsfunktion des trophotropen Systems von 1924/25 [7]. So wurden seine breiter angelegten Reizversuche an der freibeweglichen Katze seit 1929 vor allem durch Schlafexperimente bekannt, obwohl diese auch mit Skepsis aufgenommen wurden: Die Einwände amerikanischer Kritiker, die mit *Ransom* bei seinen langen Reizserien durch pulsierenden Gleichstrom elektrolytische Läsionen annahmen, konnte *Hess* jedoch widerlegen. Seine Experimente brachten 1927–1929 einen entscheidenden Anstoß für die von der Physiologie bis dahin vernachlässigte *Schlafforschung.* Hirnelektrische Korrelate des Schlafes wurden dann wenig später durch *Bergers* „Elektrenkephalogramm" (EEG) nachgewiesen, und seit 1935 machten amerikanische Forscher systematisch EEG-Ableitungen beim schlafenden Menschen.

Schwierigkeiten für die hirnphysiologische Deutung der Schlafexperimente von *Hess* lagen vor allem in der weit verstreuten unspezifischen Lokalisation der Reizpunkte, die vom medialen Thalamus bis zum Striatum reichten, und in der langen und sehr wechselnden Latenz des Schlafeffektes. Dennoch haben *Hess'* Untersuchungen eine neue Forschungsrichtung begründet, die mit der wenig später beginnenden Verhaltensforschung von *Lorenz* und v. *Holst* zum *Experimentieren am wachen Versuchstier* führte. Mit dem Schlafverhalten konnte *Hess* zum ersten Mal durch Zwischenhirnreizung eine geordnet ablaufende *Instinkthandlung* auslösen, die dem normalen Triebvorgang entspricht, der nach Ermüdung zum Ausruhen führt [8, 37]. 1943 konnte er einen umgekehrten Aktivierungseffekt, die *„affektive Abwehrreaktion"* nach Hypothalamusreizung [26], hinzufügen. Erst viel später wurde das Konzept der sog. unspezifischen Aktivierung der Hirnrinde im EEG nach Reticularis-Reizung im Mittelhirn durch *Moruzzi* und *Magoun* 1949 entwickelt. Da *Hess* sich zunächst auf Reizexperimente

oberhalb des Mittelhirns beschränkte und die späteren Reticularis-Reizungen anderer Autoren meist am narkotisierten Tier erfolgten, dauerte es ein bis zwei Jahrzehnte, bis die Befunde von *Hess* mit den hirnelektrischen Ergebnissen und dem Konzept eines unspezifischen aufsteigenden Aktivierungssystems koordiniert werden konnten.

Seit 1960 gelang es dann *Jouvet, Moruzzi* und ihren Mitarbeitern, auch die Beteiligung tieferer rhombencephaler Hirnteile an der Schlafregulation nachzuweisen. Diese Reiz- und Ausschaltungsexperimente in Pons und Oblongata und die Entdeckung der vom Hirnstamm zum Cortex aufsteigenden Systeme mit verschiedenen chemischen Überträgerstoffen zeigten, daß die Schlafregulationen viel komplizierter sind, als man in den 30er Jahren annahm. Im Prinzip hat jedoch *Hess'* Theorie, wonach der Schlaf eine trophotrope *Ruhigstellung des Großhirns* durch vom Hirnstamm aufsteigende dämpfende Impulse ist, auch heute noch ihre Gültigkeit.

Die Motorik. *Hess'* Interesse für die Bewegungsphysiologie begann schon in seiner ophthalmologischen Zeit, als er ein Schema zur Erfassung der Augenmuskellähmungen entwarf [3]. Die Augenmotorik war für ihn ein Idealfall, der die *Bewegungsordnung in den drei Raumebenen* mit drei Paaren antagonistischer Muskeln exakt darstellen ließ. Dreißig Jahre später kam er mit einer präkybernetischen Arbeit über die Motorik als Organisationsproblem [24] zur sensomotorischen Koordination zurück. Er konstruierte Blockschaltungen als Modelle der okulomotorischen Beherrschung des Blickfeldes mit einfacher und doppelter Mannigfaltigkeit, die für jede Ausgangsstellung eine Bewegungsfreiheit nach allen Richtungen entsprechend der Gesichtsfeldlokalisation ermöglichten. Diese erweiterte er für die Körpermotorik mit Überwindung der Gravitation durch propriozeptive Regulation. Nach seinen Worten sollten bei der Bewegung Rezeptorsysteme zur Störausschaltung und Muskelinnervation als „zielorientiert gruppierte Kräfte fehlerfrei zum Ziel führen". Diese Bewegungsregulation muß bei jeder neuen Stellung die Muskelzugwirkung verändern. Er postulierte im Gehirn eine *Parallelschaltung der Raumwahrnehmung mit der Bewegungskoordination.* Seine präkybernetischen Modelle verwendeten Vektorwirkungen für die richtungsmäßige Impulssummation. Gleichzeitig demonstrierte er mit seinen Hirnstammreizungen die Existenz *richtungsspezifischer Substrate im Zwischen- und Mittelhirn* der Katze [22, 35]. So konnten seine experimentellen Befunde die Realität der von vielen als spekulativ empfundenen Bewegungsorganisation nachweisen.

Seine Bewegungstheorien hat *Hess* zwei Jahre später für die *menschliche Ziel- und Stützmotorik* durch ein lebendes Modell für die praktische Bewegungsleistung ergänzt [27]. Die Wechselwirkung von Haltung und Bewegung wurde durch drei Personen dargestellt. Der Träger repräsentiert Skelet

und Schwerkraft-kompensierende Muskulatur, der Stützer die Halteinnervation rumpfnaher Muskeln und der Springer die dynamisch-ballistische Muskelaktion. Bei der aufrechten Haltung des Menschen wird die Stützmotorik vor allem zur Kompensation von Schwerkraftwirkungen eingesetzt. Damit die Zielbewegung gelingt, muß die Stützfunktion frühzeitig aktiviert werden. Diese *Antizipation* bedeutet ein Primat der Haltung für die Bewegungsbereitschaft. Träger und Stützer müssen den Moment des Sprunges *wissen,* Gewicht und Absprungkraft *fühlen* und sich an die Haltungsveränderung *anpassen.* Die Zielbewegung mißlingt, wenn der ungestützte Träger vom Absprung nicht orientiert wird. Prinzip der Stütz- und Zielmotorik sind demnach *Bereitschaftshaltung mit regelnder und steuernder Rückmeldung* entsprechend der in den folgenden Jahren entwickelten Biokybernetik [42, 43].

Hess' ungewöhnliche Terminologie von 1943, „teleokinetische Motilität" für die Zielmotorik und „ereismatische Motilität" für die Stützmotorik [27], erschwerten zunächst das Verständnis dieses Modellversuchs, so daß *Hess* ihn 22 Jahre später noch einmal mit Filmbildern zusammenfassend dargestellt hat [42, 43].

Die weitere Ausarbeitung überließ *Hess* anderen. Als seine Schüler *Wyss* und *Koella* die Labyrinthreflexe und ich die visuell-vestibuläre Koordination mit Registrierung der Augenbewegungen untersuchten, zog er sich zurück, als die Ergebnisse zu kompliziert für Modellbilder wurden. Doch verfolgte *Hess* die Reafferenz-Konzepte v. *Holst*s und andere Regelmodelle, die Blickbewegung und Wahrnehmung durch entsprechende biokybernetische Schaltbilder erklären sollten, mit wachem Interesse.

Die Psychophysiologie. Sein letztes Buch [39], das *Hess* nach seiner Emeritierung schrieb, war über Jahrzehnte geplant. Es sollte zunächst den Titel „Psychophysiologie" erhalten, den er 1962 in *Psychologie in biologischer Sicht* änderte. Seine Korrelation von psychischen und neuralen Funktionen hatte ihren frühen Ursprung in der Schrift von 1925 über psychische und vegetative Funktionen [7]. Das Psychologiebuch ist oft mißverstanden worden, besonders die Ausführungen über unbekannte „psychische Kräfte".

Im Gespräch erläuterte *Hess* die seelische Kraft und ihre unbekannte Natur viel klarer als in dem Buch: Er zog eine Parallele zur Schwerkraft in der Physik, deren Wesen auch niemand kennt, aber deren *Wirkungen* man beobachten und exakt messen kann. So meinte *Hess,* sollten auch psychische Kräfte in ihren Auswirkungen zu erkennen und *meßbar* sein, obwohl ihre Natur völlig unklar bleibt. Ein Rezensent glaubte, das Buch enthalte unwissenschaftliche Vorstellungen von psychischen Kräften ohne Korrelation mit Hirnfunktionen, obwohl *Hess* mehrfach betont hat, daß psychische Funktionen nur auf der Grundlage neuronaler Hirnprozesse möglich

sind. Eine persönliche Diskussion sollte diese Mißverständnisse vor der 2. Auflage beseitigen. Um die Verbindung mit der modernen Forschung zu erhalten, organisierte *Hess* ein kleines Symposion, bei dem Freunde und Schüler neuere Befunde mit informationstheoretischen Fragen besprachen. Diese Diskussion erschien in der 2. Auflage [39].

Über allgemeine Fragen von Hirnfunktion und Bewußtsein und seine Konzeption der psychischen Kräfte korrespondierte *Hess* zuletzt mit dem Pharmakologen H. *Fischer*. Teile dieses Briefwechsels erschienen in englischer Übersetzung 1973 kurz nach seinem Tode. Darin wird eine Lösung dieser Fragen auf empirischer Basis abgelehnt und philosophische und religiöse Gedanken werden nur als mögliche Annäherungen diskutiert. Zu den Grenzen unseres Wissens sagt *Hess:* „Wir müssen uns zufrieden geben, daß noch so vieles in der Welt existiert und vor sich geht, das unserem Verständnis entzogen ist. Darüber hinaus halte ich ein bescheidenes Schweigen als die beste Einstellung zu den aufgeworfenen Fragen."

Nebenwege der Forschung. Die rhythmischen Spontankontraktionen der Arterien verschiedener Organe und ihre humorale Beeinflussung durch vegetativ aktive Stoffe haben *Hess* über viele Jahre interessiert. Die mehr oder weniger spezifischen Veränderungen durch Adrenalin, Acetylcholin und andere Stoffe wurden von zahlreichen Doktoranden untersucht.

Große Verdienste hatte *Hess* auch für die meteorologisch-physiologische Forschung. Er gründete die *Höhenstation Jungfraujoch* und verwendete viel Zeit für die Organisation und Einrichtung, bis er sie an von *Muralt,* Bern, abgab, der die von *Hess* ehrenamtlich durchgeführte Leitung dann in eine amtliche Direktorenstelle verwandelte. Nach frühen Anregungen für die Wetterforschung durch seinen Vater hat *Hess* manche Arbeit auf diesem Gebiet veranlaßt, aber war selbst nicht auf dem meteorologisch-biologischen Gebiet tätig, das auch heute noch ungeklärt ist.

Die Wirkungen seines Forscherlebens

Der akademische Lehrer. In den ersten Jahren seiner Institutsleitung 1917–1924 widmete *Hess* viel Zeit dem Ausbau des physiologischen Unterrichts, bevor er 1924 seine Hirnforschungsarbeit begann. Er verbesserte den physiologischen Kurs mit experimentellen Demonstrationen und führte den Schmalfilm für Unterricht und Forschung ein. Die *Filmdemonstration* blieb für *Hess* seitdem wichtigstes Instrument der Demonstration und Dokumentation. Die Hauptvorlesung für alle Gebiete der Physiologie hielt er jedes Semester, auch in späteren Jahren, in denen die experimentelle Arbeit seine ganze Kraft benötigte. Seine Reizexperimente filmte er

viele Jahre selbst und erst nach 1945, als er das Personal des Institutes vergrößern konnte, übernahmen Mitarbeiter die Filmarbeit, wie Abb. 3b zeigt. Die Prinzipien der Motorik hat *Hess* vorwiegend durch Filmanalyse und Modellexperimente gefördert. Auch in den 30er Jahren, als seine Methode der Hirnreizung bei der freilaufenden Katze seine ganze Arbeitskraft in Anspruch nahm, hat er sich nicht vom studentischen Unterricht zurückgezogen, sondern grundlegende Experimente oft selbst vorgeführt wie in Abb. 2b.

Der Sprecher und Autor. *Hess* war ein guter Redner, und seine Sprache als akademischer Lehrer war klar und einprägsam. Auch in der Diskussion traf er mit wenigen, richtigen Worten den Kern der Sache. Als er auf der deutschen Physiologentagung 1960 wieder einmal die mangelnde physiologische Hirnforschung in den deutschen Instituten monierte, sagte er: „Wenn Sie es nicht machen, werden die Pharmakologen die Hirnphysiologie übernehmen, aber die Neuropharmakologie wird funktionell wichtige Zusammenhänge übersehen". Wenn *Hess* dann die gleichen Gedanken in schriftliche Form brachte, wurden die einfach erfaßten Prinzipien zwar mit konkreten Beispielen illustriert, aber sein systematisches, sich mit allen Nebenwirkungen und Widersprüchlichkeiten auseinandersetzendes Denken verführten ihn zu langen Erklärungen und komplizierten Formulierungen. Seine *Terminologie* war oft eigenwillig und erschwerte die Annahme seiner klaren Konzeptionen durch vermeintliche Ausdrucksverbesserung: z.B. die Umbenennung des anfangs „histotropen" [7] dann „trophotropen" vegetativen Nervensystems [16] in ein „endophylaktisches" System [30], das als Antagonist des ergotropen Systems funktioniert. Auch die Bezeichnung der Zielmotorik als „teleokinetisch" und der Stützmotorik als „ereismatisch" war der Anerkennung dieser wichtigen Leistungsanalyse der Bewegung und Haltung nicht günstig.

Bei Abfassung seiner Manuskripte gab *Hess* sich große Mühe und schrieb sie immer wieder um. Nach der Emeritierung war er ohne Sekretärin, und in Ascona half ihm seine Frau bei allen späteren Arbeiten unermüdlich an der Schreibmaschine. Zur Begründung mangelnder sprachlicher Eleganz sagte *Hess,* für jemand, der in der Umgangssprache Schwyzerdütsch rede, sei das „Schriftdeutsch eine Fremdsprache". Aber dies hat mich nie überzeugt, weil *Hess* auch im hochdeutschen Vortrag spontan klar und präzise sprach. Es war seine Gründlichkeit und Gewissenhaftigkeit, die den einfachen Satz komplizierte. So habe ich bei allen strittigen Fragen lieber persönlich mit ihm gesprochen, als korrespondiert oder alte Publikationen nachgelesen. 1958 wollten *Hassler* und ich, als seine Schüler, *Hess'* Konzeption der Ziel- und Stützmotorik im amerikanischen Handbuch der Physiologie darstellen: Bei unserem Besuch in Zürich gab uns *Hess* an einem Nachmittag mündlich mit einem alten Film ein klares Exposé, das aus der

Lektüre seiner zehn vorangehenden Arbeiten nur mühsam zu abstrahieren war. Der Film ließ sich in einer Schemazeichnung zusammenfassen, die *Hess* dann korrigierte und bestätigte: Haltung, Stütze und Zielbewegung war in einem Drei-Personen-Experiment anschaulicher dargestellt als es eine lange Beschreibung vermochte (vgl. S. 14).

Jede Begegnung mit *Hess* war noch bis in die letzten Altersjahre interessant und anregend, denn er blieb noch als 80jähriger produktiv mit neuen Ideen und diskutierte gern auch über neue Gebiete der Verhaltensforschung und Biokybernetik. So habe ich die früheren Zürcher Besuche, zu denen er nach kurzer Anfrage einlud, und die selteneren späteren in Ascona in schönster Erinnerung.

Die Hess-Schule und persönliche Erinnerungen. Während der vier Jahrzehnte seiner Tätigkeit im Zürcher Physiologischen Institut hatte *Hess* zahlreiche Mitarbeiter, die auf verschiedenen Gebieten der Physiologie arbeiteten und vorwiegend Schweizer Lehrstühle besetzten. Von den älteren Mitarbeitern nenne ich F. *Verzar* in Basel, A. *Fleisch* in Lausanne und O.A.M. *Wyss*, der sein Nachfolger in Zürich wurde und vorwiegend Themen der Neurophysiologie und Atmungsphysiologie bearbeitete, ferner E. *Rothlin* und W.P. *Koella*, die neurophysiologische und neuropharmakologische Forschungen in der Schweizer Pharmaindustrie förderten. Spätere neurophysiologische Schüler waren Marcel *Monnier*, der aus der Neurologie kam und nach einer kurzen Tätigkeit in Genf den Basler Lehrstuhl als Nachfolger *Verzars* erhielt und die Physiologie und Neurochemie des Schlafs bearbeitete, und R.W. *Hunsperger*, der die cerebralen Reizversuche über die affektive Abwehrreaktion fortsetzte und die Verbindungen der hypothalamischen Strukturen mit dem Rhinencephalon und dem Mandelkern klärte, Sandro *Bürgi*, der die anatomische Auswertung von *Hess'* Experimenten Ende der 30er Jahre übernahm, wurde Neurologe, aber hielt die Verbindung mit dem Institut aufrecht. Der Sohn Rudolf *Hess* jun. wechselte von der Physiologie zur klinischen Elektroenzephalographie. Konrad *Akert* war der letzte und in der Forschung aktivste Schüler, mit dem *Hess* zahlreiche Arbeiten 1945–1952 schrieb und der sein Werk mit dem Aufbau des Zürcher Hirnforschungsinstitutes fortsetzte. Nach mehrjährigen Arbeiten in verschiedenen physiologischen und anatomischen Instituten der USA kam *Akert* nach Zürich zurück, als *Hess*, enttäuscht von dem Fortgang der Hirnforschung im Physiologischen Institut die Gründung eines Hirnforschungsinstitutes erreicht hatte, das auch die hirnanatomische Abteilung v. *Monakows* fortsetzen sollte. Dieses selbständige Institut übernahm *Akert*, richtete Abteilungen für Neurophysiologie, Neuroanatomie und Neurochemie ein und konnte so die von *Hess* inaugurierte Forschungsrichtung fortsetzen und erweitern.

Von ausländischen Mitarbeitern erwähne ich den Holländer W.O.C. *Magnus,* Sohn des Utrechter Pharmakologen, den Schweden B. *Andersson,* den Italiener C. *Bartorelli* und E. *Weisschedel,* R. *Hassler* und mich selbst aus Deutschland.

Ich habe *Hess* über fast 40 Jahre gekannt, und seit meiner ersten Tätigkeit in seinem Institut 1936/37 trafen wir uns regelmäßig. Der große Altersunterschied von drei Jahrzehnten – *Hess* war damals 55 und ich 25 Jahre alt – bedeutete keine Trennung. Außer dem Lehrer-Schüler-Verhältnis entwickelte sich in den nächsten Jahrzehnten durch meine Zuwendung zur Elektrophysiologie, die *Hess* selbst nicht betrieb, ein Verhältnis gegenseitiger Anregung für die hirnphysiologische Forschung. Als *Hess* 1938 mein Laboratorium in Freiburg besuchte und ich ihm die großen, bilateral-synchronisierten EEG-Wellen beim kleinen epileptischen Anfall zeigte, rief er spontan: „Das ist die vegetativ-trophotrope Beeinflussung des Cortex aus dem Zwischenhirn". Eine ähnliche subcorticale Beeinflussung des Cortex war bei den langsamen Schlafpotentialen anzunehmen.

Selbst die Kriegsjahre brachten keine vollständige Unterbrechung unserer wissenschaftlichen Diskussion. *Hess* kam 1941 nach Frankfurt, um seine neuen Motorikuntersuchungen in den drei Raumrichtungen nach Hirnstammreizung bei *Kleist* zu demonstrieren, in dessen Lazarett ich damals arbeitete, und diskutierte klinisch-neurologische Korrelate der Wende- und Drehbewegung seiner Katzen mit uns. In den schwierigen Nachkriegsjahren, als wir in der Besatzungszeit noch ohne wissenschaftlichen Kontakt mit dem Ausland blieben, lud *Hess* hirnanatomisch interessierte deutsche Mitarbeiter wie *Weisschedel* und *Hassler* ein, an der Auswertung seiner Ausschaltungsversuche teilzunehmen [32, 35].

Unsere Reiz- und Ausschaltungsexperimente an der Substantia nigra, die wir auf Wunsch von *Spatz* bei *Hess* 1936/37 in Zürich machten, brachten nicht die erhofften Ergebnisse, da die Marchi-Methode für die Degeneration der feinen Fasern nicht ausreichte und die modernen Silberdegenerationsmethoden und die Dopamintransmitter noch nicht bekannt waren. So waren wir bei der Deutung des flachen EEG im Isocortex und der Thetawellen im Allocortex nach Sinnesreizen und Hirnstammreizungen, die ich mit *Weisschedel* und *Kornmüller* 1937 in Berlin untersuchte, anatomisch zu skeptisch gegen die von *Hess* postulierten ascendierenden Cortexprojektionen. Damit versäumten wir, das thalamo-retikuläre System zu erkennen, auf das erst 1949 *Moruzzi* und *Magoun* aufmerksam machten, und Hirnstamm-Cortex-Beeinflussungen, die jetzt für die Katecholamintransmitter anerkannt sind.

Jedes physiologische Gespräch mit *Hess* brachte neue Anregungen, Kritik und Aufmunterung. Anfangs begegnete er unseren Mikroelektrodenstudien mit Zurückhaltung, dann begrüßte er sie, riet aber mehr zu einer

Analyse der Motorik, die ihn seit 1940 vor allem interessierte. Zu dieser Arbeit kam ich erst nach seinem Tode, habe aber in den letzten Jahren seines Lebens noch einiges mit ihm diskutieren können. Nur eine Enttäuschung mußte ich *Hess* bereiten: Seinem Wunsch, den Lehrstuhl für Neurologie in Zürich zu übernehmen, zu dem mich die Fakultät 1955 berief, konnte ich nicht folgen, nachdem einige zunächst gegebene Zusagen nicht erfüllt wurden.

Das letzte Jahrzehnt. 15 Jahre nach seiner Emeritierung, als fast alle Zürcher Freunde gestorben waren und *Hess* wegen seiner zunehmenden Schwerhörigkeit nicht mehr zu wissenschaftlichen Tagungen reisen konnte, überließ er seine Bibliothek dem Institut und zog 1967 ohne Bücher und Sonderdrucke von Zürich in sein kleines Sommerhaus nach Ascona. Dort lebte er mit seiner Frau in Ruhe für die letzten sechs Jahre. Beziehungen zur Umwelt behielt er durch lebhafte Gespräche mit besuchenden Freunden und seine dauernde Freude an der Pflege seines Gartens.

Im letzten Jahrzehnt verhinderte seine Altersschwerhörigkeit alle Tagungsdiskussionen, aber in der Einzelunterhaltung blieb *Hess* aufnahmefähig und anregend wie in jungen Jahren. Die letzte Tagung, an der er noch aktiv teilnahm, war das von seinem Schüler *Akert* 1964 organisierte Schlafsymposion in Zürich, in dem er einen kurzen Überblick über seine Konzeption des Schlafes als einer aktiven Leistung des gesamten Organismus gab. In Ascona habe ich ihn seit 1967 fast jedes Frühjahr gesehen und konnte ihm 1971 zum 90. Geburtstag die Glückwünsche der deutschen Physiologen überbringen, von deren Gesellschaft er dann zum Münchener Internationalen Physiologenkongreß die Johannes-Müller-Medaille erhielt. Damals zeigte uns *Hess* den Friedhof auf dem benachbarten Berg, auf dem er begraben sein wollte. Während er sich im August 1973 an der sommerlichen Fülle seines geliebten Gartens freute, kam ein friedlicher Tod durch Herzversagen und beendete sein rastloses Forscherleben.

Literatur

Das Literaturverzeichnis von W.R. *Hess* umfaßt über 304 Arbeiten, die im Nachruf der Wiener Akademie [45] vollständig verzeichnet sind. Ich bringe daher aus der von 1903–1973 reichenden Publikationsliste nur einige wichtige Arbeiten und die zusammenfassenden Monographien in chronologischer Ordnung (A.) und eine Liste der Nachrufe für *Hess* (B.). Die Arbeiten seines Institutes für die Hirnstammphysiologie sind im Dokumentationsatlas „Hypothalamus und Thalamus" [37] zusammengestellt. Auch die „Psychologie in biologischer Sicht" [39] enthält einige thematisch geordnete Institutsarbeiten.

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Neural Organisation and Control of the Baroreceptor Reflex

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Contents

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Abbreviations

AN	Aortic nerve
BVM	Preganglionic bronchomotor neurone
C	Cervical spinal cord
CVM	Preganglionic cardiac vagal motoneurone
DLF	Dorsolateral funiculus
DLH	Di-homocysteic acid
DNV	Dorsal motor nucleus of the vagus
ECG	Electrocardiogram
5HT	5-hydroxytryptamine
IC	Intercostal
IML	Intermediolateral cell column
IMM	Intermediomedial cell column
LRN	Lateral reticular nucleus
NA	Nucleus ambiguus
NPR	Paramedian reticular nucleus
NTS	Nucleus of the tractus solitarius
SN	Sinus nerve
T	Thoracic spinal cord
TS	Tractus solitarius

1 Introduction

The baroreceptors of the aortic arch and the carotid sinuses participate in the homeostatic control of the cardiovascular system through a regulation of arterial blood pressure. The basic properties of the baroreceptors and the input-output characteristics of the reflex have been reviewed (*Heymans* and *Neil* 1958; *Kezdi* 1967; *Kirchheim* 1976). The years that span these three major reviews have seen a tremendous advance in our understanding of the central nervous control of the circulation, yet this work appears to have made very little impact on the analysis of neural control of the reflex presented in the latest of these reviews. This is likely to reflect the dominance of the concept of a medullary "vasomotor" centre through which central and peripheral inputs exert their influence on the cardiovascular system (*Bayliss* 1923; *Alexander* 1946). Accordingly, since the baroreceptor input has an important role in cardiovascular control, its role has been restricted to a control of this hypothetical "centre". Since the foundations on which both the original concept and the anatomical location of

the centre are based have been questioned (*Peiss* 1965; *Hilton* 1966, 1975; *Downman* 1972; *Smith* 1974), it becomes important to draw attention to the basic neuronal circuitry that mediates the baroreceptor reflex.

This article will endeavour to review the neurophysiological and neuroanatomical studies that have attempted to investigate the pathway within the central nervous system taken by the baroreceptor reflex. The last decade in particular has seen a rapid development in the range and specificity of neurophysiological and neurohistological techniques so that a general framework has emerged concerning the nature and extent of this pathway (Sect. 2). Secondly, an attempt will be made to summarise the available material on the baroreceptor inputs to and control of preganglionic autonomic neurones, since by analogy with the somatic nervous system they may well be a site of integration (Sect. 3). It will be necessary at this time to review the control of sympathetic and vagal preganglionic activity from other brainstem sites and the relationship of baroreceptor inputs to these controls because this may well supplement and, it is hoped, complement, the data reviewed in Sect. 2. Finally, an attempt will be made to evaluate the modifications of the reflex which may be evoked centrally or peripherally (Sect. 4). This has already received extensive review (see for example *Korner* 1971) since it has often been suspected that a central resetting of the reflex might play a role in the development of hypertension (*Kezdi* 1967). The present account will concern itself only with those modifications which have been investigated neurophysiologically. This restricted selection may, however, prove adequate, as an analysis of such a limited brief indicates that certain modifications result from a limited range of neuronal mechanisms.

Throughout, only a limited effort will be directed to neuropharmacological studies on the performance of the baroreceptor reflex, since there are few examples of direct investigation, and the expansive literature on the pharmacology of cardiovascular control has received extensive review elsewhere (for example *Day* and *Roach* 1974; *Haeusler* 1976; *Prichard* 1978).

2 The Projection of Sinus and Aortic Baroreceptors

2.1 Termination of Sinus and Aortic Nerves: Location of the First Synapse

In establishing the central pathway taken by the baroreceptor reflex, the location of the first synapse is of particular importance. Standard neuroanatomical and neurophysiological techniques are available to investigate

the projections of primary afferent sensory fibres, but although these have been applied to the problem of the baroreceptor input to the brain, until recently controversy had remained regarding the localisation of even the first relay station.

There are many reasons for this. Firstly, the afferent fibres originating from the baroreceptors do not form a homogeneous group; they range from unmyelinated to medium-sized myelinated fibres (*de Castro* 1928; *Douglas* and *Ritchie* 1956; *Douglas* and *Schaumann* 1956; *Douglas* et al. 1956; *Fidone* and *Sato* 1969). Furthermore, in the case of those innervating the carotid sinus, they are carried in the sinus nerve, mixed with afferent fibres innervating the chemoreceptors of the carotid body which have diameters within the same spectrum as baroreceptor afferents (see *de Castro* 1928; *Heymans* and *Neil* 1958; *Fidone* and *Sato* 1969). This means that it is impossible to activate preferentially either baroreceptor or chemoreceptor afferent fibres on electrical stimulation of the sinus nerve, although this has sometimes been claimed (see for example *de Groat* and *Lalley* 1974). Furthermore, the sinus nerve is a branch of the IXth cranial nerve, which contains afferents from a wide range of areas such as the pharynx, tonsil and posterior part of the tongue, in addition to efferent fibres. The sinus nerve itself contains two groups of efferent fibres: postganglionic sympathetic fibres and a group of nonsympathetic and predominantly unmyelinated fibres which relay from an unknown site in the central nervous system, i.e. true sinus nerve efferents (see *Fidone* and *Sato* 1969).

In the case of aortic baroreceptor afferents similar problems arise. In the rabbit, there are no chemoreceptors in the aortic arch (*Heymans* and *Neil* 1958), and the aortic nerve (depressor nerve) is usually independent of the cervical vagus as far as the nodose ganglion. This fortunate anatomical arrangement is not repeated in other species, and in all species the intracranial vagal rootlets contain a heterogeneous mixture of afferents which innervate a wide range of thoracic receptors, both cardiovascular and respiratory, in addition to aortic arch baroreceptors and chemoreceptors and of course efferent axons (for references see *Paintal* 1972, 1973). The cervical vagus may also contain afferents innervating a group of baroreceptors in the carotid artery but independent of the carotid sinus (*Green* 1965).

Neuroanatomical studies on the projection of the IXth and Xth cranial nerves, which have traced degenerating axons and terminals following transection, whilst not providing data concerning the projection of baroreceptors in isolation, do provide a broad estimate of the limits within which these afferents must distribute themselves (see *McAllen* et al. 1979). With the recent application of neurophysiological techniques and specifically using antidromic mapping, it has been possible to obtain a reliable

picture of the termination of sinus and aortic nerve fibres. To this it has been necessary to add unit recording coupled with natural afferent stimulation in order to identify specific baroreceptor projections.

2.1.1 Neuroanatomical Studies

The projections of aortic and carotid sinus baroreceptors have been inferred from tracing degenerating axons and terminals after sectioning the cranial rootlets of the Xth and IXth nerves respectively. An early study using the Marchi technique, which traces only degeneration in myelinated fibres, showed that following vagal rhizotomy in the cat, degenerating fibres were restricted to the area around the ipsilateral tractus solitarius (TS) of the medulla (*Foley* and *Dubois* 1934). They described that the vagal fibres descended through the tractus giving off collaterals to the main nuclear regions – the medial, circumferential and commissural nuclei – in much the same way as described for IXth and Xth afferents by *Cajal* (1909). *Ingram* and *Dawkins* (1945) also described a similar distribution in the cat, although they also showed that some fibres decussated at obex level to terminate within the contralateral commisural nucleus and a small number relayed to the ipsilateral spinal trigeminal nucleus, probably those fibres which arose from the auricular branch of the vagus. The distribution of IXth nerve afferents was broadly similar, with the absence, however, of any projection to the contralateral side. The advent of the Nauta technique, which traces degeneration in unmyelinated fibres as well as myelinated fibres (*Glees* and *Nauta* 1955), led to the description of both myelinated and unmyelinated terminal degeneration in the nucleus tractus solitarius (NTS) of many species after section of either vagal or glossopharyngeal rootlets (*Torvik* 1956; *Cottle* 1964; *Culberson* and *Kimmel* 1972; *Cottle* and *Calaresu* 1975).

In the rat, *Torvik* (1956) found terminal degeneration of IXth and Xth nerve afferents throughout the NTS, the majority of degenerating terminals being located caudal to the rostral pole of the hypoglossal nucleus. At this level the heaviest degeneration was found in the lateral division of the NTS, although a large number of finer fibres passed medially to form a plexus in the medial nucleus, especially in its dorsolateral quadrant.

The most authorative study so far is that of *Cottle* (1964) who cut rootlets of both IXth and Xth nerves and traced the resulting degeneration in the medulla of cats. She showed that the rostral third of the NTS received an input from the IXth alone; the caudal-most portion of the NTS receiving an innervation from the Xth. The greatest signs of degeneration were observed in the intermediate zone of the nucleus, which extends from obex level 2.5 mm rostrally, and this zone received degenerating fibres from both IXth and Xth nerves. This region she considered to re-

present the area receiving the baroreceptor afferent input, since vagal fibres terminating in this area had been shown in an earlier study to originate from vagal rootlets which contained fibres innervating cardiovascular receptors (*von Baumgarten* and *Arranda Coddou* 1959; *Bonvallet* and *Sigg* 1958). Other studies have indicated a marked projection of IXth afferents to this area in different species (mouse, *Aström* 1952; cat, *Kerr* 1962; cat, rat, and guinea pig, *Kimmel* and *Kimmel* 1964; monkey, *Rhoton* et al. 1966; opossum, *Culberson* and *Kimmel* 1972).

With the use of the anterograde transport of horseradish peroxidase, *Katz* and *Karten* (1979) describe the projection of aortic nerve afferent fibres to the subnucleus dorsalis of the NTS in the pigeon. The terminals appear to be restricted to a region which in this species contains catecholaminergic neurones. Using a highly sensitive technique to visualise HRP, *Berger* (1979) described the transganglionic transport of this material from the SN to the NTS in the cat. The ipsilateral medial and lateral portions of the nucleus were densely innervated. A significant contralateral projection to both the commissural and medial subnuclei and to the lateral nucleus at levels rostral to the obex was seen, although this has yet to be confirmed neurophysiologically (see 2.1.2).

The location of vagal and glossopharyngeal terminals is summarised in Fig. 1a, modified from *McAllen* et al. (1979).

2.1.2 Electrophysiological Studies

2.1.2.1 Antidromic Activation

The anatomical limits for the termination of vagal and glossopharyngeal afferents have been provided by neuroanatomical studies (see Fig. 1a), and within the broad areas thus delineated it would be expected to find the terminals of the baroreceptor afferents originating from both aortic and sinus nerves. In order to identify specifically the projection of these nerves, the technique of antidromic activation of their intracranial projections has been used, recording activity evoked in SN and AN peripherally. This technique has, however, the disadvantages of activating both fibres *en passant* as well as terminals.

In a few studies, an attempt has been made to identify whether evoked responses have resulted from stimulation within terminal fields (*Lipski* et al. 1975; *Jordan* 1977; *Jordan* and *Spyer* 1977a, 1978b). The interpretation of data based on whole nerve evoked activity remains controversial, but the threshold-depth contours obtained in these studies are broadly analogous to those of *Jankowska* and *Roberts* (1972) on single neurones in the spinal cord. More recent studies have confirmed these inferences for single, including aortic, vagal neurones (*Garcia* et al. 1979a, b). It, however, remains a possibility that responses evoked in the sinus nerve on

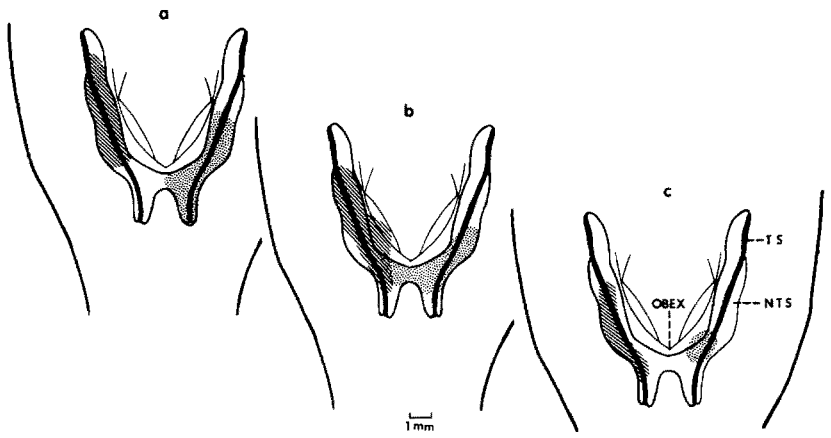

Fig. 1a–c. Diagrammatic representation of: a projection of IXth and Xth cranial nerves from degeneration studies; b projection of SN and AN afferent fibres revealed by antidromic activation; c location of neurones excited by the carotid sinus baroreceptors and pulse-rhythmically discharging neurones in the *NTS*. Cross-hatching shows projection of the IXth cranial nerve, sinus nerve afferents and carotid sinus baroreceptors. Stippled area illustrates projection of the Xth cranial nerve, aortic nerve afferents and the location of pulse synchronous neurones. (In this figure, the *TS* and *NTS* are projected onto the dorsal surface of the medulla)

stimulating within the medulla can reflect the activation of the efferent nonsympathetic neurones in the sinus nerve. These fibres are thought to be mainly small and predominantly unmyelinated (*Biscoe* and *Sampson* 1968; *Fidone* and *Sato* 1969). *Jordan* and *Spyer* (1977a) drew attention to their inability to activate two efferent nonsympathetic SN neurones on stimulating within the dorsomedial medulla [the NTS, dorsal vagus nucleus (DNV) and the area postrema].

Where this technique has been applied in studying the projections of SN and AN afferents in the cat, antidromic volleys in the SN and AN have always been evoked from the NTS and its near vicinity (*Crill* and *Reis* 1968; *Gabriel* and *Seller* 1970; *de Groat* and *Lalley* 1974; *Lipski* et al. 1975; *Jordan* and *Spyer* 1977a, 1978b; *Donoghue* et al. 1977), that is, within the limits provided by the neuroanatomical studies (see *McAllen* et al. 1979 for review). *Crill* and *Reis* (1968), however, have argued for a much wider distribution of the terminals of both SN and AN myelinated afferents. They claimed to have activated them on stimulating within the medial reticular formation in the paramedian reticular nucleus (NPR), an area corresponding to the classical medullary "depressor centre" (*Alexander* 1946). *Lipski* et al. (1975) reinvestigated the central projection of the myelinated SN afferents, but were unable to activate these fibres when stimulating anywhere but within the NTS, and even then only from a restricted portion of the NTS, primarily its ventrolateral aspect at levels

rostral to the obex. This restricted localisation of the terminals of large-diameter afferents (conduction velocity > 12.5 m/s) has since been confirmed for both the cat and the rabbit (*Jordan* and *Spyer* 1977a). It is worthwhile noting at this point that *Lipski* et al. (1975) were able to reproduce the aberrant results of *Crill* and *Reis* (1968) when recording unipolarly from the SN as in *Crill* and *Reis'* study. Conventional bipolar recordings never gave equivalent results. For the AN, neither *Donoghue* et al. (1977) nor *Jordan* and *Spyer* (1978b) could evoke antidromic responses except from the close vicinity of the NTS (see below).

Lipski et al. (1975) and *Jordan* and *Spyer* (1977) consider that this ventrolateral region of the NTS is the region containing the central afferent terminals of large myelinated SN fibres. This conclusion was reached from studying the relationship between stimulus current and depth (or position of electrode) during a penetration. In this region, the threshold for evoking a response fell abruptly to a low value, this value then being maintained over considerable depth (0.3–0.9 mm) before abruptly increasing again. This contrasts with the effect of stimulating in the region of a discrete nerve tract; at the level where the glossopharyngeal nerve fibres enter the TS, 'point' depth-threshold contours were seen (see *McAllen* et al. 1979). The presence of terminal arborisations in the NTS conforms to *Cajal*'s description of the distribution of IXth and Xth fibres once they enter and descend through the TS (see *Cajal* 1909).

Gabriel and *Seller* (1970) describe a restricted termination of both SN and AN afferents in the dorsomedial portion of the NTS just rostral to the obex in the cat. These must represent the terminals of small myelinated afferents (the latency of these responses being around 10 ms). *Jordan* and *Spyer* (1977) have mapped the projections of large myelinated fibres (conduction velocity > 12.5 m/s), small myelinated fibres (conduction velocity 2.5–12.5 m/s), and unmyelinated fibres (conduction velocity < 2.5 m/s) of the SN in both cats and rabbits. The restricted projection and termination of large myelinated fibres have already been described, the small myelinated and unmyelinated afferents being distributed over much wider areas of the NTS, extending beyond its borders especially towards the dorsal vagal nucleus (DNV in the cat, its homologue the n. alaris in the rabbit). In the cat, stimulation at a few points in the area postrema evoked responses in SN afferents of all dimensions. The significance of this projection remains uncertain (for discussion see *Jordan* and *Spyer* 1977).

In summary, SN afferents would seem to terminate only in close proximity to the NTS at levels from 0 to 3 mm rostral to obex. Only the largest myelinated afferents (conduction velocity in the range 12.5–32 m/s) have a restricted distribution within the nucleus, smaller myelinated and unmyelinated fibres projecting to much wider areas of the medulla although always in the immediate vicinity of the NTS (see Fig. 1b).

Much less attention has been paid to the projections of the AN, and most information then has come from stimulating the nerve and recording the orthodromically evoked volley in the medulla (see *Kumada* and *Nakajima* 1972). *Crill* and *Reis* (1968), however, provided the first description of the possible localisation of the projection of these afferents using the antidromic technique. Although they claimed a widespread distribution of the afferents within the medulla, complementing their description of the projection of the SN, again their observations do not conform to the anatomical description of the projection of vagal afferent fibres. Although they describe a marked representation of AN afferents, within the NTS, their figures show an abundant distribution in the rostral portions of the NTS (*Crill* and *Reis* 1968), which contradicts the restricted nature of degenerating vagal fibres described by *Cottle* (1964) amongst others, within this nucleus. *Donoghue* et al. (1977), *Jordan* (1977), and *Jordan* and *Spyer* (1978b) have provided evidence that AN fibres projecting to the NTS are found primarily in an area close to the DNV (Fig. 1b). *Jordan* (1977) and *Jordan* and *Spyer* (1978b) have shown that the area of the NTS from which antidromic responses in the AN can be evoked is restricted in both the cat and the rabbit to within 1 mm of the obex. More recent studies by *Garcia* et al. (1979a, b) have shown that single aortic baroreceptor afferents, whose activity was recorded in the nodose ganglion, project to the vicinity of the NTS. They were shown to send profuse terminal arborisations laterally in the NTS by antidromic activation. In the cat, stimulation within the commissural nucleus of the NTS, both ipsilateral and contralateral to the recording site, evoked responses in myelinated fibres (*Crill* and *Reis* 1968; *Donoghue* et al. 1977; *Jordan* 1977; *Donoghue* 1978; *Jordan* and *Spyer* 1978b). In the rabbit, aortic nerve afferents appear to project and terminate over a somewhat wider area than in the cat, relatively few terminating in the NTS and most extending from the borders of this nucleus into the nucleus alaris and nucleus intercalatus, but no evidence of a contralateral projection has yet been obtained (*Jordan* 1977; *Jordan* and *Spyer* 1978b).

2.2 Baroreceptor Reflex Pathway

From the preceding sections it would seem safe to conclude that the primary relay station in the baroreceptor reflex is located within the confines of the NTS,although its precise localisation and the characteristics of the second-order neurones remain in question. As a consequence of this and the unresolved complexity of connections within the NTS, the efferent connections from the nucleus concerned with cardiovascular control remain ill-defined. Both neuroanatomical and neurophysiological studies,

have, however, revealed something of the profusion of probable pathways, and from a combination of these approaches it is not too optimistic to expect the development of new and detailed information on the baroreceptor reflex pathway.

2.1.1 Neuroanatomical Studies

The initial neuroanatomical studies involved placing lesions in areas of the NTS and searching the central nervous system for signs of anterograde degeneration (*Kosaka* and *Yagita* 1905; *Hirose* 1916; *Morest* 1967; *Norgren* and *Leonard* 1973; *Cottle* and *Calaresu* 1975; *Palkovits* and *Zaborsky* 1977) or else placing lesions in presumed target areas of the nervous system before analysing the NTS for signs of chromalysis through retrograde degeneration (*Torvik* 1957).

Although degeneration studies have been valuable when conducted by skilled investigators, the techniques have sometimes proved capricious, and the interpretation of results is often suspect in the absence of electron microscopy. In recent years there has been a tendency to replace this type of investigation by the use of radioactive-labelled amino acids to reveal efferent connections through anterograde transport (*Loewy* and *Burton* 1978; *Ricardo* and *Koh* 1978) and by the use of horseradish peroxidase (HRP) which may be transported in both an anterograde and retrograde direction (*Kalia* 1977; *Amendt* et al. 1978; *Loewy* and *Burton* 1978; *Mesulam* 1978). Autoradiographic studies have proved particularly useful in determining whether connections between regions were significant or merely represented fibres of passage. Even though these new and apparently reproducible anterograde and retrograde methods represent a distinct advance over previous techniques, the interpretation of the resulting data requires caution, and it is desirable to confirm conclusions using both methods. Moreover, it is important to recognise that in the absence of physiological data it is not possible to determine unequivocally the relationship of specific anatomical pathways to cardiovascular control.

Morest (1967), using degeneration techniques, provided the first detailed modern description of the efferent projections of the NTS in the cat, although the study was restricted to the caudal half of the nucleus and then only its medial aspects. He emphasised the problems associated with any encroachment of lesions into the surrounding reticular formation but showed that lesions of the medial NTS at the level of the area postrema resulted in the appearance of degenerating terminals in the lateral nucleus of the NTS, the dorsolateral reticular formation of the medulla, the nucleus ambiguus (NA) and retrofacialis and the lateral reticular nucleus. He traced degeneration also to the n. intercalatus (see also *Cottle* and *Calaresu* 1975, who, however, have been challenged by *Loewy* and *Burton* 1978) and

medial reticular formation, but observed no degenerative changes in the spinal cord, or thalamus; indeed they could find no convincing evidence at all for an ascending projection to the diencephalon. *Morest* (1967) also showed that the subnucleus gelatinosa of the NTS sent efferent connections only *within* the NTS. *Cottle* and *Calaresu* (1975) described a broadly similar pattern of degeneration resulting from similar experiments, observing considerable degeneration within the DNV.

The absence of evidence for a solitariospinal projection in the study of *Morest* (1967) is countered by observations of *Torvik* (1957) in the cat. In fact, there is now overwhelming evidence in favour of direct connections from the NTS to the spinal cord, but these appear to emanate mainly from the ventrolateral nucleus (*Torvik* 1957; *Norgren* 1978; *Loewy* and *Burton* 1978). *Torvik* (1957) describes chromalytic changes in NTS neurones after spinal lesions in the rat, and *Norgren* (1978) has shown anterograde transport of labelled amino acids to the spinal cord from the ventrolateral nucleus. This descending pathway is mainly contralateral (*Norgren* 1978; *Loewy* and *Burton* 1978), but there is evidence of some ipsilateral transport of labelled amino acids (*Loewy* and *Burton* 1978). The pathway appears to be concerned primarily with medullary control of respiratory motoneurones (*Euler* et al. 1973a, b). There is, however, evidence of terminal labelling within both the intermediolateral and intermediomedial columns (*Loewy* and *Burton* 1978).

More detailed information on solitariospinal connections has been provided by the use of HRP. Neurones in the ventrolateral portion of the nucleus have been labelled by HRP injections into the contralateral thoracic and cervical spinal cord (*Loewy* and *Burton* 1978). Interestingly, the intermediate and commissural nuclei have been shown to receive bilateral labelling from injections made at cervical, thoracic, lumbar, and sacral cord levels, although the medial nucleus remains unlabelled (*Loewy* and *Burton* 1978). This latter observation has been questioned by *Seller* and his colleagues, who describe an extensive labelling in the dorsomedial part of the nucleus after HRP injections into the thoracic intermediolateral cell column (*Amendt* et al. 1978). *Loewy* and *Burton* (1978) would, however, argue that this labelling, apparently localised in the caudal part of the dorsomedial NTS, may be confused with labelling in the dorsal column nuclei.

The differences in the patterns of efferent connection of the constituent subnuclei of the NTS that are beginning to the revealed may have profound physiological significance. The ventrolateral nucleus contains the dorsal group of inspiratory neurones (*Baumgarten* and *Kanzow* 1958, and subsequently others) and nonrespiratory neurones there receive an excitatory input from the SN and carotid sinus baroreceptors (*Lipski* et al. 1975), whilst the medial nucleus receives AN and SN inputs (see Sect. 2.1.2)

but there is as yet little convincing evidence of a direct sinus baroreceptor input (*Lipski* et al. 1975). The commissural and intermediate nuclei may receive an AN input (*Jordan* and *Spyer* 1978b; *Garcia* et al. 1979a, b).

The rostral projections from the NTS are likely to be particularly important in both cardiovascular and respiratory control. In the case of respiratory control the connections with the pontine reticular nuclei, the nucleus parabrachialis and Kolliker-Fuse nuclei, shown using HRP (*Kalia* 1977; *Loewy* and *Burton* 1978) and by injections of amino acids in the NTS (*Loewy* and *Burton* 1978), are particularly significant especially as reciprocal connections may exist (see *Kalia* 1977). In a particularly extensive study, *Loewy* and *Burton* (1978) have shown not only dense projections from the NTS to these pontine nuclei but also projections ascending as far rostrally as the periaqueductal grey, the inferior colliculus and even to the bed nucleus of the stria terminalis. From other studies using HRP it is clear that the NTS projects to the contralateral locus coerulus with a small ipsilateral projection (*Cedarbaum* and *Aghajanian* 1975; *Sakai* et al. 1977); this structure is itself known to project to the diencephalon (*Loizou* 1969).

Accordingly, these observations both complement and extend the study of *Morest* (1967) whilst beginning to question the absence of a diencephalic projection (see also *Ricardo* and *Koh* 1978). They also confirm and illustrate the profusion of connections within the medulla: there are projections to the medial reticular formation, including the NPR and to the raphe complex and striking projections to the NA and lateral reticular nucleus (LRN). *Loewy* and *Burton* (1978) and *Ricardo* and *Koh* (1978) draw special attention to the connections between the NTS and the A1 group of noradrenergic neurones in the LRN (*Dahlström* and *Fuxe* 1965). In addition they illustrate a pathway from the lateral NTS to the medial accessory olivary nucleus *Loewy* and *Burton* 1978). In the context of ascending projections, the autoradiographical and HRP studies of *Ricardo* and *Koh* (1978) provide indications in the rat, at least, that the NTS sends efferent projections to the lateral subthalamus, the parabrachial area and to the paraventricular, dorsomedial and arcuate nuclei of the hypothalamus. In addition the medial preoptic area, periventricular nucleus of the thalamus, bed nucleus of the stria terminalis and central nucleus of the amygdala seem to receive an input in this species. Neurophysiological studies are now required to assess the significance of these pathways in the baroreceptor reflex and cardiovascular control.

2.2.2 Electrophysiological Studies

The limits for the projection of primary afferent fibres of the SN and AN have been inferred from neuroanatomical studies and confirmed by the

antidromic mapping experiments described in a previous section. The more traditional neurophysiological technique of recording evoked responses from a population of neurones on stimulating a peripheral nerve has also been used to obtain information on the projection of SN and AN afferents, and provides a potential advantage in evoking discharges at several levels within the reflex pathway. In this way it is possible to use the generalised field response as a marker for single unit studies. This is of particular importance in the case of the projection of SN and AN afferents, as in the former case it is possible then to use physiological stimulation of the afferent receptors, baroreceptor and chemoreceptor, so as to identify the role of neurones in specific reflex pathways.

2.2.2.1 Evoked Potentials

Lam and *Tyler* (1952), in the most important early study of this type, were able to record an evoked potential of complex waveform in the ipsilateral NTS on stimulating the cervical vagus nerve of the rabbit, primarily in its commissural and "dorsosensory" areas (using the nomenclature of *Cajal* 1909), i.e. dorsomedial portion of the nucleus. *Anderson* and *Berry* (1956), in a subsequent and more detailed study in the cat, described similar evoked responses in the NTS but showed a more widespread distribution of points within the medulla from which they could record evoked potentials in response to vagal stimulation. Indeed, they drew particular attention to the fact that they could record within the intramedullary course of vagal afferent fibres (see also *Lam* and *Tyler* 1952), a factor not always accepted as complicating many later studies. Furthermore, they observed what they considered postsynaptic activity in the spinal nucleus of the Vth cranial nerve, the gracilis nucleus, and more often in the DNV, NA, n. intercalatus and parasolitary nucleus, as well as in the lateral reticular formation. They also noted the antidromic activation at short latency of neurones in the DNV and NA on stimulating the cervical vagus, a point later reiterated by *Porter* (1963) in a similar study. Clearly, observing evoked potentials on stimulating an afferent input cannot prove a response to have been generated postsynaptically; indeed, any conclusion regarding the complexity of connection between the afferent input and the neuronal site under investigation must be viewed critically if it rests solely on the evidence of evoked potentials.

The Aortic Nerve. The earliest work concerning specifically the effects evoked on stimulating the AN was that of *Anderson* and *Berry* (1956) in the cat. They showed that electrical stimulation of the central end of the cut AN evoked activity in both the intracranial and medullary course of vagal fibres and the NTS. The negative field potential in the NTS consisted

of two major waves, which were considered to represent activity generated by the different fibre types found in the AN; *Paintal* (1972) refers to a bimodal distribution of fibre size in this nerve. Similar negative field potentials have been described by others in the NTS on stimulating the AN (*Gahery* and *Ancri* 1967; *Biscoe* and *Sampson* 1970a), although often the evoked responses were recorded outside the limits of the nucleus within the nucleus parvocellularis (see *Biscoe* and *Sampson* 1970a). *Gabriel* and *Seller* (1970) describe a response restricted to the dorsomedial portion of the NTS at a level approximately 0.5 mm rostral to the obex. This response, due in the authors' opinion to activation of only the lowest threshold afferents in the AN, had a latency of 10–11 ms, and this study never revealed responses in the latency range 2–6 ms commonly reported by other workers (*Gahery* and *Ancri* 1967; *Biscoe* and *Sampson* 1970a; *Kumada* and *Nakajima* 1972). The most detailed study so far is that of *Kumada* and *Nakajima* (1972) in the rabbit. They recorded evoked responses of widely ranging latency in the NTS and sparsely within the nucleus alaris (or DNV). They assumed that short-latency responses (< 40 ms) reflected activation of large myelinated afferent fibres and that these were likely to be generated monosynaptically. Long-latency responses (> 40 ms), seen in the NTS and elsewhere, were considered a consequence of the activation of small diameter fibres. As responses of short latency were also seen in the NA and lateral reticular formation, this distinction is hardly tenable. Such a conclusion would have a stronger basis if the afferent volley had been monitored as in the study of *Lam* and *Tyler* (1952). Even then it is impossible, on the basis of the evidence presented, to deny that both short and long latency responses might be generated over polysynaptic pathways.

In a recent study *Gahery* and *Ancri* (1967) reported an evoked response to AN stimulation in the NTS, in a region medial to TS where they had previously recorded neuronal activity with a cardiac rhythm of sinus baroreceptor origin. The latency of this evoked response fell into two latency ranges (2–3 ms and 4–6 ms).

From the Sinus Nerve. In the late 1960s, the effects of stimulating the SN on the activity of medullary neurones were investigated. *Humphrey* (1967) reported a maximal evoked response in the intermediate region of the ipsilateral NTS (0.5–2.0 mm rostral to the obex). This response (of negative polarity) had a minimum latency of 3–4 ms; since then similar responses have been observed in the NTS by numerous workers (*Miura* and *Reis* 1969a; *Biscoe* and *Sampson* 1970a; *Spyer* and *Wolstencroft* 1971; *McAllen* 1973; *de Groat* and *Lalley* 1974; *Hildebrandt* 1974; *Lipski* and *Trzebski* 1975). *Humphrey* (1967) noted that this response was not restricted to the NTS but was also seen in the subadjacent reticular forma-

tion, an observation extended by *Biscoe* and *Sampson* (1970a), who found that the most prominent effect of SN stimulation was an evoked response in the nucleus parvocellularis. *Humphrey* (1967) also noted that at the level of the obex, SN stimulation evoked responses bilaterally in the NTS, the contralateral response having a latency 3–4 ms in excess of the ipsilateral response.

Biscoe and *Sampson* (1970a) drew attention to positive-going potentials evoked in the medial reticular formation (n. gigantocellularis), which were associated with a decrease in neuronal excitability. The possibility of a major monosynaptic input of SN afferents to neurones of the medial reticular formation, particularly those of the NPR, has been a matter of controversy for a number of years. The question of a primary afferent projection has been approached using the antidromic activation of SN afferents on stimulating within the medulla (see above), and the consensus appears to be that this is unlikely to represent a significant projection. *Miura* and *Reis* (1969b), however, claimed the occurrence of a monosynaptic evoked potential within the NPR on stimulating low-threshold SN afferents. The particularly short latency (0.7–1.4 ms), together with the smooth contour and enormous magnitude of the response, seemed surprising in view of the nature of the responses evoked by others in the NTS. *Spyer* and *Wolstencroft* (1971) were unable to obtain a similar response on stimulating the SN except in cases where they had sufficient current spread to activate the neighbouring hypoglossal nerve. Only then could they record a similar potential in the region of the NPR, which is ventral to the hypoglossal nucleus. Presumably the "smooth-contoured" response reflects the antidromic potential evoked in the hypoglossal nucleus, viewed at a distance by the microelectrode.

In addition to the "early" response in the NPR, *Miura* and *Reis* (1969a) drew attention to a similar response in the intermediate portion of the NTS. They also observed longer latency response in the NTS and NPR, "late" responses (> 5 ms) being much more widely distributed through the medulla, and long latency responses (6–150 ms latency) were observed in the pons. Responses with a latency of up to 80 ms were observed in the rostral medulla (*Miura* and *Reis* 1969a), and more recently *Adair* and *Manning* (1975) have claimed to evoke activity in the perifornical region of the hypothalamus with a latency in the range from 20 to 120 ms.

Returning to the NTS, *Seller* and *Illert* (1969) and *Gabriel* and *Seller* (1970) have reported a response restricted to the dorsomedial part of the nucleus, the part where *Gabriel* and *Seller* (1970) have also described a restricted input from the AN. They attributed the response to an effect of activating the lowest threshold SN afferents but surprisingly the latency was in the range 7–11 ms, much in excess of the "early" response of *Miura* and *Reis* (1969a) or the short latency responses of others (*Humphrey*

1967; *Biscoe* and *Sampson* 1970a; *Spyer* and *Wolstencroft* 1971; *Lipski* et al. 1975). There is no obvious explanation for this discrepancy, nor indeed for the wide variations between response recorded in different laboratories. Presumably the anatomical arrangement of the SN in close proximity to other nerves relaying to the region of the NTS makes effects due to current spread a particular problem, and the wide variety of fibre size in the SN may well militate against consistent observations from one laboratory to another.

2.2.2.2 Single Unit Studies

Aortic Nerve Stimulation. The literature contains relatively few reports of the effects of AN stimulation on individual brainstem neurones. *Gahery* and *Ancri* (1967), who observed evoked potentials within the NTS on stimulating the AN, did so in areas where they had observed pulse-synchronous activity, which they considered to be of SN origin, as the animals had previously had their AN sectioned. In more recent studies, *Donoghue* (1978) and *Donoghue* et al. (1978) report that AN stimulation in cats evokes activity in medullary units with either short (< 20 ms) or long (> 20 ms) latencies. These responses are considered to be generated by activation of myelinated and unmyelinated afferents respectively. Short latency responses were observed in several regions of the medulla in addition to the medial portion of the NTS, the dorsomedial and lateral reticular formation and the NA being areas particularly affected. Those units activated at longer latencies were only observed in the dorsomedial medulla and were concentrated in the medial portion of the NTS. No responsive cells were located in the medial reticular formation. An indication that there was a convergence of input from the myelinated and unmyelinated components of the AN was obtained from observations that some neurones, located in the vicinity of NTS and NA, were activated at both short and long latency. *Biscoe* and *Sampson* (1970b) report activating a few single neurones of the NTS on stimulating the AN. Many neurones outside the limits of the NTS in the n. parvocellularis also responded to SN stimulation (as well as showing excitatory responses to other IXth and Xth nerve inputs) and showed excitatory responses to AN stimulation. *McAllen* 1973) similarly reported a convergence of excitatory inputs from SN and AN onto neurones outside the NTS (around the DVN, in the "parahypoglossal" region, and close to the NA), but within the NTS neurones were excited by either the AN or SN but never both. *Schwaber* and *Schneiderman* (1975) also observed synaptic activation at short latency of NTS neurones on stimulating the AN (latency 4–50 ms) in the rabbit. Similar synaptic effects were also noted in this study in the region of the n. alaris (or DNV). *Brickman* et al. (1977) have also observed effects of AN stimula-

tion on hypothalamic neurones. Stimulating the AN produced excitatory responses in approximately 5% of neurones recorded in the anterior hypothalamus-preoptic region. Considering the conduction distance and the inevitable involvement of a polysynaptic pathway, the latencies of these responses were often remarkably short (14–176 ms). This area would seem equivalent to the area described by *Hilton* and *Spyer* (1971) in the cat as the hypothalamic "depressor" area, whose involvement in the integration of the carotid sinus baroreceptor reflex has been demonstrated (see Sect. 2.2.3.3).

Sinus Nerve Stimulation. The picture from studies on the effects of SN stimulation on single neurones in the brainstem broadly complements the data from recordings of evoked potentials. All authors are agreed that there is a major monosynaptic input to neurones of the NTS (*Humphrey* 1967; *Miura* and *Reis* 1968, 1969a; *Biscoe* and *Sampson* 1970b; *Spyer* and *Wolstencroft* 1971; *McAllen* and *Spyer* 1972; *Weiss* and *Kastella* 1972; *Miura* 1975; *Lipski* et al. 1975; *Lipski* and *Trzebski* 1975; *Hildebrandt* 1974; *Lipski* et al. 1976; *Miura* and *Kitamura* 1979), although the extent and properties of this input vary widely in the reports from different groups. Whilst the results of *Lipski* et al. (1975) agree closely with the anatomical data and the results of their antidromic studies, i.e. the major effects of myelinated SN afferents being observed in the ventrolateral portion of the nucleus at levels rostral to the obex, *Biscoe* and *Sampson* (1970b) reported only a small proportion of activated neurones in this area, the majority being located outside the limits of the nucleus in the n. parvocellularis. *Miura* and *Reis* (1969a) reported that the majority of responses they obtained (unitary activity superimposed on evoked potentials) were in the intermediate part of the NTS, 1 mm ahead and behind the obex.

Humphrey (1967) and *Lipski* et al. (1975) drew particular attention to the paucity of neurones activated with a latency compatible with a monosynaptic input from large myelinated fibres (i.e. within 8 ms) on stimulation of the SN. *Lipski* et al. (1975) found that only 17% of neurones in the NTS were activated within 8 ms; *Humphrey* (1967) and *McAllen* (1973) consider that it is likely that many neurones are activated over both monosynaptic and polysynaptic pathways, the faster and more direct pathway sometimes requiring considerable temporal and spatial summation to make its effect noticeable (see *McAllen* 1973; *McAllen* et al. 1979). Such a complex interneuronal arrangement within the NTS confirms the impression from histological studies of *Morest* (1967) and *Cottle* and *Calaresu* (1975), as well as others discussed earlier.

The latency of responses in the NTS was, however, usually shorter than noted elsewhere in the medulla, although considerable overlap was noted.

The "parahypoglossal region" was shown to receive a major input from the SN over a relatively direct pathway, if latency can provide such evidence (*Lipski* et al. 1975; *McAllen* and *Spyer* 1972), but there is no evidence for a monosynaptic input of SN afferents of any fibre diameter to this region (*Jordan* and *Spyer* 1977). Apart from an input to this area, which lies close to the hypoglossal nucleus, *Lipski* et al. (1975) could find no excitatory (or inhibitory) input to neurones of the medial reticular formation, an area classically termed the "drepressor" area (see *Alexander* 1946) and containing the NPR, where *Miura* and *Reis* (1969a) and *Homma* et al. (1970) have claimed a significant monosynaptic input. *Humphrey* (1967) considered the presence of a polysynaptic input to this region and to the midline raphe nuclei as significant, but its influence was never seen by *Lipski* et al. (1975). In contrast, *Biscoe* and *Sampson* (1970a) describe a positive field potential in midline regions associated with a reduction in the excitability of neurones. It is worth noting at this point that *Scheibel* et al. (1955) were unable to activate neurones in this medial reticular area on stimulating the cervical vagus, and *Spyer* and *Wolstencroft* (1971), analysing the response of NPR neurones relaying to cerebellum or activated synaptically by stimulation of the cerebellar peduncles, could find *no* evidence for a convergent input, either excitatory or inhibitory, from the SN. There is, however, anatomical evidence for connections from the NTS to these areas (see above). *Miura* and *Reis* (1972a) present conflicting results arguing for a convergence of fastigiofugal fibres and SN afferents at the level of the NPR. This will be discussed later (Sect. 4.2.2).

There is much greater agreement on the lateralisation of SN effects in the medulla. Most investigators report a significant proportion of neurones in the lateral regions of the medullary reticular formation responsive to SN stimulation (*Humphrey* 1967; *Biscoe* and *Sampson* 1970b; *McAllen* and *Spyer*, 1972; *McAllen* 1973; *Davies* and *Edwards* 1973, 1975; *Hildebrandt* 1974; *Lipski* et al. 1975). In particular, responsive neurones have been reported in the vicinity of the NA (*Davies* and *Edwards* 1973, 1975; *Hildebrandt* 1974; *Lipski* et al. 1975; *Spyer* 1975), although there is some disagreement as to the nature of the input. *Lipski* et al. (1975) have shown that it is mediated by a polysynaptic pathway, the latency of responses being significantly longer than usually observed within the NTS or "parahypoglossal" region, whilst *Davies* and *Edwards* (1975) claim a monosynaptic input, i.e. a latency comparable with that also observed in the NTS. As there is *no* histological evidence for such a direct connection of either SN or AN afferents and as the antidromic mapping study of *Jordan* and *Spyer* (1977) failed to reveal a primary afferent projection of the SN to this area, it would seem best to ignore this conclusion. The significance of an influence of SN inputs on neurones of the NA will be discussed later (Sect. 3.6.2).

2.2.3 Baroreceptor Stimulation

The limits for the areas involved in the baroreceptor reflex at medullary levels have been provided by the data summarised above, but as the SN in all species contains both baroreceptor and chemoreceptor afferents, these observations are of limited value in ascribing an integrative role to these areas in baroreceptor responses. Two major approaches have been used in attempts to determine which neurones specifically mediate the baroreceptor reflex. The first arose from the premise that as this afferent input is normally pulse modulated, central neurones should have their activity sculptured by such a phasic input. Accordingly, attempts have been made to locate neurones with activity modulated by the pulse in the medulla. The second approach has involved eliciting a change in the stimulus to the baroreceptors and searching for neurones whose activity fluctuates in relationship to the experimental change in afferent barrage. At its simplest this has involved labelling neurones as "cardiovascular" in function if they either increase or decrease their discharge in response to a rise or fall in arterial blood pressure, usually induced pharmacologically. At its most elaborate it has involved controlled stimulation of the baroreceptor endings of the carotid sinus employing a "blind-sac" preparation, sometimes in association with an initial sampling of unit activity by stimulating the intact SN.

2.2.3.1 Pulse-synchronous Activity

Although there have been several attempts to identify pulse-synchronous activity in the brainstem, there are surprisingly few units adequately identified and convincingly free of artifactical modulation (see *Hellner* and *Baumgarten* 1961; *Salmoiraghi* 1962; *Smith* and *Pearce* 1961; *Werz* et al. 1974; *Langhorst* and *Werz* 1974; *Humphrey* 1967; *Stroh-Werz* et al. 1977a, b). However, there remains an isolated claim of a profusion of such neurones in the medulla (*Middleton* et al. 1973). The observation that even at the level of the NTS pulse-synchronous activity is rare in single units (*Salmoiraghi* 1962; *Humphrey* 1967; *Stroh-Werz* et al. 1977a, b) may be taken as an indication that the complexity of connections within this nucleus, referred to above, may well *smooth* what is clearly a powerful pulse-modulated input from the peripheral baroreceptors.

A detailed analysis of the firing pattern of NTS neurones, particularly those in the dorsomedial portion of the nucleus, showed that only 28 neurones of several hundred recorded in 17 dogs and 80 cats had activity clearly related to the cardiac cycle (*Stroh-Werz* et al. 1977a), but even then a single and direct baroreceptor modulation was not convincingly demonstrated. The possibility remained that the cardiac rhythm arose from cardiovascular mechanoreceptors other than arterial baroreceptors, and

indeed the major result was a convergence of vagal inputs onto neurones that received an input from extravagal fibres (presumably sinus nerve afferents although this was not directly tested). *Miura* and *Reis* (1972b), however, have recorded from 12 neurones which displayed a pattern of discharge which "often bore a striking similarity to the discharge pattern of baroreceptor afferent fibres", this activity being obliterated on bilateral carotid occlusion. Seven of these were in the dorsomedial portion of the NTS within 0.5 mm of the obex, three lateral to the TS, one in the hypoglossal nerve tract, and one just medial to it (presumably the "parahypoglossal" region, see *Lipski* et al. 1975). By constructing post-R-wave histograms of NTS unit activity, *McCall* et al. (1977) have demonstrated cardiac-related rhythmicity in several neurones. The activity of the majority of these neurones (8 out of 14) was not modulated in a simple manner, exhibiting a polymodal distribution of discharge in relation to the R wave of ECG.

The consensus from all these studies would be that distinct pulse-related activity, when present, is mainly restricted to the dorsomedial portion of the NTS (*Salmoiraghi* 1962; *Smith* and *Pearce* 1961; *Humphrey* 1967; *Miura* and *Reis* 1972b; *Middleton* et al. 1973; *Schwaber* and *Schneiderman* 1975; *Stroh-Werz* et al. 1977a, b; see Fig. 1c). Even so, it becomes clear that in only a few cases can this pattern of activity be attributed unequivocally to activation of the carotid sinus baroreceptors, although *Seller* and *Illert* (1969) recorded mass responses (and some single units) with a cardiac rhythm in this area in cats after vagotomy (see also *Gahery* and *Ancri* 1967). Indeed, many authors draw attention to background cardiac rhythmicity (see *Stroh-Werz* et al. 1977a), although the occurrence of convincing single unit responses is so rare.

The observation of a marked convergence of afferent inputs onto single neurones in the NTS (*Stroh-Werz* et al. 1977b) has led to other studies in which the "afferent spectra" of medullary neurones has been investigated. In these studies, a computer analysis of a unit's activity often reveals a cardiac rhythm when post-R-wave histograms or autocorrelogram functions are derived (see *Langhorst* and *Werz* 1974; *Langhorst* et al. 1975; *Stroh-Werz* et al. 1976; *McCall* et al. 1977), but even where this rhythm is abolished by vagal cooling or SN section or both (*Koepchen* et al. 1967, reviewed by *Langhorst* and *Werz* 1974) it is clear that there is no a priori reason for defining the unit as "cardiovascular", as other rhythms can often be distinguished simultaneously.

2.2.3.2 "Cardiovascular" Neurones

The question of the identification of "cardiovascular" neurones in the brainstem has been mooted for a number of years. On the basis that both the afferent input from the cardiovascular mechanoreceptors and the efferent outputs from the central nervous system controlling the cardiovascular system are modulated in phase with the cardiac cycle, the belief has grown that the interneurones in the baroreceptor reflex pathway are likely to have a cardiac rhythm. Indeed, it has been assumed that if a central neurone can be shown to have a rhythm in common with the sympathetic efferent output, there is an a priori connection between that neurone and the sympathetic outflow [i.e. it is part of the sympathetic-activity-generating system; see *Gootman* et al. (1975) for a detailed statement of this hypothesis]. This simplistic model rests on the hypothesis that sympathetic activity is generated solely by a tonically active medullary centre (i.e. the "vasomotor" centre), which is reflexly regulated by the baroreceptor input. The paucity of clear pulse modulation at the level of the NTS immediately produces a call for caution in using a "cardiac" rhythm as the sign of such a correlation. Indeed, the earliest claims for identifying "cardiovascular" units comes from studies in which the relative absence of pulse-rhythmic unit activity was stressed (*Salmoiraghi* 1962; *Pryzybyla* and *Wang* 1967). In the first study, "cardiovascular" units were identified as cells whose activity changed in a reciprocal manner to drug induced changes in arterial blood pressure (*Salmoiraghi* 1962); in the second study, a "cardiovascular" unit was considered to be one that decreased its activity by at least 30% for a 30 mmHg increase in arterial pressure (*Pryzybyla* and *Wang* 1967). This latter definition is a very convenient extrapolation, as these authors considered they were recording within the medullary "pressor" area (dorsolateral reticular formation), which they considered to be the sympathetic tone generating centre (cf. *Alexander* 1946).

Langhorst and his co-workers (*Langhorst* and *Werz* 1974; *Langhorst* et al. 1975), have made the most detailed analysis of the behaviour of brainstem neurones in terms of their relatonships to afferent inputs and possible efferent connections. They have demonstrated the presence of a cardiac rhythm in the activity of many neurones of the "unspecific" reticular formation (i.e. units located outside the limits of the clearly defined reticular nuclei) in the dog, using post-event time histograms and spectral analysis. They have shown that this forms only one of many afferent inputs that can modify neurone activity: they are truly *reticular*, receiving somatic inputs, respiratory influences and have patterns of activity relating to the delta-theta oscillations of the EEG. Often the cardiac-related discharge was obliterated by section of the relevant afferent input, either vagus or sinus nerve (see *Koepchen* et al. 1967). Furthermore, this rhythmic dis-

charge was not fixed rigidly: their activity could fluctuate from a rhythm state to a tonic nonmodulated discharge pattern. The most significant conclusion of this study is that no reticular neurone with a rigidly organised pattern of activity has yet been identified. Reticular neurones have multisensorial inputs, somatic as well as vegetative, and evidence of the common rhythms can be observed in both somatic and autonomic outflows. This precludes any definition of reticular neurones as "cardiovascular".

To compound this, there are also reports of pulse-related discharges in neurones in the absence of any baroreceptor input. These have been described in the medulla (*Porszasz* and *Porszasz-Gibischer* 1968), the midbrain (*Baust* and *Niemczyk* 1968) and the hypothalamus (*Baust* et al. 1963). The frequency of the delta-theta EEG oscillation may often, at least in the cat and dog, be similar to that of the cardiac rhythm, so without a full spectral analysis their separation is often impossible (see *Langhorst* et al. 1975) and these apparent cardiac rhythms may well be insignificant. None the less, if taken at face value, these observations underline the problems in using an apparent rhythm to ascribe function, in particular the fallibility of using a 3 Hz rhythm as an indication of a cardiac rhythm in establishing the central pathway of the baroreceptor reflex.

2.2.3.3 Specific Baroreceptor Inputs to the Brainstem and Hypothalamus

The baroreceptor input to the brainstem has been investigated by observing the changes in unit activity evoked by slow changes in blood pressure in units already identified as receiving an input from the sinus nerve (*Humphrey* 1967) or by observing the effects on similarly identified neurones of bilateral carotid occlusion (*Humphrey* 1967; *Miura* and *Reis* 1972b; *Nosaka* 1976). Both these physiological tests are not "pure": slowly changing levels of blood pressure will evoke changes in the activity of numerous cardiovascular receptors, whilse bilateral carotid occlusion will lead to withdrawal of the carotid sinus baroreceptor input but a concomitant excitation of the carotid body chemoreceptors. Natural baroreceptor stimulation using a "blind-sac" preparation of the carotid sinus to test the responses of units previously shown to receive an SN input is by far the most specific test (*Biscoe* and *Sampson* 1970b; *McAllen* and *Spyer* 1972; *Lipski* et al. 1975; *Lipski* and *Trzebski* 1975; *Lipski* et al. 1976). In other cases, the effects of baroreceptor stimulation alone have been used (*Trzebski* et al. 1962; *Trzebski* and *Peterson* 1964; *Spyer* 1972; *Richter* and *Seller* 1975; *Yamashita* 1977).

The Input to the Medulla. Trzebski et al. (1962) and *Trzebski* and *Peterson* (1964) described experiments in which natural stimulation of the carotid sinus baroreceptors was shown to evoke changes in the activity of medul-

lary neurones. Unfortunately details of the location of responsive neurones and the pattern of their response were not given. *Humphrey* (1967) described in detail the nature of the SN input to the medulla (Sect. 2.2.2). In particular, of 89 neurones in the NTS which were excited by SN stimulation, none had an obvious cardiac rhythm and all showed irregular spontaneous activity. Of these, 28 were investigated in detail for evidence of a hidden "cardiac" rhythm, but even after constructing post-R-wave histograms, no cardiac-related discharge was apparent (*Humphrey* 1967). This might suggest either that through the complexity of interconnections within the NTS the cardiac rhythm so apparent in the SN was "smoothed" or that these units received an input solely from chemoreceptor afferents. In 18 of these neurones, however, changes in activity correlating with slow changes in arterial blood pressure were apparent. Unfortunately none was tested for a response to sinus inflation. *Biscoe* and *Sampson* (1970b) reported on the responses of neurones in the n. reticularis parvocellularis, excited by both SN and baroreceptor stimulation: here they found the largest profusion of neurones excited on stimulating the IXth and Xth cranial nerves and their peripheral branches (see *Biscoe* and *Sampson* 1970a, b). Nine neurones excited by nerve stimulation were also depressed by sinus inflation.

Miura and *Reis* (1972b) reported that of a small population of neurones in the dorsomedial medulla the majority (9 of 12), located within the NTS at levels rostral to the obex, had their cardiac rhythm abolished by bilateral carotid occlusion. It would seem possible that these neurones were also excited by stretching the carotid artery. In a more detailed study, *McAllen* and *Spyer* (1972) and *Lipski* et al. (1975) described a baroreceptor input to a large number of medullary neurones, identified originally on the basis of their excitatory response to stimulation of the SN. Those with the shortest latency were found in the NTS and are illustrated in Figs. 1c and 2. All responded to sinus inflation before reflex changes in arterial blood pressure, and most responded abruptly with a discharge related to the sudden elevation in intrasinusal pressure, with an adapting discharge during the phase of elevated intrasinusal pressure (*Lipski* et al. 1975). A few, however, showed only gradual changes in activity.

Excited neurones were found also beyond the NTS in the n. reticularis parvocellularis (i.e. equivalent to the description of *Biscoe* and *Sampson* 1970b), many in the "parahypoglossal" region, and others in the lateral reticular formation, particularly in and close to the NA (see Fig. 2). This distribution has been confirmed in other similar but less extensive studies (*Lipski* and *Trzebski* 1975; *Lipski* et al. 1976), which stress the preponderance of responsive neurones in the ventrolateral portion of the NTS extending into the neighbouring reticular formation (*McAllen* and *Spyer* 1972; *Lipski* et al. 1975; *Lipski* and *Trzebski* 1975). The significance of

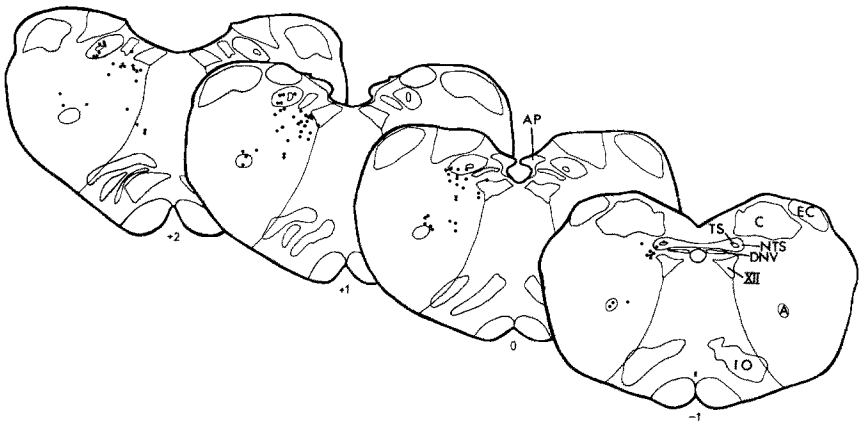

Fig. 2. Distribution of 91 identified baroreceptor-sensitive neurones plotted onto four standard sections of the medulla. *A* nucleus ambiguus; *AP* area postrema; *C* cuneate nucleus; *DNV* dorsal motor nucleus of the vagus; *EC* external cuneate nucleus; *IO* inferior olive; *NTS* nucleus of the tractus solitarius; *TS* tractus solitarius; *XII* hypoglossal nucleus. *Lipski, McAllen* and *Spyer* (1975)

the baroreceptor projection to the NA has been stressed (*Spyer* 1975, 1979) and will form an important part of a subsequent section of this review (Sect. 3.6.2), as it appears that this nucleus contains the preganglionic vagal neurones that supply the heart (see *McAllen* and *Spyer* 1976, 1977, 1978a, b). In this context it is notable that no evidence has been found of a baroreceptor input to the DNV in the cat (see *Lipski* et al. 1975).

The other major feature of the study of *Lipski* et al. (1975) was the absence of any major input to the medial reticular formation. Four neurones excited by the SN and receiving an excitatory input from the baroreceptor were found at the lateral edges of what may be loosely termed the medial reticular formation, but although the area and its more medial core were routinely penetrated no other excitatory response was identified (Sect. 2.2.2). This contrasts with results of *Humphrey* (1967) and *Miura* and *Reis* (1969a), although *Humphrey* (1967) drew particular attention to the requirement of considerable temporal facilitation to alter the activity of neurones in the medial reticular formation, relatively few responding to a single shock to the SN or NTS. Of those neurones excited or inhibited by SN stimulation, however, only 10 out of 30 gave consistent responses to carotid occlusion; even then the response was often the opposite of that predicted on the basis of the response to electrical stimulation of the SN. Only one neurone in the study of *Miura* and *Reis* (1972b) showing a sinus baroreceptor input can be said to lie in this area, and even then it was more strictly in the "parahypoglossal" region.

Lipski and *Trzebski* (1975) studied the properties of 400 medullary units, mostly located close to the NTS, found that some 89 responded to SN stimulation, 61 had a purely excitatory input and 23 purely inhibitory, with a latency of 3–21 ms. Of the irregularly firing neurones (i.e. non-respiratory neurones), 44 were excited by baroreceptor stimulation and only 3 were inhibited. Furthermore a proportion of these irregularly firing neurones projected to cervical levels of the spinal cord, although definite proof was established in only 12, of which 7 projected contralaterally and 5 ipsilaterally. The location of the spinal projecting axon was no better established, the authors noting that the intensity necessary to evoke an antidromic response was usually six times greater than required to produce synaptic activation from the cord.

The result indicates the possible involvement of a bulbospinal inhibitory pathway originating from the NTS through which the baroreceptors control sympathetic activity (Sec. 3.3). As such this represented the first direct demonstration of putative bulbospinal interneurones in the baroreceptor reflex, although the small sample and the rapid conduction velocity of its axons clearly limit its significance. Other studies reported by *Lipski* et al. (1976) may add a further question: using equivalent procedures, they showed that, of 25 nonrespiratory neurones excited by SN stimulation in this same area of the medulla, 2 responded to natural baroreceptor stimulation alone, 8 responded to *both* baroreceptor and chemoreceptor stimulation, and the remaining 15 responded to natural chemoreceptor stimulation alone. None of this sample was tested for spinal projection, but it appeared that many were located in the vicinity of the NTS and from their latency to SN stimulation appeared early in the reflex pathway. Such a marked convergence of baroreceptor and chemoreceptor inputs might seem justifiable considering the excitatory effects of both inputs on vagal efferent activity in the anaesthetised animal, but strange in view of their often antagonistic effect on sympathetic efferent activity. Since in general terms the two reflexes can be considered to act antagonistically, this apparently powerful convergence at such an early stage in the reflex pathways must be viewed with caution. The simplest explanation for this apparently anomalous effect of chemoreceptor stimulation is that it exerts a generalised excitatory influence on brainstem neurones, particularly those in the vicinity of the NTS, as part of its general arousal influence.

The demonstration in the work of *Lipski* et al. (1975) and *Lipski* et al. (1976) that SN stimulation affected respiratory neurones reinforces the effects reported by others from similar studies (*Biscoe* and *Sampson* 1970b; *Lipski* et al. 1975, 1976b, 1977) and also that baroreceptor stimulation inhibits inspiratory neurones (*Trzebski* and *Peterson* 1964; *Richter* and *Seller* 1975). Baroreceptor stimulation, however, may prolong the duration of discharge of expiratory neurones (*Trezbski* and *Peterson* 1964;

Richter and *Seller* (1975). From intracellular recordings of the activity of the lateral group of respiratory neurones, *Richter* and *Seller* (1975) have shown that whilst inspiratory neurones are powerfully hyperpolarised by baroreceptor stimulation (AN stimulation), no synaptic potentials or changes in membrane potential were noted in expiratory neurones during such stimulation. This indicates that the baroreceptor effects on these expiratory neurones are secondary to their action on inspiratory neurones, i.e. the effect represents disinhibition. Since the baroreceptors also exert an inhibitory control of the dorsal group of inspiratory neurones, the role of bulbospinal respiratory pathways in the control of sympathetic activity must be taken into account (*Lipski* et al. 1977 and Sect. 4.3).

The Effects of Lesions on the Baroreceptor Reflex. In addition to the neurophysiological and neuroanatomical data considered above, the ablation of areas of the central nervous system has provided some information on the possible role of central structures in the organisation of cardiovascular control. However, negative results are not sufficient to allow the conclusion that an area has no involvement in the integration of the baroreceptor reflex, as any modulating influence may well not be readily demonstrated in an anaesthetised preparation.

As might be expected, the most striking results have come from lesions encroaching on the dorsomedial medulla, and specifically the NTS, whether produced electrolytically or by radio-frequency current. The first clear statement on the effects of lesions of the NTS was made by *Oberholzer* (1960), who described that circumscribed electrolytic lesions of the NTS at levels rostral to the obex, in both cat and rabbit, abolished the reflex response to stimulation of the ipsilateral carotid sinus; these lesions were usually some 1 mm rostral to the obex. Similar results were later obtained in the cat by *Humphrey* (1967). *Oberholzer* (1960) also noted that more caudally placed lesions were successful in abolishing the cardiovascular responses to AN stimulation. These results broadly confirm the data cited already regarding the sites of termination of the SN and AN nerves (see Fig. 1). The effectiveness of lesions of the NTS in abolishing the carotid sinus reflex has since been confirmed by numerous authors in the cat and the rat (*Hilton* and *Spyer* 1971; *Miura* and *Reis* 1972b; *Doba* and *Reis* 1973, 1974b; *de Jong* et al. 1975a, b, 1977; *de Jong* and *Palkovits* 1976; *Palkovits* and *Zaborszky* 1977; *Reis* et al. 1977; *Zandberg* et al. 1977). *Burkhart* et al. (1977) have shown that transverse cuts through the NTS of the dog passing rostral to the obex do not abolish carotid sinus reflexes but totally abolish the responses to AN stimulation, emphasising that a lesion just rostral to the obex in the cat is sufficient to abolish carotid sinus reflexes (see *Gabriel* and *Seller* 1970; *Miura* and *Reis* 1972b; *Doba* and *Reis* 1973, 1974). It is interesting to note also that the effects of

lesions within the NTS are not merely acute but chronic; in fact the survival of rats can be severely jeopardised by NTS lesions (see *Doba* and *Reis* 1973; *Zandberg* et al. 1977), and although long-term survival is more common in the cat, blood pressure remains labile (*Reis* et al. 1977). In contrast *Barman* and *Gebber* (1978a) claim that although lesions in the NTS may abolish the baroreceptor reflex and raise blood pressure, it soon returns to control levels. It is interesting in this context that *Snyder* et al. (1978) claim that selective destruction of catecholamine terminals in the NTS of the rat results in a chronic lability of blood pressure.

The above data is of limited value in ascribing functional characteristics to the different areas of the NTS. Little is ever revealed of the precise area destroyed; it may extend considerably beyond the obvious site of ablation and may often involve the afferent input rather than the neuronal elements of the nucleus. Indeed, lesions elsewhere in the medulla are often claimed to affect the efficacy of baroreceptor reflexes and the development of hypertension and this may well result from inadvertent damage to the NTS. The claim by *Ylitalo* et al. (1974) that lesions of the area postrema produced hypertension were contested by *Hilton* et al. (1974), who drew attention to the close proximity of the NTS to the area postrema and to the failure of these workers to demonstrate whether baroreceptor reflexes were affected by their destruction of the area postrema. *Zandberg* et al. (1977) proved the validity of this questioning experimentally; lesions of the area postrema are ineffective in producing hypertension unless they extend to damage the NTS when the baroreceptor reflex is either abolished or severely attenuated.

Much of the work concerned with a possible role of other areas of the brainstem in the baroreceptor reflex pathway may well have suffered from the possibility that extensive lesions in the lower brainstem may have destroyed or damaged sinus nerve and vagal afferents *en passant* or the tractus solitarius and the surrounding nucleus in part. In this context it is not surprising that *Wang* and *Chai* (1962, 1967) and *Katz* et al. (1967) claim that only destruction of the dorsolateral medulla, the "pressor" area, is sufficient to abolish the cardiovascular response to bilateral carotid occlusion. Their lesions, as illustrated, invariably damaged or destroyed the rostral NTS and probably also its afferent input. In contrast, *Manning* (1962, 1965a, b) reported that massive lesions in the dorsolateral reticular formation *did not* abolish the reflex responses to bilateral carotid occlusion, although a subsequent decerebration did. However, *Wang* and *Chai* (1962, 1967) and *Chai* and *Wang* (1962, 1968) have claimed that decerebration at intercollicular levels in no way impairs baroreceptor function, although as *Peiss* (1965) has pointed out decerebration invariably produces some fall in arterial pressure (review even the classical studies of *Oswjannikow* 1871), which may approach as much as 20 mmHg, in which case baro-

receptor reflexes can hardly be considered to be functioning normally. Carotid occlusion is a poor test of baroreceptor function as it results in a concomitant activation of the carotid body chemoreceptors, but the distinction between results is striking. In view of the preceding discussion it is likely that Manning's lesions spared the NTS, as chemoreceptor afferents also terminate there (*Miura* and *Reis* 1972b; *Lipski* et al. 1975; *Jordan* and *Spyer* 1977a).

Manning (1962, 1965a, b) proposed that midline structures in the medulla as well as suprabulbar areas, in particular the hypothalamus, were essential for the typical sympatho-excitatory response to carotid occlusion. In view of the definition of the medial reticular formation as the "depressor" centre (*Alexander* 1946; *Bach* 1952), this would seem at first sight an attractive possibility. Unfortunately, electrolytic destruction of the medial reticular formation, including the NPR and raphe nuclei, does not abolish baroreceptor reflexes (*Löfving* 1961; *Hilton* and *Spyer* 1971; *Miura* and *Reis* 1972a, b; *Barman* and *Gebber* 1978a), although some variable effects have been reported by others. Lesions in the ventromedial medulla have been cited as abolishing the depressor (*Smith* et al. 1966, quoted by *Humphrey* 1967) or cardiac (*Lee* et al. 1972) components of the baroreceptor reflex. *Miura* and *Reis* (1972b) claim that the cardiac effects are uneffected, but that whilst the depressor response to SN stimulation is abolished by such lesions, the effects of natural baroreceptor stimulation remain uneffected. *Barman* and *Gebber* (1978a), however, leave little doubt that medial areas of the medulla are involved in only non-baroreceptor sympatho-inhibitory responses. Large medial lesions evoked an increase in renal sympathetic activity but left the cardiac rhythm in the renal nerves (postganglionic sympathetic) unaffected, and the sympatho-inhibitory response to baroreceptor activation was unaltered (*Barman* and *Gebber* 1978). It appears that lesions in the "parahypoglossal" region, which has been shown to receive both SN and baroreceptor input (*McAllen* and *Spyer* 1972; *Lipski* et al. 1975), also do not ablolish baroreceptor reflexes (*Doba* and *Reis* 1973).

The effects of laterally placed lesions are, however, much clearer. *Lee* et al. (1972) state that lesions in the NA of the cat abolish the bradycardia which normally follows the intravenous injection of either adrenaline or veratridine, whilst a lesion in the DNV was ineffective. This result, which has been confirmed for other forms of vagal bradycardia (*Kerr* 1969; *Borison* and *Domjan* 1970), argues for the fact that, at least in the cat, the vagal preganglionic supply to the heart arises from neurones in the NA (see Sect. 3.6.1). This evident lateralisation of the reflex may well extend also to its sympatho-inhibitory component. Evidence cited earlier has argued for powerful efferent projections extending from the NTS to the lateral reticular nucleus (Sect. 2.2.1), and particularly to the A1 group of

catecholamine-containing neurones (*Dahlström* and *Fuxe* 1965), which *Coote* and *Macleod* (1974a, b) consider to exert sympatho-inhibitory effects. *Hildebrandt* (1974) describes neurones in the lateral reticular formation which are excited by AN and SN stimulation whose axons can be excited by spinal cord stimulation. This will be discussed in greater detail subsequently (Sect. 3.3).

That baroreceptor function is not totally abolished by decerebration, and may even appear relatively normal, cannot be taken to imply that suprabulbar areas are not essential for a normal expression of the reflex. In fact quite the converse would appear to be the case, for evidence has accumulated that suprabulbar regions may well play an important role in the normal reflex [see *Reis* and *Cuenod* (1965) for confusing data concerning the effects of various transections of the neuraxis]. Indeed, *Hilton* and *Spyer* (1971) and *Spyer* (1969) have provided strong evidence for a role of the hypothalamus in the baroreceptor reflex. They defined an area in the anterior hypothalamus of the cat which on electrical stimulation evoked a "depressor" response qualitatively identical to the baroreceptor reflex (*Spyer* 1969; *Hilton* and *Spyer* 1971). Furthermore, *Spyer* (1969, 1972) has shown that neurones within this area of the hypothalamus are affected by carotid sinus baroreceptor stimulation (see Sect. 2.2.3.3). Bilaterally placed lesions restricted to this region of the hypothalamus reduced the efficacy of the baroreceptor reflex, but never abolished it (*Hilton* and *Spyer* 1971). Equally, lesions within the medullary "depressor" area never abolished the reflex response to stimulation of the ipsilateral carotid sinus; they usually reduced it, unless the lesion encroached upon the ipsilateral NTS. Where a significant response remained after a unilateral medullary lesion, bilateral destruction of the hypothalamic depressor area abolished the response completely. Arterial blood pressure did not remain elevated for a considerable time after these hypothalamic lesions, nor was the order of lesions important (*Hilton* and *Spyer* 1971). In the same year the importance of suprabulbar areas in the performance of the reflex was reiterated by *Kent* et al. (1971), who showed that, following decerebration, the range over which the baroreceptors can evoke a change in arterial pressure is severely restricted compared to that in an animal with intact neuraxis.

In summary, the results of lesion studies show that baroreceptors terminate in the NTS and indicate a role for suprabulbar areas in the organisation of the baroreceptor reflex (*Hilton* and *Spyer* 1971). Such a longitudinal arrangement would mirror that for sympatho-excitatory control (see *Hilton* 1975 for review) and would then conveniently encompass other data that argue strongly for hypothalamic interactions in cardiovascular control (*Gellhorn* 1957).

The Baroreceptor Input to Suprabulbar Areas. The importance of suprabulbar areas in the performance of the baroreceptor reflex has been summarised above and data illustrating the ascending projections of the NTS described. It now remains to establish the nature and extent of the baroreceptor input to these rostral structures. Recent studies have shown a baroreceptor influence on hypothalamic unit activity (*Thomas* and *Calaresu* 1972; *Yamashita* 1977; *Kannan* and *Yagi* 1978). In particular *Spyer* (1969, 1972) has described that approximately 5% of neurones investigated in the anterior hypothalamic depressor area (*Hilton* and *Spyer* 1971) received a baroreceptor input. Of the 21 neuonres studied, 15 were excited and 6 inhibited by raising the pressure of 200 mmHg in a vascularly isolated carotid sinus. In other experiments it was shown that neurones in this same area were excited on stimulating within the NTS at a latency of 20–50 ms (*Spyer*, unpublished work). In the rabbit, neurones in the equivalent area have been shown to be excited on AN stimulation, the latency often being surprisingly short (*Brickman* et al. 1977). In another study, neurones in the perifornical region of the medial hypothalamus were shown to be excited by SN stimulation (*Thomas* and *Calaresu* 1972). Of the 23 neurones affected, 7 were excited (latency 17–40 ms, mean 29 ± 3.7 ms), 16 inhibited (latency 30–140 ms, mean 68 ± 9.0 ms). Five inhibited by such stimulation were also inhibited during the pressor response to intravenous noradrenaline. These neurones would appear to be located in the region of the hypothalamus believed to integrate the defence reaction, including its cardiovascular components (see *Abrahams* et al. 1960). It is interesting that the pattern of response of neurones in this area was the converse of that seen in the hypothalamic "depressor" area (compare *Thomas* and *Calaresu* 1972 to *Spyer* 1972). An antagonistic arrangement of these two hypothalamic areas has been suggested (*Hilton* and *Spyer* 1971; cf. *Gellhorn* 1957), a relationship that may well continue throughout the length of the brainstem. These observations could be interpreted as lending indirect support to such a model.

In addition it has been known for many years that the baroreceptor (and chemoreceptor) inputs alter the release of antidiuretic hormone from the posterior pituitary. It was hence no surprise that *Barker* et al. (1971) were able to demonstrate an effect of SN stimulation on neurosecretory neurones in the supra-optic nucleus. The major effect was excitatory, but more recently *Yamashita* (1977) has shown that neurosecretory neurones in the supra-optic nucleus are excited by chemoreceptor stimulation and inhibited by inflation of the carotid sinus. Similarly *Kannan* and *Yagi* (1978) report an inhibitory effect of the carotid baroreceptors on these neurones.

In addition to baroreceptor inputs to the hypothalamus, there are indications of an AN input to the subthalamus in the rabbit. *Kaufman* et al.

(1979) have excited neurones in the zona incerta of the rabbit on AN stimulation with latencies as short as 4 ms. Whilst such latencies are dramatically shorter than previously reported for supramedullary effects and even shorter than usually observed in the medulla, they are consistent with the autoradiographic findings of *Ricardo* and *Koh* (1978) in the rat, which describe a direct projection from the NTS to the lateral subthalamic area.

In addition to this direct demonstration of a baroreceptor influence at the level of the hypothalamus it is well established that this input can have marked effects on behaviour: it can suppress the outbursts of sham rage in hypothalamic animals (*Bartorelli* et al. 1960), influence the sleep-wakefulness cycle (*Guazzi* and *Zanchetti* 1965; *Baust* and *Heinemann* 1967) and influence electrocortical activity (*Bonvallet* et al. 1953). Baroreceptor stimulation is also known to affect motor tone and activity (see *Koch* 1932; *Schweitzer* and *Wright* 1937; *Schulte* et al. 1959; *Dell* and *Bonvallet* 1966), and in a recent study *Coleridge* et al. (1976) have demonstrated that pyramidal tract neurones in the motor cortex of cats are either directly inhibited or prevailing excitatory inputs onto them are suppressed by baroreceptor stimulation. The pathway along which this effect is produced is unknown, although it is likely to involve ascending reticular pathways, which may be influenced from the NTS (*Magnes* et al. 1961; *Akimoto* and *Saito* 1966; *Klee* 1966).

3 Baroreceptor Control of Preganglionic Autonomic Activity

3.1 Sympathetic Efferent Activity

The central nervous control of the cardiovascular system is exerted primarily by means of the postganglionic sympathetic innervation of vascular beds and the heart. Together with the vagal control of the heart, these efferent pathways constitute the final efferent arm of the various cardiovascular reflexes that are considered to exert a homeostatic control on the circulation (see *Heymans* and *Neil* 1958). Hence it is not surprising that sympathetic efferent activity, particularly that of postganglionic nerves, is distinguished by its marked cardiac or pulse rhythmic discharge (*Adrian* et al. 1932; *Bronk* et al. 1940; *Alexander* 1945, 1946; *Hagbarth* and *Vallbo* 1968; *Polosa* 1968; *Cohen* and *Gootman* 1969, 1970; *Gootman* and *Cohen* 1970, 1973; *Koizumi* et al. 1971; *Mannard* and *Polosa* 1973; *Seller* 1973; *Taylor* and *Gebber* 1975; *Gross* and *Jänig* 1976; *Horeyseck* et al. 1976; *Gregor* et al. 1977). This cardiac rhythm is usually superimposed on a respiratory related pattern of activity (*Adrian* et al. 1932; *Hagbarth* and *Vallbo* 1968; *Polosa* 1968; *Cohen* and *Gootman* 1970; *Gootman* and *Cohen*

1970, 1973; *Richter* et al. 1970; *Koizumi* et al. 1971; *Seller* and *Richter* 1971; *Mannard* and *Polosa* 1973; *Seller* 1973; *Gregor* et al. 1977; *Lipski* et al. 1977; *Preiss* and *Polosa* 1977) and is considered to reflect the powerful control of sympathetic activity exerted by the baroreceptor inputs. Indeed this rhythm is usually attenuated, if not totally abolished, by baroreceptor denervation (*Gootman* and *Cohen* 1970 and others). There is, however, a claim that this apparent cardiac rhythm of postganglionic sympathetic (and of course preganglionic) activity results merely from an entrainment of the baroreceptor afferent input to an intrinsic rhythm of brainstem origin (*Taylor* and *Gebber* 1975; *Gebber* 1976; *Gebber* and *Barman* 1977).

It is well established that preganglionic and postganglionic discharge is characterised by a 3 Hz oscillation in the cat (*Green* and *Heffron* 1968; *Cohen* and *Gootman* 1970; *Gootman* and *Cohen* 1970, 1973; *Snyder* and *Gebber* 1973; *Taylor* and *Gebber* 1975; *Camerer* et al. 1977; *Gebber* and *Barman* 1977) which has usually been considered to represent the baroreceptor-related inhibitory control of sympathetic discharge. More recently a power spectral analysis of postganglionic sympathetic activity has shown that it contains two peaks at around 3 Hz in the cat (*Camerer* et al. 1977). One is related to the baroreceptor input and is abolished by baroreceptor denervation, the other is related to the delta-theta oscillation of the EEG and is abolished by decerebration (*Camerer* et al. 1977). *Gebber* and Barman (in press), however, have indications that a 2–6 c/s rhythm persists after both baroreceptor denervation and decerebration. Whether this implies that the baroreceptor input is entrained to this "central oscillator" or whether they exert their influences along independent pathways remains to be resolved.

Nevertheless, the cardiac rhythm of the sympathetic discharge survives decerebration (*Alexander* 1946; *Mannard* and *Polosa* 1973; *Camerer* et al. 1977). This cannot be taken to imply that the normal reflex control of sympathetic activity involves only a bulbar pathway. Furthermore, it is probable that not all sympathetic efferent fibres are affected in a similar manner by baroreceptor inputs. Detailed studies of the sympathetic supply to the hindlimb of the cat, investigating the inputs to hairless and hairy skin and to muscle, suggest that functional distinctions can be made on the basis of the pattern of discharge of individual neurones (*Grösse* and *Jänig* 1976; *Horeyseck* et al. 1976; *Gregor* et al. 1977; *Jänig* and *Kümmel* 1977). Indeed, it would seem convincingly demonstrated at this level of the sympathetic pathway that neurones with a vasoconstrictor function can be distinguished by their powerful cardiac rhythm, muscle vasoconstrictors having the most distinctive cardiac rhythm and inspiratory related discharge (*Gregor* et al. 1977). These neurones are usually spontaneously active, firing at a low rate, and their pattern of re-

sponse to various physiological stimuli, as well as stimulation of the neuraxis, provides at least a teleological suggestion of their probable function.

This analogy may also apply at preganglionic levels, where studies on individual fibres or recordings from the cell bodies in the spinal cord suggest that not all preganglionic neurones, when active, have either cardiac or respiratory related discharges (*Fernandez de Molina* et al. 1965; *Polosa* 1967, 1968; *Koizumi* et al. 1971; *Mannard* and *Polosa* 1973; *Seller* 1973; *Coote* and *Westbury* 1974, 1979a, b; *Preiss* et al. 1975; *Gebber* and *McCall* 1976). This immediately raises the question of identity: can preganglionic neurones be labelled as vasoconstrictor or cardio-accelerator, or is functional specialisation the reserve of postganglionic elements? As yet, a conclusive answer cannot be given; preganglionic neuronal discharges cannot yet be analysed in as much detail as postganglionic fibres, but a degree of heterogeneity has already been demonstrated by considering just the presence or otherwise of two rhythms, cardiac and respiratory (*Fernandez de Molina* et al. 1965; *Polosa* 1967, 1968; *Koizumi* et al. 1971; *Mannard* and *Polosa* 1973; *Seller* 1973; *Coote* and *Westbury* 1974, 1979a, b; *Preiss* et al. 1975; *Gebber* and *McCall* 1976).

This question of identity is not esoteric. Its importance resides in its necessity when establishing the central pathways of cardiovascular as distinct from autonomic control. It has long been considered that the sympathetic nervous system acts in a general and undifferentiated manner (cf. *Cannon* 1929, 1930, 1932), but it is becoming apparent that this is not the case. This original contention arose from two main factors: the exaggerated emotional states investigated and the fact that in most studies whole nerve activity has been recorded rather than the properties of the individual functional groups. With these factors in mind it will be necessary to review the organisation of the preganglionic sympathetic neurones, as the final common pathway within the central nervous system, to determine the synaptic complexity that is responsible for their basic firing properties and, it is hoped, to discern the pathways that mediate the powerful baroreceptor control of their activity.

3.2 Baroreceptor Control of Sympathetic Activity

The initial studies relating to baroreceptor control of sympathetic activity have involved the effects of such stimulation on on-going activity (*Gootman* and *Cohen* 1970; *Koizumi* et al. 1971; *Foreman* and *Wurster* 1973; *Seller* 1973; *Snyder* and *Gebber* 1973; *Taylor* and *Gebber* 1973; *Coote* and *Westbury* 1973, 1979a, b; *Gebber* 1976; *Gebber* and *McCall* 1976; *Gebber* and *Barman* 1977; *McCall* et al. 1977; *Barman* and *Gebber* 1978a; *Geis* et al. 1978) and somatic or visceral reflexes into these nerves (*Coote* and *Downman* 1966, 1969; *Coote* et al. 1969; *Koizumi* et al. 1971; *Seller*

1973; *Coote* and *Macleod* 1974b, 1975). In the context of the present review it is irrelevant to discuss in detail the nature and synaptic complexity of somatic and visceral reflexes into sympathetic nerves. These have been dealt with at length in the past (*Sato* and *Schmidt* 1973; *Coote* 1978; *Coote* and *Sato* 1978). The influence of the baroreceptor input on the supraspinal and spinal components of these reflexes will be raised, as this may provide considerable data on the basic circuitry of baroreceptor mechanisms.

It has been known for many years that the baroreceptors exert an inhibitory control of sympathetic efferent activity. Their cardiac rhythm is of baroreceptor origin, but the central pathways involved remained unresolved. The *central delay* of a reflex provides some indication of its synaptic complexity, although affected by the length of the interneuronal pathways, and as such the measurements of the central delay of the baroreceptor-sympathetic reflex are of value. *Kezdi* and *Geller* (1968) provided the first detailed open-loop study of the baroreceptor-sympathetic reflex in the dog. They showed that the latency to inhibition of postganglionic sympathetic activity, recorded in either renal or splanchnic nerves, varied from 150–360 ms. From preganglionic recordings in the cat during electrical stimulation of the sinus nerves, *Richter* et al. (1970) and *Seller* and *Richter* (1971) obtained a value of 181 ± 23 ms for complete inhibition of on-going sympathetic activity. *Green* and *Heffron* (1968), using natural baroreceptor stimulation, obtained values in the range of 150–300 ms, as did *Coote* and *Downman* (1969). These observations, however, leave unanswered the site of inhibition, which could be within the brainstem, or at the level of the cord, or a mixture of both.

The fact that somatic and visceral reflexes into sympathetic nerves have both a spinal and supraspinal pathway (for review see *Sato* and *Schmidt* 1973; *Coote* 1978) at least suggested the possibility that investigating the baroreceptor control of their effectiveness might shed light on the site of interaction between the baroreceptor input and sympathetic control. In fact, the controversy remains, partly no doubt owing to the variability of the early spinal reflex into sympathetic nerves, at least as far as those into the white rami are concerned, and partly to its questioned significance regarding cardiovascular control (see *Seller* 1973). This questioning has a particular relevance in this context since early or spinal reflexes are rarely seen in cardiac and renal sympathetic nerves (*Coote* and *Downman* 1966; *Coote* and *Sato* 1978), although often elicited in white rami (see above) and the cervical sympathetic nerves (*Coote* et al. 1969; *Schmidt* and *Schönfuss* 1970). It would appear that at the level of postganglionic nerves, the early response in the anaesthetised animals with intact neuraxis is variable (see *Coote* and *Downman* 1969) but is inhibited by baroreceptor stimulation along with the late supraspinal reflex. That an early response

can be recorded in the white rami and postganglionic nerves, yet the white rami responses remain unaffected by baroreceptor stimulation (*Coote* et al. 1969; *Koizumi* et al. 1971; *Seller* 1973) seems at first sight confusing since postganglionic effects have to be transmitted through these rami. *Koizumi* et al. (1971) found it difficult to record significant early (i.e. spinal) reflexes into renal or cardiac nerves; they were usually small and powerfully affected by the on-going cardiac and respiratory-related discharges of these nerves. These authors do, however, illustrate that when white rami early reflexes were present they were unaffected by baroreceptor stimulation. *Coote* and *Macleod* (1974b), however, illustrate that baroreceptor inputs powerfully inhibit the late (i.e. supraspinal) reflex in renal and cardiac sympathetic nerves, but the effects on the early spinal reflex were not entirely clear. The early reflex into cardiac nerves appeared unaffected. They were, however, able to show a baroreceptor inhibition of thoracic white rami early reflexes which contrasts to previous reports (*Coote* et al. 1969; *Koizumi* et al. 1971; *Seller* 1973). This observation has been used by *Coote* and *Macleod* (1974b, 1975) as a significant factor in their claim that the baroreceptor reflex acts, at least in part, by an inhibitory action at the level of the spinal cord (see Sect. 3.3.3.3).

In this context, it is pertinent to draw attention to a study of individual preganglionic fibres recorded in the cat; only 2 from thoracic white rami (out of 55 tested) and 24 from lumbar white rami (out of 54) showed segmental early spinal reflexes to somatic stimulation (*Seller* 1973). Furthermore, only one of these fibres showed a cardiac rhythm in its discharge, and none was silenced by the baroreceptor activation in response to an adrenaline injection.

In conclusion, the central delay of the baroreceptor-sympathetic reflex is long, generally above 150 ms, and there is no controversy regarding the ability of this input to abolish the late (supraspinal) component of somatic and visceral reflexes into sympathetic nerves. The significance for cardiovascular control of those pre- and postganglionic sympathetic neurones receiving an early (spinal) reflex remains in question although in line with the fact that *all* on-going sympathetic activity appears susceptible to powerful baroreceptor stimulation, and if these inputs are in any way concerned with the background discharge of sympathetic neurones some effects on early reflex responses appear possible.

3.3 Preganglionic Sympathetic Neurones

Preganglionic sympathetic neurones are located in the intermediolateral horn of the thoracic spinal cord, with a varying and small representation in the lower cervical and a marked representation in upper lumbar segments

of the spinal cord. Some preganglionic neurones may extend from this area into the adjacent white matter of the cord and into the intercalated area (see *Petras* and *Cummings* 1972; *Chung* et al. 1975, and detailed analysis in *Wurster* 1977). The preganglionic supply to the heart originates from T1–5 (*Wurster* 1977) with the greatest density of neurones in the intermediolateral column of the cat being in segments T1–2 and L3–4 (*Henry* and *Calaresu* 1972). Their axons are almost all myelinated and leave the spinal cord via the thoracic and lumbar ventral roots, and after passing for a short distance with the spinal nerves they separate to form the white rami. From here they pass to the sympathetic ganglia, from which unmyelinated postganglionic fibres leave to innervate end-organs. A more detailed discussion of this anatomical arrangement with particular reference to cardiac control is given in a recent review (*Wurster* 1977), and a general description is contained in a survey of sympathetic reflexes (*Coote* 1978).

In the present discussion, interest will be directed specifically at the physiological properties of the preganglionic elements but it will be necessary also to refer to the anatomical arrangements considered to represent the spinal interneuronal circuitry controlling their activity.

3.3.1 Firing Patterns

The activity of individual preganglionic neurones has been recorded by teasing single active units not only from preganglionic nerves, usually the cervical sympathetic (*Pitts* et al. 1941; *Pitts* and *Bronk* 1942; *Preiss* et al. 1975; *Preiss* and *Polosa* 1977) but also from thoracic and lumbar white rami (*Seller* 1973). In these cases, selection was dependent on the presence of spontaneous activity, which is not an ubiquitous property of sympathetic neurones. The alternative approach is to record from the cell bodies of these neurones, identifying the neurone from its antidromic response to stimulation of its axon in the white rami or other preganglionic nerves (*Hongo* and *Ryall* 1966; *Polosa* 1967, 1968; *Mannard* and *Polosa* 1973; *Taylor* and *Gebber* 1973; *Wyszogrodski* and *Polosa* 1973; *Kirchner* et al. 1975a, b; *Gebber* and *McCall* 1976; *Lipski* et al. 1977; *McCall* et al. 1977). In addition, intracellular recordings are now possible (*Fernandez de Molina* et al. 1965; *Coote* and *Westbury* 1974, 1979b).

Recordings from preganglionic fibres (*Adrian* et al. 1932; *Pitts* et al. 1941; *Alexander* 1946; *Preiss* et al. 1975; *Preiss* and *Polosa* 1977) show that these neurones fire at a low rate, often without an obvious cardiac rhythm, and it would appear that the frequency-limiting step in the sympathetic outflow is not a property of the ganglion alone but is already imposed by or before the preganglionic neurones (*Pitts* and *Bronk* 1942).

The "silent period" following a burst of activity first observed by *Pitts* and *Bronk* (1941) was defined as post-excitatory depression, i.e. an orthodromic volley producing a period of subexcitability. These authors considered this to reflect the properties of the excitatory pathways impinging on them. Conversely, *Polosa* (1967, 1968), recording extracellularly from preganglionic cell bodies in the spinal cord, suggests that the "silent period" following intense activity is a property of the neurone itself, as it may be produced by antidromically evoked spikes. He purported to eliminate the necessity for a recurrent inhibitory interneuronal pathway (Renshaw-type cell), because he provides evidence that the effect was only produced by an antidromic spike, a subthreshold stimulus to the cervical sympathetic failing to elicit a "silent period". Furthermore, in 8 out of 10 cases suprathreshold stimuli failed to affect the duration of the "silent period". Indeed in his later study *Polosa* (1968) showed that an antidromic spike would reset the on-going rhythm of a preganglionic neurone without significantly shortening the expected interspike interval. In certain cases, however, *Polosa* (1967) found indications of Renshaw-type recurrent effects on cervical sympathetic stimulation (i.e. 4 neurones), but strychnine did not block the apparent inhibition. More recently, *Mannard* and *Polosa* (1973) have extended this study and have retained the conclusion that the firing rate is broadly an intrinsic property and not determined solely by presynaptic events. Two recent studies, have, however, revived the possibility that the activity of a proportion of preganglionic sympathetic neurones may be controlled by a recurrent collateral pathway (*Barman* and *Gebber* 1978b; *Gebber* et al. 1978; *Lebedev* et al. 1980), although the appropriate interneurone has yet to be described (*Rethelyi* 1972). *Gebber* and *Barman* (1979) consider that the inhibitory interaction between preganglionic sympathetic neurones results from a cholinergic action of sympathetic neurones with C-fibre axons on the more numerous sympathetic B-fibre neurones. It is as yet unresolved whether it involves a recurrent pathway or results from dendrodendritic interactions.

Whatever mechanism(s) is responsible, there is no question that in the intact anaesthetised animal, preganglionic neurones when active fire at rates below 10 impulses/s (*Fernandez de Molina* et al. 1965; *Polosa* 1967, 1968; *Mannard* and *Polosa* 1973; *Snyder* and *Gebber* 1973; *Taylor* and *Gebber* 1973; *Coote* and *Westbury* 1974, 1979a, b; *Gebber* and *McCall* 1976, and see above for fibre recordings). Spontaneous activity appears in as few as 20% of antidromically identified neurones (*Polosa* 1968; *Mannard* and *Polosa* 1973) to as many as 60% (*Coote* and *Westbury* 1974, 1979a), most studies suggesting around 30%. Interestingly, *Mannard* and *Polosa* (1973) have shown that although the incidence of spontaneous discharge is reduced as one goes from the intact, to the spinal, and finally

to the segmental preparation, background firing remains in even this final situation (see also *Alexander* 1945).

The discharge of preganglionic neurones, recorded either from fibre or cell body usually appears irregular, but by constructing post-R-wave histograms (*Seller* 1973; *Taylor* and *Gebber* 1973; *Gebber* and *McCall* 1976; *McCall* et al. 1976, and see Fig. 3) or autocorrelogram functions (*Mannard*

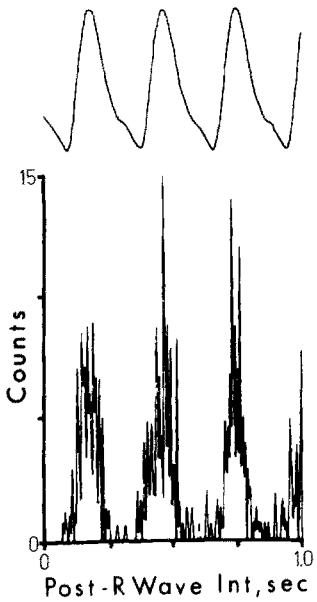

Fig. 3. Phase relationship between averaged arterial pulse wave and post-R wave TIH of antidromically identified preganglionic neurone. Sample run 256 c/s, address bin 4 ms, blood pressure 160/125 mmHg. Adapted from *Gebber* and *McCall* (1976)

and *Polosa* 1973) a clear cardiac rhythm can be shown. *Coote* and *Westbury* (1974, 1979) have constructed pulse-triggered histograms of sympathetic neuronal activity and have shown that the probability of discharge was minimal 150–200 ms after the beginning of systole. Moreover in a group of neurones the effects of inflating a blind sac of one carotid sinus was tested; the mean latency to inhibition was 148 ± 14 ms (SE, n = 15). This value for units recorded at T3 level is in close agreement with previous studies on the reflex time (see above).

At this point it is worth noting that both *Fernandez de Molina* et al. (1965) and *Coote* and *Westbury* (1979) report intracellular recordings from antidromically identified sympathetic neurones. As yet, however, no clear data have resulted on the nature of the baroreceptor control of their activity, as pulse-related changes in membrane potential have yet to be established.

3.3.2 Spinal Interneuronal Control of Preganglionic Neurones

The possibility that preganglionic neurones are under recurrent control implies the involvement of a local inhibitory interneurone (*Barman* and *Gebber* 1978b; *Gebber* et al. 1978; *Gebber* and *Barman* 1979; *Lebedev* et al. 1980). There is no anatomical support for this contention (*Rethelyi* 1972), but *Gebber* and *McCall* (1976) describe non-antidromically driven neurones in close proximity to antidromically driven preganglionic neurones (stimulating the cervical sympathetic nerve and recording at T1–5). These neurones had a cardiac rhythm (post-R-wave peak 159 ± 17 ms in 15 out of 43 studied) as against a post-R-peak of 177 ± 10 ms for preganglionic neurones (i.e. antidromically identified neurones). These 15 non-antidromically driven neurones were also inhibited by baroreceptor stimulation, as were preganglionic neurones, but in general whilst a preganglionic neurone seldom fired more than once in each cardiac cycle, "interneurones" fired in bursts of up to 4 spikes/cardiac cycle. Further, brainstem stimulation at "pressor" sites evoked excitatory responses in "interneurones" as well as preganglionic neurones, but the onset latency was shorter to the former (mean 31 ± 3 ms compared to 41 ± 6 ms for preganglionic neurones). There was no significant difference, however, in either the latency or duration of the effects of "depressor" area stimulation on their discharge. It was concluded that they represent an excitatory interneurone, presumably mediating descending excitatory (and possibly segmental reflex control) of preganglionic neurones.

In more recent studies, *McCall* et al. (1977) have described neurones in the intermediomedial region of the spinal grey with properties suggesting that they might represent inhibitory interneurones controlling preganglionic activity. It is known that neurones in this area project to the intermediolateral horn (*Bok* 1928; *Petras* and *Cummings* 1972). Twenty-nine neurones in this area were spontaneously active but silenced on bilateral carotid occlusion and had cardiac rhythm. They also received a short-latency excitatory input from the NTS (latency 8 ± 1 ms; conduction velocity 15 ± 2 m/s). These properties provide indirect evidence for their role as inhibitory interneurones but direct evidence is still lacking.

In the context of delineating the spinal organisation of the control of preganglionic activity, this tentative description of two groups of interneurone may be important in discerning the nature and involvement of descending excitatory and inhibitory pathways in mediating the baroreceptor reflex.

3.3.3 Supraspinal Influences on Sympathetic Activity

It is now well established that electrical stimulation at numerous sites within the brainstem can evoke increases in arterial blood pressure, primarily through an increase in sympathetic activity. There are, however, examples of brainstem stimulation evoking changes in sympathetic activity without concomitant alterations in arterial blood pressure (*Kahn* and *Mills* 1967).

The first direct demonstrations of brainstem influences on sympathetic discharges were those studies which showed an influence of the hypothalamus on sympathetic activity made in the 1930s and 1940s (*Bronk* et al. 1940; *Pitts* et al. 1941; *Pitts* and *Bronk* 1942). Furthermore, these studies revealed a marked interaction between these excitatory effects and baroreceptor inputs. From these and subsequent investigations, it became accepted that the activity of sympathetic preganglionic neurones was determined by the algebraic summation of excitatory and baroreceptor inputs at the level of the "vasomotor" centre. Sympathetic neurones have a low dynamic firing range, partly determined by intrinsic properties, but in general considered to result from interactions at the level of the "vasomotor centre", i.e. from its excitatory input. As such, baroreceptor control of these neurones can be considered to result from disfacilitation through a withdrawal of descending excitatory drives.

This model has come under determined experimental attack in recent years, and it is now established that sympathetic control involves far more than this stereotyped mechanism (reviewed by *Peiss* 1965; *Hilton* 1965, 1966, 1975, 1977; *Smith* 1974). It is now apparent that simple summation at the level of the medulla cannot explain all observations. There are circumstances where the baroreceptor input can be totally over-ridden, in such a way that even non-linear summations are unlikely to provide all the answer (see Sect. 4.4). In addition some sympatho-excitatory effects appear insensitive to baroreceptor inhibition (see *Kahn* and *Mills* 1967). It is also becoming clear that inhibitory effects can occur within the spinal cord, on or near to the final common pathway, the preganglionic neurone. It remains controversial whether this spinal inhibitory mechanism is responsible for baroreceptor control of sympathetic activity, but it does imply an integrative action within the cord and presumably an integrative function for preganglionic sympathetic neurones.

3.3.3.1 Brainstem Inputs to the Cord

The fact that stimulating within the brainstem can excite the sympathetic motoneuronal pool has led to the conclusion that there is a relatively stereotyped bulbospinal excitatory system (see above, and *Alexander* 1946). Recent studies indicate that the sympatho-excitatory pathways are not homogeneous. *Gebber* and his colleagues have provided evidence for two

distinct excitatory systems (*Gebber* et al. 1973; *Snyder* and *Gebber* 1973; *Taylor* and *Gebber* 1973; *Gebber* and *McCall* 1976) divided into the pattern first described by *Kahn* and *Mills* (1967) and subsequently *Nathan* (1972). This conclusion rested on the fact that although electrical stimulation at sites in the medulla (*Gebber* et al. 1973; *Snyder* and *Gebber* 1973; *Taylor* and *Gebber* 1973; *Gebber* and *McCall* 1976), midbrain and hypothalamus (*Gebber* et al. 1973; *Snyder* and *Gebber* 1973) excite sympathetic activity, two patterns of response can be discerned: one is a short latency and relatively constant response, and the other, which may be evoked concomitantly from the same site, has a longer latency and is variable in appearance. In addition, the "early" response is resistant to baroreceptor stimulation and the "late" is totally suppressed by baroreceptor inputs. This suggests that the inhibition of the late response is mediated within the spinal cord. Other evidence to support this model will be reviewed below (see Sect. 3.4). The resistance of the "early" excitatory input to sympathetic neurones to baroreceptor stimulation, may not be total. *Coote* and *Macleod* (personal communication) have shown that "early" excitatory responses evoked in thoracic white rami by stimulation in descending sympatho-excitatory tracts of the cervical cord can be inhibited during powerful baroreceptor stimulation.

Medullary Pathways. The "pressor" area is considered to lie in the lateral areas of the medulla (see *Alexander* 1946). *Gebber* et al. (1973) showed that stimulating within this area, particularly within the n. reticularis ventralis and the LRN, evoked discharges in the postganglionic external carotid nerve over two pathways. Furthermore, *Taylor* and *Gebber* (1973) have described the effects of such stimulation on single preganglionic neurones, the early response (latency 21.4 ± 1.0 ms) as against the late response (55.4 ± 3.8 ms) was resistant to both baroreceptor activation and to stimulation in depressor areas of the medulla. In addition, later experiments have shown that stimulating in these areas of the medulla also excited non-antidromically driven sympathetic "interneurones" located close to preganglionic neurones (T1–5) identified by their antidromic response to stimulating the cervical sympathetic (*Gebber* and *McCall* 1976, and see above). The division into sympathetic preganglionic neurones and "interneurones" may not be as firm as *Gebber* and *McCall* claim; all that the authors can conclude with certainty is that the "interneurones" do not have an axon running in the cervical sympathetic nerve.

These apparently distinct descending excitatory systems are differentially affected by stimulation in "depressor" areas of the medulla (*Taylor* and *Gebber* 1973; *Snyder* and *Gebber* 1973; *Gebber* and *McCall* 1976). The pathway responsible for the early excitatory response (which is resistant to "depressor" area and baroreceptor stimulation) conducts at around

5 m/s, and the pathway whose effects are powerfully suppressed by both baroreceptors and the "depressor" area conducts at up to 2 m/s. *Seller* (1973) describes the effects of stimulation of the brainstem on sympathetic preganglionic neurones with a latency broadly compatible with the range described above, but without discerning functionally distinct effects.

Considerably faster pathways exerting excitatory effects on sympathetic activity have been described (*Alanis* et al. 1966; *Calaresu* and *Henry* 1970; *Henry* and *Calaresu* 1974a–d). In particular, stimulation in the parahypoglossal area (*Alanis* et al. 1966; *Calaresu* and *Henry* 1970) excites sympathetic neurones (of the inferior cardiac nerve) with a latency of 3–10 ms (conduction velocity 45 m/s). It has already been shown that this area of the medulla receives a baroreceptor input (*Lipski* et al. 1975), but since this is an excitatory input, it is difficult to formulate an explanation for the relationship of this excitatory input to this sympatho-excitatory pathway. *Alanis* et al. (1966) argue that it represents a descending pathway (i.e. fibre tract) arising from the hypothalamus, so there may be no significant connection between the baroreceptor input to and the efferent effects of stimulation of the parahypoglossal area.

In alternative studies *Henry* and *Calaresu* (1974a) have described field potentials and unit responses in the NPR and LRN with a latency of around 1.7 ms on stimulating within the intermediolateral cell column of upper thoracic levels at points which evoked cardio-acceleration. They considered that they were activating descending excitatory and inhibitory pathways converging onto sympathetic preganglionic neurones (*Henry* and *Calaresu* 1974a–d), but since the calculated conduction velocities of these putative pathways were around 60 m/s it is impossible to reconcile them with the observations of others (see above). Even more serious was their failure to demonstrate that they were not activating fibres *en passant*, without direct functional connection to sympathetic preganglionic neurones. This is especially likely, as the intermediolateral horn is adjacent to the lateral funiculus. In this context, the conduction velocities quoted are very similar to those of the bulbospinal respiratory neurones, whose axons traverse the lateral funiculus (see *Bianchi* 1971; *Euler* et al. 1973a, b; *Merrill* 1974; *Richter* et al. 1975, and others).

In an attempt to reconcile their results with those of others, *Henry* and *Calaresu* (1974d) have stimulated at cardio-accelerator and cardio-inhibitory sites in the medulla recording in the intermediolateral horn at T2. They claim two patterns of response, one of short latency (2.4–5.0 ms, mean 3.0 ms) and another of long latency (12–40 ms, mean 20 ms), which they consider to act at spinal interneurone and preganglionic neurone respectively, but they provide no physiological identification of the neurones investigated. Unfortunately their presumed interneuronal response, which is equivalent to their previous data in terms of latency (*Henry* and *Calaresu*

1974a), is at variance with the data of *Gebber* and *McCall* (1976), where the interneuronal response is within the overall range of that seen in preganglionic neurones although the modal latency is somewhat less (31 ± 3 ms compared to 41 ± 6 ms for preganglionic neurones). *Henry* and *Calaresu*'s observations can only have any significance if there are complex propriospinal pathways (see *Kirchner* et al. 1975a) but this has yet to be convincingly demonstrated.

Hypothalamic Pathways. The first demonstrations of brainstem control of sympathetic activity were those showing that simulation of the hypothalamus could evoke increases in the activity of post- and preganglionic sympathetic fibres (*Bronk* et al. 1940, and subsequently others). In the main, studies have since been concerned more specifically with the pathways from the hypothalamus affecting arterial blood pressure (see *Abrahams* et al. 1960; *Schramm* and *Bignall* 1971, amongst many others). Most results suggest that the efferent pathways involve connections within the medulla, but anatomical evidence is accumulating that there may be direct connections from the hypothalamus to the spinal cord, and particularly to the intermediolateral horn of the thoracic and lumbar cord (*Beattie* et al. 1930; *Smith* 1965; *Kuypers* and *Maisky* 1975; *Saper* et al. 1976).

More recent studies using spinal injections of HRP (*Kuypers* and *Maisky* 1975; *Saper* et al. 1976) are particularly revealing because they suggest a pathway from perifornical regions of the hypothalamus descending directly to the intermediolateral column of the thoracic cord. Moreover, *Saper* et al. (1976) have demonstrated the anterograde transport of labelled amino acids from the hypothalamus to this region of the cord, arguing for true terminal endings in the intermediolateral column. They have also shown that pathways from the hypothalamus terminate within regions of the midbrain and medulla previously implicated in cardiovascular control. The relationship of these areas of the midbrain and hypothalamus to those stimulated in former studies that resulted in sympathetic activation (see *Gebber* et al. 1973) remains unresolved.

3.3.3.2 Spinal Sympatho-Excitatory Pathways

A specific locus of a sympatho-excitatory pathway has been identified in the spinal cord of the cat. This pathway descends in the dorsolateral funiculus (*Illert* and *Gabriel* 1972; *Gebber* et al. 1973; *Coote* and *Macleod* 1974a, b; *Foreman* and *Wurster* 1973; *Henry* and *Calaresu* 1974b, c; *Kirchner* et al. 1975; *Barman* et al. 1976; *Szulcyck* 1976; *Achari* et al. 1978; *Geis* et al. 1978). Lesions in this pathway have been shown to reduce blood pressure and to abolish the cardiovascular responses to bilateral carotid occlusion in acute experiments in the cat (*Foreman* and *Wurster* 1973), but chronic experiments in the dog show that blood pressure reverts

to normal levels although the response to carotid occlusion remains absent (*Geis* et al. 1978). The interpretation of these data may be complicated by the fact that this part of the dorsolateral funiculus also contains descending axons of at least two sympatho-inhibitory pathways, one of which has also been implicated in mediating the inhibitory control of sympathetic activity during the baroreceptor reflex (see Sect. 3.3.3.3).

In addition to this established pathway, there is evidence that central respiratory drive, and in particular inspiratory drive, can effect sympathetic efferent activity (*Polosa* 1968; *Mannard* and *Polosa* 1973; *Preiss* et al. 1975; *Preiss* and *Polosa* 1977; *Lipski* et al. 1977). Since the excitability of preganglionic, and indeed postganglionic, vasoconstrictor neurones (see above) is so powerfully influenced by inspiratory activity, it is likely that the bulbospinal pathways from medullary respiratory neurones are involved in a control or background drive to sympathetic neurones, mediated no doubt by spinal interneurones (see for example *Lipski* et al. 1977).

3.3.3.3 Descending Inhibitory Control

The medulla, and indeed other levels of the neuraxis, have been known to be capable of reducing arterial blood pressure through an inhibition of sympathetic activity. The medullary "depressor" area was considered to encompass the medial reticular formation, extending medially from the intramedullary course of the hypoglossal nerve tract (*Alexander* 1946). Its action was supposed to be mediated by an inhibitory action on the "pressor" area (see above), and in consequence baroreceptor control of sympathetic activity was mediated by this medullary reciprocal network. In fact data have accumulated showing that it is very unlikely that the medial reticular formation and the midline raphe system are involved in baroreceptor reflexes. Lesions of this area have been shown to leave baroreceptor reflexes unaffected (see Sect. 2.2.3.3). There is, however, little doubt that the medial regions of the medulla, i.e. the classical "depressor" area, can evoke profound changes in the discharge of sympathetic neurones (*Gootman* and *Cohen* 1971; *Taylor* and *Gebber* 1973; *Gebber* et al. 1973; *Kirchner* et al. 1975a, b; *Gebber* 1976; *Gebber* and *McCall* 1976) and can exert a tonic control of somato-sympathetic reflexes (*Coote* and *Sato* 1978, and others).

In this section an attempt will be made to evaluate the role of this area in the control of sympathetic activity and to establish whether other areas of the medulla can exert a significant inhibitory control of sympathetic activity. The role of these areas in mediating baroreceptor reflexes will also be discussed.

The Nucleus of the Tractus Solitarius. The connections of the NTS with the spinal cord were described in Sect. 2.2.1. It seems that there may be pathways independent of the bulbospinal respiratory pathway, descending

from the NTS to the spinal cord and which may have a role in baroreceptor-mediated inhibition (*Hildebrandt* 1974; *Lipski* and *Trzebski* 1975; *McCall* et al. 1977).

In this context *Lipski* and *Trzebski* (1975) have shown that some baroreceptor-sensitive neurones in the vicinity of the NTS can be activated antidromically on stimulating within the cervical spinal cord. This pathway conducted at 29 ± 5.2 m/s, but as it was activated by stimulation at C4 no details of its termination, and in particular of its relevance to sympathetic control, were obtained. *McCall* et al. (1977) have provided evidence for a pathway from the NTS to the intermediomedial zone of the spinal grey, the pathway having a conduction velocity of 15 ± 2 m/s. They have illustrated that the firing patterns of neurones in the two areas have similar post-R-peaks and are similarly excited by electrical stimulation of sympathetic afferent fibres in the inferior cardiac nerve. These intermediomedial neurones have been considered as candidates for a role as spinal inhibitory interneurone in the baroreceptor reflex pathway (see McCall et al. 1977).

Paramedian Reticular Nucleus; Ventromedial Medulla. There is considerable evidence that stimulating in the vicinity of the NPR and ventromedial medulla produces an inhibition of sympathetic activity (*Coote* and *Downman* 1969; *Gootman* and *Cohen* 1971; *Gebber* et al. 1973; *Taylor* and *Gebber* 1973; *Coote* and *Macleod* 1974b, 1975; *Henry* and *Calaresu* 1974d; *Kirchner* et al. 1975a, b; *Gebber* 1976). In many studies the latency of the evoked inhibition has been shown to be brief, in fact of an order of magnitude less than the central delay of the baroreceptor reflex (see *Coote* and *Downman* 1969; *Gootman* and *Cohen* 1971; *Coote* and *Macleod* 1974b, 1975; *Henry* and *Calaresu* 1974a; *Gebber* and *McCall* 1976). It would appear that the descending pathway from this region passes in the ventral funiculus of the spinal cord (*Henry* and *Calaresu* 1974b; *Coote* and *Macleod* 1975), and that this must be sectioned to permit the increase in the spinal component of somato-sympathetic reflexes, especially in the case of those into the cardiac sympathetic nerves (*Coote* and *Sato* 1978). In other words, it would appear to mediate a tonic inhibition of the spinal component of somato-sympathetic reflexes.

It would seem that this pathway conducts at a fairly rapid rate (ca. 12.0 m/s – see *Gebber* and *McCall* 1976) and the short latency would make its involvement in the baroreceptor reflex, where the central delay is so long, unlikely (see Sect. 3.3). To this must be added the fact that lesions, which may be extensive, in this area of the medulla (see *Löfving* 1961; *Hilton* and *Spyer* 1971; *Barman* and *Gebber* 1978a, and others) do not impair baroreceptor function. These observations are particularly significant because in other circumstances Gebber and his colleagues argue that

the inhibition evoked from this area is analogous to baroreceptor-mediated inhibition of sympathetic activity (see *Snyder* and *Gebber* 1973; *Taylor* and *Gebber* 1973, 1975; *Gebber* and *McCall* 1976; *McCall* et al. 1977).

Raphe-Spinal Neurones. The inhibition that may be evoked from the midline, mainly in the n. raphe pallidus, has a long latency (*Scherrer* 1966; *Coote* and *Macleod* 1974a, b, 1975). This long latency is in complete disagreement with the latencies quoted by *Henry* and *Calaresu* (1974a). *Coote* and *Macleod* (1974a) have provided evidence that 5-hydroxytryptamine-(5HT)-containing neurones may make up the sympatho-inhibitory pathway descending from the raphe which passes via the dorsolateral funiculus. Subsequent studies have shown that lesions of this part of the spinal cord abolished the inhibitory effects of stimulating in the raphe on IC9 to T10 WR reflex (*Coote* and *Macleod* 1975), but *Henry* and *Calaresu* (1974b) concluded that the fast-conducting pathway originating from the raphe traversed the ventral funiculus! In view of the many other discrepancies between this latter study and those of all other groups, it is probably advisable to treat this observation with caution. Pharmacological depletion of this pathway using p-chlorophenylalanine or 5-, 6-dihydroxytryptamine affected neither ongoing sympathetic activity nor baroreceptor control of sympathetic discharge (*Coote* et al. 1978).

Ventrolateral Sympatho-Inhibitory Neurones. There is evidence that stimulating within LRN can produce falls of arterial pressure and a reduction in sympathetic efferent activity (*Coote* and *Macleod* 1974a), although there is also evidence of sympatho-excitatory effects from stimulating in this area (*Thomas* et al. 1977). *Coote* and *Macleod* (1974a) have shown that the area producing these inhibitory effects corresponds to the area in which the A1 group of noradrenaline-containing neurones are located (*Dahlström* and *Fuxe* 1965). These bulbospinal neurones are small and have mainly unmyelinated axons, which agrees with the long latency of the sympatho-inhibitory effects produced by stimulating in this area (*Coote* and *Macleod* 1974a, b). From the use of 6-hydroxydopamine lesions (*Coote* and *Macleod* 1977) and surgical transections (*Coote* and *Macleod* 1975, 1977), it appears that these neurones relay in the dorsolateral funiculus, in the area where *Illert* and *Gabriel* (1972) described a sympatho-inhibitory pathway but where there is also evidence for a sympatho-excitatory pathway (see above and Fig. 4). The inhibitory effects of stimulating in the ventrolateral medulla on the spinal component of somato-sympathetic reflexes has been shown to be abolished by both surgical and pharmacological destruction of this pathway (*Coote* and *Macleod* 1974a, b, 1975, 1977). There is now convincing neuroanatomical data, from studies using both the retrograde transport of HRP and the anterograde transport

of labelled amino acids, that axons from the LRN terminate in the intermediolateral cell column (*Martin* et al. 1979).

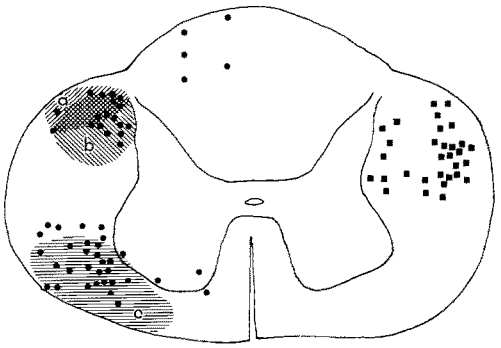

Fig. 4. Diagram of a transverse section of spinal cord (C 3–4) to show distribution of points, obtained in seven experiments, where electrical stimulation caused either an inhibition (●) or an excitation (■) of renal nerve activity. Unanaesthetised decerebrate cats, spinalised at C1. Figure has been modified to illustrate *a* course of bulbospinal noradrenergic neurones descending from LRN; *b* raphe-spinal neurones; *c* descending pathway from the ventromedial medulla. See text for further details. Adapted from *Coote* and *Macleod* (1974a)

The Spinal Course of Inhibitory Pathways. The preceding sections have described the three main medullary areas with bulbospinal inhibitory projections. The anatomical location of these pathways in the spinal cord and their characteristics have been established by several studies (*Illert* and *Seller* 1969; *Illert* and *Gabriel* 1972; *Coote* and *Macleod* 1974a, 1975; *Kirchner* et al. 1975a, b) and are summarised in Fig. 4.

The implication is that pathways from the medulla can act either directly or via spinal interneurones on the preganglionic sympathetic neurones. It is now widely accepted that somato-sympathetic reflexes, which involve a spinal pathway as well as a supraspinal loop (reviewed by *Sato* and *Schmidt* 1973) are under bulbar inhibitory control. For example, recent studies in which the upper cervical cord has been cooled to block descending inhibitory (and for that matter excitatory pathways) have revealed both an increase in the magnitude and shortening of the latency of intercostal to T3 or T4 white rami reflex (*Dembowsky* et al. 1978). Naturally this type of experiment will not reveal which pathway or pathways are involved, but *Coote* and *Sato* (1978) have demonstrated that, with respect to somatic (and visceral) reflexes into cardiac sympathetic nerves, sections of the dorsolateral funiculus are ineffective in releasing the spinal component of the reflex. This would implicate the ventromedial medulla and its efferent pathway through the ventral funiculus in the control of these reflexes (see *Coote* and *Macleod* 1975). It would seem that destruction of

this ventral pathway is ineffective in altering the baroreceptor reflex control of sympathetic activity (*Illert* and *Seller* 1969; *Coote* and *Macleod* 1975). However, there is little doubt that the other two inhibitory systems can equally well affect somato-sympathetic reflexes, but presumably they do not exert a tonic control.

For baroreceptor control of sympathetic activity, previous considerations must lead to a discussion of the role of the dorsolateral funiculus as the pathway for its action. This could result from the interplay of both descending excitatory and inhibitory pathways (see *Illert* and *Seller* 1969; *Foreman* and *Wurster* 1973; *Coote* and *Macleod* 1974b, 1977; *Geis* et al. 1978).

With respect to the involvement of descending inhibitory pathways, the noradrenergic neurones in the LRN (sending axons in the dorsolateral funiculus) are a strong candidate (*Coote* and *Macleod* 1974b, 1977). At present the conclusion must rest on the fact that the spinal component of IC 10 to T9 WR reflex is partially suppressed by the electrical stimulation of the sinus nerve and that this suppression is reduced by lesions in the dorsolateral funiculus (*Coote* and *Macleod* 1974b) or by pharmacological destruction of noradrenergic neurones (*Coote* and *Macleod* 1977).

However, other data have been used to counter, or at least question, this claim. Electrical stimulation of the sinus nerve evokes concurrent activation of both chemoreceptor and baroreceptor afferents, the former evoking an increase in sympathetic activity. Accordingly, the apparent depression could result from a "silent period" following the excitatory effect of chemoreceptor stimulation. *Szulczyk* (1976) has shown that the excitatory effects of sinus nerve and hypoglossal nerve stimulation are blocked by DLF section (cf. *Foreman* and *Wurster* 1973 for the effects of such lesions on the response to bilateral carotid occlusion). To distinguish which interpretation is correct, it would seem there is no option but to use single unit recordings.

In the one case in which single sympathetic units have been studied during stimulation of the dorsolateral funiculus, the results are complicated by the fact that this region contains both excitatory and inhibitory pathways (*Kirchner* et al. 1975a). Stimulation normally evoked an early excitatory response followed by a long-lasting "silent period", although in three cases a pure inhibition was seen. As the recordings were made extracellularly at T2 and several of the neurones were activated by the iontophoretic application of glutamate, it would seem likely that the "silent period" could result from a direct inhibitory action. These authors also showed that the inhibition evoked from this area of the cord was present in chronic spinal animals, as judged from effects on somatic reflexes into white rami at lumbar levels and the renal nerve (*Kirchner* et al. 1975b).The authors consider that this makes a direct monosynaptic inhibitory action

unlikely to be the only mechanism for spinal inhibition but indicates the involvement of propriospinal pathways (see also *Kirchner* et al. 1975a).

In contrast, *Coote* and *Macleod* (1974b, 1977) argue for a direct noradrenergic inhibitory innervation of sympathetic neurones from bulbospinal neurones. This would be a surprising situation as most long-circuited inhibitory effects are mediated by an inhibitory interneurone close to the target neurone. In support of their claim is the fact that the iontophoretic application of noradrenaline to sympathetic preganglionic neurones depresses their activity (*Coote* and *Macleod,* unpublished work), although *Hongo* and *Ryall* (1966) have provided less clear-cut results on the effects of noradrenaline. There is, however, evidence that the α-agonist clonidine, given systemically, reduces the size of spinal reflexes onto sympathetic neurones (*Dembowsky* et al. 1978; *Haeusler* 1977). As yet the iontophoretic studies would seem to be at an early stage, and the use of specific antagonists to NA on the effectiveness of baroreceptor inputs to the preganglionic neurones would be indicated. Certainly, since baroreceptor stimulation can affect the performance of somato-sympathetic reflexes (see refs. above and *Fussey* et al. 1973a), an effect that can be produced by activating any of three inhibitory pathways so far identified, there can be little doubt that at least part of the baroreceptor reflex is mediated by an inhibitory action with the cord.

3.4 Integrative Control of Sympathetic Activity

There are indications that two general processes are involved in baroreceptor control of sympathetic activity. The first process is not at variance with the generally accepted view that the baroreceptors act by inhibiting descending excitatory pathways. Its extension is that it does not limit this action to a control of medullary excitatory pathways but opens the possibility that there may be parallel channels from the hypothalamus and midbrain which may pass without synaptic connections in the medulla. The second process is the possibility that active inhibition occurs at the level of the spinal cord. From the various studies referred to in the previous sections, a general conclusion can be made that there are pathways, of unknown synaptic complexity, which descend through the spinal cord and can exert a powerful inhibitory control of sympathetic activity. As yet there is no conclusive evidence that the baroreceptor influence is mediated by such a system, although the ability of the baroreceptor input to suppress both medullary and spinally evoked sympatho-excitatory responses is striking. It is probably not too naive to argue that the baroreceptors which have been known to exert such a powerful control of vasoconstric-

tor and cardio-accelerator "tone" through the sympathetic nervous system are likely to utilise both systems.

Accepting then the premise that baroreceptor control of sympathetic activity may be exerted by both disfacilitation (i.e. control of descending excitatory inputs) and active inhibition within the spinal cord, is it possible to speculate usefully on the connections, at least those acting within the cord, that integrate such a control? It is probably justified for a review to pose such a question, and to conclude this section, two simple models will be proposed as a challenge for subsequent experimental work (see Fig. 5).

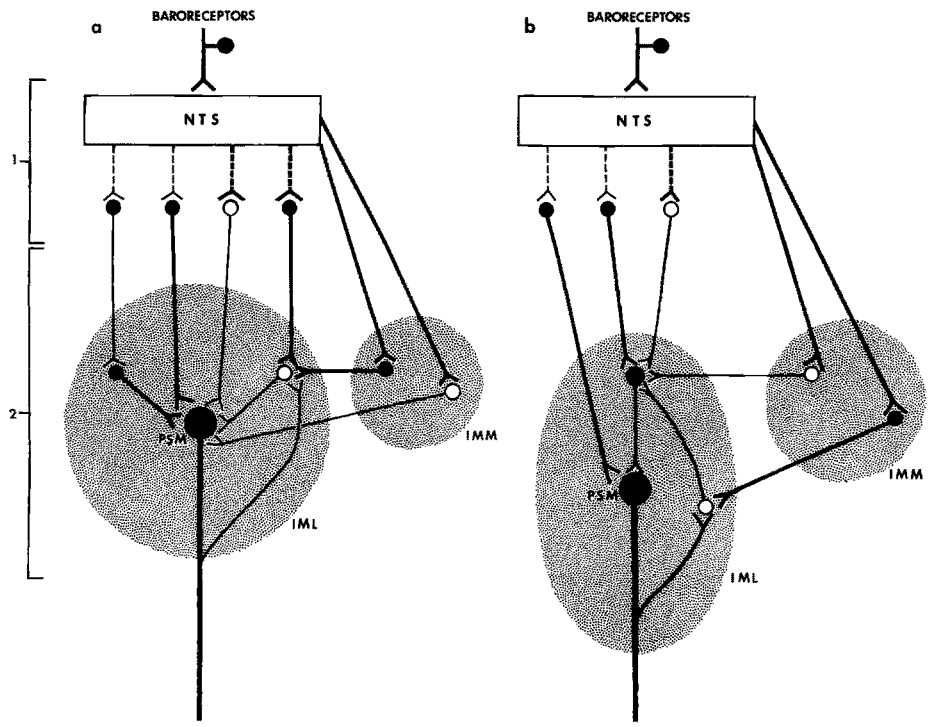

Fig. 5a, b. Diagrams of the relationship of bulbospinal spinal pathways in the mediation of the baroreceptor reflex. ● neurones exerting an excitatory function; ○ neurones exerting an inhibitory function. *1* medulla; *2* spinal cord; *NTS* nucleus of the tractus solitarius. *PSM* preganglionic sympathetic motoneurone; *IML* intermediolateral cell column; *IMM* intermediomedial cell column. In **a** the site of convergence is at the level of the PSM, in **b** an excitatory interneurone forms an important site of integration. *Dotted lines* refer to pathways of unknown synaptic complexity. Further details in the text

In considering baroreceptor regulation of sympathetic activity we are really only questioning the integrative role of these preganglionic neurones (Fig. 5a). In this model, their output is determined by the interplay of in-

hibitory and excitatory inputs at the cell body (and presumably its dendrites) of the sympathetic neurone. This does not preclude interactions further back in multisynaptic pathways onto them, but draws an analogy to the situation in the somatic system. Unfortunately there is insufficient data, as yet, to give credence to the presence of excitatory or inhibitory interneurones in the intermediolateral column that impinge on sympathetic preganglionic neurones. The evidence in favour of an excitatory interneurone is the stronger and received indirect support from a study using intracellular recordings from sympathetic neurones (*Coote* and *Westbury* 1974, 1979b). In the latter study the membrane potential was marked by random EPSPs of relatively small amplitude and short duration, with no evidence of large slow potential changes. This observation may be taken as evidence for the fact that their control is exerted by an excitatory interneurone alone (Fig. 5b). In this situation, inhibitory control, either baroreceptor or recurrent, could be exerted by convergence onto this interneurone.

In both models, it is possible to envisage that some descending excitatory control is exerted directly on the preganglionic neurone, in view of the baroreceptor-insensitive excitatory effects that may be elicited from the brainstem (see Sect. 3.3.3.2). It is, however, unlikely that these inputs are totally baroreceptor-insensitive; their apparent insensitivity probably represents only a more synaptically secure input than other descending excitatory systems. Accordingly, its failure to excite sympathetic activity at heightened levels of baroreceptor stimulation would result from the reduced excitatory input, i.e. disfacilation, (see Fig. 5b) or from the power of the induced inhibitory control of sympathetic activity (Fig. 5a).

To complete an already complex arrangement, the neurones of the intermediomedial nucleus may also function as interneurones in the baroreceptor reflex (*McCall* et al. 1977). It is very simple to accommodate their action in either of the schemes presented in Fig. 5. It may be that a combination of these two models will present the most adequate approximation to reality; detailed experimental studies using conventional neurophysiological and neuroanatomical techniques can be expected to resolve this question in due course.

3.5 Vagal Control of the Heart

Nervous control of the heart is mediated by the reciprocal discharges of its sympathetic (see above) and vagal innervations. The role of the vagus in exerting a negative chronotropic influence is so well documented that citation is superfluous. In the context of the present review its significance rests on the abundant demonstration that the baroreceptor control of the heart is mediated primarily by the vagal outflow (see *Heymans* and *Neil*

1958; *Schaeffer* 1960; *Kirchheim* 1976; *Levy* 1977). This basic control mechanism appears to function relatively normally in the decerebrate animal, but until the present the basic circuitry linking the baroreceptor afferent input to the vagal outflow, i.e. the preganglionic vagal neurones, remained in doubt (for discussion see *McAllen* and *Spyer* 1978; *Spyer* 1979). This uncertainty resulted from the fact that although the vagus had been known for at least the last hundred years to have two motor nuclei in the medulla of mammals, controversy had remained concerning which contains the cell bodies of the preganglionic innervation of the heart (*Mitchell* and *Warwick* 1955; *McAllen* and *Syper* 1976, 1978a; *Spyer* 1979). Accordingly, most data relating to vagal control has been obtained from the effects of the baroreceptors on heart rate or the activity of preganglionic vagal fibres in the cervical vagus or cardiac branches of the thoracic vagus.

The studies referred to above have been reviewed extensively (*Heymans* and *Neil* 1958; *Kirchheim* 1976; *Levy* 1977), and it is unnecessary to reiterate in detail that in animals with heart rates less than 180 beats/min the vagal innervation exerts a beat-by-beat control of cardiac function (*Levy* 1977). However, since neuroeffector delays are long, in the region of 0.3 ms (*Warner* and *Cox* 1962), this type of study will provide little of value regarding the central integrative responses underlying the observed changes. It is for this reason that the subsequent discussion will concern the activity and control of preganglionic vagal neurones, firstly with respect to fibre recordings and finally with a discussion of recent studies relating to recordings from the cell bodies of these neurones.

3.6 Preganglionic Vagal Cardiomotor Neurones

Preganglionic vagal fibres with presumed cardio-inhibitory function have been described as having distinctive firing patterns. They have a variable pulse rhythm, which can be seen as a burst of discharge synchronous with each cardiac cycle, or revealed by constructing histograms of their pulse-triggered or post-R wave-triggered activity (*Magruth* et al. 1951; *Green* 1959; *Schaeffer* 1960; *Okada* et al. 1961a, b; *Weidinger* et al. 1962; *Jewett* 1964; *Katona* et al. 1970, 1977; *Kunze* 1972). This cardiac rhythm of baroreceptor origin is usually superimposed on a respiratory-related rhythm; they normally fire in phase with expiration (*Rijlant* 1936a, b; *Weidinger* et al. 1962; *Iriuchijima* and *Kumada* 1963, 1964; *Jewett* 1964; *Katona* et al. 1970, 1977; *Neil* and *Palmer* 1975; *Davidson* et al. 1976). Their overall discharge frequency is low: in the cat vagal "tone" is especially low (see *Kunze* 1972; *McAllen* and *Spyer* 1976, 1978a), whilst in the dog spontaneous activity is more conspicuous. Even so, the overall characteristics of discharge have similarities, and it is rare for vagal efferent

fibres to the heart to fire at greater than 20 impulses/s (*Iriuchijima* and *Kumada* 1963, 1964; *Jewett* 1964; *Katona* et al. 1970, 1977; *Kunze* 1972). However, with arterial pressure elevated to around 200 mmHg, activity may reach 30–40 Hz (see *Jewett* 1964; *Katona* et al. 1970, 1977; *Kunze* 1972), although *Okada* et al. (1961b) claim recording discharges with up to 26 impulses/s per cardiac cycle, at a mean frequency of 120 Hz, in the cardiac branches of the cat.

It is pertinent at this point to question the number of cardiac efferent fibres present in the cervical vagus. It is likely that a very few can have a marked effect on heart rate (*McAllen* and *Spyer* 1976, 1978a), and it is known that in the cat there are only some 500 B fibres in the cervical vagus which appear to pass to the thoracic vagus or its various branches (*Agostini* et al. 1957). It is established beyond reasonable doubt that, in mammals, cardio-inhibitory neurones have B fibre axons (*Heinbecker* 1930; *Heinbecker* and *O'Leary* 1933; *Brown* and *Eccles* 1934a, b; *Grundfest* 1939; *Middleton* et al. 1950). This has been shown by graded electrical stimulation of the cervical vagus, recording the evoked volley and noting the efferent effects on the heart (see also *McAllen* and *Spyer* 1978a). There are, however, equally strong indications that among the population of B fibres so activated are those destined for the lungs, which have a bronchoconstrictor function (*Widdicombe* 1961, 1966; *Jewett* 1964) and the oesophagus (*Jewett* 1964), so that the total number of cardiac efferents is likely to be very much smaller.

Attempts have been made to assess the complexity of connections between the arterial baroreceptors and these vagal efferent fibres by studying either the nature of their response to electrical stimulation of the sinus nerve (*Iriuchijima* and *Kumada* 1963, 1964; *Kunze* 1972) or the properties of their cardiac rhythm (*Jewett* 1964; *Katona* et al. 1970, 1977; *Kunze* 1972). Both these approaches and the data accrued will be discussed later, but as in both cases efferent conduction time is unknown and in the latter afferent conduction time is also unknown, the reflex times obtained can give little indication of the central delay of the reflex and hence of its neuronal complexity. For this purpose it is necessary to have the possibility of recording from the cell bodies of preganglionic vagal neurones.

3.6.1 Location of Preganglionic Vagal Neurones

3.6.1.1 Anatomical Studies

The existence of two vagal nuclei in the medulla of mammals has been appreciated for at least a hundred years. There had at first been controversy whether one was sensory and the other motor but by the early part of this century it was agreed that both the dorsal (DNV, dorsal motor nucleus of the vagus) and the ventral (NA, n. ambiguus) had motor functions (see

Mitchell and *Warwick* 1955 for discussion). By the same token, it became accepted that the DNV was a visceral-motor nucleus, the NA having a somatomotor function (*Mitchell* and *Warwick* 1955). For this reason, the consensus was that the DNV contained the cardio-inhibitory vagal neurones (*Mitchell* and *Warwick* 1955, and most current textbooks of neuroanatomy), although dissenting voices have remained (*Kosaka* 1909; *Szentagothai* 1952).

The major evidence for the DNV as the location for these vagal cell bodies was from studies observing the chromalytic changes produced in the vagal nuclei following section of the vagus and its peripheral branches (*Mitchell* and *Warwick* 1955; *Smolen* and *Truex* 1977 for review). The alternative technique of observing peripheral changes after central destruction has provided contrasting results. *Szentagothai* (1952) showed that lesions within the NA of the cat were followed by signs of Wallerian degeneration in the vagal cardiac branches; similar discrete lesions in the DNV were ineffective in producing such changes (see also *Kosaka* 1909; *Kerr* 1967, 1969). The implication is that the cell bodies of cardio-inhibitory neurones are located in the NA. These results are unfortunately not without certain limitations, as the technique of central destruction will destroy fibres *en passant* as well as cell bodies, and it is known that efferent axons from the DNV pass close to the NA, whilst the axons of the NA may pass dorsomedially towards the DNV (*Cajal* 1909).

There are as yet few studies on the transport of HRP from the vagal cardiac branches to the medulla (*Bennett* et al. to be published; *Garcia* et al. to be published; *Nosaka* et al. 1979), but several studies have shown the retrograde transport of HRP from the cervical vagus to both vagal nuclei in the medulla (*Devito* et al. 1974; *Miller* 1976; *Robertson* et al. 1976; *Geis* and *Wurster* 1978). In general, labelling is more apparent in the DNV than the NA by factor of at least ten (*Miller* 1976; *Robertson* et al. 1976). In one study, medullary labelling has been observed after placing HRP on the sinoatrial and atrioventricular nodes of the heart in the cat (*Todo* et al. 1977) on the basis that this would label preganglionic vagal neurones. Unfortunately this is not without serious inherent problems: HRP is readily transported in the blood and would be expected to enter the central system whenever the blood-brain barrier is ineffective. It is hence not surprising that labelling was seen in the vicinity of the NTS and DNV close to the area postrema, particularly as no evidence was provided that the material was intracellular.

In a similar study, *Geis* and *Wurster* (1978) have shown that epicardially placed HRP is transported to the brainstem. The majority of labelled neurones (78%) were seen in the NA, just 5% in the DNV and the rest in between these nuclei. Similarly, *Bennett* et al. (to be published) achieved equivalent neuronal labelling from identified cardiac branches in both NA

and DNV, whilst *Garcia* et al. (to be published) noted that labelling from cardiac branches was mostly restricted to the NA, although pulmonary branch axons appeared to originate from neurones in both NA and DNV. *Nosaka* et al. (1979) have identified labelled neurones in both the DNV and NA of the rat, after embedding cardiac vagal branches in HRP, and also in the region between these two nuclei. Since it is apparent that cardiac branches are often contaminated with fibres destined for the lungs, it is impossible to conclude very much from these studies in the absence of physiological data. The labelling in the DNV from cardiac branches might represent the efferents with unmyelinated axons described by *McAllen* and *Spyer* (1976) and demonstrated to be profuse by *Bennett* et al. (to be published).

3.6.1.2 Destructive Lesions in the Medulla: Cardiac Effects

The effects of electrolytic lesions in the medulla on vagally mediated bradycardia were summarised earlier (Sect. 2.2.3.3). Broadly, destruction of the DNV is ineffective in abrogating such effects (*Kerr* 1967, 1969; *Borison* and *Domjan* 1970), whilst lesions in the NA were effective in the cat (see *Lee* et al. 1972).

3.6.1.3 Neurophysiological Studies

Electrical Stimulation. Physiological studies concerning the site of origin of preganglionic vagal neurones supplying the heart, based on electrical stimulation of the medulla, have favoured either or both vagal nuclei (*Miller* and *Bowman* 1915; *Chiurugi* and *Mollica* 1954; *Calaresu* and *Pearce* 1965b; *Gunn* et al. 1968; *Thomas* and *Calaresu* 1974a; *Chen* and *Chai* 1976; *Dugin* et al. 1976). It is worth recalling that the efferent axons from each nucleus may pass in close proximity to the other nucleus (*Cajal* 1909) and hence may account for at least part of the confusion. Equally, current spread from the point of stimulation may account for at least some of the observed changes. This is particularly so in the case of the DNV, which is located close to the NTS, where baroreceptor afferents terminate. Accordingly, bradycardia mediated by vagal fibres can result from stimulating any part of the baroreceptor reflex pathway. Stimulation elsewhere in the CNS may well evoke a bradycardia by a similar process.

There may well be a species difference in the location of these vagal cardio-inhibitory neurones, which may also account for some of the differences in the literature. In the cat, vagal bradycardia can be obtained by stimulating the NA (*Gunn* et al. 1968; *Thomas* and *Calaresu* 1974a; *Chen* and *Chai* 1976) but not the DNV (*Calaresu* and *Pearce* 1965b; *Gunn* et al. 1968). In the dog, *Gunn* et al. (1968) report eliciting vagal bradycardia from both sites. In contrast there are claims that vagal bradycardia can be evoked from stimulating the DNV in the cat (*Miller* and *Bowman*

1915; *Chiurigi* and *Mollica* 1954; *Dugin* et al. 1976). It is worth noting that the bradycardia elicited from the NA is abolished by ipsilateral vagotomoy in the cat whilst that evoked from the NTS and DNV is only partially reduced by ipsilateral vagotomy (*Thomas* and *Calaresu* 1974a).

Recording Experiments. Calaresu and *Pearce* (1965a) were unable to record activity correlated with the cardiac cycle in the DNV of the cat. This was perhaps not unexpected in view of the data from stimulating and lesion studies (see above). In conclusion, in the cat it appears likely that the NA would contain vagal cardio-inhibitory neurones. This has been confirmed directly in recent studies (*McAllen* and *Spyer* 1975, 1976, 1977, 1978a, b). In the cat, they have been shown that there are neurones in the NA which can be antidromically activated by stimulating cardiac branches at intensities which evoke cardiac slowing (*McAllen* and *Spyer* 1976, 1978a) and that these neurones have axons which are in the range of B fibres on the basis of calculated conduction velocity. In the same study similar neurones were not found in the DNV; furthermore, on studying a large number of neurones in the DNV relaying to the cervical vagus, none with B fibres was found to relay into the cardiac branches (*McAllen* and *Spyer* 1976; Fig. 6). Three neurones with axons in the C fibre range were,

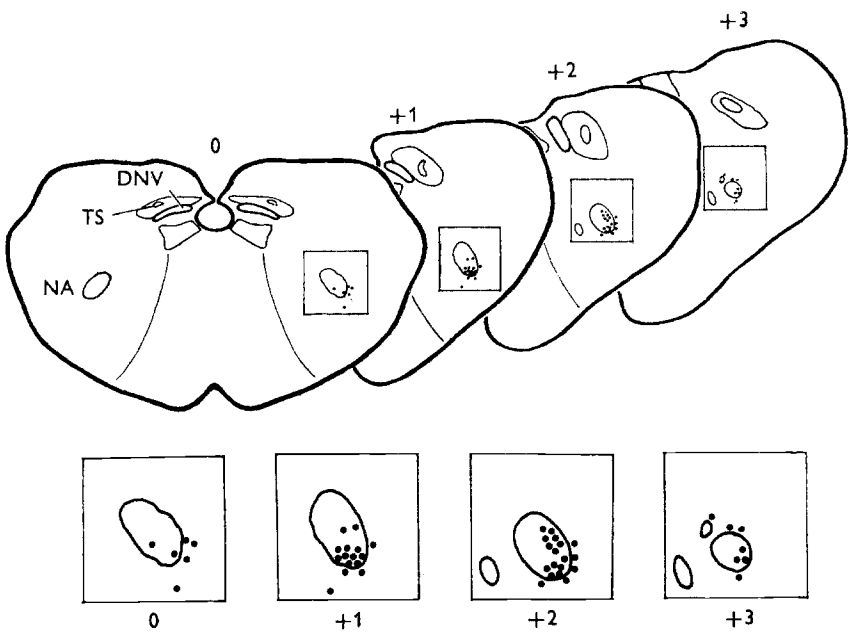

Fig. 6. The positions of 46 cardiac efferent neurones are shown on four standard sections of the medulla taken at obex level, and at 1-mm intervals rostrally. Inserts, 2 mm square, show details of their relation to the structure of the nucleus ambiguus. *TS* tractus solitarius; *DNV* dorsal motor nucleus of the vagus; *NA* nucleus ambiguus. *McAllen* and *Spyer* (1976)

however, seen to relay to the cardiac branches, which could explain certain of the observations of *Todo* et al. (1977), *Geis* and *Wurster* (1978) and *Bennett* et al. (to be published).

This demonstration that vagal neurones with B fibre axons originate in the NA does not on its own prove a cardio-inhibitory function. Among the B fibres in the thoracic vagus are bronchoconstrictor vagal neurones (*Widdicombe* 1961, 1966; *Jewett* 1964) and oesophageal-motor vagal neurones (*Jewett* 1964). Physiological studies have added still further support to the original suggestion (*McAllen* and *Spyer* 1977, 1978a, b). These have involved analysing the firing patterns of identified cardiac-branch-projecting neurones, firing patterns from both spontaneously active neurones, and those induced to fire by the iontophoretic application of DL-homocysteic acid (DLH) or glutamate. A major group of neurones with an expiratory firing pattern (the majority were usually silent until the expulsion of excitant amino acid) have been observed and were shown to have a cardiac rhythm of baroreceptor origin in their discharge (*McAllen* and *Spyer* 1978a, b). These neurones, when activated by amino acid, were capable of slowing the heart (*McAllen* and *Spyer* 1977, 1978a), which confirms the impression that they represent cardiac vagal motoneurones.

A second group of neurones with B fibre axons were also identified as projecting to either cardiac branches or lung branches of the thoracic vagus. These neurones were usually spontaneously active, discharging with an inspiratory rhythm. They were not excited by the arterial baroreceptors (*McAllen* and *Spyer* 1978a) but were excited by laryngeal stimulation and would seem equivalent to the vagal efferent fibres described by *Widdicombe* (1961, 1966) as bronchoconstrictor in function. There was also a degree of spatial separation of the two classes of vagal preganglionic neurone within the NA (see Fig. 7). The bronchoconstrictor neurones tended to be more rostrally and dorsally placed in the nucleus, extending into the n. retrofacialis.

As suggested previously there may be species differences regarding the location of cardiac vagal motoneurones. In the pigeon it is clear from neurophysiological studies that they are located in the DNV (*Schwaber* and *Cohen* 1978a, b), but it is generally considered that this species has a single vagal motor nucleus, the DNV. In the dog there is evidence that the NA contains cardiac vagal motoneurones, i.e. neurones activated antidromically from cardiac branches of the right vagus (*McAllen* and *Spyer* unpublished work), but no data exists regarding the DNV. In the rabbit, however, there is evidence in favour of their localisation in the DNV. *Schwaber* and *Schneiderman* (1975) and *Kaufman* et al. (1979) have described in the DNV of the rabbit neurones whose axons projected in the cervical vagus and which were, on the basis of conduction velocity, B fibres. These they considered to be cardio-inhibitory: their spontaneous

and evoked discharge varied inversely, but proportionally, with heart rate and they were located in the area of the DNV which elicited a low-threshold bradycardia on electrical stimulation. Moreover, the discharge of these neurones evoked by the iontophoresis of DLH elicited a bradycardia (*Jordan* et al. 1979). In a recent study, *Jordan* et al. (1979) have described a population of vagal neurones with B-fibre axons which are located in both DNV and NA. These neurones have been shown to have identical properties to CVMs described in the cat (see above).

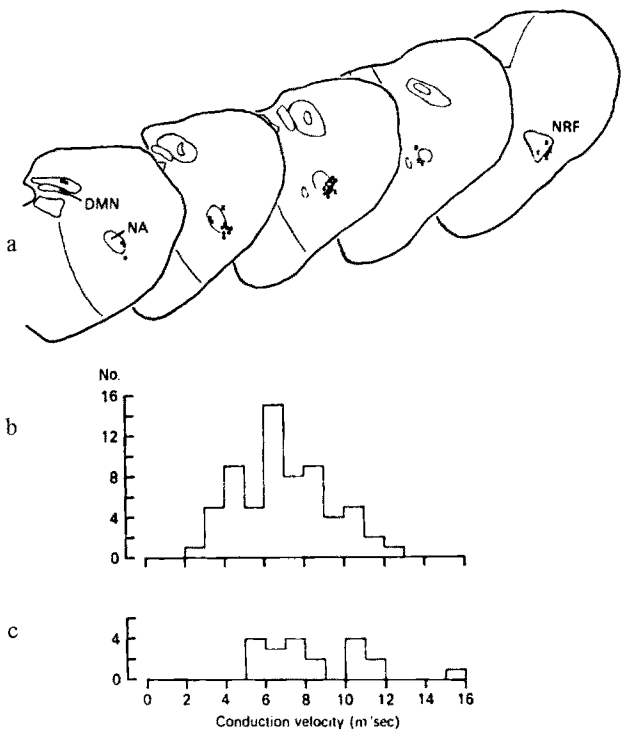

Fig. 7. a The position of 21 CVMs (•) and nine BVMs (X) on five standard sections of the medulla taken at obex level, 1, 2, 3 and 4 mm rostral to the obex. *DMN* dorsal motor nucleus of the vagus; *NA* nucleus ambiguus; *NRF* nucleus retrofascialis. **b** and **c** show histograms of the conduction velocities of cardiac and bronchomotor units, respectively. *McAllen* and *Spyer* (1978a)

3.6.2 Baroreceptor Input to Preganglionic Vagal Neurones

The influence of the arterial baroreceptors on vagal preganglionic neurones is well documented (*Marguth* et al. 1951; *Green* 1959; *Schaeffer* 1960; *Okada* et al. 1961a, b; *Weidinger* et al. 1962; *Jewett* 1962, 1964; *Iriuchijima* and *Kumada* 1963, 1964; *Katona* et al. 1970, 1977; *Davidson*

et al. 1976), but there is considerably less quantitative data available on this subject. Furthermore, even the quantitative information available is in a form which does not allow any conclusions to be drawn regarding the central mechanisms and pathways linking the baroreceptor afferent input to these neurones.

In the main, studies have fallen into two categories. Firstly, the effects of electrical stimulation of the SN on vagal efferent fibres located in the cervical vagus (*Iriuchijima* and *Kumada* 1964) and vagal cardiac branches (*Iriuchijima* and *Kumada* 1963; *Kunze* 1972) have been observed. Secondly, attempts have been made to analyse the pulse-related discharge of similar vagal efferent fibres (*Jewett* 1962, 1964; *Weidinger* et al. 1962; *Katona* et al. 1970, 1977; *Kunze* 1972).

In the cat, *Kunze* (1972) has shown that stimulation of the SN excites efferent fibres in the vagal cardiac branches with a latency in the range of 26–90 ms, and their probability of discharge was maximal at 70–400 ms, in different units, after the rise in systolic pressure. With increases in arterial pressure the discharge of neurones rose to a peak instantaneous frequency of up to 40 Hz. In similar experiments in the dog, *Iriuchijima* and *Kumada* (1963) report a latency of 60–100 ms for evoked responses in cardiac branch fibres and 50–100 ms for fibres in the cervical vagus (*Iriuchijima* and *Kumada* 1964) on stimulating the SN. They also noted that the stimulus was most effective during expiration, responses rarely being observed from stimuli occurring during inspiration (*Iriuchijima* and *Kumada* 1964; for discussion see Sect. 4.3).

There is general agreement that the pulse-related discharge of vagal efferent fibres in the cervical vagus occurs some 50–250 ms after the systolic rise in aortic pressure (*Jewett* 1964; *Katona* et al. 1970). *Jewett* (1964) showed that the first peak in histograms of post-R-wave-triggered vagal activity occurred some 60–240 ms after the systolic rise in pressure, a second peak related to the dichrotic notch following some 180–300 ms after the first peak. *Katona* et al. (1970) describe the first peak at 50–40 ms (mostly around 80 ms), the second 80–200 ms after the dichrotic rise in pressure. This contrasts with observations of *Weidinger* et al. (1962), in the cat, which suggest that the peak in vagal activity follows 45–55 ms after the R wave of the ECG. Since the aortic pressure starts to rise some 60 ms after the R wave of the ECG (see *Jewett* 1964; *Katona* et al. 1970), it is unlikely that the cardiac rhythm of these multifibre preparations can result from inputs generated from the arterial baroreceptors, except in the case where the peak is related to the preceding arterial pulse, which might be possible at rapid heart rates.

In order to overcome the problems in interpreting the above data in terms of the reflex time of the baroreceptor-vagal reflex, *McAllen* and *Spyer* (1978b) have made accurate timings of the probability of discharge

of CVMs, in relation to the arterial pulse. These were recorded in the NA of the cat, the afferent barrage from the carotid sinus also being monitored. In a proportion of their preparations the aortic baroreceptors had been denervated, and as the cardiac rhythm of CVMs was then obliterated by bilateral carotid occlusion, it was possible to conclude that this rhythm depended on an input from sinus baroreceptors alone. The pulse-related peak followed the increase in SN activity by from 20–110 ms in individual neurones (*McAllen* and *Spyer* 1978b, see Fig. 8). In a proportion of these

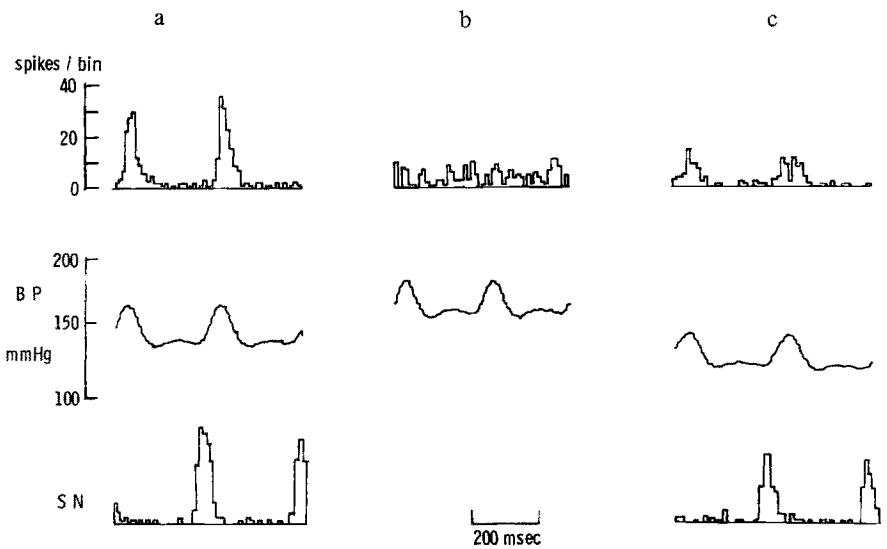

Fig. 8a–c. The cardiac rhythm of a CVM (aortic baroreceptors denervated). Pulse-triggered histograms (256 cycles superimposed, 10 ms bin width) of CVM activity *(upper trace)* and sinus nerve activity *(lower trace)*. Femoral pulse wave form was averaged simultaneously with the same bin width *(middle trace)*. **a** Before, **b** during and **c** after bilateral carotid occlusion. The unit was firing in response to 17 nA DLH. *McAllen* and *Spyer* (1978b)

neurones the effect of SN stimulation was also tested. Invariably the latency of the response was significantly shorter than that measured for natural baroreceptor stimulation (*McAllen* and *Spyer* 1978b; *Spyer* 1979). With the reservation that these values of reflex time are not an accurate measure of central delay (see *Spyer* 1979 for discussion), they do provide an indication of the complexity of connection in the reflex pathway. The reflex time at physiological levels of blood pressure is surprisingly long, considering that these values eliminate efferent conduction (see Fig. 8). This makes it unlikely that the baroreceptor-vagal reflex involves a simple fast-conducting disynaptic pathway (*McAllen* and *Spyer* 1978b; *Spyer* 1979). Baroreceptor afferents are known to terminate in the NTS (Sect.

2.1 and 2.2), and the NTS projects to the NA (Sect. 2.2), but the complexity of connections within both the NTS and NA remains unresolved (*Spyer* 1975, 1979; *McAllen* et al. 1979) so it is not as yet possible to eliminate a role for supramedullary connections in the normal reflex pathway.

3.6.3 Supramedullary Inputs to Preganglionic Vagal Neurones

The previous sections have outlined the putative ascending projections in the baroreceptor reflex pathway and have indicated a role for suprabulbar and diencephalic areas in the reflex. Some of the pathway between the baroreceptor input and CVMs has been indicated above, and it is sufficient at this point to emphasise that there is both anatomical and physiological evidence for hypothalamic pathways descending to areas of the medulla known to contain preganglionic vagal neurones. From the use of retrograde transport HRP and the anterograde transport of tritiated amino acids, *Saper* et al. (1976) described pathways emanating from the hypothalamus and ending in the NA, NTS, and close to the DNV. *Swanson* (1977) has further demonstrated that descending fibres from the paraventricular nucleus of the hypothalamus containing the carrier protein neurophysin project to or through the NA, DNV, NTS, and lateral tegmental field at the nucleus intermedius. The role of these connections remains to be resolved, and the physiological data relating to suprabulbar control of vagal activity will be considered in subsequent sections (see also Fig. 13, p. 100).

4 Modulation of the Baroreceptor Reflex

The previous sections have detailed the current position concerning the central pathways involved in mediating the baroreceptor control of sympathetic and vagal efferent activity. The details are, however, as yet incomplete. A further set of experimental studies have provided information on both the organisation and control of the baroreceptor reflex. These have involved studies on the interaction between the different baroreceptor afferent inputs, between baroreceptors and other peripheral afferent inputs, and finally the influence of stimulation within the brainstem and cerebellum on the efficacy of the baroreceptor reflex. These approaches are diverse, yet the observations have revealed some physiological phenomena that may indicate common synaptic processes in the integration of these various inputs.

4.1 Interactions Between Carotid Sinus and Aortic Arch Baroreceptor Inputs

From numerous reports it has been accepted that there is a broad degree of similarity in the receptor properties of the baroreceptors of the carotid sinus and aortic arch (reviewed by *Kirchheim* 1976), although there may be differences in their dynamic sensitivity (see *Landgren* 1952; *Angell-James* 1971a,b), and it has been suggested that they may act over different ranges of pressure (*Pelletier* et al. 1972; *Shepherd* 1973). Since this latter suggestion depended on observations of whole nerve activity, its applicability to the normal in vivo situation is questioned; *Samodelov* et al. (1979) consider that the working ranges and sensitivities of individual receptors from the two areas are in fact similar, at least in the cat.

There is, however, good evidence that the quantitative effects of the two groups of baroreceptors on vasomotor activity and the heart may be different. *Angell-James* and *Daly* (1970) have shown that at static pressures within the physiological range, vascular resistance is reduced to a greater extent by a change in sinus pressure than an equivalent change in pressure in the aortic arch. Such differences were not seen during perfusion with pulsatile pressures. These quantitative differences may reflect either differences in the distensibility properties of the two areas or a central phenomenon (*Angell-James* and *Daly* 1970). The latter could be due to afferent density or differential effects on central neurones, or both. These authors also demonstrated that simultaneous stimulation of the aortic arch and carotid sinus baroreceptors evoked responses of greater magnitude than stimulating either alone, although the apparent summation resulted in an effect that was less than the algebraic sum of the individual effects. This type of summation has been demonstrated by others (*Stegemann* and *Müller-Büton* 1966; *Kotter* et al. 1970; *Warzel* and *Brattström* 1972; *Katona* and *Tan* 1975).

Such interactions in the control of vascular resistance imply a form of central summation, but *Wang* and *Borison* (1947b) argue for an occlusive interaction between baroreceptor inputs from the two carotid sinuses, although they readily demonstrated facilitation in the baroreceptor-cardiac reflexes mediated by the vagal efferents. Such a facilitation of vagally mediated cardiac effects appears not uncommon, representing either an intrinsic property or extrinsic control of the vagal preganglionic neuronal pool.

In an earlier section (2.2) the termination of AN and SN afferents in the medulla was described, and mention was made of attempts to identify the convergence of these inputs onto second-order neurones in the NTS. Suggestions for convergence have resulted from monitoring evoked potentials concurrently at the same site on stimulating the AN and the SN

(*Hellner* and *Baumgarten* 1961; *Biscoe* and *Sampson* 1970a; *Gabriel* and *Seller* 1970), but single unit studies have as yet failed to demonstrate convergence at this level of the brainstem (*McAllen* 1973). It is, however, often observed on medullary neurones located beyond the confines of the NTS (*Biscoe* and *Sampson* 1970b; *McAllen* 1973), which presumably represent later stages in the reflex pathway.

Direct studies on the interactions of SN and AN inputs are few (*Biscoe* and *Sampson* 1970b; *Gabriel* and *Seller* 1970; *McAllen* 1973; *Jordan* 1977; *Jordan* and *Spyer* 1978b), and all are complicated by the fact that electrical stimulation of SN evokes a concomitant activation of chemoreceptor afferents (as also occurs with AN stimulation in the cat). *Gabriel* and *Seller* (1970) have shown that the evoked response to electrical stimulation of the SN recorded in the NTS is modified by a conditioning stimulus to the AN, and vice versa. Equally, the response to one input can be modified by a conditioning stimulus to the same nerve, the response to SN stimulation at 10 Hz being only 50% of that observed at 1 Hz (*Seller* and *Illert* 1969; *Gabriel* and *Seller* 1970). Similarly, contralateral inputs from SN and AN can modify the responses to ipsilateral inputs (*Gabriel* and *Seller* 1970). It may be that the first synapse represents a frequency-limiting step in the reflex pathway, since the cardiovascular responses to SN stimulation are maximal at 20–30 Hz, while those from stimulating the NTS are maximal at 120 Hz (*Seller* and *Illert* 1969). These apparently occlusive interactions provide an explanation for the observations of *Wang* and *Borison* (1947a, b) on the vascular component of the baroreceptor reflex, but are clearly at variance with the simultaneous observations of summation (or facilitation) in the cardiac arm of the reflex. These studies may thus indicate an early decussation of the reflex, which was also implied by the observation of *Lipski* et al. (1976) on chemoreceptor-baroreceptor interactions in or close to the NTS.

If the data from evoked potentials can be taken to indicate a convergence of these baroreceptor inputs at the first synapse, the interaction is most certainly postsynaptic. *Gabriel* and *Seller* (1970) and *Jordan* and *Spyer* (1978b) have failed to reveal presynaptic interactions of SN and AN afferent fibres. Conditioning stimuli in either AN or SN failed to alter the magnitude of the antidromically evoked potential in the other nerve of the pair elicited by stimulation in the NTS (*Gabriel* and *Seller* 1970; *Jordan* and *Spyer* 1978b). Under a number of different circumstances, *Jordan* and *Spyer* (1977, 1978a, 1979) have failed to demonstrate presynaptic influences on either SN and AN afferent terminals in the medulla, a result which confirms the impression of *Rudomin* (1968) that although AN inputs could evoke presynaptic influences on other vagal afferent inputs at this level, they were themselves not amenable to presynaptic modulation. Thus, within the limits of the techniques so far applied, it would seem

that interactions between AN and SN occur postsynaptically at the first synapse or at subsequent synapses in the reflex pathway.

In resolving the connections within the NTS that may account for convergence, it would appear that there are many complicating factors. For SN inputs alone it appears that some neurones may receive both monosynaptic and polysynaptic input (*Humphrey* 1967; *McAllen* 1973). Furthermore, any interaction between SN and AN inputs will reflect the relative potency of each input onto recipient neurones, which may vary greatly across the population of NTS neurones. Equally, the functional effectiveness of the pattern of convergence will be dependent on the efferent projection of these recipient neurones.

There is anatomical and neurophysiological evidence that the intermediate portion of the NTS contains afferent terminals of both the SN and AN (Sect. 2.1.2), particularly in the case of small myelinated and unmyelinated fibres (see *Jordan* and *Spyer* 1977a, 1978b, among others). It is interesting to note that unmyelinated cardiac vagal afferents appear to excite neurones in this area also (*Fussey* et al. 1973b; *Donoghue* 1978). Since stimulation of these fibres evokes a pattern of response qualitatively the same as baroreceptor stimulation (*Öberg* and *Thoren* 1973a, b; *Little* et al. 1975), some form of convergence may be indicated at this level. In addition the activation of myelinated cardiac afferents has been shown to activate neurones in the NTS (*Baertschi* et al. 1975; *Keith* et al. 1975; *Ward* et al. 1977).

4.2 Cardiac Component of the Baroreceptor Reflex

4.2.1 Facilitation

In reviewing only the interactions of baroreceptor inputs it appears that there are considerable difference in the integration of the vascular and cardiac components of the response. In the previous section, evidence was cited which showed summation, and even implied facilitation, in the cardiac arm of the reflex. Since baroreceptor control of the heart is exerted primarily by its vagal innervation (*Wang* and *Borison* 1947a, b; *Heymans* and *Neil* 1958; *Levy* and *Zieske* 1969; *Levy* 1977), it is clear that we are concerned with mechanisms related to the control of vagal preganglionic activity. This is reinforced by the demonstration that whatever the level of ongoing sympathetic activity, vagal efferent activity is the major determinant of heart rate (*Levy* and *Zieske* 1969; *Levy* 1977).

The relationship between vagal efferent activity, as inferred from stimulation frequency, and heart rate is nonlinear (see Fig. 9), the slope being especially steep at low frequencies, and it is clear that convergent inputs may well produce enhanced effects, since vagal discharge is usually low.

This may well account for the facilitation that can sometimes be observed between any two inputs that evoke a vagal bradycardia. This has been claimed for inputs from the two carotid sinuses (*Wang* and *Borison* 1947b), baroreceptors and sinus arrhythmia (*Schweitzer* 1935), chemoreceptors and nasal receptors (*Angell-James* and *Daly* 1969, 1973, 1975a, 1978; *Daly* et al. 1978, among numerous authors), the "diving" response and the baroreceptor and chemoreceptor reflexes (*Angell-James* and *Daly* 1975b; *Elsner* et al. 1977; *Angell-James* et al. 1978), superior laryngeal nerve stimulation and baroreceptor inputs (*Lopes* and *Palmer* 1976a, 1978; *Angell-James* and *Daly* 1978), and the effects of central ischaemia and medullary stimulation (*Borison* and *Domjan* 1970). There is a respiratory related control of the excitability of preganglionic vagal neurones (*McAllen* and *Spyer* 1978b; *Spyer* and *McAllen* 1979; *Spyer* 1979; see Sect. 4.3), which may contribute to the low firing of these neurones and hence may be partly responsible for the pattern of interaction demonstrated above.

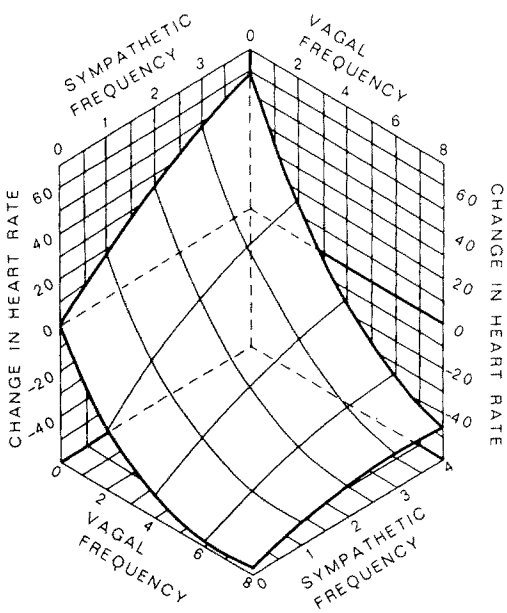

Fig. 9. Change in heart rate as a function of the frequency of vagal and sympathetic stimulation frequency in Hz. The response surface represents the mean data from 10 anaesthetised dogs. *Levy* and *Zieske* (1969)

Aside from the facilitation of the baroreceptor-cardiac reflex by other peripheral afferent inputs (see above), it has often been noted that electrical stimulation at sites within the central nervous system also facilitates its effects. In the 1950s Gellhorn published a monograph proposing that the anterior hypothalamus facilitated the baroreceptor reflex (*Gellhorn* 1957). Direct evidence for such an interaction has since come from studies in which the anterior hypothalamus-preoptic region and the septum have been stimulated electrically in the cat (*Klevans* and *Gebber* 1970; *Gebber*

and *Klevans* 1972; *Lopes* and *Palmer* 1978). Part of this area would appear to correspond to the anterior hypothalamic "depressor" area identified on the basis of the similarity of the response evoked to the baroreceptor response (*Hilton* and *Spyer* 1971). This has been broadly confirmed in the rabbit, where hypothalamic stimulation at sites which evoke a vagal bradycardia either summate with the response to AN stimulation or evoke facilitation (*Evans* 1977; *Gimpl* et al. 1976). Moreover such stimulation has been shown to excite presumed vagal preganglionic neurones in the DNV and interneurones excited by AN stimulation.

Gebber and *Klevans* (1972) describe a facilitation of the baroreceptor-vagal reflex evoked in the cat from the amygdala and septum. In addition it would seem that this component of the reflex can be facilitated by stimulation in the midbrain and hippocampus (*Hockman* et al. 1969). *Kaufman* et al. (1979) argue for a role of the lateral subthalamus (zona incerta) in the vagal bradycardia evoked by AN stimulation, because stimulation in this area excites presumed cardio-inhibitory neurones in the DNV (and close to the NTS in the rabbit. Neurones in the zone incerta were also excited by AN stimulation at remarkably short latency (as short as 4 ms) and an anatomical connection between the NTS and this subthalamic area has been demonstrated (*Ricardo* and *Koh* 1978), therefore a facilitatory loop in baroreceptor/vagal control appears likely.

Such apparent facilitation of baroreceptor-vagal reflex may again reflect the respiratory effects of central stimulation. *Hilton* and *Spyer* (1971) drew attention to the inhibition of respiration evoked from the hypothalamic "depressor" area, and even baroreceptor stimulation alone is known to powerfully suppress inspiration (see Sect. 2.2.3.3). The anterior hypothalamus can evoke a pattern of response very similar to the baroreceptor reflex and its destruction can attenuate the reflex (*Hilton* and *Spyer* 1971), and this argues powerfully for its involvement in the integration of the baroreceptor reflex. That its stimulation may facilitate the cardiac component of the reflex (*Klevans* and *Gebber* 1970; *Gebber* and *Klevans* 1972; *Lopes* and *Palmer* 1978) or summate with it (*Jordan* et al., unpublished work) provides additional support for this contention.

4.2.2 Inhibition

Just as there are well-documented instances where the cardiac component of the baroreceptor reflex can be facilitated by peripheral or by central input, so there is plentiful evidence for its suppression by other inputs. This inhibitory effect could result either from influences on the excitability of the preganglionic vagal neurone pool, i.e. disfacilitation, or from a simple summation of antagonistic drives at their membranes. Alternatively, the baroreceptor reflex input might itself be gated, a possibility that has been

tested experimentally (see Sects. 4.3 and 4.4). Equally, these mechanisms may not be mutually exclusive; the apparent suppression of the cardiac arm of the reflex could result from a mixture of disfacilitation, summation, and a true reflex "gating". In this context, lung inflation, with resulting activation of lung stretch afferents, may provide a valuable indication of the mechanisms where by the baroreceptor-cardiac reflex is modified. Lung inflation has been shown to suppress baroreceptor control of heart rate (*Haymet* and *McCloskey* 1975; *Davidson* et al. 1976; *Angell-James* and *Daly* 1978; *Gandevia* et al. 1978) and vagal efferent fibre discharge (*Davidson* et al. 1976), as well as affecting resting heart rate. Since it is more appropriate to consider the influence of respiration, both the central patterning and afferent feedback together, discussion will be considered later (Sect. 4.3).

However, there are plentiful examples of other peripheral inputs, such as sciatic nerve stimulation (*Quest* and *Gebber* 1972; *Kumada* et al. 1975), evoking an increase in arterial blood pressure and a simultaneous suppresson of the cardiac component of the baroreceptor reflex. This effect, which may simply represent an alerting stimulus, would be expected to excite those areas of brainstem involved in the integration of the defence reaction (Sect. 4.4). In very much the same way a powerful stimulation of the peripheral chemoreceptors may also block the cardiac component of the baroreceptor reflex through eliciting a defence response (*Marshall* 1977).

In addition to peripheral inputs evoking a suppressive effect on the cardiac arm of the reflex, stimulation at certain sites in the brainstem, amygdala, and hypothalamus also exert a significant inhibitory control of vagally evoked bradycardia.

It is well illustrated that stimulation at many sites in the hypothalamus, particularly in medial and posterior regions, can suppress the vagal arm of the baroreceptor reflex (*Hilton* 1963; *Feigl* et al. 1964; *Folkow* et al. 1964, 1968; *Djojosugito* et al. 1970; *Gebber* and *Snyder* 1970; *Kylstra* and *Lisander* 1970; *Bagshaw* et al. 1971; *Humphreys* et al. 1971; *Wilson* et al. 1971; *Coote* and *Perez-Gonzalez* 1972; *Thomas* and *Calaresu* 1974b; *Kumada* et al. 1975; *Lopes* and *Palmer* 1975; *Keith* et al. 1976; *McAllen* 1976; *Jordan* and *Spyer* 1977b, 1979; *Coote* 1978; *Coote* et al. 1979), while the vascular arm of the reflex either remains unaffected (*Feigl* et al. 1964; *Folkow* et al. 1964, 1968; *Djojosugito* et al. 1970; *Gebber* and *Snyder* 1970; *Kylstra* and *Lisander* 1970; *Bagshaw* et al. 1971; *Humphreys* et al. 1971; *Wilson* et al. 1971; *Kidd* and *Penna* 1976) or is even potentiated (*Kumada* et al. 1975). The vascular effects are usually considered to represent an algebraic stimulation of the baroreceptor response and the centrally evoked sympatho-excitatory response, although stimulation in the defence area may well block both cardiac and vascular components of

the baroreceptor reflex (see Sect. 4.4.1). The common features of the centrally evoked response are a rise in arterial pressure, sometimes an increase in heart rate and usually an increase in respiration (see above references). Similar effects are also observed during stimulation in the midbrain (*Kumada* and *Sagawa* 1974) and amygdala (*Schlör* and *Stock* 1978; *Timms* 1977) and are accompanied by a suppression of the vagal arm of the baroreceptor reflex. Stimulation within the medulla may also evoke blocking of the baroreceptor reflex (*Perez-Gonzales* and *Rojas* 1976). In the rabbit, stimulation within the posterior hypothalamus usually suppresses the vagal bradycardia accompanying baroreceptor or AN stimulation (*Brickman* et al. 1977; *Gimpl* et al. 1976), although hypothalamic stimulation itself may not increase either heart rate or blood pressure.

In addition to these effects elicited from the brainstem it is clear that cerebellar stimulation can affect the baroreceptor reflex. As long ago as 1938, *Moruzzi* suggested that electrical stimulation in the cortex of the anterior lobe of the cerebellum could reduce the respiratory and cardiovascular response to both vagal stimulation and bilateral carotid occlusion (*Moruzzi* 1938, 1940, 1947, 1950). Although such stimulation might affect respiration, it appeared to have no effect on resting arterial blood pressure (*Moruzzi* 1940). Since the inhibitory effect of cerebellar stimulation was manifest on the effects of chemoreceptor excitation, it may be that the effect on the response observed during bilateral carotid occlusion represents an effect on this reflex rather than on the baroreceptor reflex. Indeed it could represent a secondary influence evoked through its inhibitory influence on respiration (see Sect. 4.3). Even allowing for these problems of interpretation these studies represented the first controlled investigation of cerebellar influences on the cardiovascular system. Since then interest has focussed more onto the role of the fastigial nucleus.

Zanchetti and *Zoccolini* (1954) described that stimulation in the fastigial nucleus evoked both a pressor response and bursts of sham rage in the thalamic cat. Subsequently several reports describe a characteristic pressor response elicited from the rostral pole of the fastigial nucleus in anaesthetised cats (*Achari* and *Downman* 1969, 1970; *Miura* and *Reis* 1969b, 1970, 1972a; *Lisander* and *Martner* 1971a, b, 1973). There is also an accompanying suppression of the cardiac component of the baroreceptor reflex, whether evoked through the injection of noradrenaline (*Achari* et al. 1973) or by vagal or sinus nerve stimulation (*Hockman* et al. 1970; *Gurevitch* and *Vyshatira* 1973) or distension of an isolated carotid sinus (*Lisander* and *Martner* 1971b).

There may be important functional implications in these observations: it would appear that fastigial stimulation evokes bursts of sham rage, which is equivalent to a defence reaction (*Zanchetti* and *Zoccolini* 1954; *Moruzzi* 1947), while stimulation in the white matter of the anterior lobe sup-

pressed the autonomic components of the defence reaction (*Lisander* and *Martner* 1971a). In view of the profound effects of the defence reaction on the baroreceptor reflex, which will be reviewed later (Sect. 4.4) this implies that either the anterior lobe evokes a generalised inhibitory action on reflexes or else that its inhibitory action is concerned with chemoreceptor reflexes, which may themselves evoke defence reactions, having no influence of importance on the baroreceptor reflex except via its effect on the defence reaction. In essence, cerebellar influences may be considered to represent the antagonistic balance between cerebellar cortex and fastigial nucleus influences on the defence reaction. *Lisander* and *Martner* (1973) discount this possibility on the basis that fastigial stimulation might suppress the cholinergic vasodilatation in skeletal muscles evoked in the defence reaction, although vasoconstrictor effects were clearly facilitated (*Lisander* and *Martner* 1973; *Achari* et al. 1973). Behavioural components may similarly fail to show facilitation in conscious animals (*Achari* et al. 1973), so this apparent discrepancy cannot be taken to result from a suppressive effect of anaesthesia and caution is required in attributing a functional significance to any of the observations made so far.

It has been suggested that the anatomical and physiological connections described between the fastigial nucleus and the paramedian reticular nucleus (see *Jansen* and *Brodal* 1954; *Spyer* and *Wolstencroft* 1971; *Ghelarducci* et al. 1974, among many others) may mediate both the cardiovascular responses and this apparent suppression of vagally mediated bradycardia of the baroreceptor reflex (*Miura* and *Reis* 1972a). This may well prove insignificant: the role of this medullary nucleus in mediating the baroreceptor reflex has been shown to be highly questionable, its stimulation usually evoking a suppression of sympathetic activity (Sect. 3.3.3), and the interactions at the neural level appear confusing (*Miura* and *Reis* 1972a).

There is also a report that stimulating in the motor area of the cerebral cortex evokes increases in heart rate and blood pressure as well as a suppression of the bradycardia of the baroreceptor reflex (*Achari* and *Downman* 1978). Another study, however, indicates that stimulation in the motor cortex exerts little, if any, direct effect on the cardiovascular system, the changes being secondary to evoked movement (*Hilton* et al. 1975, 1979). Since, either directly or through evoked movement, respiratory changes may accompany stimulation in the motor cortex, the observed change in the efficacy of the reflex may again manifest only its powerful control by respiratory activity.

The most important observation may prove to be the fact that stimulating in the various brainstem sites, cerebral, cortical and cerebellar loci that profoundly modify or suppress the baroreceptor-cardiac reflex, invariably also evokes an increase in ventilatory drive. It would seem advisable at this juncture to consider the respiratory influences on the baroreceptor reflex,

for such consideration may provide at least a partial answer to the nature of the synaptic mechanisms responsible for these apparent suppressive influences and the facilitatory interactions discussed previously.

4.3 Respiratory Influences on the Baroreceptor Vagal Reflex

In considering the ability of peripheral and central inputs to suppress or facilitate the cardiac arm of the baroreceptor reflex, indications have been obtained that central respiratory drive might be responsible in part for this apparent gating of the reflex. Lung inflation was also described as a potent stimulus to the suppression of vagal efferent discharge. Indeed, the influence of respiration on the heart, and by implication vagal efferent activity, has been appreciated since 1936, when *Anrep* et al. (1936a, b) showed that the respiratory related fluctuations in heart rate were effected through two mechanisms. The first had a central origin and was related to the genesis of respiratory activity (*Anrep* et al. 1936b); the second was the result of an inhibitory input related to lung inflation (*Anrep* et al. 1936a). These two mechanisms are normally in phase and the result is sinus arrhythmia (see also *Katona* and *Jih* 1975). Accordingly, if the excitability of CVMs is the key to their ability to respond to excitatory inputs, a respiratory "gate" at their membrane might explain all the apparent inhibitory influences on the baroreceptor cardiac reflex.

This argument for an effective respiratory gating of the baroreceptor reflex was first made by Koepchen and his colleagues (*Koepchen* et al.

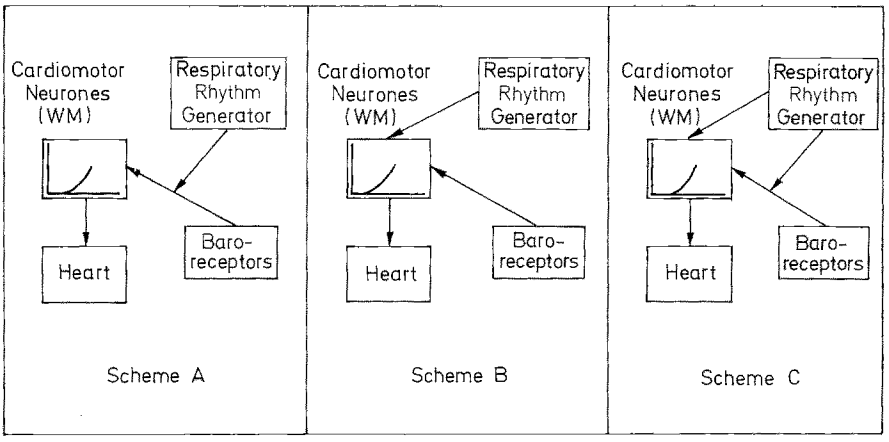

Fig. 10. A scheme of the mechanisms responsible for the respiratory modulation of the sinus baroreceptor control of the heart (for explanation see text). (Taken from *Koepchen* et al. 1961b)

1961a, b). In their studies of the SN and baroreceptor control of heart-period, they demonstrated that a stimulus to the SN was effective in prolonging heart-period only if timed to occur within expiration and was ineffective, or considerably less effective, if timed to occur during inspiration. Accordingly, three explanations were tendered to account for the observation (see Fig. 10): it could result from a "gating" of the afferent input to the vagal neurones (Fig. 10a), a respiratory related control of the excitability of CVMs (Fig. 10b), or a combination of both (Fig. 10c). These pioneering observations on heart rate (*Anrep* et al. 1936a, b) and baroreceptor control of heart rate (*Koepchen* et al. 1961a, b) have been confirmed by numerous groups. It is now generally accepted that a brief stimulus to the carotid sinus baroreceptors evokes a bradycardia only if timed to occur during expiration, an equivalent stimulus in inspiration being ineffective (*Iriuchijima* and *Kumada* 1963; *Katona* et al. 1970; *Haymet* and *McCloskey* 1975; *Neil* and *Palmer* 1975; *Davidson* et al. 1976; *Lopes* and *Palmer* 1976; *McAllen* and *Spyer* 1975). Consequently the same is true for the baroreceptor input to vagal efferent neurones (*Iriuchijima* and *Kumada* 1963; *Katona* et al. 1970; *Davidson* et al. 1976; *McAllen* and *Spyer* 1978b; see Fig. 11). Furthermore a chemoreceptor stimulus will only evoke a bradycardia and activate vagal efferent fibres if timed to occur during expiration (*Davidson* et al. 1976).

Considering then the possible explanations for this apparent "gating" of the reflex, we can eliminate a presynaptic control of the central terminals of the baroreceptor afferents within the NTS. *Jordan* and *Spyer* (1978a, b, 1979) have shown that the excitability of SN and AN afferent

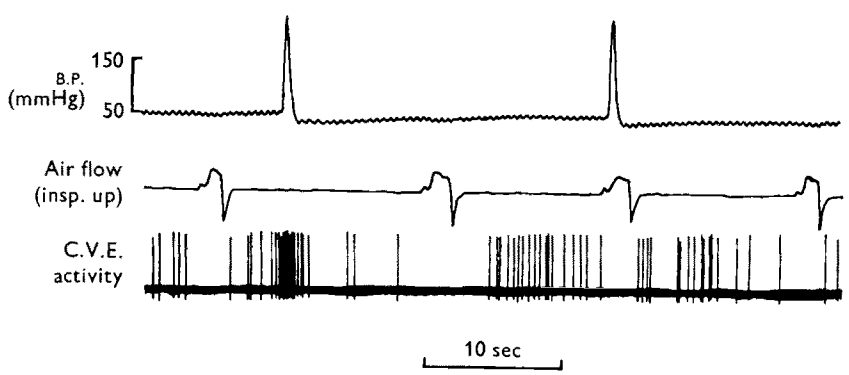

Fig. 11. Dog. Chloralose and morphine. Records of carotid sinus blood pressure, respiratory air flow and the activity of single cardiac vagal efferent nerve (CVE) are shown. A burst of firing in the cardiac efferent nerve was evoked by a baroreceptor stimuls timed so as to occur in the expiratory pause. No firing was evoked when a similar stimulus was given during inspiration. *Davidson* et al. (1976)

terminals (without distinguishing them as either baroreceptor and chemoreceptor afferents) does not alter in phase with central respiratory activity. This was demonstrated in both cats and rabbits, in artificially ventilated and paralysed preparations, with central inspiratory activity being recorded from the phrenic nerve. Antidromic potentials evoked in the SN and AN by stimulating within the NTS showed no variation in amplitude (or threshold) in phase with central respiratory drive, nor were changes observed in phase with lung inflation, although this was not tested with large lung inflations.

It remains possible that a "gate" may occur at a postsynaptic site within the NTS, as many neurones there show both respiratory and cardiac rhythm (*Stroh-Werz* et al. 1977a, b). In contrast, many neurones receiving SN and baroreceptor input have no obvious respiratory rhythm (*Lipski* et al. 1975).

If such a "gate" exists, it cannot represent an "all or none" mechanism. The evidence for this conclusion is shown in Fig. 12. In this experiment *McAllen* and *Spyer* (1978b) took advantage of the fact that by recording

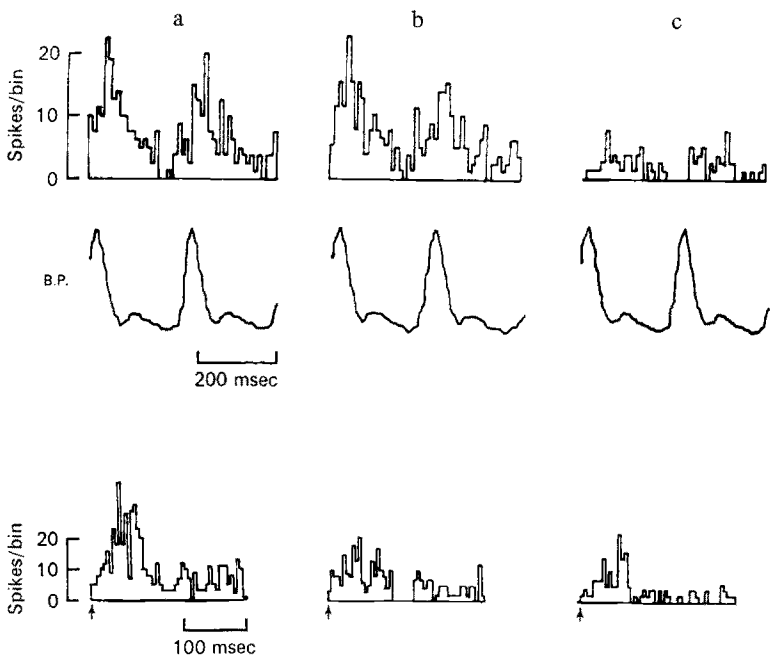

Fig. 12a–c. Cardiac rhythm of a CVM and its response to stimulation of the sinus nerve. Trace from top downwards: pulse-triggered histograms of CVM activity (120 cycles, 10 ms bins) with femoral pulse wave on same time scale, histograms of response to sinus nerve stimulation (0.1 ms pulse at 2 V, 128 cycles, 5 ms bin width). a Analysed throughout the respiratory cycle; b analysed in expiration; c analysed in inspiration. Unit firing in response to 60 nA DLH. *McAllen* and *Spyer* (1978b)

from CVMs directly and altering their excitability by the iontophoresis of DLH they could induce CVMs to fire during inspiration, when they are normally silent and inexcitable by reflex inputs, as well as during expiration. By analysing the firing patterns of CVMs, a pulse rhythm of baroreceptor origin was observed in both inspiration and expiration (see Fig. 12; *McAllen* and *Spyer* 1978b). Furthermore, stimulation of the SN was effective in both inspiration and expiration in this situation of heightened excitability. The implication is that CVMs receive an excitatory baroreceptor input throughout the central respiratory cycle but that it is normally subliminal during inspiration (*McAllen* and *Spyer* 1978b; *Spyer* and *McAllen* 1979; *Spyer* 1979). Hence the "gate" in the baroreceptor-cardiac reflex is essentially at the level of the CVM. This does not eliminate the possible influence of other respiratory related mechanisms acting on the pathway to CVMs but it does imply that these are relatively ineffective. To accommodate the role of lung inflation inputs, *McAllen* and *Spyer* (1978c) studied open-chest artificially ventilated cats, where central respiratory activity was out of phase with the respiratory pump; it is only necessary to suggest that such inputs act via a pathway that impinges on CVMs.

The question of the synaptic mechanisms responsible for the respiratory related control of CVM activity has been raised (*Lopes* and *Palmer* 1976, 1978; *McAllen* and *Spyer* 1976, 1978b; *Spyer* and *McAllen* 1979; *Spyer* 1979) and the simplest explanation would seem to be that it is related to central inspiratory drive. *Lopes* and *Palmer* (1976, 1978), from a range of indirect observations, have suggested that the Rβ inspiratory neurones of the NTS might be the ideal candidate, since they have a central inspiratory rhythm and they are excited by lung inflation (*Baumgarten* and *Kanzow* 1958, and subsequently others). In the cat, they certainly project to the NA, where CVMs are located (*Merrill* 1974).

More directly, *McAllen* and *Spyer* (1978b) and *Spyer* and *McAllen* (1979) have argued for a role of the inspiratory neurones of the NA, among which CVMs are located (*McAllen* and *Spyer* 1976, 1978b). The pattern of discharge of CVMs firing either spontaneously or in response to the iontophoresis of DLH does not resemble the recruiting discharge of central expiratory activity (see *Merrill* 1974; *Sears* 1964), and the firing pattern of CVMs could be best explained by an inhibitory sculpturing of their activity through an inspiratory related inhibitory input (*Spyer* 1979). Indeed, more positive evidence in favour of such a mechanism has arisen from the demonstration of *Garcia* et al (1978) that atropine applied iontophoretically blocks both the inhibitory action of acetylcholine exerted on CVMs by iontophoretic application and the inspiratory related depression of activity of CVMs firing in response to DLH. *Katona* et al. (1977) had previously reported that small doses of atropine, considerably smaller than

those normally used to block vagal efferent effects on the heart, evoked both an increase in vagal efferent activity and a fall in heart rate, but only if the animal had central respiratory activity. This postulated synaptic mechanism has the added attraction that it conveniently explains both the apparent "gating" of the baroreceptor reflex and the phenomenon of sinus arrhythmia. It also leaves the original contention that the major excitatory input to CVMs arises from the arterial baroreceptors, its effectiveness being adjusted by the excitability of the CVM. Hence, any input that promotes inspiratory drive will reduce the excitability of CVMs, and any mechanism which reduces inspiratory drive will increase vagal efferent excitability. This observation does not, however, exclude the participation of other inhibitory controls that are independent of the "inspiratory gate".

On the basis of these observations alone it may be premature to discuss the synaptic mechanisms responsible for the inhibitory control of CVM activity. It could involve a direct cholinergic innervation from inspiratory neurones or be mediated via a neighbouring inhibitory interneurone which also receives an excitatory input from CVM axon collaterals, i.e. in this circumstance ACh would excite the interneurone, which would also have an inspiratory rhythm.

It would be wrong to leave the impression that only the vagal arm of the baroreceptor reflex is influenced by the respiratory cycle. The excitability of sympathetic preganglionic neurones is altered in phase with respiratory activity (Sect. 3.3.1; *Lipski* et al. 1977). Accordingly it is not surprising that the baroreceptor control of the heart mediated by sympathetic efferents is powerfully affected by the respiratory cycle (*Seller* et al. 1968; *Richter* et al. 1970; *Seller* and *Richter* 1971; *Davis* et al. 1977). The changes in heart rate evoked by the baroreceptors in vagotomised dogs are reduced during inspiration, and the effecitveness of the baroreceptor control of sympathetic activity shows quantitative differences during the respiratory cycle (*Seller* et al. 1968; *Seller* and *Richter* 1971; *Davis* et al. 1977). The duration of the silencing of sympathetic activity evoked by the baroreceptors was shown to be minimal in the middle of the phrenic nerve discharge and maximal shortly after the end of inspiration. Since there is plentiful support for an inspiratory related excitatory input to sympathetic preganglionic neurones, it is possible that the disfacilitation of these neurones at the end of inspiration is sufficient to explain their heightened sensitivity to the baroreceptor inhibitory input at that time. In effect there is no respiratory "gate" in the baroreceptor-sympathetic reflex, merely a changing sensitivity to its inhibitory action and, accordingly, a quantitative reduction in effectiveness. Thus the control of the activity of sympathetic neurones falls into the pattern described by *Pitts* et al. (1941), where summation was considered a suitable explanation of their control.

4.4 Total Central Inhibition of the Baroreceptor Reflex

In the previous section, the baroreceptor cardiac reflex was seen to be profoundly modified by both peripheral and central drives. In particular the portion of the reflex mediated by vagal efferent neurones was shown to be particularly sensitive to respiratory related factors, a mechanism that was seen as part of direct control of CVM excitability by respiration. In contrast, the baroreceptor sympathetic reflex showed quantitative variations during the respiratory cycle but there was no evidence of an "all-or-none" gating of this arm of the reflex. The quantitative variations in efficacy of baroreceptor control of sympathetic activity with respect to the respiratory cycle seemed to be explicable on the basis of an algebraic summation of baroreceptor inhibitory inputs and on-going excitatory inputs not dissimilar from the interactions between baroreceptor inputs and the excitatory drive from the hypothalamus first described by *Pitts* et al. (1941) and *Pitts* and *Bronk* (1942).

It is now generally accepted that the cardiac component of the baroreceptor reflex is particularly sensitive to other inputs, but there are two centrally evoked patterns of response that appear to include a total suppression of the baroreceptor reflex. This central inhibition is considered an integral part of the defence reaction (*Hilton* 1963, 1965, 1966) and can also be evoked on stimulating in a restricted portion of the inferior olive (*Smith* and *Nathan* 1966).

4.4.1 The Defence Reaction

It is beyond the scope of this review to describe in detail the physiological and anatomical arrangement of limbic and hypothalamic integration of defensive or aggressive behaviour, but it is important to underline that the autonomic component of such responses involves a characterisitc pattern of cardiovascular response easily distinguished from more general pressor responses evoked by central stimulation. This response, which may be elicited on electrical stimulation of the hypothalamus of anaesthetised animals, involves an increase of mean and pulse pressure, tachycardia, and a generalised peripheral vasoconstriction, although the blood flow through skeletal muscle increases dramatically (for refs. see *Hilton* 1966). In the cat, this hindlimb vasodilatation involves both an activation of sympathetic cholinergic vasodilator fibres and a reduction in vasoconstrictor tone (*Eliasson* et al. 1951; *Abrahams* et al. 1960). The concomitant increase in heart rate and arterial pressure suggests a modification, or at least a resetting, of the baroreceptor reflex. Indeed, *Hilton* (1963) claimed that the reflex was totally suppressed during the hypothalamically induced defence response. This preliminary report triggered off considerable controversy

and a spate of reports claiming that although the cardiac component of the baroreceptor reflex was suppressed during the defence reaction, the vascular component was either unaffected (*Feigl* et al. 1964; *Folkow* et al. 1964, 1968; *Djojosugito* et al. 1970; *Kylstra* and *Lisander* 1970; *Bagshaw* et al. 1971; *Humphreys* et al. 1971; *Wilson* et al. 1971; *Kidd* and *Penna* 1976) or even potentiated (*Kumada* et al. 1975) and that the two inputs might act synergistically in producing the characteristic hindlimb vasodilatation of the defence reaction (*Djojosugito* et al. 1970). Behaviourally the effects of the two drives are opposite (see *Hilton* 1975) and may even be mutually inhibitory, so a synergistic relationship between their effects on the cardiovascular system would seem surprising.

The case for a synergistic interrelationship rested on the observations of *Folkow* et al. (1964) and *Bolme* et al. (1967) that vasoconstrictor tone has to be more or less totally eliminated before cholinergic vasodilatation can be fully developed. They argued that the powerful vasoconstrictor drive to other vascular areas, with an accompanying increase in cardiac output and hence blood pressure, led to a baroreceptor-mediated suppression of the vasoconstrictor supply to skeletal muscle (*Djojosugito* et al. 1970). This extrapolation has since been shown to be unnecessary. *Coote* et al. (1973) have shown in the cat that stimulating in part of the descending pathway for the defence reaction, in a narrow strip close to the dorsal surface of the medulla, evokes an increased hindlimb flow that is independent of both cholinergic vasodilator fibres and baroreceptor inputs but is abolished by guanethidine; hence it is likely to result from an active withdrawal of vasoconstrictor tone specifically in skeletal musculature. Moreover, *Horeyseck* et al. (1976) have shown that stimulation in areas of the hypothalamus which evoke a cholinergic vasodilatation in hindlimb skeletal muscles, evokes a discharge in normally silent postganglionic neurones (putative cholinergic sympathetic neurones) and a complex pattern of response in postganglionic vasoconstrictor neurones. These latter neurones may be silenced briefly, followed by a burst of activity which precedes a second and prolonged suppression, at a time when cholinergic vasodilator fibres are most conspicuously active.

The argument of *Folkow* et al. (1964) is further handicapped by the fact that their observations would demand a differential effect on vasoconstrictor activity of different vascular beds. It is now well documented that renal sympathetic activity is powerfully excited during defence are stimulation (*McAllen* 1976; *Jordan* and *Spyer* 1977b, 1979; *Coote* et al. 1979) and that this remains elevated *throughout* stimulation. Stimulating at sites beyond this integrative area similarly elevates sympathetic activity but the response is not maintained. Furthermore, baroreceptor inputs are ineffective in lowering or silencing sympathetic activity during such defence area stimulation (*McAllen* 1976; *Coote* et al. 1979). Since the effects of SN

stimulation are also blocked by such stimulation (*Jordan* and *Spyer* 1977, 1979; *Coote* et al. 1979), it is clear that the mechanism involves a central suppression and cannot be explained by a sympathetic mediated resetting of the baroreceptors themselves, as remained a possibility from the observations of the effect of sympathetic activity on baroreceptors (*Koizumi* and *Sato* 1969).

It would thus appear that the central mechanism underlying the interaction between baroreceptors and the defence reaction is more than a simple saturation effect due to the enormous excitatory drive to the sympathetic neuronal pool evoked on hypothalamic stimulation. Increases of sympathetic activity of comparable magnitude evoked from other sites in the hypothalamus, for instance, remain buffered by the baroreceptors (*Coote* et al. 1979).

There has been much speculation on the nature of the mechanisms responsible for this complete suppression of the reflex. The receptors themselves do not appear to be significantly affected, and it has been proposed that the afferent terminals in the medulla might be under a presynaptic control (*Weiss* and *Crill* 1969). They claimed that stimulation within the fields of Forel, an area of the hypothalamus which is not a part of the integrative matrix of the defence reaction, evoked a depolarisation of SN afferent endings in the NTS. *Jordan* and *Spyer* (1977, 1979) have looked directly at the effect of conditioning stimuli delivered within the hypothalamic defence area on SN and glossopharyngeal afferent terminals in the NTS. They could show no effect on SN terminals, although glossopharyngeal afferents were markedly affected by stimulation at hypothalamic sites which totally suppressed the cardiovascular responses to SN stimulation. There are, however, indications that the excitatory responses of NTS neurones to both baroreceptor and SN stimulation may be blocked by conditioning stimuli delivered to the hypothalamic defence area (*McAllen* 1976). On the basis of the latency of the response of these neurones to SN stimulation it would seem that they were located within one or two synapses of the afferent input (*McAllen* 1976). The specificity of this action is in question: *Adair* and *Manning* (1975) claim to have blocked the normal excitatory response of NTS neurones to SN stimulation on stimulating in the hypothalamus, although the hypothalamic site of stimulation and its effect on the baroreceptor reflex were never analysed. These observations indicate that at least part of the block of the baroreceptor reflex during the defence reaction may be effected close to the termination of baroreceptor afferents. In this type of interaction we are concerned with the functioning of polysynaptic pathways, and it is likely the synaptic processes mediating these changes may involve actions at several levels of the neuraxis, including the hypothalamus (*Gellhorn* 1957; *Hilton* and *Spyer* 1971; *Hilton* 1975).

The block of the cardiac component of the reflex during the defence reaction may be elicited through the respiratory "gate" (Sect. 4.3). Defence area stimulation certainly evokes hyperpnoea, with an especially powerful inspiration drive. However, *Lopes* and *Palmer* (1978) have suggested that hypothalamic inputs might exert an additional tonic inhibitory control of CVM activity. *Jordan, Khalid, Schneiderman* and *Spyer* (unpublished work) have since shown that stimulation in the defence area of the hypothalamus of the cat inhibits both on-going CVM activity (i.e. that induced by the iontophoresis of DLH) and AN inputs to CVMs and that this inhibitory action is not blocked by the iontophoresis of atropine although this did block inspiratory related inhibition. Accordingly, hypothalamic descending inhibition is likely to be mediated, at least partly, by a mechanism independent of the inspiratory-gate. Furthermore, it appears that at least a portion of the CVM neuronal pool is amenable to recurrent inhibition (*Jordan* et al., unpublished work), an influence that is antagonised by iontophoresis of atropine. Although at a preliminary stage, the observations together provide an indication of the nature of the inhibitory mechanisms that control vagal efferent discharge (see Fig. 13).

The defence area influence on the sympathetic and vascular components of the baroreceptor reflex is not necessarily an all-or-none phenome-

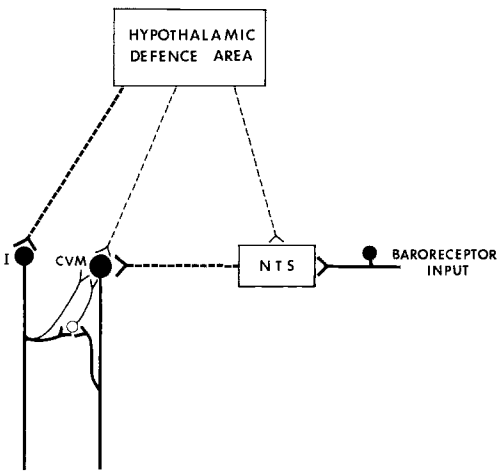

Fig. 13. Diagram illustrating the control of the baroreceptor input to cardiac vagal motoneurone *(CVM)*. Inspiratory neurones of the NA *(I)* exert an inhibitory control of CVM either directly, or via an interneurone which may also receive recurrent collateral inputs from CVMs. This inhibitory mechanism is sensitive to atropine. The hypothalamic defence area may inhibit CVM activity and block their baroreceptor input through this mechanism, but also by an alternative mechanism. This may involve a direct inhibitory control of CVM, or via a modification of transmission through the *NTS*. See text for further details. *Dotted lines* represent pathways of unknown synaptic complexity, excitatory pathways are shown by *thick lines*, inhibitory by *thin lines*

non. The temporal relationship between these antagonistic stimuli is important. *Stock* (pers. communication) has shown that if a baroreceptor stimulus is timed early in a defence response elicited by amygdala stimulation, it is totally blocked, but delaying the test stimulus until later during the defence response allows the vascular component to reassert itself although the cardiac component remains suppressed. The fatigue of cholinergic sympathetic dilatation has been documented (*Djojosugito* et al. 1968), and the slowly increasing vasoconstrictor tone in the supply to skeletal muscle may well provide a basis on which to explain this observation (*Horeyseck* et al. 1976). Also, many of the interactions may be reserved for the level of the preganglionic sympathetic neurones, so the temporal and spatial nature of descending inputs may play an important role in the pattern of interaction observed.

4.4.2 The Inferior Olive

It has been suggested that a region in the dorsomedial portion of the inferior olive exerts an inhibitory control of the baroreceptor reflex (*Smith* and *Nathan* 1966). Stimulation of this region evokes no obvious change in arterial blood pressure or heart rate but completely blocks the effect of carotid sinus inflation. *Smith* and *Nathan* (1966) suggested that this area of the medulla might mediate the defence area inhibition of the baroreceptor, and more recent neurohistological studies have indicated a descending pathway from the perifornical region of the hypothalamus to this part of the olivary complex (*Saper* et al. 1976). *Smith* and *Nathan* (1966) implied that the inhibitory control might be mediated via the cerebellum, since *Moruzzi* (1938, 1940) and subsequently others (*Hoffer* et al. 1966) had indicated that the anterior lobe of the cerebellum might exert an inhibitory control of autonomic reflexes in general and the baroreceptor reflex in particular. In some unpublished studies, *Coote* et al. have confirmed the original observation of *Smith* and *Nathan* (1966) but have shown that the inhibitory effect on the baroreceptor reflex survives cerebellectomy. They also have evidence that bilateral lesions in the olive, destroying the specific region from which this effect can be elicited, in no way impair the suppressive effect of the hypothalamic defence area on the baroreceptor reflex. Interestingly, these restricted lesions alone produce an enormous increase in both mean arterial blood pressure and pulse pressure, which developes slowly and is maintained. Furthermore, against a background of high sympathetic tone produced by bilateral carotid occlusion, stimulation in the olive may evoke a small fall in arterial pressure. It seems remarkable that despite blocking the baroreceptor reflex at normal levels of background blood pressure, olivary stimulation is ineffective in evoking obvious cardiovascular responses and so is apparently leaves ongoing baroreceptor

inputs unaffected. At this stage, the pattern of effect can best be described as interesting: further studies will be required before the significance of the olive in cardiovascular control can be assessed.

5 Concluding Remarks

This review has endeavoured to consider the baroreceptor reflex as a mechanism with a distinctive input-output relationship whose central pathway might shed light on basic problems concerning the nervous control of the heart and circulation. As such, it has dealt mainly with establishing the central connections mediating the baroreceptor control of sympathetic and vagal preganglionic neurones, but the survey has been extended to discern the synaptic processes responsible for the modification of the pattern of reflex response that occurs in different physiological states. This latter, relatively restricted discussion may in fact hold the most important clues for understanding the integrative basis of the baroreceptor reflex and consequently the nervous control of arterial blood pressure.

These rather broad generalisations can be supported by some significant conclusions that arise from such a survey of the literature. For example, there is now abundant evidence in favour of an essential role of the NTS in the mediation of the baroreceptor reflex and in cardiovascular and respiratory control. It remains to resolve whether this involves simply an ordered organisation of the diverse afferent inputs which impinge on this nucleus or whether the output from this nucleus in response to, say, baroreceptor stimulation can be modified by other afferent inputs to this area, both those arising from peripheral receptors and from central structures. Such modification would imply an integrative function and could be expected to result in differential effects on the heart and vasculature under different physiological situations. There are techniques currently available to solve this problem which are analogous to those neurophysiological and neuroanatomical approaches being used so successfully in studying the processing of afferent information in the dorsal horn of the spinal cord.

A start has certainly been made in this direction with the recent reappraisals of the anatomical description of this area and its efferent connections, to which has been added neurophysiological data on the inputs to the NTS. In this context probably more is known of the baroreceptor innervation of the NTS than for any other of its afferent inputs, yet its interactions at this level with other afferents have, as yet, barely been approached.

From this first relay in the NTS, there are indications of a complex series of connections that mediate the baroreceptor reflex and extend

through divergent areas of the brainstem. This effectively diffuse pathway finally converges to control the activity of the autonomic preganglionic neurones, the sympathetic and vagal neurones. A major advance has been achieved in the last decade with the realisation that these neurones have an integrative function. In this, their baroreceptor input over a polysynaptic pathway forms just one of the many inputs that modify their excitability, but such an organisation can certainly be seen to minimise the role of any distinctive and restricted "vasomotor centre" in the control of the circulation. The many links in the baroreceptor pathway may still remain uncertain, but we have reached a stage where analytical rather than simply qualitative studies can be undertaken to identify the action of the baroreceptors and their interactions with other inputs on the activity of these neurones.

The divergent nature of the baroreceptor input may well have contributed to our failure to identify more precisely the interneuronal matrix of the reflex. In fact connections with little direct relevance to the basic reflex may well have obscured its most important connections, since so many of its influences appear to involve the reticular formation. As a reasonable working hypothesis, it is possible to suggest that the baroreceptor input may have a preferential pathway through the reticular formation related to cardiovascular control and an indirect influence on both this and behaviour through more general effects on the reticular formation. The "preferential" system would seem to offer the most immediate challenge to neurophysiological investigation; certainly a series of possible reticulospinal connections have been revealed which may contribute to the baroreceptor control of sympathetic efferent activity. The latter and more generalised effects may well also alter the excitability, and hence effectiveness, of the preferential pathway, but except in a few instances little has yet been achieved in investigating the more general effects of the baroreceptor input on the reticular formation.

An involvement of the baroreceptors in the regulation of reticular mechanisms, such as sleep-wakefulness, has been described. The marked cardiovascular changes in these states certainly imply interactions, but whether these are at the level of the brainstem, at the final common pathway, the preganglionic neurone, or at both remains to be resolved.

An attempt has been made to assess how certain patterns of physiological behaviour evoked from the central nervous system can influence the effectiveness of baroreceptor inputs. Indeed, studies on the influence of central respiratory activity and the defence reaction on the efficacy of the baroreceptor control of vagal and sympathetic activity have shed considerable light on the basic mechanisms underlying the reflex. Furthermore, since these two patterns of activity are so powerfully affected by peripheral

inputs and behavioural state, they may well offer particularly valuable clues to the basic mechanisms underlying not only the integration of the baroreceptor reflex, but also the nervous control of circulation.

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Event-Related Slow (DC) Potentials in the Human Brain*

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Contents

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Introduction

The study of event-related slow (DC) potentials of the human brain is at the same time fascinating and disappointing. It is fascinating because obvious correlations exist between these electrical phenomena of the brain with higher psychic functions and processes. But it is disappointing because these correlations remain "phenomenological", and little is known about the actual underlying brain mechanisms. Historically, *Caton* (1875) first observed event-related slow (DC) potentials in response to sensory stimulation and motor acts. Later studies ignored DC potentials due to the use of low frequency filters. Renewed interest in these problems started with *Davis* et al. (1939), who tried to correlate slow (DC) potentials with variations in depth of sleep. *Goldring* and *O'Leary* (1951a) studied stimulus-evoked slow (DC) potentials, and *Köhler* and *Held* (1949) and *Köhler* et al. (1952) demonstrated slow (DC) potentials connected with complex visual stimuli.

Event-related slow (DC) potentials occurring after external stimulation as well as prior to behavioural responses have been extensively described by *Caspers* (1961, 1963, 1965). DC potentials related to mental activity were found by *Bechtereva* (1967, 1968, 1974) in different subcortical structures of the brain. Slow potentials related to conditioned responses have been observed by *Rowland* (1960, 1967, 1968), and sound-evoked slow negative potentials were recorded from auditory cortex by *Gumnit* (1960, 1961).

Late responses in the form of long latency, slow evoked potentials have been described as being associated with "information delivery" (*Sutton* et al. 1965) and with unpredictably occurring stimuli as a kind of central orienting response (*Haider* et al. 1968b; *Ritter* et al. 1968). These late responses have been variously designated "P 3" or "P 300" (*Ritter* et al. 1968); "late positive component" (LPC) (*Ritter* and *Vaughan* 1969) and "association cortex potential" (ACP) (*Vaughan* 1974).

Contingent responses have been observed as slow (DC) potential changes between a warning or conditional stimulus (S_1) and an imperative or unconditional one (S_2) with which the subject is "engaged" in the form of action or decision. *Walter* et al. (1964), in such an experimental design, observed a slow increase in surface negativity and called it "contingent negative variation" (CNV) or "expectancy wave" (E-wave).

Slow (DC) potentials preceding a voluntary movement have been observed by *Kornhuber* and *Deecke* (1965), who called this slow potential shift *Bereitschaftspotential* (BP) or "readiness potential" (RP). The potential changes associated with motor action have been named "motor potential" (MP) by *Gilden* et al. (1966) and *Vaughan* et al. (1968).

Our review deals with these three groups of phenomena, namely the late potentials associated with orienting and information processing, the contingent potentials associated with expectancy and the movement-related potentials associated with voluntary movement and motor control. First we will survey the terminologies and abbreviations which unfortunately are used very inconsistently in this field. Then we will describe some methodological aspects, which seem to be necessary since different methods for registration and analysis have been proposed. After comments on electrogenesis and physiological significance we will describe results of research with corticography and stereo-electro-encephalography. The later parts of the review will then be devoted to topographical and maturational aspects and related psychological processes, as well as the application in clinical studies and research on drug effects and toxic influences.

2 Terminology and Definitions

Concerning terminology, abbreviations and definitions we will try to work out some unifying principles and recommendations for further usage. A basic discrepancy already exists between researchers recording directly from the cortex, working mainly on the animal brain, and researchers recording from the human scalp. The first group has decided that the term DC potentials, derived from the application of directly coupled amplifiers,

would be most unprejudiced and that this nomenclature should be adopted in future publications (*Caspers* 1974).

The second group, in the title of its congress papers, uses the term "event-related slow potentials" (*McCallum* and *Knott* 1973).

In our title we have combined both terminologies by adding DC in the sense of direct coupling, in parantheses, and also by using the term "event-related slow (DC) potentials". This combined term has already been used by *Lindsley* (1969). A general review of the different terminologies and abbreviations used in this field is given in Tables 1 and 2.

Table 1. General terminology and abbreviations for event-related slow (DC) potentials [a]

	Descriptive terms related to	
Technological terms	Potential characteristics	Events
DC (directly coupled)	SP (slow potentials)	ERP (event-related potentials)
DC (direct current)	SPC (slow potential change)	
DC recordings	SPS (slow potential shift)	
	DC change	
	DC shift	
	Standing potential	
	Steady potential	
	Sustained potential	

[a] Terms used as main headings in this paper and recommended for future usage are enclosed.

At the time terminologies must remain largely descriptive and not explanatory. We therefore use as main headings in this review and propose for further usage the general descriptive terms "slow potentials" (SP) and "event-related potentials" (ERP) and as specific descriptive terms, "late potential" (LP) or "information-related potential" (IRP), "contingent potential" (CP) and "movement-related potential" (MRP).

We are not concerned in this review with the early and middle components of evoked potentials. Late potentials (LP) may include positive as well as negative potentials between 200 and 500 ms, depending on the experimental situation. The best usage seems to us therefore to designate the main component of the late responses according to its polarity and latency. In many cases this will be a positive wave with a peak latency around 300 ms, as originally described by *Sutton* et al. (1965) and designated as P 3 or P 300 by *Ritter* et al. (1968) or LPC (late positive component) by

Table 2. Situation-specific terms and abbreviations for event-related slow (DC) potentials [a]

Phenomenological terms	Topographical terms	Descriptive terms related to Potential characteristics	Events
OP (orienting potential)		LP (late potential)	IRP (information-related potential)
	ACP (association cortex potential)	LPC (late positive component)	PWSP (post warning signal positivity)
		SNP (slow negative potential)	
		$P_3 = P_{300}$ (positive wave with peak latency 300 ms)	
E-wave (expectancy wave)			CP (contingent potential)
Imaginary potential			CNV (contingent negative variation)
Imagination potential			RCPV (rewarding contingent positive variation)
			PINV (post imperative negative variation)
I-wave (intention wave)			MRP (movement-related potential)
			RRP (response-related potential)
			AMP (average movement potential)
			RP (readiness potential, i.e. BP, *Bereitschafts-potential*)
			PMP (premotor positive potential)
			MP (motor potential)
			GDMP (goal-directed movement potential)

[a] Terms used as main headings in this paper and recommended for future usage are enclosed.

Ritter and *Vaughan* (1969). In other cases the main potential components may be a negative wave with latencies of about 250 ms, as described by *Haider* et al. (1968b). In other studies, still other prominent waves or wave complexes may be seen which could all be summed up under the descriptive heading of "late potentials". Since all components seem to be related to different aspects of information processing we propose the term "information-related potential" (IRP).

Similarly, the term "contingent potential" (CP) could be used for a whole group of responses described by *Walter* (1975) as "potential changes whose appearance is contingent on the association of signals and/or action or decision by the subject." The most obvious of these is the contingent negative variation (CNV). Again, this more specific term applies to a special situation in which a negative potential appears.

But sometimes the variation may be positive. *Marczynski* (1972) described a reward-contingent positive variation (RCPV). In some parts of the brain (frontal of the thalamus) even the typical experimental situation for a CNV leads to slow positive variations (*McCallum* et al. 1976).

Under the heading "movement related potentials" (MRP), at least three main components are described: a slow rising readiness potential *(Bereitschaftspotential),* premovement phasic components and a late positive wave. Recently, *Zielbewegungspotentiale* (goal-directed movement potentials, GDMP) have been found over the precentral and parietal cortex (*Grünewald-Zuberbier* et al. 1978a; *Grünewald-Zuberbier* and *Grünewald* 1978). In these instances the premotion negativity increases and remains during the goal-directed movement until the target is reached.

It must be emphasized that some authors (*Gilden* et al. 1966; *Vaughan* et al. 1968) use the term "motor potential" for all potential components associated with movements, whereas other authors (*Kornhuber* and *Deecke* 1965; *Deecke* et al. 1969) call only the negative peak "motor potential". There is no agreement as to what part of the trace the term N_2 applies and to what part, the term "motor potential". *Gerbrandt* et al. (1973) use the term "average movement potential". A group attending the symposium on motor control [Fourth International Congress on Event-Related Slow Potentials, *Otto* (ed.) 1978] therefore proposed the following taxonomy of movement-related brain macropotentials (*Papakostopoulos,* 1978).

1. Potentials related to the state of the sensory motor system at rest (resting potentials – RTPs)
2. Potentials related to functions during the preparatory period (preparatory period (preparatory potentials – PPs)
3. Potentials related to the initiation period (initiation potentials – IPs)
4. Potentials related to the execution of the movement (movement-execution potentials – MEPs)

5. Potentials related to the termination of the movement (termination potentials – TPs)

Future research must show the extent to which these terms are useful in handling our knowledge of motor control from different disciplines. In this review we take the term "movement-related potentials" as the best descriptive term and propose it for further usage. How far the different components of these movement-related potentials, according to their time sequence, are related to preparation, initiation, execution and termination of movements will be discussed in this review.

3 Potential Characteristics and Methodology

3.1 The Biological Signal

3.1.1 Late Potentials

Sutton et al. (1965) described a rather slow late positive potential component with a peak latency of about 300 ms which appeared to be related more to complex psychological variables than to the physical characteristics of the stimulus. Further experiments showed that this phenomenon of late potential changes with peak latencies between ~200 and ~400 ms seem to be related to similar psychological variables (*Haider* et al. 1968b; *Ritter* et al. 1968). Multiple late potential components have also been described (*Harter* and *Salomon* 1972; *Squires* et al. 1975; *Courchesne* et al. 1975). Some characteristic wave forms of late potentials, drawn according to the published curves of different authors, are compared in Fig. 1.

There have also been reports of cerebral potentials occurring at about the time of an expected but absent stimulus. Stimulus absence provided information or is salient for the subject. These potentials consist mainly of a positive peak occurring about the same time as the p 300 and is referred to as an "emitted p 300" potential (*Klinke* et al. 1968; *Weinberg* et al. 1974; *Ruchkin* et al. 1975).

The original construct that one unifying psychological variable is responsible for these potential changes which are elicited in a wide variety of situations such as uncertainty, information delivery, signal significance, orienting, inhibition, selective recognition, awareness or salience, has been replaced by some authors with the concept of several independent late potential components. This second concept is supported mainly by topographical data.

The technical problems involved in defining LP on the basis of individual trials are considerable (see Sect. 3.6.2) and sometimes impossible (low signal-to-noise ratio).

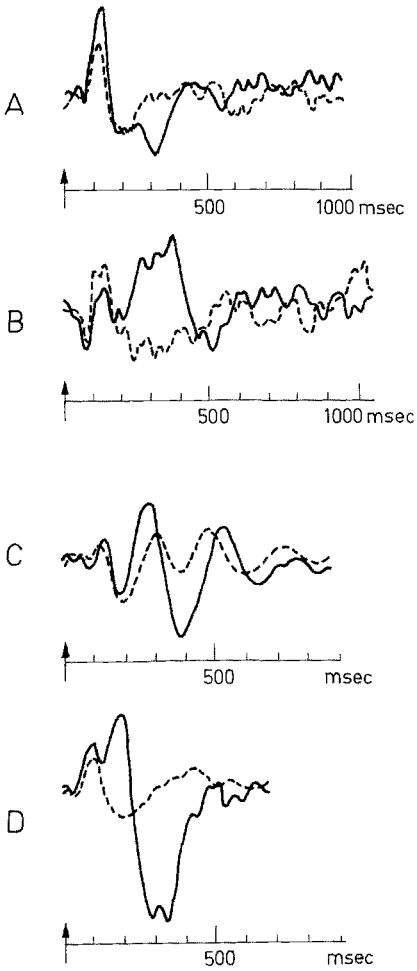

Fig. 1 A–D. Late potentials found by different authors for unexpected stimuli compared with expected stimuli. ——unexpected stimuli; - - - - - - expected stimuli negativity upwards; ↑ stimulus onset. **A** *Ritter* et al. (1968); **B** *Haider* et al. (1968b); **C** *Squires* et al. (1973); **D** *Courchesne* et al. (1975)

Late potentials normally are extracted from the raw EEG by different methods of averaging (methods that increase the signal-to-noise ratio).

3.1.2 Contingent Potentials

The contingent negative variation derives its name from being a slow potential shift in the EEG baseline which typically occurs on the association (contingency) of successive stimuli. As mentioned previously, it was first described by *Walter* et al. (1964), as developing between the warning signal and the imperative signal in a constant foreperiod reaction time task. The contingent negative variation appears within the intersignal interval as a surface negative shift with respect to a mastoid reference.

Meanwhile, it has been demonstrated that the CP can be elicited by many different experimental designs. It is not dependent on stimulus

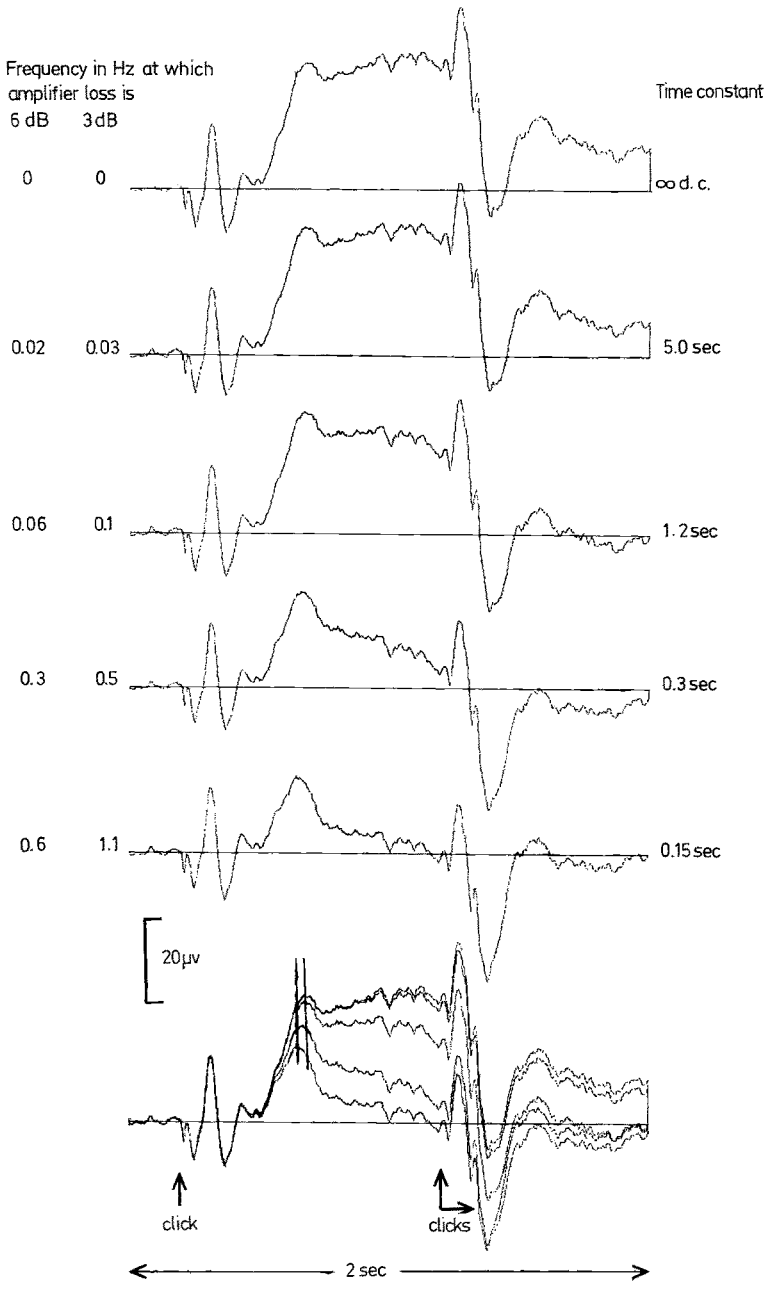

Fig. 2. Contingent negative variation *(CNV)* in the standard paradigm (reaction time experiment with foreperiod) and the effect of time constant on the contingent variation. Note also the apparent variations in latency of the first peak of CNV. A warning signal (S_1) is followed by repetitive clicks which were terminated by the press of a button. Each trace is the average of 50 trials recorded simultaneously but with different time constants. Negativity upwards. (*Cooper* et al. 1974)

modality or intensity, nor are overt motor acts essential for a contingent variation. The reasons for the sometimes considerable changes in CP morphology and amplitude as well as for changes in peak latency variations are discussed in Sect. 8.

The CP is not readily seen in the raw EEG traces of most normal adults. Therefore, different averaging techniques are used to enhance CP amplitude relative to background EEG. In the last years some mathematical models have also been discussed for CP evaluation as alternatives to the averaging methods, which include some theoretical difficulties.

The maximum negative voltage, compared to the iso-electric direct current prestimulus baseline, ranges from 10 μV to 50 μV with an approximate mean of 20 μV (*Walter* 1967b). The termination of the CP can be slow and inconsistent as well as immediate.

The terminating potential decline limb of the CP may overshoot the baseline. The time course for the development of CP may vary from 0.5 s to many seconds. It is reported to persist as long as 20 s under special conditions, if the subject is highly motivated. When using RC-coupled amplifiers the time constant may reduce the amplitude of slow potentials. This is demonstrated in Fig. 2, which presents a typical example of a CP simultaneously recorded with different time constants in a classic experimental paradigm.

3.1.3 Movement-Related Potentials

Voluntary movements are preceded and followed by slow electrical brain potentials of different latency and amplitude characteristics. There is general agreement as to the morphology of this MRP and its division in four components: a slowly rising negativity (N_1), an inconsistently appearing small positivity (P_1), a fast negative deflection (N_2) and a large, rather slow final positivity (P_2).

Characteristic examples of movement-related potentials for right and left unilateral finger movements are shown in Fig. 3, which demonstrates that the fast negative deflection (motor potential, according to *Deecke* and *Kornhuber* 1977) occurs contralateral to the moving hand.

The N_1 component, generally called *Bereitschaftspotential* (BP), is a bilateral, slowly increasing surface negative potential. In scalp derivations it starts on the average about 0.8 s prior to the onset of a movement. The amplitude of the average BP is between 5 and 7 μV. There is small intraindividual but large interindividual variability in latency. Amplitudes are dependent on several individual and experimental parameters.

Similar to the CP the BP occurs in preparatory situations. Therefore, the question sometimes arose whether CP and BP would not be the same electrophysiological phenomenon. There is now, however, general agree-

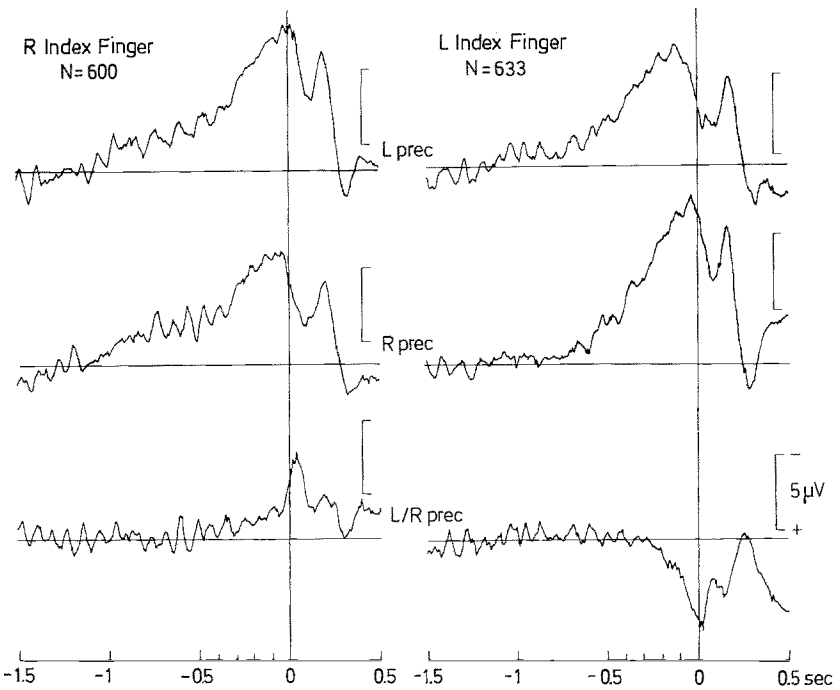

Fig. 3. Examples of voluntary movement-related potentials (*Deecke* et al. 1976b). Comparison of right unilateral *(R)* and left unilateral *(L)* index finger movements in the same experiment. With right index finger movement there is more negativity over the left precentral region *(R)*; with left index finger movement there is more negativity in the right precentral lead *(L)*. Bipolar recording (left versus right precentral) in the bottom trace

ment that CP and BP are correlates of different psychophysiological mechanisms. *Deecke* and *Kornhuber* (1977) ascribe different topographical distribution, morphology and amplitudes to CP and BP. Similar differences between BP and CP were described by *McCallum* (1978) for cortical derivations.

A small positive-going wave whose deflection time is 90–80 ms before the start of movement as defined by EMG onset is sometimes registered. Average amplitude of this wave is about 1.7 μV. This P_1 component appears to be bilateral and widespread and is described as occurring inconsistently across and within subjects (*Gerbrandt* et al. 1973; *Vaughan* et al. 1968). *Deecke* and *Kornhuber* (1977) found this premotor positivity in about two-thirds of their subjects. *McCallum* (1978) was not able to analyse this potential component.

A fast negative deflection following the P_1 component was described by *Kornhuber* and *Deecke* (1965) and is called N_2 or motor potential (MP). The negative MP is restricted to the contralateral precentral area. It

starts 60–50 ms prior to EMG onset and has an average amplitude of about 1.6 μV. The MP starts before the onset of movement. The N_2 component described by *Deecke* and *Kornhuber* does not correspond to the N_2 component described by *Gerbrandt* et al. (1973), who found that this component arises after movement onset. This difference obviously depends on electrode linkage and position.

In cortical derivations during stereotactic surgery the motor potential has now been observed as a restricted, localized phenomenon at the proper motor cortex, area 4 (*Ganglberger* et al. 1980).

During smooth goal-directed hand movements the premotion negativity increases and remains during movement until the target is reached. An example is shown in Fig. 4.

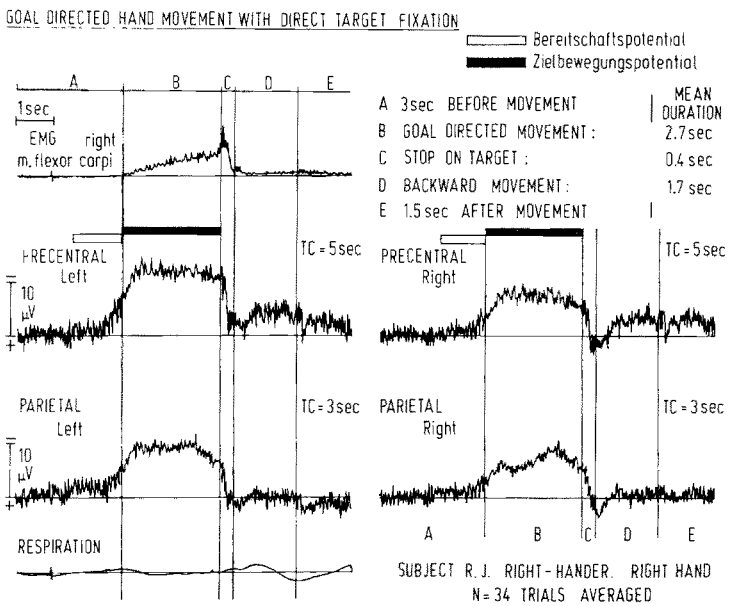

Fig. 4. Negative potentials during goal-directed movements, *Zielbewegungspotential* (*B* ▬) reach double amplitudes of *Bereitschaftspotential* before movement (*A* ▭). In *B* the right hand guides the rod to the visualized goal during maintained target fixation. Reference: linked mastoids. (*Grünewald-Zuberbier* et al. 1978a)

The negativity is very large and widespread and has maximal amplitudes over the vertex. Over the precentral cortex they are larger contralaterally, but over parietal cortex an ipsilateral preponderance is sometimes seen.

Potential changes during such goal-directed movements are of higher amplitude than potential changes during voluntary finger movements and very often may be seen in the raw EEG. *Grünewald-Zuberbier* et al.

(1978a), *Grünewald-Zuberbier* and *Grünewald* (1978) were the first to describe the phenomenon under the term "goal-directed movement potential".

3.2 Reliability of Biological Signals

The reliability of a measurement is a crucial factor in determining its usefulness. Generally the reliability is expressed as the correlation between repeated measurements. Information on test-retest reliability *(TRR)* of averaged slow potential changes is limited, and the results of different investigations may not directly be compared. Different authors use various experimental designs and parameters for potential descriptions. This probably accounts for some of the diverging results.

The test-retest reliability of different EP components is reported to be between 0.87 and 0.97 (*Shagass* and *Schwartz* 1961; *Callaway* et al. 1965; *Kooi* and *Bagchi* 1964; *Ellingson* et al. 1973; *Soskis* and *Shagass* 1974).

Smaller reliability coefficients were found by *Roth* et al. (1975) (r = 0.78 amplitude; latencies 0.63). For longer test intervals smaller correlation coefficients in the range 0.55–0.66 were found. There is general agreement on higher reliability for earlier potential components than for the later ones. There is so far no agreement whether latency measurements or amplitude measurements are more reliable (*Kooi* and *Bagchi* 1964; *Roth* et al. 1975).

There are only few experimental data on CP reliability. *Straumanis* et al. (1969) found a rather low reliability of 0.32 for a normal population and 0.05 in a psychiatric population. It has to be mentioned, however, that different experimental designs were used as test and retest.

Cohen (1969) reports a reliability coefficient of 0.80 for "average maximum vertex amplitude", using test intervals of 2–8 days. The median subject consistency in retests separated from 5 min to 8 days was 0.68 as reported by *Roth* et al. (1975).

Timsit-Berthier et al. (1978) studied CP reliability using two groups of psychiatric patients (those with permanent behaviour disorders and those with important changes in their clinical state) and retest intervals of 1–2 months and 1–2 years. Correlation coefficients for amplitude measures were 0.66 (1–2 months) and 0.55 (1–2 years), respectively ($P < 0.05$). For qualitative evaluation of CNV termination, retest reliability was even higher (0.88–0.78).

Tests for personality traits which by definition are stable over time have TRRs ranging between 0.9 and 0.6 for intervals of several weeks. The CP reliability is therefore lower than expected for measurement of trait reliability but much higher than measurements of individual variables fluctuating with different states of the individual.

3.3 Variability of Biological Signals

The interindividual variability of the EP component shows a slight but progressive increase for waves I–III and is very high for the late potential components. This occurs in the peak latencies as well as in amplitude measurements (*Storm van Leeuwen* et al. 1975).

There is considerable interindividual variability in phenomena related to contingent potential development. In raw EEG traces, CP's are to be seen in about 20% of subjects. The range of CP amplitude found among normal individuals is between 8 and 50 μV in standard CP paradigms.

Changes in the experimental design (i.e. omission of S_2, distraction from S_2) may evoke different reactions in different subjects, i.e. decrease in CP amplitude for some subjects and augmentation for others.

In summary, the interindividual variability of CP parameters in standard situations is already great. Introduction of supplementary behavioural aspects into the situation increases the interindividual variability considerably.

Average EPs in the same subject under identical conditions are very stable over a long period of time: the intra-individual variability is small. Studies of *Aunon* and *Cantor* (1977) have shown that the intrasession variability for EP components is significantly smaller than the intersession variability within the same subject. Interlaboratory standard deviation was found to be over twice as large as the intralaboratory standard deviation measured over an 8-week period.

3.4 Recording System

3.4.1 Characteristics of Electrodes for Registration of Slow (DC) Potential Changes

Reversible electrodes should be used for registration of steady or slowly changing potential differences; i.e. electrodes having low values for R_F, the faradic resistance of the chemical change and the Warburg impedance. Using reversible electrodes a small increase or decrease of potential above or below the electrode potential will cause the discharge of ions at a considerable rate. This means that such electrodes have a low resistance to steady or slowly changing potentials.

Reversible electrodes commonly used in EEG investigations are reversible with respect to anions. In this case a metal is in contact with one of its insoluble salts immersed in a solution of a soluble salt of the same anion (*Geddes* 1972; *Cooper* et al. 1974).

The choice of the metal used for electrodes cannot only be determined by the susceptibility to polarization. Many metals cause inflammation

when they are in contact with tissue for longer periods. Therefore, especially for chronical intracerebral recordings, metals such as stainless steel or gold must be used whose recording characteristics are poor when DC recordings have to be made and conventional EEG amplifiers are used. The low frequency activity is attenuated by a factor determined by the values of the electrode impedance and the amplifier impedance. EEG amplifiers with high input impedance (100 MΩ) make possible the registration of slow potential changes with such electrodes without too much loss. In animal experiments, electrolyte-filled glass pipettes in connection with sintered Ag/AgCl pellets seem to be a good alternative (*Rebert* and *Irwin* 1973).

Electrode potentials often change with time. Slow drifts may be caused by several sources; for instance, differences between electrodes, skin potentials or potential changes at the skin as a result of the conducting jelly can be in the range of mV and therefore much higher than the EEG phenomenon under investigation. Because of these instabilities one should carefully consider whether DC recordings with all their difficult technical aspects are really required or whether AC amplifiers with very long time constants (25 s) will suffice.

3.4.2 Number and Location of Electrodes

There is general agreement that as many electrodes as possible should be used in EP experiments. The number and location of electrodes must be decided according to the specific goal of the experiment and the technical availabilities of the recording system. Further limitations are set by the capacity of the data-analysing equipment. For experiments dealing with the relationship between EPs and complex psychological processes, the following ranking of electrode placements in order of desirability was proposed by *Donchin* et al. (1977) if scalp electrodes are used. Electro-oculogram EOG and the encephalogram from the location C_Z should always be recorded followed by derivations from P_3 and P_4 (P_Z), C_3, C_4, then F_3, F_4 (or F_Z), O_1 and O_2 and finally, T_5 and T_6. For specification of electrode placement the international 10–20 electrode placement system (*Jasper* 1958) should be used. Electrode positions which vary for scientific reasons from the 10–20 system should also be specified in terms of the standard coordinate system.

3.4.3 Recording Montages

For deriving EEG recordings from an electrode array, three main methods are described:

1. In the bipolar method potential differences are measured between two electrodes, both of which are affected by EEG potentials ("active" electrodes).

2. In a common reference (unipolar, monopolar) derivation each amplifier is situated between one "active" electrode and the so-called common reference which is placed so as to minimize the possibility of picking up brain potentials ("inactive" electrode).
3. In a common average reference system (Goldman-Offner method) usually all the electrodes on the scalp (sometimes with the exclusion of some electrodes thought likely to produce artefacts) are connected through equal resistors to a single point which is then used as a common reference. The potential of this point will be the average of the potentials at the scalp electrodes. Each amplifier is then connected between one active electrode and this common average "inactive" reference).

It is not possible to make a general recommendation as to which recording method is preferable. In investigations of slow potential changes there seems to be, however, a preference for common reference derivations using "linked ears" as the "inactive" electrode site.

3.5 Artefacts

"By definition an artefact in electroencephalography is any recorded electrical potential which does not originate in the brain" (*Cooper* et al. 1974). Artefacts arise because of two main factors: technical and physiological. Many technical artefacts arise at the junction between the electrodes and the patient's scalp. Movement of the electrode relative to the scalp results in a change of contact resistance or disturbance of the electrode potential. Imperfect electrode contact or contamination of the different junctions (electrode clipjacket) may cause further artefacts.

Several physiological potentials originating from extracerebral sources may be recorded from the scalp electrodes used to detect the EEG and the time-locked cerebral potential it contains. Some of them, such as muscle activity or artefacts from the EEG, are rather easily recognized in the raw EEG. Galvanic skin response and respiratory effects may seriously confound the activity originating from the brain, especially when event-related slow (DC) potential shifts are under investigation.

Low et al. (1966a) reported that a consistent pattern of involuntary eye movements could accompany behavioural tasks used to elicit the CNV or other CP.

The most serious difficulty, however, is undoubtedly presented by the corneoretinal potential which generates the EOG. The fact that the EOG is sometimes time-locked to stimuli has led to serious errors, especially in slow potential investigations. This EOG potential is large in comparison to cerebral potentials and may significantly contaminate recordings taken from points as distant as the vertex and sometimes the occiput (*Rowland* 1968).

Different methods for EOG elimination have been proposed:

1. Requiring the subject to fix his gaze during the recording period is reported to be effective in about 50% of subjects (*Rowland* 1968; *Wasman* et al. 1970); *Hillyard* and *Galambos* (1970) found this method "generally" effective.
2. A variation of the gaze-fixation technique using a special device for stimulus presentation has been shown to virtually eliminate involuntary ocular rotations (*Borda* and *Hablitz* 1973).
3. Techniques which favour rejection of eye-movement contaminated trials are:
   a) Electrographical monitoring of eye-movements and subsequent elimination from further analysis of trials during which eye movements occurred, based on either visual monitoring or automatic EOG recognition in off-line analysis (*Debecker* and *Carmeliet* 1974) with analogue equipment or on-line by a general purpose computer.
   b) Rejection of mechanically detected eye-movement contaminated trials in on-line analysis using a mechanical transducer to sense movements of the eye equivalent to 3° or more has been suggested by *Papakostopoulos* et al. (1973).

The behavioural significance of such "cleaned" CPs must be discussed as it is very likely that in some situations CP trials accompanied by eye movements represent a special situation.

4. Mathematical adjustment of CNV amplitude based on the correlation between magnitude of eye movements and magnitude of "pseudo-CNV" recorded on the vertex (*Hillyard* and *Galambos* 1970).
5. On-line technique for separating eye movement potentials from EEG potentials by electronically subtracting a fraction of both the horizontal and the vertical EOG potential from the raw EEG (*Girton* and *Kamiya* 1973).

3.6 Data Analysis

3.6.1 Averaging and its Limitations

Since *Adrian* (1941) demonstrated that an evoked response to a flash in the ongoing activity of the EEG was tied in time to the stimulus, with latencies of about 100 ms one assumed that earlier signal-evoked events were also almost certainly present though masked by the ongoing EEG. The problem of selecting these evoked responses from the ongoing EEG is one of increasing the signal-to-noise ratio. A technique was consequently developed by which the recorded potential change is time locked to a pulse coincident with the stimulus. Repetition of the same signal situation and

averaging the resultant record was, for a long time, the only method of enhancing the signal-to-noise ratio.

Different parameters of these averaged evoked responses are used for descriptive and statistical purposes. The parameters most often used in slow potential studies shall be discussed.

One way to define the size of LP components, contingent variation or movement-related potentials, is the measurement of amplitude. There is presently no general agreement as to whether the amplitude of EP components should be measured from a baseline or as an absolute distance between peaks of adjacent components (peak-to-peak measurement). Measurements from the baseline present some difficulties. First, one must define the baseline and, second, measurements from the baseline introduce special complexities in the interpretation of data, for example when negative-going potentials peak at levels more positive than the baselines.

When using peak-to-peak amplitude measures one need not be concerned by the fact that there are sometimes difficulties in determining a baseline and also that the baseline and the whole EP may be superimposed on a (very) slow wave. However, measuring peak-to-peak does not take into account that adjacent components may be differently affected by the introduced variables. Thus, those measurements may blur the true relationship.

Investigations of late potential components generally refer to a baseline prior to stimulus onset (5%–10% of total sweep time is recommended). In both baseline measures and peak-to-peak measures, the points for amplitude evaluations are determined by the peak latencies and the number of late potential components.

In CP studies baseline considerations are dependent upon the general definition of the contingent variation which can be either (a) the absolute level of negativity/positivity, measured in relation to an absolute baseline (in this case prestimulus baseline is used); or, alternatively (b) a potential change with respect to the level upon which the warning stimulus falls. Here baseline would be adjusted from a point 400 ms following the first stimulus (*Rebert* and *Knott* 1970).

The difference between these two definitions of CP becomes important whenever the evoked response to the first stimulus is associated with a pronounced positive shift, followed by a small negative-going potential shift which in fact may never exceed the absolute baseline (i.e. the stimulus baseline).

The use of the late positive-going potential shift of the first signal for baseline evaluation or peak-to-peak measurements would imply that this component is not affected by the same variables as the contingent variation. Some investigations, however, have shown that such activity evoked by the first stimulus has considerable effect on the CNV (*Otto* and *Leifer* 1973).

There are two different ways for amplitude evaluation commonly used in contingent variation studies. Some workers measure amplitude just before or at the time of the presentation of the imperative stimulus (*McCallum* and *Walter* 1968), whereas others use maximum amplitude wherever it happens to occur in the interstimulus interval.

Further amplitude measures used in most CNV studies are the values for the post-warning signal positivity measured either in relation to absolute baseline or as peak-to-peak measure in relation to previous negative potential peak.

Amplitude measures of movement-related potential changes refer to a prepotential baseline and also to peak-to-peak measures. Because the onset time of the slowly developing *Bereitschaftspotential* (readiness potential) changes according to different parameters of the performed movement, no general assumption can be made for the length of the necessary premovement registration time. (In experiments using the general experimental designs of voluntary finger movement 2-s premovement and 1-s postmovement registration should be enough for baseline evaluation and measurement of slow potential components.)

No general solution can be advanced when amplitude measures are of concern. Each experiment, however, should examine these data both as measured from the baseline prior to stimulus onset and also from "peak-to-peak".

Low and *McSherry* (1968) proposed to use the integration of the area above or under the baseline between arbitrarily defined points as a measurement of the size of potential components. This method should only be used when digital computation is available. There are some typical integration limits, generally used by experimentors, which correspond in some way to the most frequently used points of amplitude measurement. Because less data are discarded by the use of area measures than by amplitude measurement, this method offers some advantages.

Neither amplitude nor area measures are able to take the shape of the contingent variation or movement-related potentials. As a matter of fact a great variety of wave shapes exists. For the CNV, *Tecce* (1972) has discussed at least three major types, each showing a large individual variability.

Some evidence, however, is emerging that the slope of the ascending limb might be equally as important as other CNV measures. In this connection the use of "latency to peak" or some other rise time measures could be helpful. Attempts to relate the cut-off or descending part of the curve with diagnostic measures have already been successful, and it will be necessary to perform further work on these problems.

The concept of signal averaging implies that a signal must be extracted which may not be observed in its entirety in the raw data. It implies at the

same time that each reaction in the nervous system in response to the same stimulus should be the same. This assumption is certainly not true, since the stimuli occur at different times and are therefore presented to a different state of the nervous system. Different reactions should result. For some parameters, systematic changes during successive presentations of the same event are known. In those cases, variability may be thought of as a dependent factor.

The most important limitation of signal averaging is the inability of this method to give specific information about the specific influence of the single trials on the central tendency both with respect to amplitude and latency differences which may exist.

Knowledge of the consistency of potential changes is necessary, however, to any statement of reliability. Therefore measures of variability are now often used as routine qualification of the average. The most commonly used measure is "variability of voltage at the same time". But as long as those measurements refer to the mean or the sum of potentials, the variability in the amplitude of the signal may not be distinguishable from variability in latencies.

3.6.2 Alternatives to Averaging

One alternative to signal averaging is the method of superimposition, which assumes that the same variability would emerge with an equal number of randomly selected single trials. Superimposition of single trials, on the other hand, does not yield results if the signal-to-noise ratio is low. In both, the eye is used as a device for estimating mean and variability.

Discriminant and factor analysis techniques were proposed. These methods are based on the same assumption as average methods, namely that single trials represent variability in respect to a "real signal".

Fourier analysis has also been used for the analysis of averages as well as for that of raw data. Fourier analysis gives very little information about the time when the signal is occurring, but this difficulty may be partially solved by using successively smaller epochs within the record of interest.

4 Electrogenesis and Physiological Significance

The discussion of electrogenesis and physiological significance will be kept brief as *Caspers* and *Speckmann* will give an extensive account in one of the following volumes of "Reviews of Physiology". At present such a discussion can be only hypothetical. The main problem is to bridge the gap between our knowledge of sensory, neuron and membrane physiology as

well as neurochemical mechanisms on the one hand and the slow DC potential phenomena on the other hand.

4.1 Even-Related Slow (DC) Potentials

Slow surface potentials of evoked responses are assumed by some authors (*Watanabe* et al. 1966; *Creutzfeld* and *Kuhnt* 1966, 1967) to reflect the summated postsynaptic potentials of cortical cells as well as the potentials originating in synchronous afferent and efferent fibre activity. Expanding this theory to cover slow DC potentials *McSherry* (1973) assumes a combination of prolonged superficial axodendritic excitatory postsynaptic potential volleys and prolonged deep axosomatic inhibitory postsynaptic potential volleys, and he presumes distant cortical and subcortical centres to supply the steady barrage of inhibiting and excitatory input. In accordance with this view, *McSherry* and *Borda* (1973), in a study using monkeys, found intracortical, positive correlates to the slow rising surface negativity. *Rebert* (1973) described different active and inactive brain regions during the training of monkeys on a reaction time task. Some stereotactic studies using humans demonstrated the involvement of different subcortical brain structures in the genesis of slow DC potentials (*Haider* et al. 1968a, 1972; *Groll-Knapp* et al. 1968, 1977; *McCallum* et al. 1976).

Other authors stress the possibility that neurons and glia may contribute to slow DC potentials. *Goldring* (1974) concludes that evoked DC shifts will reflect either sustained hyperpolarization of neurons in cortical depth, predominantly glial depolarization, or a blend of both neuronal and glial depolarization.

Since gross recordings of slow DC potentials probably reflect the average potential fluctuations in a large number of individual units, investigations of the origin of DC potentials have focussed on special experimental conditions, such as seizure activity, in which the majority of individual generators are forced into synchronized action. Studies with such models have shown that DC changes are paralleled by membrane-potential changes of single neurons and of glia cells (*Karahashi* and *Goldring* 1966; *Glötzner* and *Grüsser* 1968; *Grossman* and *Hampton* 1968; *Caspers* and *Speckmann* 1970; *Speckmann* et al. 1972). Since *Kuffler* and *Nichols* (1966) pointed out that glial depolarization will occur due to local release of potassium as a result of neural activity, it seems possible that a linkage between neuronal and glial activity represents a complex generation of slow DC potentials. The extent to which such models may be applied to late responses, contingent responses and movement-related potentials awaits further study.

The possibility of an involvement of cholinergic mechanisms in the genesis of slow DC potentials is suggested by laminar DC studies of acetyl-

choline-activated epileptiform discharges in cerebral cortex (*Ferguson* and *Jasper* 1971) and the cholinergic influences on reward-contingent positive variations (*Marczynski* et al. 1971). Obviously many questions with respect to neurochemical mechanisms and their association with slow DC potentials in different brain regions need further explication. Because an "ascending cholinergic reticular system" from the brain stem, with dorsal and ventral tegmental pathways extending to the anterior thalamus and septal regions with important projections to the limbic system and cerebral cortex has been described (*Shute* and *Lewis* 1967; *Lewis* and *Shute* 1967), it may be speculated that thalamic slow DC potentials as observed by *Haider* et al. (1968a, 1972), *Rebert* (1972), *McCallum* et al. (1976) and *Groll-Knapp* et al. (1977) may also be cholinergically mediated.

It should be mentioned that some authors (*Wurtz* and *O'Flaherty* 1967; *Besson* et al. 1970) assume a vascular origin for DC potential shifts related to sleep, arousal and drug influences. The time course of vascular changes is however much too slow to account for the event-related slow DC potentials discussed herein.

4.2 Late Potentials

Assumptions about the physiological significance of late potentials are complicated by the fact that different experimental situations lead to different topographical distributions of these responses. Therefore it cannot easily be concluded that they all depend on an unitary physiological mechanism arising from a single cerebral generator system. Some authors (*Waszak* and *Obrist* 1969; *Karlin* et al. 1970) noted an augmentation of localized late responses in situations with an inhibitory context. *Papakostopoulos* et al. (1976) and *McCallum* et al. (1976) explain these findings as being due to an increased spatial distribution in the cortex, resulting in an augmentation of amplitude when recorded from the scalp, and they interpret late responses as electrophysiologically indicating an inhibitory brain function. These authors also find a spread of late responses generally located parietally to prefrontal cortex in situations demanding alterations of a preset plan and discuss this as being compatible with frontal lobe functions and with the special perceptual motor deficits after frontal lobe damage. *Desmeth* and *Debecker* (1979a, b) interpret the P_{350} as a post-decision event resulting from a phasic inhibition exerted by prefrontal cortex on the mesencephalic reticular formation at the closure of a cognitive processing epoch.

4.3 Contingent Potentials

In speculating about the physiological significance of contingent responses, *Walter* (1975) suggests that the underlying electrochemical processes may act as cortical "primers", ensuring prompt and economical firing of the central effector mechanisms. He mentions that such slow DC potential phenomena arise in brain regions closely connected to the motor area and that the amplitude of such potentials is related inversely to motor reaction times. During the 200–300 ms before the imperative stimulus, when the contingent response is at its peak, the amplitude of responses to intracerebral electrical stimuli is 30% larger than at other times, the latency of responses to interpolated sensory stimuli is slightly shorter at this phase and the threshold for the H-reflex is lower (*Papakostopoulos* et al. 1973).

Concerning the connection of contingent responses and the energy exchange system of the brain, *Walter* (1975) maintains that a local rise in available oxygen starts about 10 s after the response and peaks at about 20 s. Such local variations in oxygen availability may be measured with noble metal electrodes (*Cooper* et al. 1966). On the hypothesis that they are due to changes in blood flow and that this is mediated by variations in CO_2 as a result of glycolysis, it is supposed that the electrical phenomena of contingent responses are associated with local increases in brain metabolism.

4.4 Movement-Related Potentials

The physiological significance of movement-related potentials has been proposed on the basis of different timing for the main components. The readiness potential (RP, or *Bereitschaftspotential*) obviously resembles the contingent responses (*Kornhuber* and *Deecke* 1965; *Gilden* et al. 1966) and represents physiological activity related to conation or preparation for performance of a motor act (*Low* et al. 1966a). *Vaughan* (1975) showed that the negative shift recorded in the classic situation for contingent responses conforms to the topographical distribution of the readiness potential and is more closely time locked to the motor response than to the stimulus.

On the other hand it has to be pointed out that slow (DC) potentials may be observed even when no motor response is required. The subject may only anticipate a meaningful presentation (*Cohen* 1969) or the "response" may only be a decision (*Haider* et al. 1968b). Some clarification may be found in the observation that tasks requiring sensory discrimination are associated with potential distributions consistent with their generation in sensory areas, whereas tasks with establishment of a preparatory

motor set are characterized by potentials arising from motor cortex (*Vaughan* and *Costa* 1968; *Vaughan* 1969). The premovement phasic components are considered to represent cortico-subcortico-motor-cortical loops with cerebellar neurons being active prior to the motor cortex as well as the corticospinal discharge immediately preceding motor contraction. With subdural electrodes during stereotactic surgery in humans a "localized motor potential" is observed at area 4 over the representation of hand or finger movement (*Ganglberger* et al. 1980). The corticomuscular delay, i.e. the interval between onset of cortical potentials and electromyograph (EMG) activity varies according to the length of neural pathways between brain and contracting muscle (*Ganglberger* 1962; *Vaughan* et al. 1968). The late positive wave of movement-related potentials has been considered to represent kinesthetic feedback (*Kornhuber* and *Deecke* 1965). Later, *Vaughan* et al. (1968) have shown that deafferentiation of the upper extremity failed to alter the configuration of motor potentials. Sometimes, especially in mental patients, the late positive components are absent and sometimes they last very long. It may be postulated therefore that these later portions of movement-related potentials may reflect primarily central mechanisms.

5 Electrocorticography and Stereo-Electro-Encephalography

5.1 Electrocorticographical Studies

The term "electrocorticography" refers to the recording of electrical activity through the dura (the term "electrodurogram" is seldom used), directly from the cortical surface, using electrodes placed in different cortical layers or with a transcortical electrode arrangement.

5.1.1 Late Potentials

Late potentials have been observed localized mainly over the parietal and frontal cortex during stereotactic brain surgery (*Groll-Knapp* et al. 1968; *Papakostopoulos* and *Crow* 1976). These studies show that late potentials are cerebral events, independent of stimulus modality and with a localization slightly different from contingent responses. In the most frequently used experimental situation the maximal amplitude of LP is localized over the parietal cortex. Under special circumstances, for instance in situations where the subject is asked to alter a preset plan, the late potentials may also be recorded over more frontal and prefrontal localizations.

5.1.2 Contingent Potentials

Contingent potentials, in most situations, are electrocortigraphically recorded over a widespread central and frontal area (*Haider* et al. 1968c; *Papakostopoulos* and *Crow* 1976; *McCallum* 1978). The distribution for contingent responses is usually similar though not identical to the distributions of late potentials and readiness potentials. Contingent potentials are symmetrically distributed and slightly more prominent anteriorly then late responses and readiness potentials. In animal studies under special circumstances, for instance during waiting periods (*Donchin* et al. 1971, 1973) or following periods of food deprivation (*Borda* 1973), some authors observed a central or postcentral dominant potential. In the usual stimulus-response paradigm, most authors (*Low* et al. 1966b; *Rebert* 1972, 1973; *Borda* 1973) found a frontal premotor dominant potential. *McSherry* and *Borda* (1973) concluded from their work with animals that contingent potentials are not uniformly distributed throughout the frontal lobe, but rather are a local phenomenon and consist of a superficial cortical negative shift or an intracortical positive shift or, at some locations, both a superficial negative and an intracortical positive shift.

5.1.3 Movement-Related Potentials

Cortical recordings of movement-related potentials should be instrumental in providing additional insight into the questions related to preparation, initiation, execution and termination of movement. At the moment the information is meagre and partially contradictory. *McCallum* (1978) demonstrated that the readiness potential is distributed weakly asymmetrically, showing increased negativity over the hemisphere contralateral to the operative muscles, the largest values occurring pre-Rolandically. In no case was a premotion positivity observed by *McCallum*. *Papakostopoulos* and *Cooper* (1976) found cortical negativity to be completely paralled with EMG recordings up to the point of movement and concluded that these potentials may be the result of movement. *Groll-Knapp* et al. (1977) and *Haider* et al. (1979) extracted some patterns of movement-related cortical potentials: one early positive potential shift in the parietal and the frontopolar cortical region, a slow negative potential change occurring on the premotor region and marked phasic potential shifts around the time of movement in the proper motor cortex.

A premovement positivity followed by a negative small "motor potential" can be observed locally at the region of area 4 indicating hand or finger movement. If the electrode is near or at the postcentral area, only a prominent positive wave is seen. These specific localized changes are depicted in Fig. 5 in which the different curves are grouped according to the different representation fields.

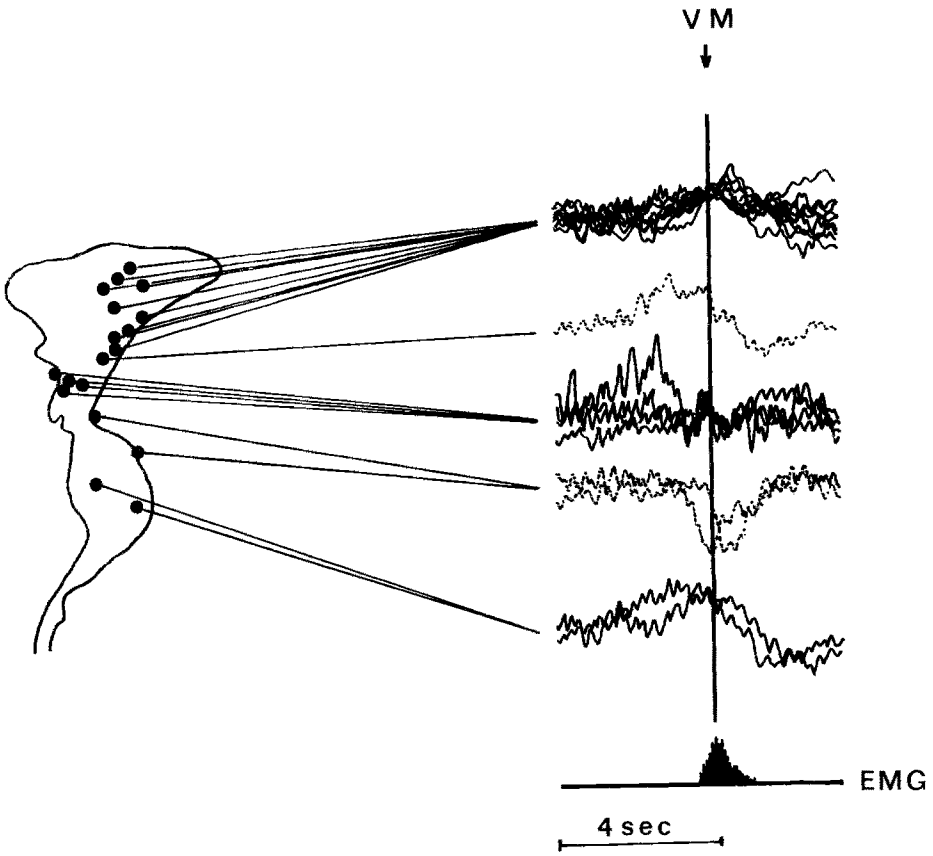

Fig. 5. Voluntary movement-related potentials from different localizations in area 4. The eight individual traces are grouped and superimposed according to representation fields. Negativity upwards, button trace: averaged EMG activity. ↓ trigger point at time of the button press

5.2 Stereo-Electro-Encephalographical Studies

The term stereo-electro-encephalography (SEEG) has been proposed for the recording of electrical activity from different intracranial levels with the help of stereotactic procedures for localizing the different brain structures (*Bancaud* 1975). The localization procedures that make it possible to determine intracranial and especially subcortical brain structures rather precisely in animals cannot be transposed directly to man. Functional stereotactic investigations in man were dependent on the publication of atlases providing the spatial coordinates of the different brain structures. With the help of special methods and electrodes, it is possible in any patient to reach the intracranial targets previously determined. Investigations

are based either on chronically implanted electrodes or recordings made during acute stereotactic surgery. In both situations location of electrodes and duration of investigations are limited according to the medical indication.

5.2.1 Late Potentials

Late potentials for different subcortical structures have not been systematically studied up to now. A series of experiments by *Groll-Knapp* et al. (1968) and *Haider* (1970) showed in man, however, that evoked potentials recorded in nuclei of motor thalamus after unexpected acoustic stimuli clearly differentiate from evoked potentials after regular stimulation. The

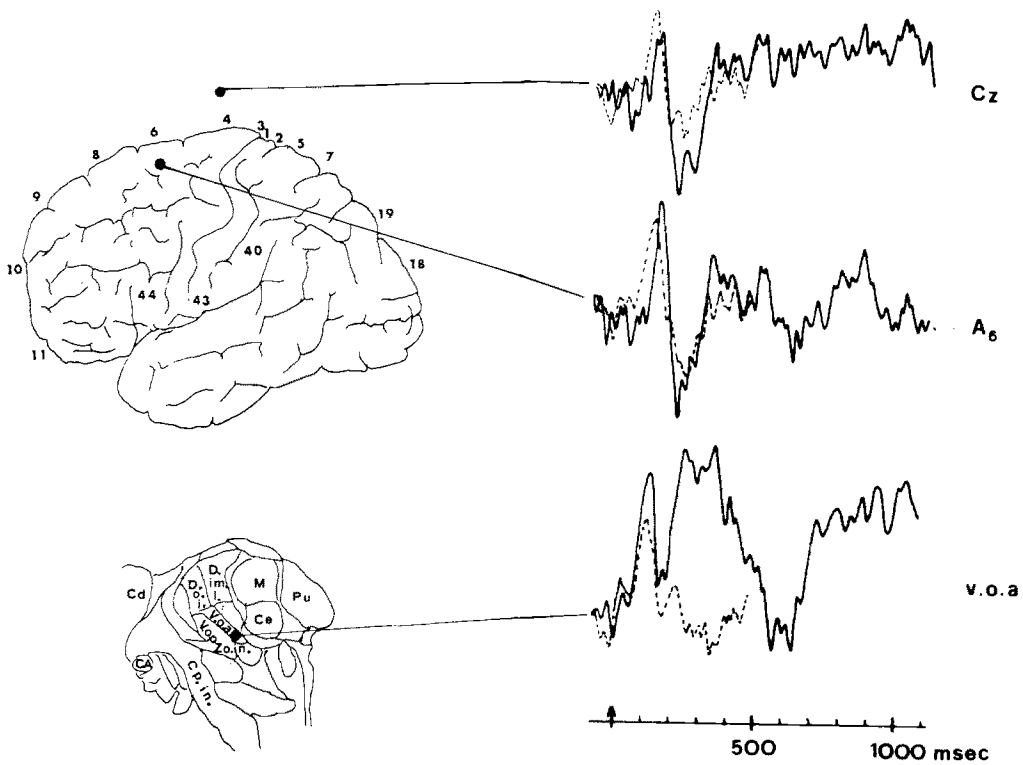

Fig. 6. Evoked potentials on vertex (scalp), in area 6 (subdural) and in the motor thalamus (nucleus ventralis oralis anterior, *v.o.a.*) after unexpected (———) and expected (- - - - -) stimuli. Reference: linked mastoids; negativity upwards.

V.o.a. = Nc. ventro-oralis anterior
V.o.p. = Nc. ventro-oralis posterior
Zo.in = zona incerta
Ce = Nc centralis thalami (centre median)
Pu = Pulvinar thalami
M = Nc. medialis thalami
D.im.l = Nc. dorsalis intermedius thalami
D.o.l. = Nc. dorsalis oralis thalami
Cd = Nc. caudatus
CA = Commisura anterior
Cp.in = Capsula interna
Cz = Vertex

differences consisted of longer latencies and higher amplitudes of the prominent wave in the orienting situation. The late potentials in the motor thalamus demonstrate the involvement of the central motor system in orienting reactions. Fig. 6 gives examples of late potentials in motor thalamus, premotor cortex and scalp derivation.

Acoustically evoked potential shifts in motor thalamus have also been reported by *Ganglberger* et al. (1971) and by *Fukushima* et al. (1976).

The differential effect of attention and task relevance on late subcortical somatically evoked potentials (SEPs) was previously mentioned by *Ervin* and *Mark* (1964) and recently studied by *Velasco* et al. (1975) in a group of Parkinson's disease patients. *Ervin* and *Mark* (1964) reported SEPs at the medial thalamus (CM) with long-lasting rhythmic after-discharges. Significant amplitude reduction of late SEP components was found by *Velasco* et al. (1975) when patients shifted from attention to distraction or habituation. No such changes occurred in early components. In contrast to the early SEP components the late components occurred rather widespread in thalamic lemniscal, prelemniscal and reticular regions.

5.2.2 Contingent Potentials

For several years contingent responses have been generally regarded as cortical phenomena, primarily because it was possible to record contingent potentials directly from the cerebral cortex (see Sect. 5.2.1). Recordings taken from thalamic nuclei in a standard CNV paradigm during acute stereotactic surgery indicated, however, a close relationship between the thalamic and the cortical electrophysiological event connected with expectancy (*Haider* et al. 1972, 1979; *Groll-Knapp* et al. 1970). These results are shown, together with similar results reported by *Iliukina* (1977) and *Tsubokawa* and *Moriyasu* (1978), in Fig. 7.

In Fig. 7 contingent responses reported by different authors for different patients during stereotactic brain operations can be seen. The vertex and cortical leads show the typical CNV pattern. In the thalamus, clear local differences may be observed. In the motor thalamus [ventrooralis posterior (v.o.p.) and ventrolateralis (VL) regions] only late potentials after the first stimulus (orienting potentials) and between the second stimulus and the response occur, but no slow rising negativity is seen.

In the nucleus medialis, or dorsomedialis, as well as in the centre median and intralaminar nuclei a clear slow negative potential shift is seen in most cases. This potential shift has a short deflection time and precedes the slow rising negativity of cortical and vertex derivations in its sequential development. This may show that in humans the whole medial thalamus and the mediothalamic-frontocortical system are involved in the generation and control of slow DC potentials of the cortex.

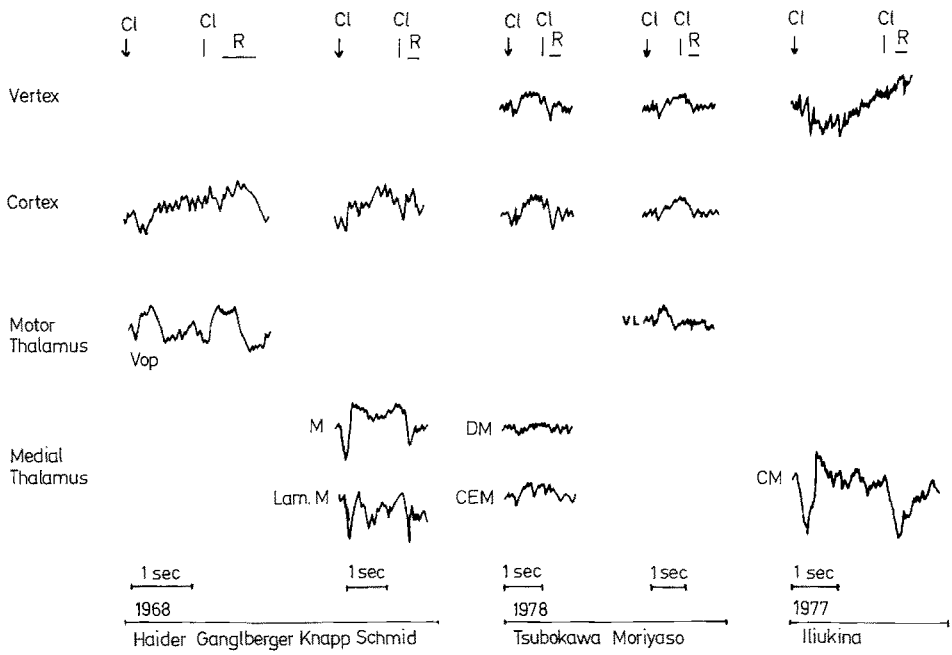

Fig. 7. Contingent potentials in a CNV paradigm with a warning and an imperative stimulus *(Cl-Cl-R)*, found by different authors in *vertex, cortex, motor thalamus* (*V.o.p.*, ventro-oralis posterior, *VL*, ventrolateralis), medial *(M)* or dorsomedial *(DM)* nucleus and non-specific thalamic projection nuclei (*CM*, centre median; *Lam*, lamella medialis). Negativity upwards; ↓ trigger point; *R*, time of reaction

These conclusions are supported by the observation of *Tsubokawa* and *Moriyasu* (1978) that ventrolateral thalamotomy has no effect on the amplitude of cortical contingent potentials, whereas medial thalamotomy causes suppression of contingent potentials. One could speculate that this mechanism of suppressing attention and expectancy for exogenous stimuli may be involved in the relief of intractable pain after medial thalamotomy.

McCallum and his colleagues (1976) studied DNV distribution with multiple implanted gold electrodes in brain stem structures. Widespread slow (DC) potential changes were observed for brain stem derivations, those from the most rostral electrodes being positive and those from the most caudal (mesencephalic electrodes) negative. These slow subcortical potential shifts look very similar to the contingent responses recorded from some parts of the cortex. In thalamic nuclei little evidence of contingent responses was found.

Some common features in all studies seem to be that complex cortical events are mediated at subcortical levels. Many thalamic nuclei show no slow DC potential changes such as contingent responses, but in some thalamic structures, especially the medial thalamus, slow potential shifts ac-

companying the beginning and the duration of the cortical slow (DC) events are observed.

Several experiments using animals support the still rather limited findings in human studies. Slow potentials were recorded in different animals from a variety of subcortical nuclei during different experimental paradigms. *Rebert* (1972, 1973, 1976), in macaque monkeys, found negative potential shifts in several non-specific projection nuclei (midbrain reticular formation, nucleus reuniens, posterior hypothalamus), whereas positive shifts developed in the caudatum, amygdala and nucleus dorsomedialis, thus confirming earlier assumptions that positive shifts occur in rhinencephalic structures. For some structures the coincidence of negative shifts with increased multiple unit activity and of positive shifts with decreased unit activity could be demonstrated. The earliest indication of learning (defined by the occurrence of slow potentials) was found in non-specific ascending reticular structures and not in cortical regions.

A series of studies in cats (*Skinner* 1971; *Skinner* and *Lindsley* 1973; *Yingling* and *Skinner* 1977; *Skinner* and *Yingling* 1977) demonstrate the involvement of the mediothalamic frontocortical system in the generation of cortical slow DC potentials. Bilateral cryogenic blockade in the inferior thalamic peduncle (ITP) with interruption of connections between medial thalamus and frontal cortex abolished all SP changes in the cortex after novel stimuli as well as SP after strong cutaneous stimulation or SP in a tone-shock conditioning paradigm. Slow potential changes in nucleus reticularis thalami are unequally affected. While conditioned slow potential shifts and slow potentials evoked in the reticular thalamic nucleus after medial thalamic stimulation are abolished during ITP blockade, SPs after medioreticular formation stimulation and after strong cutaneous shock remain unaffected.

5.2.3 Movement-Related Potentials

The distribution of movement-related potential shifts throughout the midbrain and brain stem was studied with implanted gold electrodes (*McCallum* et al. 1976). Similar to their CNV results the authors found little evidence for movement-related potential changes in thalamic nuclei. In the rostral derivations MRP were positive, whereas in the caudal derivations negative shifts could be demonstrated.

In recent studies *Groll-Knapp* et al. (1977) and *Haider* et al. (1979) reported voluntary movement-related slow potential changes in different subcortical nuclei. Subcortical target points – according to the indication for stereotactic surgery – were in different thalamic nuclei (Nuclei medialis, centre median, v.o.a, V.o.p, L.Po., V.c.pc; see Fig. 8 for explanation of

abbreviations), in the tractus spinothalamic, fornix and amygdala [nomenclature of *Hassler* (1959), stereotactic atlas of *Schaltenbrand* and *Bailey*].

Voluntary movement-related slow (DC) potential changes for various thalamic specific and non-specific nuclei and other subcortical structures are shown in Fig. 8.

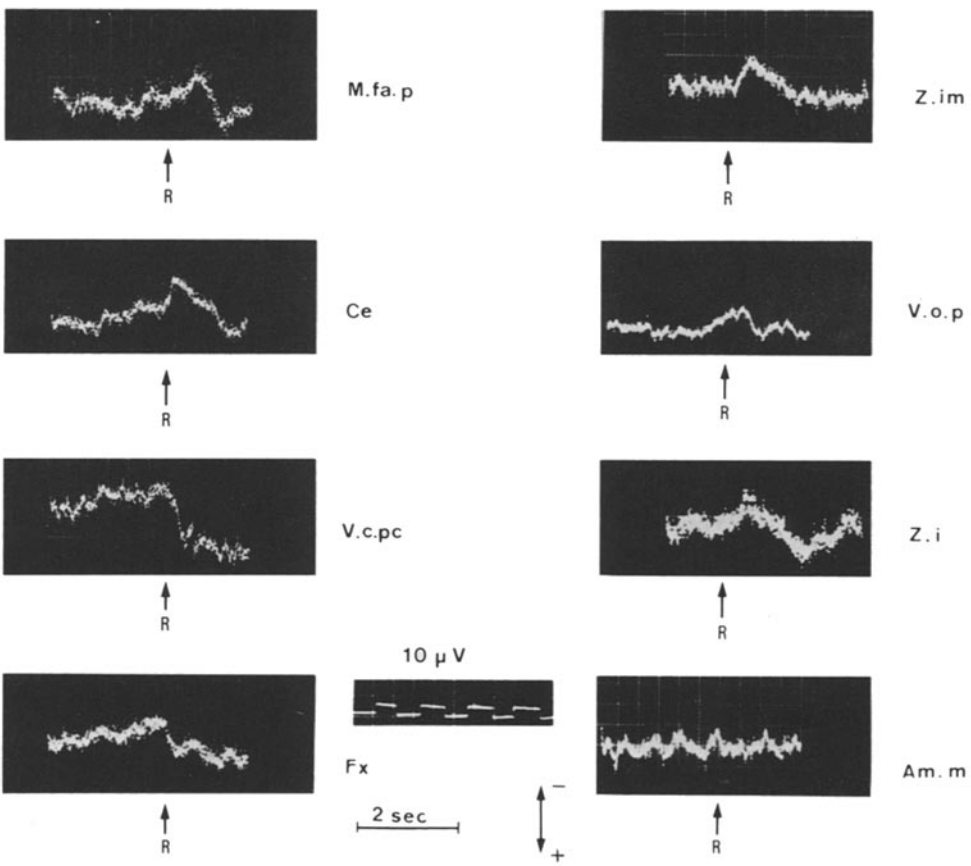

Fig. 8. Voluntary movement-related potentials from various thalamic nuclei and other subcortical structures. *M.fa.p*, Medialis fasciculus posterior; *Ce*, nucleus centralis or centre median of *Luys; V.c.pc*, ventrocaudalis parvocellularis; *Fx*, fornix; *Z.im*, nucleus centralis intermedius; *V.o.p*, ventro-oralis posterior; *Z.i*, zona incerta; *Am.m*, nucleus medialis amygdalae. The different beginnings of the traces are due to the different tape speeds during the instantaneous opisthochronic analysis; *R*, reaction and trigger point

In the specific motor relay nuclei and the zona incerta the negativity starts shortly before motor action and is followed by a relatively sharp increase. The peak is reached after the trigger mark produced by thumb press. In the nucleus medialis or dorsomedialis, as well as in the centre

median, a clear slow negative potential shift starts earlier and shows a higher amplitude than those recorded from the motor thalamus. In recent studies we observed greatly enhanced motor thalamic potentials during goal-directed movements, which were sustained until the target was reached.

According to our findings four patterns of cortical and subcortical event-related slow potential changes may be differentiated:

1. Early positive potential shifts in parietal and frontopolar cortex associated with beginning negative potential changes in medial thalamus;
2. Widespread slow negative potential rises in premotor and parietal cortex, increasing during goal-directed movements;
3. Localized potential changes on proper motor and sensory cortex, motor thalamus and other subcortical nuclei around the time of movement. Some of these potentials are greatly enhanced and sustained during goal-directed movements; and
4. Positive potential declines in most cortical and subcortical electrode sites after movements, decisions or responses.

On the basis of time relationships of these four possible patterns it may be speculated that designs or "ideations" are accompanied by early potential changes in parietal cortex and the mediothalamic-frontocortical system. These potential changes, together with widespread negative potential rises over premotor and parietal cortex (readiness potentials), constitute the preparatory period for judgements, decisions and responses. In the initiation period a premotion positive decline over premotor cortex as well as localized potential changes in motor cortex and motor thalamus are sometimes seen. In the part of area 4 representing hand or finger movements, premotion positivity (PMP) and motor potentials (MP) are seen (*Ganglberger* et al. 1980). Near or at the sensory cortex only a prominent positive wave occurs. In the upper and lower parts of area 4 a slowly rising negativity reaching its peak around the time of actual movement or shortly afterwards is observed. These negative peaks of motor cortical and motor thalamic potentials are greatly enhanced and sutained during goal-directed movements until the target is reached. Since the motor thalamus is integrated in motor feedback loops from the cerebellum and basal ganglia to the motor cortex, these potentials may be related to the control and internal monitoring of programming activities during initiation and execution of movement. The final post-movement-positive potential decline may represent central mechanisms related to termination of movements and re-afferent signals from the periphery.

Many of these interpretations are still highly speculative, but our studies, based on acute stereotactic surgery, demonstrate some mechanisms of summation and integration of the multiple local generators in the cortex to the common patterns of event-related responses emerging from

studies using scalp electrodes. Moreover, these studies reveal subcortical involvement in the regulation of cortical activity and the interrelationship between subcortical and cortical electrophysiological events.

6 Topographical Aspects (Scalp Distribution)

6.1 Late Potentials

Studies by *Vaughan* and *Ritter* (1970) suggested for LPs a dipole layer source with axes perpendicular to the surface of the scalp and centred upon the parietotemporal association area. In accordance with this suggestion the largest amplitude for late potentials has been reported at the parietal electrodes (*Donchin* et al. 1975). The same modality non-sepcific distribution with a maximum over the parietal region has been found for the "emitted potentials" from missing stimuli. The distributions and presumptive sources of negative and positive components of visually evoked potentials and for potentials after missing stimuli are shown in Fig. 9.

The topographical analyses seem to show that the earlier components have distributions compatible with sources in and near the primary cortical projection area, whereas the potential components for missing stimuli similar to all late potentials have a distribution compatible with a cortical origin in the inferior parietal lobule. The main localization for late potentials has also been found in electrocorticographical studies to be at the parietal cortex (see Sect. 5). Because the topographical distribution suggests an origin in secondary cortical projection areas and in association cortex, *Vaughan* (1975) uses the term "association cortex potential (ACP)".

Since late potentials are not a uniform wave component but consist of a variety of negative and positive waveforms, we must also take into account the possibility of different sites of generation, depending for instance on the task and experimental design (see Sect. 8.1). Late potential components, with distributions largest over posterior regions, have been described during an acquisition task (*Poon* et al. 1974). On the other hand a large frontal positive component following a negative orienting potential was observed for novel stimuli (*Courchesne* et al. 1975). One may speculate, therefore, that different topographical field distributions for late potentials reflect different functions of cortical and subcortical sites with respect to novelty and information processing.

Stereo-electro-encephalographical studies (see Sect. 5) clearly demonstrate that the source of late potentials is not purely cortical. Therefore one has to consider that either subcortical or combined cortical-subcortical sources may account for the reported scalp distribution. Intracranial

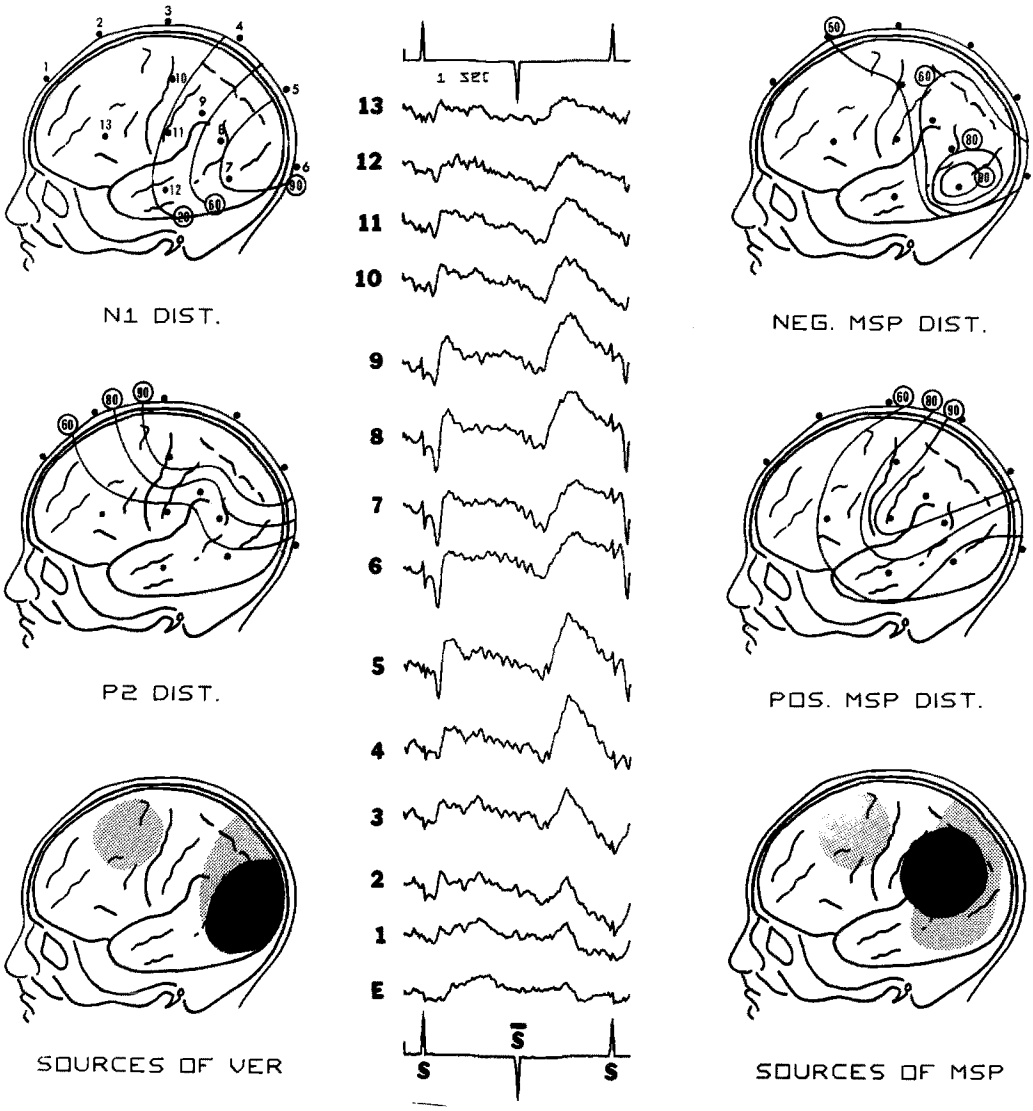

Fig. 9. Averaged responses *(VER)* to 1-s light flash *(S)* and brain potentials missing stimulus potentials *(MSP)* associated with unexpected deletion of a flash *(S)*. Potentials are grand means of 11 responses obtained from eight subjects. Isopotential maps on left depict the negative (N_1) and late positive (P_2) components of the *VER*, respectively, together with the estimates of intracranial sources inferred from these data. Maps on the right indicate the distribution and presumptive sources of the missing stimulus paradigm (*Vaughan* 1975)

studies during stereotactic surgery (*Groll-Knapp* et al. 1968, 1970; *Haider* 1970; *Ganglberger* et al. 1971; *Velasco* et al. 1975) have shown that quickly habituating late potentials for unexpected (orienting) stimuli are widespread in different thalamic nuclei, even in the motor thalamus. This may explain to a certain degree why late potentials show modality non-specific distributions without polarity inversions in scalp and cortical depth recordings and with maximum amplitudes deep in the brain and not near the cortical surface (*Wood* et al. 1979).

6.2 Contingent Potentials

There may be three approaches to the analysis of differences in contingent potentials, recorded from different localizations of the scalp. Some authors consider contingent potentials to be unitary phenomena, while others see them as being composed of several different waves, converging on local recording sites. A third group assumes that each potential is characteristically generated at the local site from which it is recorded (*Weinberg* and *Papakostopoulos* 1975).

Early studies (*Walter* et al. 1964; *Low* et al. 1966a) reported contingent potentials with maximal amplitudes at frontal sites. Later studies reported a gradient of change in the anterior-posterior axis. Many authors (*Cant* et al. 1966; *Walter* 1967a, b; *Cohen* 1969; *Gullickson* 1970) suggested a bilateral symmetrical distribution with maximum at the vertex, being smaller in the frontal region and smallest in posterior areas.

In tasks involving the processing of verbal and spatial information, the amplitudes of contingent potentials were larger at parietal areas compared to frontal and temporal sites (*Marsh* and *Thompson* 1973).

In conditioning experiments differences in location have been found related to the different stages of training. In early training phases a central dominant potential was seen; during overtraining periods a frontal dominant wave was observed (*Borda* 1970; *Hablitz* 1973).

That contingent potentials may indicate functionally different processes in more frontal or more posterior areas is suggested by different studies. Task dependency has been demonstrated by frontal dominant potentials in an auditory discrimination task and central dominant potentials prior to motor movements (*Järvilehto* and *Fruhstorfer* 1970).

Correlation studies of contingent potentials and reaction times showed poor matching of frontal and vertex waveforms contrasting with good matches of central and parietal with vertex waveforms. Moreover, there was a lack of correlation between contingent potentials and reaction times in prefrontal areas but some correlation in central-parietal areas (*Papakostopoulos* and *Fenelon* 1975). Similarly, *Weinberg* and *Papakostopoulos*

(1975) used a pattern recognition technique to determine the form differences of contingent potentials in frontal, parietal and vertex sites. Frontal potentials were the smallest and were different in form from vertex, central and parietal sites.

One conclusion to be gained from all these studies seems to be that the wave-form of contingent potentials to a certain degree maps the processing of information under the recording area. In this respect contingent potentials show similarities to late potentials. But besides topographical differences there are differences in the kind of information processing and its outcome. Late potentials are post stimulus and therefore are most sensitive to immediate outcomes of information processing, whereas contingent potentials occur prior to critical stimuli and may reflect changes in different cerebral sites as a result of accumulated information.

6.3 Movement-Related Potentials

The topography of voluntary movement-related potentials was first studied systematically by *Vaughan* et al. (1968) and *Deecke* et al. (1969). *Gerbrandt* et al. (1973), *Becker* et al. (1973), *Deecke* et al. (1973, 1979), and *McCallum* et al. (1976) have also investigated this problem.

There is still some controversy about the topographical distribution of movement-related potentials. Different spatial distribution of maximal amplitudes and onset of the main three potential components preceding the movement, as well as for the post-movement positivity, have been found.

The individual differences in both the prominence and degree of symmetry of the MRP are substantial and greater than for the CNV. These variations could perhaps partly account for some of the discrepancies in the above-mentioned studies. Differences in experimental design and especially in the measurement technique may also explain diverging results.

Deecke et al. (1969, 1973), *Deecke* and *Kornhuber* (1977) and *Becker* et al. (1973) report that the slow surface negative potential (readiness potential , RP) is maximal at the vertex and that this potential is nearly symmetrical in the pre- and postcentral region. It is sometimes larger over the contralateral than over the ipsilateral precentral region, mainly when the dominant hemisphere is involved in the movement. The readiness potential declines in amplitude in more anterior derivations. In frontal and basal leads, however, *Deecke* and *Kornhuber* (1977) found this potential to be positive.

The difference in the distribution of the RP compared to that of the CNV indicates that the slow surface negative potential reflects the general facilitating process which pre-activates the brain regions needed in the

ensuing situation. During a premovement time the frontal lobe might be inactive (no negative shift) or even inhibited (positive RP).

Premovement positivity was also found to be symmetrically distributed and rather widespread over the scalp. In contrast the additional rising negativity occurring shortly before the onset of EMG activity (motor potential, MP) had its maximum over the contralateral precentral motor region, sometimes may only be recorded there and is a very circumscribed phenomenon. This has now been directly demonstrated by our corticographic studies as shown in Fig. 5 (Sect. 5.1.3).

There is rather good agreement among different authors that the final component of the movement-related potential, the relatively large and complex positive (P_2)-negative wave occurring after the movement, is largest and most asymmetrical predominantly over the motor cortex and that these components are mainly due to the input from joint receptors. Several authors (*Vaughan* et al. 1968; *Deecke* et al. 1969; and *Gerbrandt* et al. 1973) mention the close relationship between the P_2 peak and the "vertex potential" of the somatically evoked potential. The authors have developed their concepts about physiological origin and the physiological relevance of the potential components according to scalp distribution and the time relations of the movement-related potential components. *Vaughan* et al. (1968) report that movement-related potential components are directly connected to motor cortex activity. In contrast, *Gerbrandt* et al. (1973) states that the motor origin of the different components of the "average movement potential" components indicates different aspects in the preparation and execution of a motor movement. Taking into account the results of cortical and subcortical investigations of humans (*Groll-Knapp* et al. 1977; *McCallum* 1978) mentioned in the previous section this concept now seems the most appropriate.

7 Maturational Aspects

7.1 Theoretical Problems of Developmental Studies

Developmental studies in slow potential research involve some theoretical problems. Age is generally taken as the independent variable in developmental studies, but the question remains to what extent chronological age is a relevant parameter for a process, such as slow potential changes, which is so clearly linked to behaviour. The great interindividual differences, mainly in children, between chronological age and behavioural age point out this difficulty. There exists no complete parallel between psychological and behavioural maturation, on the one hand, and biological and neurol-

ogical development on the other. One should therefore try to find other criteria, perhaps based on behavioural tests, to form homogeneous groups for developmental investigations.

Compared to the general explosion of research relating to the CNV since its discovery, only a few investigations have attempted to study ontogenetic aspects of SP. It is only in the last years that the number of relevant publications has increased, due mainly to the fact that SP research was introduced to psychiatric research. In this connection one expects that the study of SP in normal subjects can provide the normal data base necessary for comparative evaluation of SPs in psychiatric populations and for the development of adjuvant procedures for the evaluation of higher-order functions in clinical populations.

7.2 Late Potentials

The various long latency waves (> 100 ms) seem to be unequally affected by age. Peak latencies of wave components between 140 and 300 ms are reported to be shortest for teenagers and young adults (*Dustman* and *Beck* 1969; *Lüders* 1970; *Schenkenberg* 1970, unpublished work; *Buchsbaum* et al. 1974). Young children (*Dustman,* 0–4 years; *Buchsbaum,* 6–9 years) and older people show longer latencies. *Courchesne* (1979) did not find any change in latencies of these potential components between 6 and 36 years of age. Amplitudes of these components generally decline at higher ages (*Dustman* and *Beck* 1969; *Lüders* 1970; *Buchsbaum* et al. 1974; *Courchesne* 1979).

Wave components occurring after 300 ms were observed by *Kurtzberg* et al. (1979) for children in paradigms similar to P_3 paradigms used for studies of adults.

Recently *Courchesne* (1979) reported on a series of experiments with subjects between 6 and 36 years of age. When events occurred which were not explicitly pre-categorized, subjects of different ages produced ERPs dominated by different waves. In adults P_3 waves were the most prominent, while large negative components with peak latencies at about 700 ms and positive peaks at about 1000 ms were characteristic for 6-month-old infants (*Courchesne* et al. 1977) and for children between 6 and 17 years (*Courchesne* 1979). In this latter group, the P_3 component, which was not clearly developed in infants, had peak latencies at about 700 ms and decreased with age to approximately 400 ms.

In studies in which subjects are actively involved, significant age-dependent changes were not seen (*Marsh* 1978). Higher activity for older subjects was found if a cumulative voltage measure was taken between 200–500 ms (*Schenkenberg* 1970, unpublished work).

Linear correlation coefficients were calculated for ten normal children (5.7–12.7 years; $\bar{X}$ = 9.5 years) between age and cumulative voltage measures referred to prestimulus baseline for positive shifts occurring during the encodement interval in a three-stimulus paradigm "protracted p 300 waves" (*Otto* et al. 1976). Substantial negative correlations were found for all measurement epochs during the S_2–S_3 (encodement interval) and for the 320-ms epoch preceding S_2. Young children tended to show positive shifts during the warning and encodement interval while older children showed negative shifts similar to CNV.

Positivity after the warning signal in a classic CNV paradigm was found to be developmentally related (*Karrer* and *Ivins* 1975, 1976). Postwarning stimulus positivity (PWSP) was determined in relation to prestimulus baseline and occurred with a latency of about 300–500 ms. There were significant differences between the two groups under experiment. Younger children (9–12 years; $\bar{X}$ = 11.1) had significantly larger PWSP than older children (13–18 years; $\bar{X}$ = 15.1) on the vertex. The same trends were not significant in frontal areas. The larger PWSP in young children is interpreted within the p 300 conceptualization as reflecting greater conscious effort to control irrelevant activity and greater uncertainty in responding.

Late negative postwarning stimulus activity was observed during foreperiod experiments by *Loveless* and *Sanford* (1974). These authors found a negative-going potential shift peaking about 1 s after the warning signal. No significant difference in this component was found between two age groups, one with a mean age of 21.0 (20.2–22.7) and a second with a mean of 66.9 years (58.1–75.1). Form and latency of this negative peak were not affected by the use of different sets of foreperiods, and this uniformity strongly suggests that this negative peak is a constant effect of the warning signal and is interpreted by the authors to be part of the orienting response.

Similar postwarning signal activity showed an age dependence for younger subjects in the study by *Klorman* (1975) insofar as this component tended to habituate over several trial blocks in 19-year-olds, but not in 10- and 14-year-olds.

7.3 Contingent Potentials

Compared to the few reports on the age dependence of late potentials the literature on contingent potentials is more systematic and covers a broader span of age. *Walter* (1967a, b), using a constant foreperiod reaction time paradigm, could not observe CNVs in children under 3 years. Nevertheless, it seems possible to elicit contingent variations in very young and immature children (i.e. 3 years). In a systematic study of preschool children, clear

CNVs were recorded by the use of coloured patterns and novel auditory patterns as S_2 without the occurrence of a motor response. Probably the children's general interest, attention, motivation and cooperation were higher due to the different experimental design (*Gullickson* 1973a).

Between the ages of 5 and 15, CNV is rather unstable. Either no CNVs, in the usual sense, are observed or only small inconsistent negative shifts, sometimes even a positive-going shift in the S_1–S_2 interval and a post-S_2 negativity (*Low* and *Stoilen* 1973; *Timsit-Berthier* and *Hausman* 1973). *Papani* and *Zappoli* (1973) found "tent-like" CNVs for this age.

In general there seems to exist a positive correlation between CNV amplitude and age during childhood up to the time when the adult contingent variation is established. Table 3 (*Cohen* 1973) demonstrates the age dependency of the CNV.

Table 3. Mean amplitude of peak CNV in 6–18-year-old subjects in frontal, vertex and parietal derivations

Age of child	Vertex	Frontal		Central		Parietal	
		L	R	L	R	L	R
6	11	6	6	11	10	12	11
7	13	9	8	12	13	12	11
8	13	9	9	12	13	12	12
9	15	11	10	13	12	13	12
10	14	10	11	13	12	12	11
11	16	12	13	13	14	11	11
12	15	12	14	14	13	11	12
13	16	14	12	13	14	11	10
14	17	13	13	15	14	12	12
15	21	15	13	15	16	12	13
16	20	14	15	17	17	13	12
17	21	15	14	17	18	14	13
18	22	16	15	18	19	13	12

No agreement has so far been reached about the age at which "adult-like CNV" can be observed. Several authors assume a rather clearly maturation of CNV, at an age of about 10–11 years (*Low* et al. 1966a; *Timsit-Berthier* and *Hausman* 1972, 1973; *Low* and *Stoilen* 1973; *Lancry* 1976; *Karrer* and *Ivins* 1976; *Karrer* et al. 1978). These authors found either immature CNV forms for children younger than 10 years; and the usual configuration for older ones, or no correlation between age and CNV parameters after age 12.

A later age for the maturation of the CNV is suggested by *Klorman* (1975), who did not find the usual CNV configuration in subjects younger than about 14. In the investigations of *Cohen* and his group the adult peak

amplitude of approximately 20–22 μV and pattern was reached by age 15 (*Cohen* 1973). In earlier studies an even later age was proposed (*Cohen* 1970, 16–18 years; *Cohen* et al. 1967a, 20 years).

Whereas in adults CNV typically declines abruptly to baseline upon responses to S_2, in children this termination of CNV is usually gradual and has been suggested as an index of maturation (*Cohen* et al. 1967b; *Low* and *Stoilen* 1973).

Investigations of CNV in older populations were done by *Loveless* and *Sanford* (1974a), *Marsh* and *Thompson* (1973) *and Marsh* (1978). *Loveless* and *Sanford* have shown equal orienting responses for a group with a mean age of 21 and for one with a mean age of 66.9, but much reduced CNV responses at long foreperiod intervals (up to 15 s) for older subjects. The main age difference consisted in a rise of slow potential initiated either immediately following the warning signal or after a brief period and then sustained at a fairly constant but low level throughout the foreperiod.

Marsh and *Thompson* (1973) compared CNV parameters of a young group (19–21 years) with those of an elderly group (68–80 years). The absence of any consistent age difference agrees with the findings of *Thompson* and *Nowlin* (1971), but conflicts with the results of *Loveless* and *Sanford* (1974a). If one assumes that CNV reflects the level of arousal, the data suggest that elderly subjects are capable of showing central arousal levels similar to those of the young when the experimental situation requires a high arousal level.

There is an interesting relationship between age and CNV distribution over the scalp. As previously discussed the usual topography of the CNV consists of maximum amplitude on the vertex and higher CNV amplitudes in frontal areas, compared to posterior regions. The anterior-posterior distribution and the amplitude changes with age can also be seen in Table 3. The CNV attains its earliest peak amplitude in younger children in the parietal region. There is a shift to central and frontal maximum amplitude for older children and adults. After 11 years of age the adult pattern of higher CNV in the frontal areas emerged (*Cohen* 1973). This shift in topographical distribution is due to an increase in frontal CNV, whereas parietal CNV amplitude remains essentially the same between 6 and 10 years of age. Other investigations support these findings, showing clearer CNV in posterior brain areas of young people than in adults (*Walter* 1967b) and a higher correlation for older children (between frontal and vertex derivation) (*Karrer* and *Ivins* 1976). *Low* and *Stoilen* (1973) occasionally found parieto-occipital dominant waves in children age 10 and over, though the configuration of CNV was already classified as mature.

As in adults contingent potentials in children appear to be bilaterally symmetrical over the hemispheres (*Cohen* 1973).

7.4 Movement-Related Potentials

There has been little study of the development of voluntary movement-related potential changes. A readiness potential preceding the motor act was clearly seen by *Gullickson* (1973b) in 3-year-old children. For children up to 14 years, he found premovement negativity to be smaller than the postmovement positivity. Between the age of 12–14, the preparatory potential becomes the dominant negative potential. *Karrer* et al. (1978) also found different wave-forms for children 6–8 years old as compared to young adults (16–18 years). Whereas the slowly rising negativity in adults begins 500–700 ms before EMG onset, in young children a positive-going wave was initiated at this time. This wave was followed by a negative shift peaking about 150–300 ms pre-EMG and a second positive shift.

Three mechanisms are possibly responsible for this clearly divergent wave-form in young children in contrast to the wave-form of adults in polarity and amplitude. First, the second positivity could be a correlate of the requirement of greater activity for the initiation and may reflect an enhanced PMP. Second, the positivity occurring in adults after the movement could be shifted forewards. A third speculation is that the young

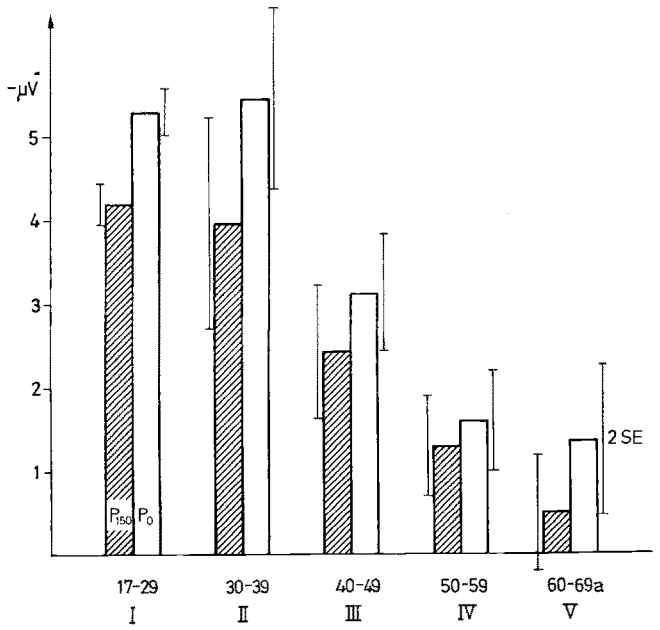

Fig. 10. Mean *Bereitschaftspotential* (BP) amplitude in different age groups. *White columns*, BP amplitude at movement onset (first action potential in the EMG); *hatched columns*, BP amplitude 150 ms prior to EMG onset. (*Deecke* et al. 1978)

child may need some verbal control to organize his motor response. Activity preceding speech has a relatively large positive component.

Only *Deecke* et al. (1978, 1979) have systematically investigated about movement-related potential development in higher age groups. The average BP amplitude is relatively constant from age 17 until the end of the 4th decade (39 years) and then gradually declines. In the higher age groups very small BP amplitudes are observed; above age 60 positive BP can occur. Such positive BP are found in younger people only in frontal leads. For subjects between 30 and 69 the correlation coefficient between age and amplitude P_{150} was $r = 0.58$ ($p < 0.01$) and for P_0, $r = 0.66$ ($p < 0.001$). In contrast, no significant reduction of the motor potential was observed (see Fig. 10).

Gullickson (1973b) describes the anterioposterior distribution of change occurring with age. The maximum preparatory potential was observed at the vertex for all ages. In young children the frontal response was larger than the parietal, whereas in subjects between 12 and 16 years, parietal response surpasses the frontal in magnitude.

Age-dependent changes in the topographical distribution were also found by *Karrer* et al. (1978), who described an increase in the coherence of BP measures between different derivations at higher ages.

8 Psychological Correlates

Many psychological processes have been related to slow (DC) brain potentials, and the whole field is as yet ill defined. It is impossible to cover the literature completely and therefore only the main lines of scientific developments and neuropsychological theorizing or model building will be outlined.

8.1 Late Potentials as Information-Related Potentials

Substantial increase of late potential components of evoked potentials to various stimuli have been related by many investigators to the amount of information carried by the stimulus (*Chapman* and *Bragdon* 1964; *Sutton* et al. 1965, 1967). Depending on the experimental design the late changes were elicited in a variety of situations and have been interpreted in terms of decision making (*Hillyard* 1969; *Smith* et al. 1970), cognitive evaluation (*Ritter* and *Vaughan* 1969), template matching (*Squires* et al. 1973, 1975, 1977), reduction of arousal (*Karlin* 1970), stimulus uncertainty (*Paul* and *Sutton* 1972), change in preparatory set (*Karlin* and *Martz* 1973)

and selective attention (*Hillyard* et al. 1973). The late potential in all these studies is interpreted as being dependent upon the recognition of known, task-relevant stimuli. Some authors, however, found no differences in P_3 latency and amplitude between task-relevant and task-irrelevant signals (*Roth* et al. 1976).

In another development some authors observed late potentials evoked by novel, rare or unexpected stimuli. This was related to the concept of orienting responses or "what is it" reactions. Examples are demonstrated in Fig. 1. The orienting potentials were independently described by *Haider* et al. (1968b) and *Ritter* et al. (1968). *Haider* et al. observed a late negative-positive wave complex with negative peak latencies between 250 and 350 ms evoked by unexpected changes of stimuli in a time series as well as unexpected changes of sense modalities (Fig. 1A). *Ford* et al. (1973) found a modification of late negative waves with peaks between 190 and 280 in response to relevant or irrelevant stimuli from a relevant modality or to novel stimuli. *Ritter* et al. (1968) as well as *Ritter* and *Vaughan* (1969), observed P_3 waves correlated with unpredictable changes in pitch (Fig. 1B). *Demaire* and *Coquery* (1977) showed that in the absence of any task to be performed by the subjects after the occurrence of stimuli, a N_2–P_3 complex is the most conspicuous component of the evoked potential to be differentially affected by stimuli to expected and unexpected modalities. Prominent negative-positive wave complexes with latencies between 210 and 450 ms have been described by *Squires* et al. (1975 and 1977). The negative peaks occurred in response to rare stimuli, regardless of whether these were task relevant (Fig. 1D). The positive component P_{350} is enhanced when the stimulus is rare and task relevant. A slow wave component following the P_{350} is related to the same variables but with a different scalp distribution. *Courchesne* et al. (1975) found a negative late potential component, similar to that described by *Haider* et al. (1968b) as largest for novel stimuli, which are most likely to produce an orienting response (Fig. 1C). This negative wave was followed by a large frontal positive component (330–360 ms). Another, more posteriorly evoked positivity (380–430 ms) was evoked by recognizable, simple stimuli. *Courchesne* mentions cases of an atypically high amplitude negative process (onset at 200 ms and a duration of 450 ms) similar for all types of unexpected stimuli. Other researchers have reported large negative deviations in response to complex visual patterns (*Cohen* and *Walter* 1966; *Lifschitz* 1966; *Symmes* and *Eisengart* 1971). An orienting potential with an onset latency of 300–350 ms and a peak about 450–460 ms following the warning signal in a classic CNV paradigm has been interpreted by *Loveless* and *Sanford* (1974) as a cortical component of the orienting response to the warning signal. This orienting response was not affected by instructions such as "sensory set" or "motor set". Finally it has been shown that orienting

which contains motor elements in the sense of readiness for movements enhances the late negative potential. This is demonstrated through experiments in which subjects had to make a direct or a delayed response (*Kok* 1980; *Ritter* and *Vaughan* 1980).

The great variety of situations evoking late potential changes and the correlations between psychological processes and different potential components are extensively discussed in recent review articles by *Donchin* (1979) and *Sutton* (1979).

It may be concluded from all these studies that the late potential is not a unitary phenomenon, but consists of multiple components, each related perhaps to different aspects of cognitive behaviour. We therefore proposed in Sect. 2 that all these potential components may be summed up under the heading of "information-related potentials". This term may also include the "emitted potentials" occurring at about the time of an expected but absent stimulus when the event of stimulus absence provided information or was salient for the subject (*Rusinov* 1959; *Haider* 1965; *Sutton* et al. 1967; *Klinke* et al. 1968; *Barlow* 1969; *Weinberg* et al. 1970, 1974; *Ruchkin* and *Sutton* 1973; *Picton* and *Hillyard* 1974). Emitted and evoked potential components are similarly affected by variations in event probability (*Rushkin* et al. 1975).

Concerning the differences of polarities, latencies and topographies of information-related potentials one may speculate that the negative components and the frontally localized positive late component constitute a central orienting response, with motor readiness being most prominent in situations using rare stimuli, with novelty and unpredictability, and even without task relevance. Such late potential components have been observed by us in motor thalamus and motor as well as frontal cortex (Fig. 6).

Especially in motor thalamus a quick habituation occurred, showing that the whole motor control system is involved in the response of the organism to novelty. The different positive components located more posteriorly at the vertex and parietal regions seem more related to task-relevant information processing probability aspects of the stimuli and stimulus categorization. In some situations different negative and positive potential components may produce potential peaks which follow each other in a sequence of cognitive processing; in others, one component may outweigh the others. The potential peaks occurring in a certain situation depend on many factors. The peak latency is dependent on the internal event to which it is related, which may at least be partly independent of stimulus and response. The polarity is dependent on the basic DC level, which may to a certain degree represent the level of cortical activation.

8.2 Contingent Potentials and Psychological Variables

Contingent potentials occur in a great variety of situations in which perceptual, cognitive and motor acts are prepared, anticipated or conditioned. The paradigms in which CPs are generated may tentatively be classified into four general types: (1) holding a motor response in readiness; (2) preparing for a perceptual judgement; (3) anticipation of a positive or negative reinforcer; and (4) preparing for a cognitive decision (*Hillyard* 1971, 1973). In highly motivated and stressful situations contingent potentials are clearly seen in EEG records without averaging. One such example, from a musician who had to play a horn solo in an open performance, is demonstrated in Fig. 11.

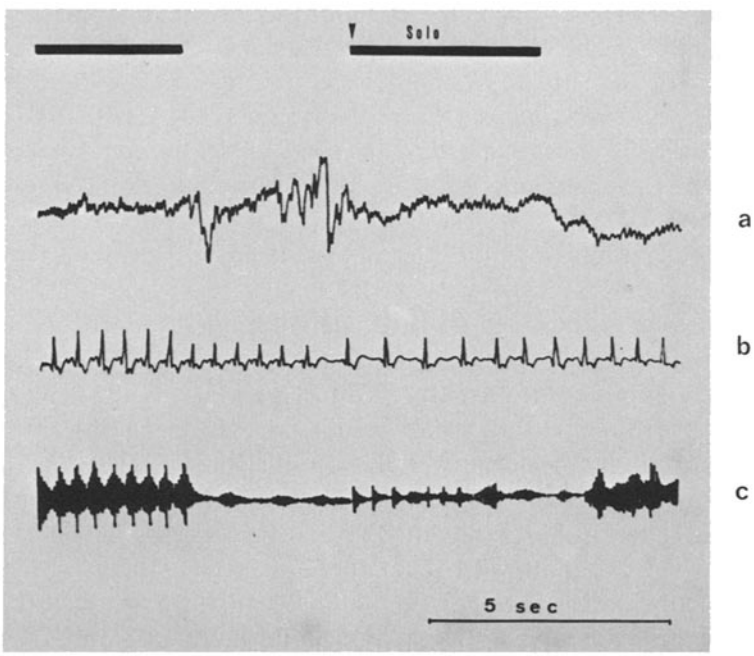

Fig. 11a–c. Contingent variation in on-line EEG of a horn player prior to his solo performance during a concert. **a** EEG (P_3-linked mastoid), negativity upwards; **b** ECG; **c** Sonogram. (*Haider* and *Groll-Knapp* 1971)

For the interpretation of empirical results, psychological constructs and theoretical concepts related to learning and memory, expectancy, conation, motivation and attention have been used.

Slow potential shifts related to learning and conditioning are reported by *Rowland* (1960, 1967). Cortical slow potential shifts to non-reinforcing stimuli disappeared with loss of novelty and to reinforcing stimuli

diminished with drive reduction. In learning the slow (DC) potentials to non-reinforcing stimuli are acquired in some cortical loci and become drive dependent. It has recently been shown that the slow (DC) potentials may be conditioned operantly in humans by appropriate visual and acoustical feedback (*Birbaumer* et al. 1978; *Bauer* and *Lauber* 1979).

The contingency of reinforcement was also important in early theorizing on CNV. The basic paradigm for generating a CNV involved a first stimulus (the warning stimulus, or S_1) followed by a second stimulus (the imperative stimulus, or S_2). When S_2 was omitted, CNV amplitude was reduced or "exstincted" after several trials (*Walter* et al. 1964; *Low* et al. 1966b). This was interpreted in terms of "expectancy processes". Expectancy was defined as "subjective probability" or relative certainty that S_2 will follow S_1, and the CNV was phenomenologically called "expectancy or E-wave" (*Walter* 1964; *Walter* et al. 1964). Obviously this expectancy hypothesis leaves unexplained the many changes occurring in contingent potentials with unchanged statistical association between S_1 and S_2.

That the intention to perform an act ("conation") is a main determinant for the development of contingent potentials is demonstrated by the finding that the amplitude of such potentials is significantly elevated when a motor response is given to S_2 compared with the absence of a response (*Irwin* et al. 1966; *Jus* et al. 1968; *Low* et al. 1966a; *Peters* et al. 1970; *Small* and *Small* 1970; *Straumanis* et al. 1969). In addition the potential magnitude was found to be directly proportional to be amount of anticipated force needed for a response (*Rebert* et al. 1967; *Low* and *McSherry* 1968). Furthermore, amplitude changes proportional to the anticipated speed of movement in response to S_2 were described by *Grünewald* et al. (1979a). When the response terminates S_2 and helps to avoid a shock, CP amplitude is significantly enhanced (*Peters* et al. 1970; *Cant* and *Bickford* 1967). All these results provide evidence that motivational states and response intentions are important for the development of contingent potentials. But it has been shown in other experiments that systematic changes in such potentials may occur without changes in the response parameters or even with no overt response (*Irwin* et al. 1966; *Gullickson* 1970).

Attention as an anticipatory selective function has been related to CNV development by different lines of experimentation. The correlation between fast reaction times (RT) and large CNVs has been interpreted to signify that CNV is a sign of attention (*Hillyard* and *Galambos* 1967). But later work on the relations of RT to CNV shows conflicting results. Some authors (*Walter* et al. 1964; *Hillyard* and *Galambos* 1967; *Rebert* and *Sperry* 1973) reported significant correlations. Others (e.g. *Waszak* and *Obrist* 1969) failed to find such correlations, and *Rebert* and *Tecce* (1973) concluded in their review that CNV and RT are essentially unrelated events. *Papakostopoulos* and *Fenelon* (1975) found few intra-individual

correlations, but some correlations in average data across subjects in the central-parietal areas, contrasting with a lack of correlation in prefrontal areas.

A second line of evidence for the influence of attentional factors on CP comes from correlations found between CNV amplitudes and measures of perceptual accuracy. Such results have been attained in auditory signal detection (*Hillyard* 1969, 1971), auditory intensity discrimination (*Wilkinson* and *Haines* 1970), visual pattern recognition (*Cohen* 1973) and visual position discrimination (*McAdam* and *Rubin* 1971). But there have also been studies in which no association between perception and CNV in auditory discrimination (*Järvilehto* and *Fruhstorfer* 1970) and auditory signal detection (*Paul* and *Sutton* 1972) was found.

A third group of results involves changes of attention to S_2, for instance by reducing the intensity of this expected signal to near threshold level. In these cases higher CNV amplitudes have been found (*Low* et al. 1967; *Rebert* et al. 1967; *Faidherbe* et al. 1969). The increased CNV may indicate a facilitation of sensory processing in these instances, but other factors such as motivation and activation or arousal may also be involved.

A fourth group of findings is that distracting stimuli produce concurrent reduction in CNV and response effectiveness. CNV magnitude has been decreased by such extra stimulation as conversation and reading (*Walter* 1964), irrelevant tones (*McCallum* and *Walter* 1968), presenting and remembering letters (*Tecce* and *Hamilton* 1973) and background music (*Miller* et al. 1973). In the latter study, CNV amplitude was decreased only when S_2 had a different sense modality than the extra stimulation. The results of all these studies have been interpreted as CNV distraction effects and as support for an attention hypothesis of CNV development (*Tecce* 1972; *Tecce* and *Hamilton* 1973; *Tecce* et al. 1976). Studies with sustained cognitive activity produced, in addition to the CNV changes, significant elevations in heart rate levels and also increased frequency of eye blinks (*Tecce* et al. 1976). In the frame work of a distraction-arousal hypothesis these result were interpreted as indicating heightened autonomic arousal which accompanies and mediates the disruption of CNV development.

In conclusion one has to admit that the CNV does not in general predict subsequent behavioural performance with a high degree of reliability (*Hillyard* 1973). Since it occurs in preparation for very diverse types of perceptual, motor and cognitive acts, the results may be conceptualized in a hierarchical model of activation and related behavioural events (*Haider* 1969, 1970). In Sect. 11 we will try to elaborate such a hierarchical theoretical model of slow (DC) potentials, activation and behavioural states.

The topographical differences in scalp derivations (Sect. 6.2) as well as in cortical and subcortical leads described in Sect. 5 seem to show that

contingent potentials are not a unitary process but rather may be differentiated into several task-specific event-related potential components. *Järvilehto* and *Fruhstorfer* (1970) distinguished a central premotor dominant and a frontal dominant CNV accompanying auditory discrimination, and *Cohen* (1973) reported a more posteriorly distributed negativity preceding a visual discrimination. Electrocorticographical studies on animals (*McSherry* and *Borda* 1973) and man (*Groll-Knapp* et al. 1977; *Haider* et al. 1979; *Papakostopoulos* and *Crow* 1976) demonstrated that contingent responses are not uniformly distributed over the cortex but consist of a complex of rather local phenomena. The common pattern emerging from studies with scalp electrodes obviously indicates an integration of various cortical and subcortical mechanisms. Since the results of split brain experiments showed only slight deviations of bilateral symmetry it has been proposed (*Hillyard* 1973) that each type of human contingent potentials contains a bilaterally symmetrical, diffuse component, possibly under reticular and non-specific thalamic control, to which is added a process-specific negativity distributed across the cortex according to which thalamocortical pathways are active.

The return to baseline after the motor performance has been called CNV resolution. Some variables have been shown to accelerate this return. Using complex tasks and a paradigm with more than two stimuli, it has been shown that CNV resolution was caused neither by the overt response, nor by the final decision concerning the nature of the stimulus, but probably by the first coarse identification of the stimulus (*Wilkinson* and *Spence* 1973). It was also shown that the negativity was sustained during periods of unconfounded expectant attention, and it was suggested that a sustained negativity, sometimes seen in behaviour pathology, may be attributable to the attempt of subjects to continue processing information after S_2 and the response have occurred (*Weinberg* 1973).

8.3 Psychological Aspects of Movement-Related Potentials

It has been mentioned in the last section that the amplitude of contingent potentials depends on response variables. The amplitude is elevated when a movement is made and especially when the response has an operant quality and motor readiness potential occur together and form a complex, "hybrid" wave. But when subjects are required to perform a voluntary movement in the absence of external stimuli, the motor readiness potential is influenced by similar psychological variables such as the contingent potential, which increases with greater involvement in the experimental task (*Kornhuber* and *Deecke* 1965; *Kornhuber* et al. 1969) and varies with different motivational and attentional states. The amplitude can, for in-

stance, be elevated by monetary reward (*McAdam* and *Seales* 1969) and correlates with perceptual accuracy (*McAdam* and *Rubin* 1971). The readiness potential preceding a verbal response seems to be largest over Broca's area (*McAdam* and *Whittaker* 1971). During a retrieval task, differences between words recognized on a list and words not recognized occurred over the temporal lobe. Effects of physical aspects of movements (speed, duration and force) on the movement-related potentials have been demonstrated by different authors (*Hazemann* et al. 1968; *Kutas* and *Donchin* 1977; *Becker* and *Kristeva* 1980; *Grünewald* et al. 1979a).

With forearm extensions against different forces opposing the movement, a surface negative-positive deflection appeared after movement began (*Wilke* and *Lansing* 1973). The greater force condition produced greater amplitude of this wave. Similarly, slow waves following movements were seen after clenching the fist or articulating words (*Lelord* et al. 1973). With imperative instructions, contingent potentials could be conditioned to the slow activity evoked during and after movements.

Recently it has been reported that during smooth goal-directed hand movements the premotion negativity increases and remains during movement until the target is reached. In a feedback task this goal-directed movement potential showed an increased negativity and a large positivity after the feedback stimulus. It is suggested that the bilateral component of the negative slow potential shift during goal-directed movements is related to processes of intention and expectancy and that the lateralized components reflect cortical activity specific to the movement execution (*Grünewald-Zuberbier* et al. 1978a, b; *Grünewald* et al. 1979b).

The motor thalamus exhibits only a small wave during short ballistic movements at the time of movement. This is greatly enhanced and extended during the period of goal-directed movements, thus showing that thalamocortical interactions are important in the execution of aimed and goal-directed motor acts (*Knapp* et al. 1980).

9 Psychiatric and Neurological Studies (Clinical Application)

Many clinical psychiatric and neurological investigations have been carried out, the results being somewhat different, sometimes equivocal, sometimes even contradictory. Consequently the diagnostic value of studying the various forms of slow potential phenomena remains open for discussion. Several authors even discuss the possibility whether the differences found are caused only by varying degrees of attention of the subjects.

Some of the various results attained by different groups of investigators may be explained by the means of selection of psychiatric patients and

also by national differences in classification of psychopathology. Differences in method may also play a role.

In the earliest stages of CNV investigation, some irregularities were noted in mentally disturbed patients and neurotics. Patients with anxiety or phobias were reported to develop CNVs very slowly and with smaller amplitudes, the E-waves being more sensitive to equivocal presentations. Psychopathic delinquents showed "little or no sign of an E-wave", but rather an augmentation of the non-specific (late) components of the EP (*Walter* 1964; *McCallum* 1966, 1967a).

Patients with compulsive-obsessive disorders showed irregularities, especially in relation to the effect of the operant response, i.e. slow return to baseline after S_2, and single subjects even showed what was later called a postimperative negativity while failing to develop a CNV (*Walter* 1964, 1966a, b; *Timsit-Berthier* et al. 1971).

In highly anxious patients smaller CNVs were found and distraction considerably attenuated the amplitude, which was also seen to a lesser degree in normal controls. Obsessive neurotics had slightly higher CNVs and showed faster recovery of amplitude after distraction (*Walter* 1964, 1966a, b, 1967; *McCallum* 1967b; *McCallum* and *Walter* 1967a, b); the higher amplitude was also confirmed by other groups (*Dongier* and *Bostem* 1967; *Timsit* et al. 1970).

Slightly smaller CNVs had been found in chronically anxious neurotics and in schizophrenic patients (*McCallum* 1966, 1967a). When mild distraction was introduced (irregular tones as a background), the amplitude could be reduced considerably. After elimination of distraction, normal controls recovered quickly, recovery being delayed in highly anxious neurotics and schizophrenics. Obsessive neurotics, on the other hand, showed recovery of the CNV similar to that of non-patients. After successful treatment of highly anxious neurotics the CNV amplitude increased and also became more resistant to distraction. The probability was pointed out "that the common psychological factor shared" by neurotics and schizophrenics with small CVNs "is a failure of attention" (*McCallum* 1967a).

No correlation of anxiety with amplitude of CNV was found by others (*Low* et al. 1967; *Bostem* et al. 1967; *Dongier* and *Bostem* 1967), while attenuation of amplitude in a high anxiety group was found only under stress (*Knott* and *Irwin* 1968, 1973), females being more sensitive to stress than males (*Knott* and *Peters* 1974).

The tendency of mental patients to show prolonged CNVs has been reported by *McCallum* (1969), who had also published traces of post-imperative negativity in a schizophrenic patient, after-distraction showing an independent post-imperative negativity. The significance of this was pointed out later by *Dongier* et al. (1973), who also stated the necessity of averaging epochs of 8 s (*Timsit* et al. 1970) for studying prolonged CNV or

post-imperative negative variation (PINV). At the same time the question has been raised whether a PINV is necessarily a prolonged CNV.

Timsit et al. (1970) compared CNVs of normal controls, neurotics (hysterics and obsessives) and psychotics (early and chronic schizophrenics and manic-depressives). Amplitude of CNV was found to be generally larger in obsessives than in hysterics (in agreement with *Walter* 1966a), while the highest incidence of prolonged CNV was found in psychotics (in agreement with *McCallum* 1969) and the lowest in normal controls. The authors concluded that the probability of the occurrence of a prolonged CNV increases with the severity of the psychological disturbance.

No difference in amplitude between neurotics and normals was later reported (*Timsit-Berthier* et al. 1971) and no prolongation of the *Bereitschaftspotential* was found in these cases. Psychosomatically ill patients were found to have a greater CNV amplitude than normals (*Dongier* and *Koninckx* 1970).

Different types of CNVs, including post-imperative negativity, were worked out by *Timsit-Berthier* et al. (1973). The highest incidence of small CNVs was found in psychotics (in agreement with *McCallum* 1966, 1967b; *McCallum* and *Walter* 1968; *Small* and *Small* 1971; *McCallum* and *Abraham* 1973; *Abraham* et al. 1976). The highest incidence of prolonged CNVs was found in psychotics (in agreement with *McCallum* 1969; *Timsit* et al. 1970).

Studying the motor readiness potential (RP) in normals, neurotics and psychotics, the Liege group found, mainly in psychotics, and less frequently in neurotics, a smaller motor RP with slow and only gradual return to baseline after the voluntary movement.

Dongier et al. (1973) found the highest incidence of abnormal and prolonged CNVs in psychotics. The prolongation was reported to shorten with clinical improvement.

Contrary to earlier statements of the Liege group the difference in amplitude of CNVs between hysterical and obsessive neurotics was not confirmed in this series, which also found that psychotics tended to have a prolonged motor RP. Also not found by this group was the small amplitude of CNV in psychopathic criminals, contrary to the findings of the group in Bristol, which may be explained by a different selection of subjects.

In subjects suffering from phobic neurosis, CNV was found to be of higher amplitude and of longer duration when phobogenic stimuli were used, while at the same time RT after S_2 was found to be shortened (*Barbas* et al. 1978).

Schizophrenics showed slightly attenuated amplitudes together with a high trial-to-trials variability (*McCallum* 1966, 1967a, b, 1969). Another study confirmed these earlier observations (*McCallum* and *Abraham* 1973).

Especially florid cases of early schizophrenia showed small mean CNV amplitudes in the "acquisition condition", together with further reduction in the "distracting condition". The initial amplitude was smaller and the reduction by distraction was more pronounced in cases with more severe symptoms. In a more recent study (*Abraham* et al. 1974, 1976) using another group of schizophrenics, acquisition and distraction amplitude, prolongation and parietal spread [amplitude difference between vertex (C_z) and postcentral midline derivation (P_z)] were investigated, the subjects being without medication at the first test. The earlier observations were confirmed: prolongation tended to disappear with treatment and improvement. Patients with more florid symptoms showed less differences in amplitude values between C_z and P_z than normal controls.

That post-imperative negativity could be selectively attenuated by hyperventilation without seriously affecting CNV amplitude and duration was shown by *Dubrovsky* et al. (1973).

Total sleep loss for one night reduced CNV amplitude considerably; sleep loss for two nights abolished it (*Naitoh* et al. 1971; *Naitoh* and *Hilbert* 1976).

Contingent negative variation in cases with known brain lesions was investigated by several groups. *McCallum* et al. (1970) and *McCallum* and *Cummins* (1973) reported reduction of amplitudes over unilateral lesions, while cases with bilateral lesions and bilateral Parkinson's disease patients showed generally small amplitudes, the latter sometimes showing a tendency to inverse polarity.

The *Bereitschaftspotential* in Parkinson's diesease patients was found to be severely attenuated over both hemispheres in bilateral cases, while hemi-Parkinson's diesease subjects showed severe attenuation contralaterally to the akinesia-affected side of the body (*Deecke* et al. 1976a).

Zappoli et al. (1976) reported that absent CNV in cases with frontal space-occupying lesions could be restored after surgery in some cases. This group also investigated patients who had previously undergone extensive prefrontal lobotomy. Of the small number of eight patients, five had "fairly typical" CNVs. In these subjects the actual extent of the interruption of the mediothalamic-frontocortical system was deduced only from surgical reports, the anatomical evidence of the extent of interruption remaining open (*Zappoli* et al. 1976, 1980).

Children with poor abilities to concentrate showed longer latencies and smaller amplitudes of the late components of EPs and smaller CNVs (*Grünewald-Zuberbier* et al. 1978b; *Grünewald* et al. 1978).

In dyslexic children CNV was found to be attenuated or even diminished when a visually presented word was used for S_2 (*Fenelon* 1968).

Differences in CNV between normals and stutterers were reported to be found over inferiofrontal regions by *Zimmermann* and *Knott* (1974).

There was no difference in vertex CNV when stutterer spoke normally, but a less hemispheric asymmetry was found in stutterer over inferiofrontal regions. When stuttering occurred no vertex CNV was seen.

In an examination of aphasic, dyslexic and normal children, using a three-stimulus paradigm, *Otto* et al. (1976) found greater positivity in aphasic and dyslexic children in the interval between warning and encodement.

10 Drug Effects and Toxic Influences

Some observations of drug effects on CNV were initially mentioned by *Walter* (1964). Deprivation of (the accustomed intake of) caffein attenuated the CNV which was restored by administration of caffeine sodium citrate. The same result was found with amphetamine. In one subject administered 100 μg LSD-25, the E-wave following single flashes "was enormously augmented and spread to nearly all regions" (*Walter* 1964).

Low (1969) saw no apparent effect on CNV amplitude in subjects given amphetamine or chlordiazepoxide. An increase of CNV amplitude was seen by *McCallum* (1969) in those administered methedrine. After administration of large doses of dextro-amphetamine *Tecce* and *Cole* (1974) found reduced CNV amplitudes in subjects who showed a paradoxical drowsiness in the 1st hour. Others, with increased alertness, showed increased CNV amplitudes.

The influences of marijuana and alcohol, methamphetamine and secobarbital have been studied by *Kopell* et al. (1972), *Low* et al. (1973), and by *Roth* et al. (1977). Flurazepam was found to cause a marked reduction of the EP to S_1 while the CNV amplitude was only slightly attenuated (*Hablitz* and *Borda* 1973). *Ashton* et al. (1974) compared the effects of caffeine, nitrazepam and cigarette smoking on the CNV. The mean amplitude of the CNV was clearly increased by administration of 300 mg caffeine citrate; it was significantly decreased by 2.5 mg nitrazepam. In smokers the change of CNV amplitude differed between individual smokers, some smokers showing an increase and others a decrease in amplitudes. In a later study (*Ashton* et al. 1978), the effect of nicotine was studied after smoking and after intermittent intravenous administration of 150 μg nicotine in volunteers. Initial small doses increased CNV amplitude while repeated small doses decreased the amplitude. The biphasic effect of nicotine (small doses stimulating, larger doses acting as a depressant) was found also during cigarette smoking and was dependent on individual smoking habits.

Increase of the late components of visual evoked potentials (VEP) during tobacco smoking was found by *Friedmann* et al. (1974), while the auditory evoked potential (AEP) tended to be reduced.

Low doses of carbon monoxide were found to attenuate the CNV amplitude, though this effect was not as clearly seen in a more recent study (*Groll-Knapp* et al. 1972, 1978), which also showed that with low level carboxyhemoglobin (COHb) the VEP remained unchanged while there is a marked effect on the somatosensory evoked potential (SEP), which was lessened with higher COHb levels.

In a collaborative pilot study between investigators in Bristol and Newcastle-upon-Tyne, the CNV was studied under interference with the action of some putative neurotransmitters by intramuscular administration of antagonists and a placebo (physiological saline solution). Atropine was used as antagonist of acetylcholine, thymoxamine against noradrenalin, and metoclopramide as an antagonist of dopamine.

Atropine and metoclopramide produced a steady fall in CNV amplitude, a minimum amplitude was reached earlier with atropine, followed by partial recovery during the experiment. No significant change of mean CNV was produced by thymoxamine or the placebo. At the same time of the S_2 response reaction time (RT) was measured. There was no change with atropine and placebo. Reaction time was lengthened with metoclopramide and shortened by thymoxamine, which had no effect on CNV amplitude.

The handicap of the very short plasma life of thymoxamine was also discussed. It was suggested that there is more than one putative neurotransmitter involved in the genesis of the CNV (*Thompson* et al. 1978).

In shoe industry workers exposed to chronic poisoning with adhesive solvents the CNV proved to be of no clinical value, while the raw EEG showed slowed α-rhythms and diffuse abnormalities, and the motor nerve conduction velocity was decreased in accordance with the clinical polyneuropathy (*Zappoli* et al. 1978b).

In conclusion it may be stated that the evidence concerning the relation between biochemical and toxicological effects and slow (DC) potential changes in the brain is currently scarce and inconsistent. One may hope that more biochemists and toxicologists become interested in event-related brain potentials and contribute to a more coherent theoretical and empirical approach in the future.

11 Concluding Remarks: a Hierarchical Model of Slow (DC) Potentials, Activation and Behaviour

In reviewing the research field of event-related slow (DC) potentials one gets the impression that much data have been accumulated, but that the experimentor is still faced with problems and questions similar to those of 20 years ago. We obviously need more principal data and new theoretical

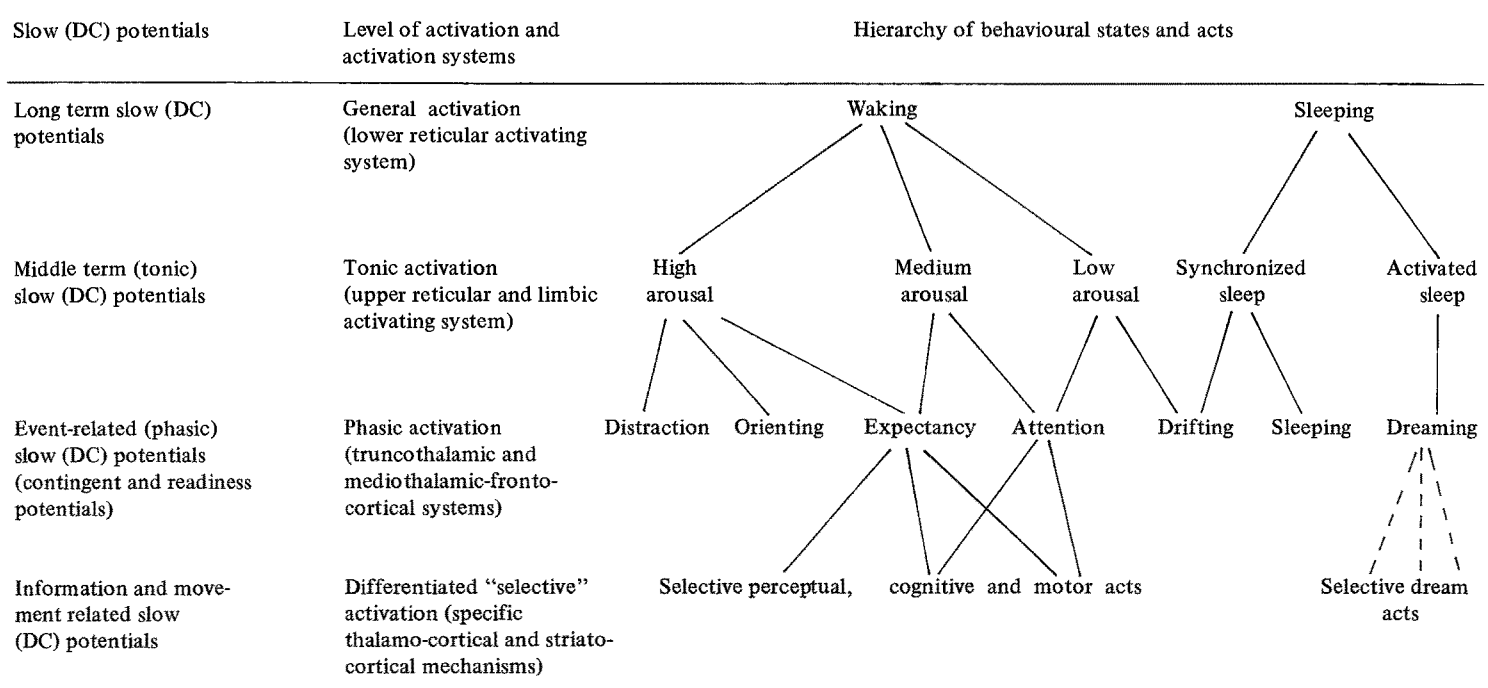

Fig. 12. Hierarchical model of slow (DC) potentials, activation and behaviour, provided as an aide in conceptualizing in a very simplified manner some relationships between different, long- and short-term slow (DC) potentials *(left)*, some activation mechanisms *(middle)* and some behavioural states *(right)*

approaches, and we must try to analyse psychological data which is as complex as neurophysiological data. On the one hand we must try to understand the basic neurophysiological mechanisms to be able to use event-related potentials as better indicators for psychological theory. The potentials clearly depend to some degree on psychological states and processes, but the question is how specifically they represent them. Obviously we are able to attend to certain stimuli and to learn and perform motor acts without reliably occurring slow potential changes. This may be disappointing but it demonstrates on the other hand the great adaptability of our neural functions. The brain may solve different problems by using different strategies. All we can expect therefore is to find dynamic patterns of activity with some sequential development in time.

Within a certain period of time we assume that different slow (DC) potentials occur in the brain with different slopes, different time courses and different amplitudes. The potential changes, recorded in a specific situation, depend on many variables such as the state of the brain and the experimental design. We must try to conceptualize the functional relations of all the different slow (DC) potentials in some kind of a theoretical model and to combine the study of general, long-term potential changes with event-related short-term changes.

Many investigators interpreted slow (DC) potentials to be a consequence of altered levels of cortical activation (*Goldring* and *O'Leary* 1951; *Caspers* 1965; *O'Leary* and *Goldring* 1964; *Walter* et al. 1964; *Rowland* 1960, 1967). Findings on event-related potentials suggest that more differentiated activation processes are involved (*Routtenberg* 1968; *Rebert* 1973; *Tecce* 1972; *Desmedt* and *Debecker* 1979a, b) and results of stereo-electroencephalographic studies, summarized in Sect. 5, demonstrate the importance of subcortical, reticular, thalamic and striatal mechanisms.

In Fig. 12 we show a first approach for a hierarchical model of slow (DC) potentials in relation to concepts of activation and behaviour. A hierarchical system of activation was proposed earlier (*Haider* 1969, 1970).

First we have some general activation or arousal mechanisms, regulating wakefulness and sleep. Related to these are long-term slow DC potentials which occur with gross transitions from one state of the brain to another, such as the sleep-wakefulness cycle (*Caspers* 1961, 1963) or seizure activity (*Speckmann* and *Caspers* 1979).

We then have "tonic" activation with long latencies and durations, slowly changing the state of the organism between low and high arousal; reticular and limbic activation mechanisms mediate these changes. Related to this may be middle term (tonic) slow (DC) potentials, observed, for instance, in some studies of *Bechtereva* (1974).

Next there are "phasic" activation or arousal mechanisms with shorter latencies and durations. They are mediated by the diffuse thalamic projec-

tion system (*Jaspers* 1960) and the truncothalamic system, including a striatopallidal neuronal chain (*Hassler* 1978). Event-related (phasic) slow potentials related to expectancy, attention and motor readiness (contingent and readiness potentials) may be strongly connected to the functioning of these systems as well as to the mediothalamic-frontocortical system. It is now well established by studies of different authors that during stereotactic surgery in humans contingent potentials (CNVs) occur in all parts of these systems (*Groll-Knapp* et al. 1977; *Haider* et al. 1968a, 1979; *Iliukina* 1977; *McCallum* et al. 1976; *Tsubokawa* and *Moriyasu* 1978).

Finally we have to consider a highly "differentiated and selective" activation related to selective perceptual, cognitive and motor acts, without any gross changes in arousal level. For instance, some components of information-related and motor potentials may depend on the more specific thalamocortical and striatocortical mechanisms involved in these processes. These mechanisms for the most part are feedback mechanisms so that one should really use the terms "thalamocortical-thalamic" or "striatothalamic-corticostriatal", etc. Striatocortical mechanisms include pathways to the neurons of the pallidum which send off ascending non-specific or semi-specific pathways which travel through the rostral pole of the thalamus and run through specific and non-specific afferents to almost all cortical fields (*Hassler* 1978). By stimulating the pallidum or the motor thalamus (v.o.a.) or the anterior thalamus during stereotactic surgery a "psychmotor advertance mechanism" may be elicited. This consists of turning the head, directing attention to the contralateral side and dilating the pupil. This may be related to "orienting" potentials which we found in the motor thalamus.

Motor thalamus and motor cortex also show clear motor potentials which at the proper motor cortex (area 4) are demonstrable only very specifically and are localized on the parts representing hand- or finger movements (*Ganglberger* et al. 1980). Concerning the focussing of attention it should be mentioned that a well-organized corticostriatal feedback mechanism with glutamate as the transmitter has been described. This mechanism, especially in relation to the function of the putamen, may be involved in focussing attention to one single perceptive, cognitive or motor act and fading out all other events (*Hassler* 1978). Information- and movement-related potentials may in this connection indicate which thalamocortico-thalamic or striatothalamic-corticostriatal pathways are open and active during a specific mental act.

In a hierarchical system of activation it must be assumed that each level of the hierarchy influences and determines the next one and vice versa. To be able to perform selective perceptional, cognitive and motor acts we need a waking organisms with optimal (medium) arousal and with attentiveness to a specific class of stimuli. Physiologically the upper levels of

the hierarchy determine the polarity of potential changes at lower levels by regulating the basic activation-related DC level (*Speckmann* and *Caspers* 1979). Low levels of epicortical DC negativity (low activation) lead to predominantly negative event-related slow potentials and high levels to predominantly positive components.

Empirically the generality or specificity of activation may be operattionally defined by the number of variables differentiating the different levels. The more indicators vary with a certain level the more general it is. The change from sleeping to waking is accompanied by a great variety of physiological changes, amongst others by changes in body temperature, pulse rate, EEG and slow (DC) potentials. Distracting influences on contingent potentials may be an effect of heightened autonomic arousal, as shown by the elevations in pulse rate (*Tecce* et al. 1976). Some event-related slow (DC) potential changes are accompanied by phasic changes in EEG activity. For instance, an inverse relation between α-activity and contingent potentials was found (*McCallum* and *Walter* 1968; *Pfurtscheller* and *Aranibar* 1977).

Finally, some information- and movement-related potential components are obviously related to specific mechanisms without any change in the intrinsic EEG rhythm or in other indications of arousal.

Many of the assumed relationships in the hierarchical model outlined here are arbitrary and speculative.

With refined methods and experimentation the functional relations will be more precisely definable in future experimentation. What we need in the whole field for the future is not so much phenomenology but a more theoretical and neuroscientific framework within the broad context of brain systems and brain functions, including event-related slow (DC) potentials together with psychological states and processes.

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α-Adrenoceptor Subclassification

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Contents

1 Introduction

In this review the classification of α-adrenoceptors into two major subgroups is discussed, an idea which derived primarily from studies on the pre- and postsynaptic α-receptors at junctions between postganglionic sympathetic neurones and smooth muscle cells. The terms α_1 and α_2, analogous to β_1 and β_2, were loosely suggested (*Delbarre* and *Schmitt* 1973), subsequently used to refer to pre- and postsynaptic α-receptors (*Langer* 1974), and finally generalized (*Berthelsen* and *Pettinger* 1977).

Different names are given to receptors when the sites at which they recognize and bind agonists and competitive antagonists differ structurally

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and when, hence, for a given drug the drug–receptor dissociation constants differ. We must then examine the methods used to determine the drug–receptor dissociation constant or, in other words, the *affinity* of a drug for the receptor, which is *proportional to the reciprocal of the dissociation constant.* One way is to measure the binding of radioactive drugs to receptors and the competitive inhibition of this binding by nonradioactive congeners. This yields dissociaton constants for the radioligand and for the competitor. Receptor properties may change, however, during the homogenization and incubation involved in such assays.

Affinities can also be determined in functional experiments in which the biological response of the tissue indicates the drug–receptor interaction. The interpretation is straightforward for antagonists. Receptor theory (see *Ariens* 1964; *Furchgott* 1964, 1972; *Waud* 1968) shows that the antagonist concentration which shifts the log concentration–response curve of an agonist to the right by the factor 2 is equal to the antagonist–receptor dissociation constant. The interpretation is less straightforward for agonists. In most studies only the EC_{50} is determined, i.e., the concentration that produces 50% of the maximal response obtainable with the agonist; only the *potency* of the agonists is thus evaluated, which is *proportional to the reciprocals of the* EC_{50} *values.* In general, the function relating response or potency to receptor occupation or affinity is not known. The EC_{50} of an agonist is not necessarily the concentration at which 50% of the receptors are occupied. Moreover, the relative potencies of a series of agonists at a receptor are not necessarily equal to the relative affinities for that receptor. The latter is only the case when the response is proportional to the 'stimulus' generated by the drug–receptor interaction, or when the agonists have equal efficacies (see *Stephenson* 1956; *Furchgott* 1972). Procedures have been worked out for functional determination of agonist–receptor dissociation constants, but have seldom been applied to α-adrenoceptors (e.g., *Besse* and *Furchgott* 1976).

The present review is not the final presentation of a universally accepted theory, but a provisional account of a young and rapidly growing field of research. Contradictions are not only inevitable but welcome. In particular, the definition of α_1- and α_2-adrenoceptors given in Table 1 is open to correction and improvement. It incorporates most of the available data from the radioligand binding as well as from the functional studies that will be discussed at length. The drugs were chosen because they have been used in both kinds of studies. Agents that are more selective at α_1- or α_2-receptors may eventually lead to a better definition. It can be seen that the relative *potencies* of agonists in general agree with their relative *affinities.* An exception that will be discussed in Chap. 5 is the high affinity but low potency of clonidine relative to phenylephrine at α_1-adrenoceptors.

Table 1. Proposed definition of α_1- and α_2-adrenoceptors

α_1-Adrenoceptor		
Agonist affinities and potencies		
Affinity and potency of (−)-noradrenaline	3–10	times affinity and potency of α-methylnoradrenaline [a]
Affinity and potency of (−)-noradrenaline	2– 8	times affinity and potency of (−)-phenylephrine
Affinity of clonidine	4–15	times affinity of (−)-phenylephrine
Potency of clonidine	0.1– 1	times potency of (−)-phenylephrine
Antagonist affinities		
Prazosin ≫ corynanthine, yohimbine > rauwolscine		
α_2-Adrenoceptor		
Agonist affinities and potencies		
Affinity and potency of (−)-noradrenaline	0.1– 0.6	times affinity and potency of α-methylnoradrenaline [a]
Affinity and potency of (−)-noradrenaline	15 – 150	times affinity and potency of (−)-phenylephrine
Affinity and potency of clonidine	50 –1000	times affinity and potency of (−)-phenylephrine
Antagonist affinities		
Rauwolscine, yohimbine ≫ corynanthine, prazosin		

[a] The stereoisomers of α-methylnoradrenaline are not always indicated unequivocally in the literature. It can be assumed that the racemate or the levorotatory form of the *erythro*-isomer was used

Some aspects of the α_1/α_2 subclassification have already been reviewed by *Berthelsen* and *Pettinger* (1977), *Starke* (1977), *Wood* et al. (1979) and, most extensively, *Wikberg* (1979b).

2 Functional Studies: Pre- and Postsynaptic α-Adrenoceptors at Sympathetic Nerve–Muscle Junctions

Presynaptic α-adrenoceptors mediate the autoinhibition of transmitter release from noradrenaline neurones (see *Starke* 1977; *Westfall* 1977; *Vizi* 1979). That they differ from postsynaptic α-adrenoceptors was first suggested by observations on rabbit hearts and cat spleens. In the rabbit heart, the relative potencies of phenylephrine, oxymetazoline, and naphazoline

Table 2. Comparison of effects of agonists and antagonists at pre- and postsynaptic α-adrenoceptors in the pulmonary artery of the rabbit [a]

Agonist	EC_{20} pre (n*M*)	EC_{50} post (n*M*)	$\frac{EC_{20}\ pre}{EC_{20}\ post}$	Antagonist	EC_{30} pre (n*M*)	K_B post (n*M*)	$\frac{EC_{30}\ pre}{K_B\ post}$
(±)-Methoxamine	24 000	2 700	32.5	Prazosin	> 100	2	> 50
(−)-Phenylephrine	1 700	250	30.9	Corynanthine	10 000	250	40
(±)-Isoprenaline	12 000	10 000	4	Clozapine	900	37	27
(−)-Noradrenaline	12	56	1.6	Azapetine	1 300	110	12
(±)-Metanephrine	> 10 000	26 000	> 1.4	Phentolamine	85	32	2.7
(−)-Adrenaline	1.9	13	0.58	Mianserin	550	250	2.2
Naphazoline	16	120	0.41	Piperoxan	600	870	0.69
Oxymetazoline	3.1	87	0.17	Dihydroergokristine	15	32	0.47
Clonidine	10	380	0.15	Tolazoline	700	3 900	0.18
(−)-*erythro*-α-methylnoradrenaline	8.1	300	0.13	Dihydroergotamine	4	28	0.14
Tramazoline	3.7	230	0.066	Yohimbol	115	1 000	0.12
				Yohimbine	8	400	0.020
				β-Yohimbine	15	760	0.020
				Rauwolscine	5	1 300	0.0039

[a] Artery strips were superfused with medium that contained propranolol, cocaine and corticosterone to block β-adrenoceptors and the neuronal and extraneuronal uptake of noradrenaline, respectively. For the investigation of postsynaptic effects concentration–response curves of agonists and the displacement of the curves to the right by antagonists were determined. For the investigation of presynaptic effects, the strips were preincubated with ^{3}H-noradrenaline (in the absence of propranolol, cocaine and corticosterone); the sympathetic fibres were stimulated transmurally at 2 Hz; the evoked overflow of tritium under these conditions reflects the release of noradrenaline. EC_{20} pre, agonist concentration that reduced the evoked overflow of tritium by 20%. EC_{50} post and EC_{20} post, concentrations that produced 50% and 20%, respectively, of the maximal contractions obtainable with the agonist. EC_{30} pre, antagonist concentration that increased the evoked overflow of tritium by 30%. K_B post, dissociation constant of the antagonist-postsynaptic receptor complex, calculated according to *Arunlakshana* and *Schild* (1959) or a similar method. From *Starke* et al. 1974, 1975b; *Borowski* et al. 1977; *Endo* et al. 1977; *Weitzell* et al. 1979; and unpublished results

at the presynaptic, release-inhibiting receptors did not agree with their relative potencies at the postsynaptic, contractility-enhancing receptors (*Starke* 1972). In the cat spleen, phenoxybenzamine was more potent in blocking the postsynaptic than in blocking the presynaptic receptors (*Langer* 1973). In both studies it was explicitly concluded that the neuronal receptors differed from the classic postsynaptic receptors of the muscle cells.

Pre- and postsynaptic effects of agonists and antagonists in the pulmonary artery of the rabbit were compared in detail. Table 2 shows that the presynaptic receptors fulfil α_2 criteria and the postsynaptic receptors α_1 criteria. From the effective concentrations postsynaptic/presynaptic potency ratios were calculated (Table 2; note that a *presynaptic/postsynaptic concentration* ratio such as $EC_{20\ pre}/EC_{20\ post}$ yields a *postsynaptic/presynaptic potency* ratio). Given the same kind of receptors pre- and postsynaptically (and, for agonists, linear stimulus–response functions or the same efficacies), the ratios should be equal. In fact, however, they vary 500-fold for agonists and more than 10 000-fold for antagonists. The ratios also demonstrate that some drugs are quite selective. Clonidine, α-methylnoradrenaline, and tramazoline preferentially activate the presynaptic α_2-receptor, whereas phenylephrine and methoxamine preferentially activate the postsynaptic α_1-receptor. After it had been classified as selectively presynaptic in the rabbit pulmonary artery (*Starke* et al. 1974), clonidine was widely used not only for the activation of α_2-adrenoceptors in functional experiments but also for their labelling in radioligand-binding studies. Yohimbine was the first preferentially presynaptic antagonist to be recognized (*Starke* et al. 1975a). One of its diastereomers, namely rauwolscine, is even more selective. Prazosin (*Cambridge* et al. 1977; Cavero et al. 1977; *Doxey* et al. 1977), the yohimbine diastereomer corynanthine, clozapine, and azapetine preferentially block the postsynaptic α_1-receptor. Phenoxybenzamine also primarily blocks postsynaptic α-receptors in the pulmonary artery but, being an irreversible antagonist, is not listed in Table 2.

The postsynaptic/presynaptic potency ratio is an essential feature of a drug, deciding how the drug affects the transmission of information through neuroeffector junctions (with postsynaptic receptors of the α type). α_1-Selective agonists such as phenylephrine act mainly postsynaptically, where their effect *is additive to* that of sympathetic nerve stimulation. In contrast, α_2-selective agonists such as clonidine at low concentrations mainly diminish the release of noradrenaline and thereby *reduce* the response to sympathetic nerve stimulation. Furthermore, α_1-selective antagonists like prazosin always *inhibit* the transmission of information. In contrast, low concentrations of α_2-selective antagonists such as yohimbine primarily interrupt presynaptic autoinhibition, facilitate the release

Table 3. Comparison of effects of α-adrenergic agonists at pre- and postsynaptic α-adrenoceptors

Presynaptic effect [a]	Postsynaptic effect	Postsynaptic/presynaptic potency ratio	Reference
In vitro			
Rabbit heart, inhibition of noradrenaline overflow	Rabbit heart, increase in force of contraction	Phenylephrine > naphazoline, oxymetazoline	*Starke* (1972)
Rabbit pulmonary artery, inhibition of noradrenaline overflow	Rabbit pulmonary artery, contraction	Methoxamine, phenylephrine ⩾ noradrenaline > naphazoline > oxymetazoline, clonidine, α-methyl-noradrenaline > tramazoline	*Starke* et al. (1975b) [b]
Rabbit ear artery, inhibition of contraction	Rabbit ear artery, contraction	Phenylephrine > clonidine > xylazine	*Drew* (1979) [b]
Rat vas deferens, inhibition of contraction	Rat vas deferens, contraction	Noradrenaline ⩾ clonidine	*Doxey* et al. (1977) [b]
Rat vas deferens, inhibition of contraction	Rat vas deferens, contraction	Methoxamine, phenylephrine ⩾ xylazine, naphazoline, clonidine, oxymetazoline	*Drew* (1977b)
Rat anococcygeus muscle, inhibition of noradrenaline overflow	Rat anococcygeus muscle, contraction	Methoxamine, phenylephrine, naphazoline > oxymetazoline ⩾ clonidine	*Leighton* et al. (1979)
Mouse vas deferens, inhibition of contraction	Mouse vas deferens, contraction	Phenylephrine > noradrenaline > clonidine	*Marshall* et al. (1978)
In vivo			
Rabbit autoperfused hindlimb, inhibition of vasoconstriction	Rabbit autoperfused hindlimb, vasoconstriction	Phenylephrine > tramazoline	*Steppeler* et al. (1978)
Pithed rat, inhibition of tachycardia [c]	Pithed rat, increase in blood pressure	Phenylephrine, methoxamine, naphazoline > oxymetazoline > clonidine > xylazine	*Drew* (1976)

Pithed rat, inhibition of tachycardia [c]	Spinal rat, increase in blood pressure	Methoxamine > oxymetazoline > clonidine	*Pichler* and *Kobinger* (1978)
Pithed rat anococcygeus muscle, inhibition of contraction [c]	Pithed rat anococcygeus muscle, contraction	Naphazoline, oxymetazoline ⩾ clonidine ⩾ guanfacine	*Doxey* (1979) [d]
Cat, inhibition of reflex increase in blood pressure	Cat, increase in blood pressure	Phenylephrine > methoxamine > noradrenaline > oxymetazoline > tramazoline	*Walland* (1978)
Cat autoperfused hindlimb, inhibition of vasoconstriction	Cat autoperfused hindlimb, vasoconstriction	Methoxamine > oxymetazoline, clonidine	*Pichler* and *Kobinger* (1978)
Dog, inhibition of tachycardia	Dog, increase in blood pressure	Phenylephrine, noradrenaline > α-methylnoradrenaline	*Lokhandwala* et al. (1979) [b]

A comma between two drugs indicates that they had similar postsynaptic/presynaptic potency ratios or that their ratios were not differentiated.

[a] The response inhibited by activation of presynaptic α-receptors was evoked by electrical stimulation of the sympathetic pathway except in the experiments of *Walland* (1978) where a reflex increase in blood pressure was elicited by afferent stimulation.

[b] Noradrenaline uptake mechanisms and/or β-adrenoceptors blocked.

[c] Preganglionic stimulation of the sympathetic pathway.

[d] Similar results were obtained for the anococcygeus muscle in vitro.

of noradrenaline and thereby may *enhance* the transmission of information. This seemingly paradoxical effect of yohimbine was observed long ago (*Bacq* 1935).

Postsynaptic/presynaptic potency ratios found in other tissues are shown in Table 3. The rank orders agree well. In all studies phenylephrine has a high ratio and is rather selective for postsynaptic α-receptors, and clonidine has a low ratio and is rather selective for presynaptic α-receptors. Tramazoline, xylazine and guanfacine may surpass clonidine in selectivity (see Table 3; but see *Wikberg* 1978b), as may 2-(3,4-dihydroxyphenylimino)imidazolidine (*Hieble* and *Pendleton* 1979), 2-amino-6-allyl-5,6,7,8-tetrahydro-4H-thiazolo-(5,4-d)-azepin (B-HT 920; *Kobinger* and *Pichler* 1980), and azepexole (B-HT 933; *Pichler* et al. 1980). Some dopamine derivatives also are preferentially presynaptic α-adrenergic agonists in certain preparations (*Hicks* and *Cannon* 1979; *Steinsland* and *Hieble* 1979).

The findings with antagonists in cat spleen (*Langer* 1973; see above) and rabbit pulmonary artery (Table 2) have also been substantiated. Phenoxybenzamine preferentially blocks postsynaptic α-receptors in many tissues (*Cubeddu* et al. 1974; *Dubocovich* and *Langer* 1974; *Drew* 1976; *Doxey* et al. 1977), as does prazosin (*Constantine* et al. 1978; *Lefèvre-Borg* et al. 1978), whereas yohimbine preferentially blocks presynaptic α-receptors (*Doxey* et al. 1977; *Constantine* et al. 1978; *Kapur* and *Mottram* 1978; *Marshall* et al. 1978; *Walland* 1978; *Drew* 1979; *Leighton* et al. 1979). Other mainly postsynaptic antagonists are thymoxamine (*Drew* 1976, 1977b; *Marshall* et al. 1978; *Rhodes* and *Waterfall* 1978), labetalol (*Blakeley* and *Summers* 1977), some butyrophenones (*Göthert* et al. 1977), indoramin (*Algate* and *Waterfall* 1978; *Rhodes* and *Waterfall* 1978), 2-[(2′,6′-dimethoxyphenoxyethyl)-aminomethyl]1,4-benzodioxane (WB 4101; *Butler* and *Jenkinson* 1978; *Kapur* and *Mottram* 1978), and 2-[2-(4-o-methoxyphenyl-piperazine-1-yl)ethyl]-4,4-dimethyl-1,3(2H,4H)-isoquinolinedione (AR-C 239; *Mouille* et al. 1979, 1980). Slight presynaptic or slight postsynaptic or no preference has been reported for phentolamine (*Cubeddu* et al. 1974; *Borowski* et al. 1977; *Doxey* et al. 1977; *Kapur* and *Mottram* 1978; *Rhodes* and *Waterfall* 1978), piperoxan (*Borowski* et al. 1977; *Blakeley* and *Summers* 1978) and mianserin (*Borowski* et al. 1977; *Doxey* et al. 1978; *Robson* et al. 1978; *Cavero* et al. 1979b), indicating perhaps that these drugs occupy an intermediate position with no marked selectivity. In the rabbit pulmonary artery, tolazoline and dihydroergotamine have lower presynaptic than postsynaptic threshold concentrations, but have very flat presynaptic log concentration–response curves; high presynaptic affinity may be coupled with a presynaptic partial agonist effect that curtails the α-adrenolytic facilitation of noradrenaline release (*Borowski* et al. 1977).

Before a general conclusion is drawn, some critical comments seem appropriate.

1) Only some of the studies reviewed here were carried out in vitro under optimal conditions for receptor characterization (*Furchgott* 1972), for instance in the presence of β-adrenolytic drugs and inhibitors of neuronal and extraneuronal noradrenaline uptake. Other studies were aimed at clarifying the consequences of selective receptor activation under near-normal conditions; these were of course performed in vivo and without auxiliary drugs. Some relevant details are specified in Table 3.

2) Presynaptic receptors modify the release of noradrenaline. In only a few studies was release measured as directly as possible, namely as 'overflow' into the medium (see Table 3). More frequently, the postsynaptic response was taken to reflect noradrenaline release. The postsynaptic response, however, may be modified by the postsynaptic as well as by the presynaptic action of a drug (see *Starke* 1977). For instance, a marked discrepancy between the effect on noradrenaline release and the effect on the response of the effector cells has been demonstrated for the α-adrenergic imidazoline derivative cirazoline (*Dubocovich* et al. 1980).

3) Whenever drug effects on the depolarization-evoked release of noradrenaline are investigated, the transmitter itself is inevitably present in the biophase at rather high concentrations. This leads to underestimation of the presynaptic potency of α-receptor agonists and antagonists (*Starke* et al. 1974), whether release is determined as overflow or by the postsynaptic response.

4) The term EC_x is normally used for the concentration that produces x% of the maximal response obtainable with the same drug; such EC_x values are suitable for calculation of relative potencies. The $EC_{20\ pre}$ and $EC_{30\ pre}$ values of Table 2 do not conform to this definition, since they do not refer to the individual maxima (see also, e.g., *Drew* 1976). Maximal presynaptic α-receptor effects could not be determined for many drugs because at high concentrations they exerted marked side effects, e.g., displacement of stored noradrenaline. Of course these side effects also occur, although unnoticed, when postsynaptic responses are used to detect presynaptic effects, and are a possible source of error. It seems unlikely that the use, in Table 2, of presynaptic concentrations unrelated to the individual maxima greatly distorts the potency ratios.

5) The sympathetic pathway was sometimes stimulated preganglionically, and ganglionic actions of drugs cannot be excluded (see some papers in Table 3). For studies on the vas deferens one has to recall that the motor transmitter may not, or not only, be noradrenaline, in which case the presynaptic receptors may be located on non-noradrenergic neurones.

6) Potency ratios of agonists are the same as their affinity ratios only when their efficacies are equal (or in the rare event that the responses are

proportional to the stimulus). The agonists in Tables 2 and 3, however, include some with high postsynaptic efficacy, e.g., noradrenaline, and some with low postsynaptic efficacy, e.g., clonidine (see Chap. 5). Clonidine and oxymetazoline may also have a lower presynaptic efficacy than noradrenaline (*Starke* et al. 1974; *Rand* et al. 1975; *Stjärne* 1975; *Medgett* et al. 1978). Part of the variability in potency ratios may thus reflect differences in agonist efficacies rather than affinities, although the size of the variability makes it unlikely that efficacy differences are the only reason. Moreover, the postsynaptic/presynaptic ratios of antagonists vary even further, and this can hardly be explained by anything but differences in affinity.

7) Although, on the whole, all studies agree, there are discrepancies in details. This is illustrated by the postsynaptic/presynaptic potency ratio of clonidine. *Drew* (1976) calculated the ratio of the dose which in pithed rats reduced the tachycardia evoked by sympathetic nerve stimulation by 50 beats/min, and the dose which increased blood pressure by 50 mmHg; the ratio was 1.4 and close to the ratio 0.5 that *Pichler* and *Kobinger* (1978) found in similar experiments. *Starke* et al. (1975b) calculated the ratio of the concentration that decreased the evoked overflow of noradrenaline from strips of the rabbit pulmonary artery by 20%, and the concentration that elicited 20% of the maximal contraction obtainable with clonidine; the ratio was 0.15. From experiments by *Leighton* et al. (1979) on the rat anococcygeus muscle in vitro two ratios can be calculated: one, namely 0.3, from the EC_{50} for inhibition of the evoked overflow of noradrenaline and the EC_{50} for the direct postsynaptic effect; the other, namely 0.03, from the EC_{50} for inhibition of stimulation-evoked contractions and the postsynaptic EC_{50}. Finally, *Medgett* et al. (1978) compared the EC_{50} for inhibition of the evoked overflow of noradrenaline from guinea-pig atria with the EC_{50} for contraction of rabbit aorta; the ratio was 0.0025. The ratios differ enormously. Nevertheless, all studies show that clonidine has a far lower postsynaptic/presynaptic potency ratio than other agonists such as naphazoline and phenylephrine. Much of the discrepancy is probably attributable to the arbitrary choice of potency parameters (see the two values of *Leighton* et al. 1979) and to the factors discussed under points 1–6. For instance, the presynaptic potency reported by *Medgett* et al. (1978) may be particularly high because these authors stimulated the atrial sympathetic nerves with only 5 pulses at 1 Hz. This yields low perineuronal concentrations of noradrenaline, little reduction in the apparent potency of clonidine (point 3), and a good approximation to the 'true' potency.

These comments question certain aspects of the work summarized here. On the whole, however, the evidence for differences between the pre- and the postsynaptic α-adrenoceptors at sympathetic nerve–muscle junctions

is overwhelming. Moreover, in all tissues examined so far, the presynaptic receptors appear to be similar to those of the rabbit pulmonary artery and, hence, at least predominantly α_2, whereas the postsynaptic receptors appear to be at least predominantly α_1. This conclusion does not imply that all noradrenergic axons possess only α_2-receptors and all smooth and cardiac muscle cells only α_1-receptors. There is now evidence for heterogeneity. Contraction-eliciting, α_2-like adrenoceptors seem to occur on some smooth muscle cells such as those of rat blood vessels (Chap. 3). One reason, perhaps, for the high postsynaptic/presynaptic potency ratio of clonidine found by *Drew* (1976) and *Pichler* and *Kobinger* (1978) is that in rats clonidine causes vasoconstriction in part via smooth muscle α_2-receptors. Presynaptic α-receptors may be heterogeneous as well (*Doxey* and *Everitt* 1977; *Constantine* et al. 1978; *Roach* et al. 1978; *Dubocovich* 1979). For instance, the clonidine-induced inhibition of the tachycardia evoked by sympathetic nerve stimulation is antagonized by prazosin in dogs, cats and, according to some but not all investigators, rats (*Constantine* et al. 1978; *Lefèvre-Borg* et al. 1978; *Roach* et al. 1978; *Cavero* et al. 1979a; *Mouillé* et al. 1979; *Timmermans* et al. 1979b), suggesting that the neurones may possess both presynaptic α_2- and prazosin-sensitive α_1-receptors (*Cavero* et al. 1979a; see also *Kobinger* and *Pichler* 1980). On the other hand, there is evidence that prazosin at high doses blocks α_2-receptors, and that at least in rats, the cardiac sympathetic nerves contain only the α_2 type (*Docherty* and *McGrath* 1980).

Presynaptic receptors of noradrenergic neurones other than those supplying muscle have rarely been investigated. In slices of rat brain cortex, yohimbine and rauwolscine increase the stimulation-evoked release of noradrenaline at much lower concentrations than does corynanthine (*Starke* and *Stamm*, unpublished results), and prazosin has no effect (*Dubocovich* 1979). Thus, the receptors satisfy α_2-criteria. On the other hand, in brain slices phentolamine is more potent than yohimbine, and piperoxan is almost equipotent with yohimbine (*Taube* et al. 1977; *Delini-Stula* et al. 1979), whereas in the rabbit pulmonary artery yohimbine is much more potent than its congeners (Table 2), casting some doubt on the similarity between the two kinds of presynaptic receptors.

3 Functional Studies: α_2-Adrenoceptors Outside Noradrenergic Axons

Observations on pre- and postsynaptic α-receptors at noradrenergic synapses gained a new dimension when receptors resembling the presynaptic ones were found on structures other than noradrenergic terminal axons.

The terms α_1- and α_2-receptors had been proposed as synonyms for post- and presynaptic α-receptors (*Langer* 1974). The existence of the α_2 type elsewhere made it necessary to use these prefixes solely for receptors with different affinities for drugs regardless of location or function (*Berthelsen* and *Pettinger* 1977; *Cedarbaum* and *Aghajanian* 1977; *Drew* 1977a, 1978; *Wikberg* 1978a, b; *Starke* and *Langer* 1979). The following examples are just a selection, to illustrate the wide range of potential α_2-adrenoceptor locations.

3.1 Cholinergic Neurones

α-Adrenergic agonists inhibit the release of acetylcholine from central, preganglionic autonomic, and postganglionic parasympathetic neurones; they facilitate the release of acetylcholine from motor neurones to skeletal muscle (see *Vizi* 1979). The poperties of the α-receptors in the intestine have been the subject of most frequent study. α-Receptor agonists can inhibit intestinal cholinergic activity at three sites at least, namely preganglionic terminals, the cell bodies of the cholinergic neurones of the enteric plexuses, and the axon terminals of these neurones. Much of the inhibition is probably exerted at the latter two sites (*Paton* and *Vizi* 1969; *Kosterlitz* et al. 1970; *Drew* 1978). An early, unexplained observation was that methoxamine failed to inhibit acetylcholine release (*Paton* and *Vizi* 1969), whereas naphazoline, xylazine, and clonidine were potent inhibitors (*Oberdorf* and *Kroneberg* 1970; *Deck* et al. 1971). Retrospectively, this is easily understood from the character of the receptors, which differ from classic smooth muscle α-adrenoceptors (*Wikberg* et al. 1975), and were eventually shown to be of the α_2 type (*Drew* 1977a, 1978; *Wikberg* 1978a, b).

Table 4 summarizes potencies of agonists, relative to noradrenaline, in inhibition of acetylcholine outflow or cholinergic transmission in the guinea-pig ileum. The receptors fulfil α_2 criteria. In the terminal ileum phenylephrine fails to inhibit cholinergic transmission (Table 4, column c), but competitively antagonizes the effect of noradrenaline. Its affinity can, therefore, be estimated; it is low, the dissociation constant being 63 μM (*Wikberg* 1978a).

Similar experiments with agonists suggest that α_2-receptors occur on cholinergic neurones of the rabbit jejunum (*Wikberg* 1979a), the chicken stomach (*Seno* et al. 1978), the guinea-pig gallbladder (*Lee* and *Fujiwara* 1977), the cat submaxillary gland (*Green* et al. 1979), and perhaps the cerebral cortex of the rat (*Vizi* 1979).

The α_2 character is confirmed by experiments with blocking drugs. Yohimbine is a potent antagonist at the α-receptors of the cholinergic neu-

Table 4. Relative potencies of agonists at α-adrenoceptors of the cholinergic neurones of the guinea-pig ileum

	Potencies relative to noradrenaline				
	a	b	c	d	e
Clonidine	9.1	10	20	10	18
(−)-*erythro*-α-methylnoradrenaline	3.2				
Tramazoline	2.9				
Naphazoline	2.2				
Oxymetazoline	1.7	2.2	3		
(−)-Noradrenaline	1	(1)	1	1	1
(−)-Phenylephrine	0.0089	0.0004	0	0.001	0.018
(±)-Methoxamine	0.0004	0.0002			

The effect measured was the inhibition of contractions of the ileum evoked by electrical stimulation (columns a–d) or the inhibition of the stimulation-evoked outflow of acetylcholine (column e). *a)* From *Wikberg* (1978b). Ilea from reserpine-pretreated guinea pigs were mounted in medium containing sotalol, cocaine and corticosterone. With the author's consent, attention is drawn to the fact that this paper contains some printing errors that confuse the meaning, especially in Fig. 1 where the drugs are coded. For instance, α-methylnoradrenaline is 4l, not 4k. *b)* From *Drew* (1978). Ilea were mounted in medium containing propranolol. Since the paper contains no data for noradrenaline, the potency of clonidine was taken to be 10. Effect of phenylephrine and methoxamine not reversed by piperoxan. *c)* From *Wikberg* (1978a). Terminal ilea were incubated in medium containing sotalol. *d)* From *Ennis* et al. (1979). Enantiomers not indicated. *e)* From *Vizi* (1979). Stereoisomers not indicated.

rones of the guinea-pig ileum (*Drew* 1978; *Andréjak* et al. 1980) and the cat submaxillary gland (*Green* et al. 1979). Tolazoline and piperoxan are also potent antagonists in the ileum, whereas for phentolamine divergent results have been reported (*Paton* and *Vizi* 1969; *Drew* 1978; *Wikberg* 1978a). The α_1-selective antagonists labetalol (*Drew* 1978), prazosin and AR-C 239 (*Andréjak* et al. 1980) fail to block the receptors. Interestingly, the facilitatory α-receptors at skeletal muscle motor nerve endings are more akin to α_1- than to α_2-receptors (*Malta* et al. 1979).

Some of the critical comments of Chap. 2 also pertain here. For instance, not only acetylcholine but also noradrenaline is released by field stimulation of the guinea-pig ileum. Noradrenaline then inhibits the release of acetylcholine as shown by the fact that yohimbine and tolazoline increase the evoked release of acetylcholine (*Kilbinger* and *Wessler* 1979). The presence of noradrenaline may lead to underestimation of the potency of exogenous α-receptor agonists and antagonists as discussed earlier. Moreover, drugs may affect the release of acetylcholine indirectly by changing primarily the release of noradreanline.

Wikberg (1978b) avoided this by depletion of the noradrenaline stores by reserpine. Moreover, in his experiments β-adrenoceptors as well as the

neuronal and extraneuronal uptake of noradrenaline were blocked. *Wikberg* (1979b) calculated the correlation of the relative potencies of agonists at inhibiting cholinergic transmission in the guinea-pig ileum (Table 4, column a) and at inhibiting noradrenaline release in the rabbit pulmonary artery (Table 2). The very close correlation ($r = 0.96$) is good evidence for the similarity of these receptors.

3.2 Noradrenergic Cell Bodies

α-Receptor agonists inhibit the firing of the noradrenergic cells of the locus ceruleus and hyperpolarize sympathetic ganglion cells. The receptors involved appear to be α_2 (*Cedarbaum* and *Aghajanian* 1977; *Brown* and *Caulfield* 1979). For instance, the effect of agonists on sympathetic ganglia was reduced by yohimbine but not by up to 10 μM prazosin (*Brown* and *Caulfield* 1979). Phenylephrine was only slightly less potent in hyperpolarizing the ganglia than was noradrenaline (*Brown* and *Caulfield* 1979), and this might be taken as evidence against a pure α_2-receptor population. The experimental conditions of the authors did not, however, exclude release of noradrenaline by phenylephrine and, hence, an indirect mode of action. From these observations and those discussed in Chap. 2 the general picture emerges that central and peripheral noradrenaline neurones may be endowed with inhibitory α_2-adrenoceptors, in other words inhibitory α_2-autoreceptors, in both their soma-dendritic and their terminal region.

3.3 Central Nervous System

Interest in central α-adrenoceptors rose steeply when it became clear that these receptors were important sites of action of clonidine and related drugs as well as of α-methylnoradrenaline, the active metabolite of α-methyldopa (*Delbarre* and *Schmitt* 1969; *Andén* et al. 1970; *Heise* and *Kroneberg* 1970, 1973; *Hoyer* and *van Zwieten* 1971; *Kobinger* and *Walland* 1971; *Schmitt* et al. 1971). As has been mentioned, electrophysiological and brain slice experiments indicate that cerebral noradrenergic neurones possess soma-dendritic and presynaptic α_2-adrenoceptors. These studies concerned relatively isolated structures and simple responses. The involvement of α-receptor subtypes in more complex functions of the central nervous system is, of course, very difficult to elucidate. The blood–brain barrier impedes drug access, and drugs may act simultaneously at many sites. All conclusions are tentative, and only selected aspects will be discussed here (see also *Berthelsen* and *Pettinger* 1977; *Schmitt* 1977; *Starke* 1977).

Clonidine and related compounds reduce the synthesis and utilization of noradrenaline in rat brain and spinal cord (*Andén* et al. 1970; *Scholtysik* et al. 1975; *Fuller* et al. 1977). Low doses of clonidine are required. Its effect is strongly counteracted by yohimbine, piperoxan and tolazoline, but only weakly by phenoxybenzamine and not at all by prazosin. In the case of another α-adrenergic effect upon the central nervous system, namely the increase in strength of the flexor reflex of acutely spinalized rats, the pattern of drug effects is quite different. High doses of clonidine are needed, and its effect is strongly counteracted by phenoxybenzamine and prazosin, but only weakly by yohimbine, piperoxan and tolazoline (*Andén* et al. 1976, 1978). Since both the biochemical and the motor effect occur in the spinal cord, the contrasting patterns are probably not due to differing access of the drugs to the receptors. Rather, the receptors differ. Those mediating the inhibition of noradrenaline neurones appear to be α_2, whereas those mediating the increase of the reflex appear to be α_1.

The reflex-enhancing receptors are probably located on non-catecholamine neurones (*Andén* et al. 1976). The turnover-decreasing receptors might be identical with the α_2-autoreceptors of noradrenergic neurones. However, this is by no means certain. The turnover-decreasing receptors may well be located on non-noradrenergic neurones and may depress the noradrenergic neurones via a neurone chain (*Andén* et al. 1976). The question of identity with the α_2-autoreceptors always arises when a central drug effect is supposed to be α_2-adrenergic. It is stressed that the α_2 properties of a central receptor do not imply that it is a soma-dendritic or presynaptic receptor of noradrenergic neurones or that the effect it mediates involves central noradrenergic pathways.

The central receptors responsible for the cardiovascular depression caused by clonidine-like drugs and α-methyldopa appear to differ from smooth muscle α-receptors (see *Schmitt* 1977; *Kobinger* 1978) and may be of the α_2 type (*Berthelsen* and *Pettinger* 1977; *Starke* 1977). The recently reported antagonism by prazosin does not exclude this possibility, since high doses of prazosin were given (*Timmermans* et al. 1979b). Whatever the subtype, most but not all of the receptors are probably located on non-catecholamine neurones because clonidine and related compounds retain much of their central autonomic effect after near-complete catecholamine depletion (*Haeusler* 1974; *Kobinger* and *Pichler* 1974; *Reynoldson* et al. 1979; *Pichler* et al. 1980).

Sedation is a prominent side effect of clonidine-like drugs and of α-methyldopa and is probably mediated by central α-adrenoceptors. The following findings suggest that these receptors may be α_2.

1) In chicks with incomplete blood-brain barrier the potency of agonists in inducing sleep declines in the order clonidine $\gg$ α-methylnoradrenaline, naphazoline $>$ noradrenaline (*Fügner* and *Hoefke* 1971).

2) Sleep caused in chicks by clonidine is antagonized by phentolamine, tolazoline, piperoxan, and yohimbine, but not by azapetine and phenoxybenzamine (*Delbarre* and *Schmitt* 1969, 1971, 1973; *Fügner* 1971). Similar results were obtained in mice where the agonists prolong the chloral hydrate sleeping time (*Delbarre* and *Schmitt* 1971, 1973).

3) In rats the sedative potencies of intracerebro-ventricularly injected agonists decline in the order clonidie $\gg$ xylazine, naphazoline $>$ methoxamine; phenylephrine is inactive. The sedation induced by clonidine is antagonized by intraventricular injection of phentolamine, piperoxan, yohimbine and tolazoline, but not by injection of labetalol, prazosin and thymoxamine (*Drew* et al. 1979). Essentially similar results were obtained in rats by other authors (*Clineschmidt* et al. 1979, 1980; *Delini-Stula* et al. 1979; *Nomura* et al. 1980).

The question again arises as to whether the sedation-mediating sites, if α_2, are autoreceptors. Since sedation and inhibition of noradrenaline turnover are produced by similarly low doses, this does seem possible. In further support of this view, clonidine no longer causes sedation after catecholamine depletion, but, on the contrary, causes locomotor stimulation (*Zebrowska-Lupina* et al. 1977; see also *Strömbom* and *Svensson* 1980).

Effects of clonidine related to sedation include suppression of conditioned avoidance responses, of self-stimulation, and of the fear-potentiated startle reflex. These effects also seem to be mediated by α_2-receptors and, moreover, by inhibition of central noradrenaline neurones (*Franklin* and *Herberg* 1977; *Hunt* et al. 1978; *Robson* et al. 1978; *Davis* et al. 1979; *Hawkins* and *Monti* 1979).

Like noradrenaline neurones, central *adrenaline* pathways can be modulated via α-receptors belonging to the α_2 group (*Scatton* et al. 1979).

3.4 Blood Platelets

Adrenaline, noradrenaline, and α-methylnoradrenaline induce an α-adrenergic aggregation of human platelets. Non-catecholamine agonists do not share this effect with the three catecholamines but may enhance the aggregation produced by other stimuli (see *Grant* and *Scrutton* 1979; *Hsu* et al. 1979). The catecholamines also inhibit platelet adenylate cyclase. Non-catecholamine agonists fail to do so or are only partial agonists (*Jakobs* et al. 1978; *Tsai* and *Lefkowitz* 1978). All α_2-receptors discussed hitherto were probably constituents of the cell membrane of neurones. The platelet α-receptors may be an example of non-neuronal α_2-receptors.

α-Methylnoradrenaline is twice and clonidine 15 times as potent as noradrenaline in enhancing ADP-induced aggregation, whereas phenylephrine and methoxamine have little effect (*Hsu* et al. 1979). Yohimbine

and phentolamine, but not up to 100 μM prazosin, counteract adrenaline-induced aggregation (*Glusa* et al. 1979; *Hsu* et al. 1979; *Lasch* and *Jakobs* 1979). Non-catecholamines that have little or no effect of their own do antagonize adrenaline-induced aggregation as well as the inhibition of adenylate cyclase (*Hsu* et al. 1979; *Lasch* and *Jakobs* 1979; *Rossi* et al. 1979); oxymetazoline, naphazoline, and clonidine are much more potent in this respect than is phenylephrine (*Lasch* and *Jakobs* 1979). These findings are compatible with the view that platelets possess an α_2-receptor through which only adrenaline, noradrenaline, and α-methylnoradrenaline act with full efficacy (*Glusa* et al. 1979; *Hsu* et al. 1979; *Lasch* and *Jakobs* 1979). They may, however, in addition contain an α_1-receptor which does not contribute much to the response to adrenaline but which may mediate the aggregation-enhancing effect of phenylephrine (*Grant* and *Scrutton* 1979). The observation that α-methylnoradrenaline is only half as potent as noradrenaline in eliciting aggregation and inhibiting adenylate cyclase would be unusual for a pure α_2 population.

3.5 Smooth Muscle

Perhaps the most unforeseen α_2-receptors, or α_2-like receptors, have recently been detected in smooth muscle cells, the α-receptors of which had served as α_1 prototypes. The initial observation was that prazosin antagonized the contractile effect of noradrenaline strongly in human visceral arteries, but at best only slightly in digital arteries. There seemed to be a prazosin-sensitive and a prazosin-resistant group of contraction-mediating vascular α-adrenoceptors (*Moulds* and *Jauernig* 1977; *Jauernig* et al. 1978). Following up the idea that the two groups might be α_1- and α_2-receptors, *Drew* and *Whiting* (1979) showed that in cats and rats prazosin strongly counteracted the hypertensive effect of phenylephrine, but much less markedly counteracted the effect of noradrenaline. Conversely, yohimbine was slightly more potent against noradrenaline than against phenylephrine. The effect of noradrenaline was also relatively prazosin-resistant in the isolated cat hindlimb and mesenteric vascular beds but not in the renal vascular bed. *Drew* and *Whiting* (1979) concluded that phenylephrine constricts blood vessels solely via the prazosin-sensitive α_1-receptor, whereas noradrenaline, except in cat kidney, possesses an additional, prazosin-insensitive site of action. Although they hesitated to classify the latter site as α_2, other experiments support this possibility. For instance, in pithed rats prazosin, at a dose which abolishes the pressor effect of high doses of phenylephrine, only reduces the pressor effect of clonidine and does not change that of the highly α_2-selective agonist xylazine; yohimbine antagonizes the effect of all three agonists, but antagonizes xylazine more than

phenylephrine (*Docherty* et al. 1979; *Docherty* and *McGrath* 1980). There are, by now, numerous analogous observations, the most clear-cut and consistent findings being that contractions of smooth muscle caused by agonists with a strong α_2-component are at least partly resistant to α_1-selective antagonists, and that the resistant contractions can be blocked by α_2-selective antagonists and, hence, are probably mediated by α_2-adrenoceptors (*Timmermans* et al. 1979a; *Constantine* et al. 1980; *Drew* 1980; *Flavahan* and *McGrath* 1980; *Kobinger* and *Pichler* 1980; *Madjar* et al. 1980; *Timmermans* and *van Zwieten* 1980).

A cautionary remark must be added. None of the studies summarized above was carried out under optimal conditions for receptor characterization (see *Furchgott* 1972). Only in one published abstract has differentiation of smooth muscle α_1- and α_2-receptors under strictly controlled in vitro conditions been reported; α_2-receptors were found in dog veins but not arteries (*De Mey* and *Vanhoutte* 1980). Further such in vitro experiments are necessary before the occurrence of smooth muscle α_2-receptors can be considered as established.

4 Radioligand-Binding Studies

α-Adrenoceptors have been labelled with several radioactive ligands. In the present context, ^{3}H-dihydroergokryptine, ^{3}H-clonidine, ^{3}H-WB 4101, and ^{3}H-prazosin are especially important.

4.1 ^{3}H-Clonidine, ^{3}H-WB 4101 and ^{3}H-Prazosin

In the studies summarized in Tables 5 and 6, membrane fractions of tissue homogenates were incubated with low concentrations of the radioligands in 25–30 m*M* Tris–HCl buffer pH 7.4–8.0. Nonspecific binding was measured in the presence of high concentrations of unlabelled ligands and was subtracted from total binding. The remaining specific binding was saturable and of high affinity, as shown by the dissociation constants K_D of the radioligand–receptor complexes in the Table legends. The Tables contain dissociation constants K_i of nonradioactive drugs that competed with the radioligands for specific binding.

The rank orders of affinities of agonists and antagonists for the ^{3}H-clonidine-binding site agree well in the various tissues and studies (Table 5). The rank orders of affinities for the ^{3}H-WB 4101 site resemble the rank orders for the ^{3}H-prazosin site and are therefore presented together

Table 5. K_i values (n*M*) for the inhibition of the binding of ^{3}H-clonidine to α-adrenoceptors

	Rat brain minus cerebellum a	Rat brain minus cerebellum b	Rat cerebral cortex c	Rat cerebral cortex d	Calf cerebral cortex e	Rabbit duodenum f	Guinea-pig ileum g	Guinea-pig kidney h
Agonists								
(−)-Phenylephrine	270			390	260		2300	4200
(−)-Noradrenaline	17	10.2		25.2	16	27	58	170
α-Methylnoradrenaline	7.7	1.5		8.7			18	
Clonidine	5.7	0.9		4.8	1.2	8.5	5.7	27
Naphazoline	5.7			5.4	0.9			30
Tramazoline	4.2			10.4			6.9	
Oxymetazoline	1.9			4.6	1.6			780
Antagonists								
Phentolamine	22	5.2	2.1	78	1.2	300	12	24
Piperoxan	95	325						430
Rauwolscine			41				57	
Yohimbine	150	253	47	360			82	220
Tolazoline	180							
WB 4101	200	985	110	2560	27		230	
Prazosin		6960	5000	3430			5400	1400
Corynanthine			6200				5800	
Indoramin	6500		6500					

Tissues were homogenized and incubated with 0.4–20 n*M* ^{3}H-clonidine. K_D for ^{3}H-clonidine was 2–11 n*M*. *a) U'Prichard* et al. (1977). *b) Miach* et al. (1980). *c)* Phentolamine, WB 4101, prazosin and indoramin from *U'Prichard* et al. (1978); rauwolscine, yohimbine and corynanthine from *Tanaka* and *Starke* (1980). *d) Hornung* et al. (1979). *e) U'Prichard* and *Snyder* (1977). *f) U'Prichard* and *Snyder* (1979). *g) Tanaka* and *Starke* (1979). *h) Jarrott* et al. (1979); phenylephrine enantiomer not specified.

Table 6. K_i values (n*M*) for the inhibition of the binding of ^{3}H-WB 4101 and ^{3}H-prazosin to α-adrenoceptors

	Rat brain a	Rat cerebral cortex b	Rat cerebral cortex c	Calf cerebral cortex d	Rat vas deferens e	Rat brain minus cerebellum f	Rat brain minus cerebellum g	Rat cerebral cortex h	Guinea-pig lung i
Agonists									
(−)-Phenylephrine	2 600					1 400		16 000	110 000
(−)-Noradrenaline	1 000		4 200	1 300	470	900	5 615	10 200	1 400
α-Methyl-noradrenaline	2 800						36 474	56 000	
Clonidine	430		1 162	450	850	340	2 315	950	2 200
Naphazoline	110		226			43		320	
Tramazoline	110					290		1 000	
Oxymetazoline	24					23		630	
Antagonists									
Phentolamine	3.6	3.6	74.8	1.2	5.3		304	30	6.6
Piperoxan	180				150	360	5 775		770
Rauwolscine		2 200							
Yohimbine	480	419			480	1 000	8 906	800	3 100
Tolazoline	2 100					2 000			
WB 4101	0.6	0.3	2.7	0.3		1.0	3.8	8	0.8
Prazosin		0.5				0.1	0.3	0.6	0.1
Corynanthine		170							
Indoramin	5.9	5.9				5.0			4.0

Tissues were homogenized and incubated with 0.2–8 n*M* ^{3}H-WB 4101 (a–e) or 0.1–2 n*M* ^{3}H-prazosin (f–i). K_D values were 0.3–2.7 n*M* for ^{3}H-WB 4101 and 0.2–0.5 n*M* for ^{3}H-prazosin. *a) U'Prichard* et al. (1977). *b)* Phentolamine, WB 4101, prazosin and indoramin from *U'Prichard* et al. (1978); rauwolscine, yohimbine and corynanthine from *Tanaka* and *Starke* (1980). *c) Davis* et al. (1978). *d) U'Prichard* and *Snyder* (1977). *e) U'Prichard* and *Snyder* (1979). *f) Greengrass* and *Bremner* (1979); phenylephrine enantiomer not specified. *g) Miach* et al. (1980). *h) Hornung* et al. (1979). *i) Barnes* et al. (1979)

in Table 6, but they differ from the rank orders for the ^{3}H-clonidine site. There are, however, many discrepancies between absolute K_i values. For instance, the K_i values of agonists for inhibition of ^{3}H-prazosin binding to rat brain membranes found by *Hornung* et al. (1979; Table 6, column h) exceed the corresponding values for inhibition of ^{3}H-prazosin binding found by *Greengrass* and *Bremner* (1979; column f) and for inhibition of ^{3}H-WB 4101 binding found by *U'Prichard* et al. (1977; column a) by factors of between 2 and 27. The K_i values of agonists for inhibition of ^{3}H-clonidine binding reported by *Jarrott* et al. (1979; Table 5, column h) also are higher than corresponding values (in columns a–g); the discrepancy for oxymetazoline is particularly large, as pointed out by the authors. Surprisingly different constants have been published for phentolamine. Its K_i for ^{3}H-clonidine binding varied between 1.2 and 300 n*M* in one laboratory (Table 5, columns e and f) and between 2.1 and 22 n*M* even in one tissue, namely rat brain (columns a and c).

The K_i values reveal two characteristic properties of the binding sites. Firstly, agonists tend to have much higher affinities for the ^{3}H-clonidine site than for the ^{3}H-WB 4101 and ^{3}H-prazosin sites, whereas the reverse holds true for antagonists. This was noted even in the first experiments by *Greenberg* et al. (1976), *U'Prichard* and *Snyder* (1977), and *U'Prichard* et al. (1977). These authors concluded that either there was a single α-adrenoceptor that could take agonist- and antagonist-preferring conformations, or, more probably, that there were two distinct, non-interconvertible α-adrenoceptors, one with high affinity for agonists (the 'agonist receptor site'), the other with high affinity for antagonists (the 'antagonist receptor site', see also *Greenberg* and *Snyder* 1978; *Greenberg* et al. 1978; *Peroutka* et al. 1978).

With growing functional evidence for two major α-receptor subtypes, the second property of the binding sites became obvious, namely that the ^{3}H-clonidine site satisfies α_2-, whereas the ^{3}H-WB 4101 site and the ^{3}H-prazosin site satisfy α_1-receptor criteria (*U'Prichard* et al. 1978; *Greengrass* and *Bremner* 1979; *Hornung* et al. 1979; *U'Prichard* and *Snyder* 1979). Comparison of Tables 1, 5, and 6 makes this plain.

How are the two properties related? Is the ^{3}H-clonidine site an α_2-receptor, and is this receptor simultaneously an agonist-selective receptor? Is the ^{3}H-WB 4101 and ^{3}H-prazosin site (if both drugs label the same site) an α_1-receptor, and is this receptor simultaneously an antagonist-preferring receptor?

The predilection of antagonists for the ^{3}H-WB 4101 and ^{3}H-prazosin site is not without exception. In the experiments of *U'Prichard* et al. (1977) tolazoline, piperoxan, and yohimbine had higher affinity to the ^{3}H-clonidine site (the presumed agonist site) than to the ^{3}H-WB 4101 site (the presumed antagonist site). Similar results were obtained by *Hornung* et al. (1979) and *Miach* et al. (1980; see Tables 5 and 6). *U'Prichard* et al.

(1977) explained this by a partial agonist character of the three antagonists. Although the explanation may hold good for tolazoline, there is no evidence for a partial agonist effect of yohimbine and piperoxan at α-adrenoceptors. Even more striking are recent observations with the yohimbine diastereomer rauwolscine. Rauwolscine had 40–54 times higher affinity for the ^{3}H-clonidine site in guinea-pig ileum and rat cerebral cortex (Table 5, columns c and g) than for the cerebrocortical ^{3}H-WB 4101 site (Table 6, column b). Since rauwolscine, yohimbine, tolazoline, and (not consistently) piperoxan preferentially block α_2-adrenoceptors, all these findings fit in with the ^{3}H-clonidine site being an α_2-receptor but not an agonist receptor.

There is as yet no exception to the predilection of agonists for the ^{3}H-clonidine site. Yet, Tables 5 and 6 show that the K_i values of phenylephrine for ^{3}H-clonidine binding (260–4 200 n*M*) and for ^{3}H-WB 4101 and ^{3}H-prazosin binding (1 400–110 000 n*M*) overlap, indicating that the preference of this drug for the presumed agonist site is small. On the whole, the available data suggest that the ^{3}H-clonidine site is identical with the α_2-receptor found in functional studies, whereas the ^{3}H-WB 4101 and ^{3}H-prazosin sites are identical with the α_1-receptor. There is a marked tendency for agonists to bind mainly to the ^{3}H-clonidine site and for antagonists to bind mainly to the ^{3}H-WB 4101 and ^{3}H-prazosin sites *under the conditions of the binding assays*. This, however, is not generally valid, and the sites should not be called the agonist and antagonist site, respectively.

Given this conclusion, a major difficulty remains. In the binding studies all agonists except phenylephrine have much higher affinity for the α_2- than for the α_1-receptor. From the data of *U'Prichard* et al. (1977) the following α_1/α_2 affinity ratios can be calculated (columns a of Tables 5 and 6): phenylephrine 0.10; noradrenaline 0.017; α-methylnoradrenaline 0.0028; clonidine 0.013; naphazoline 0.052; tramazoline 0.038; oxymetazoline 0.079). Functionally, however, the agonists are not so much more potent at α_2- than at α_1-receptors; some are equipotent (like noradrenaline) and some actually more potent at α_1-receptors (like phenylephrine). For instance, comparison of the affinity ratios with the postsynaptic/presynaptic (α_1/α_2) potency ratios of Table 2 shows that the latter are about 10 times higher than the affinity ratios for the imidazolines, and about 100 times higher than the affinity ratios for the phenylethylamines. Comparison of α_1/α_2 affinity ratios with the α_1/α_2 potency ratios of agonists in guinea-pig aorta (α_1) and in cholinergic neurones (α_2; *Wikberg* 1978b) yields essentially similar values. As will be discussed in detail in Chap. 5, two factors may account for this discrepancy. Firstly, in physiological media the affinity of agonists to the α_2-receptor may be lower than in the Tris buffer media used in the binding assays; secondly, in intact tissues a moderate affinity to α_1-receptors may be translated into a high potency.

4.2 ^{3}H-Dihydroergokryptine

In several tissues the number of ^{3}H-dihydroergokryptine-binding sites is equal to the sum of the numbers of ^{3}H-clonidine and ^{3}H-WB 4101 binding sites. ^{3}H-Dihydroergokryptine binds to the ^{3}H-clonidine site and to the ^{3}H-WB 4101 site with similar affinity. These and other observations were first interpreted in terms of agonist and antagonist α-receptors and a partial agonist character of dihydroergokryptine (*Greenberg* and *Snyder* 1978; *Peroutka* et al. 1978). It now seems more likely that ^{3}H-dihydroergokryptine binds with about equal affinity to α_1- and α_2-adrenoceptors (*Miach* et al. 1978; *U'Prichard* et al. 1978; *Hoffman* et al. 1979; *U'Prichard* and *Snyder* 1979; *Wood* et al. 1979). The binding of ^{3}H-dihydroergokryptine to α_1- and α_2-receptors in tissues in which both occur is inhibited by other ligands in a typical manner. If the unlabelled ligand has similar affinity to either receptor, the log concentration–inhibition curve is monophasic and steep, as one would expect from the competition of two drugs for *one* site. If, however, the ligand is selective for one receptor, the curve becomes shallow or overtly biphasic. In experiments on brain membranes, steep monophasic curves are obtained with phentolamine (*Miach* et al. 1978), but biphasic curves with clonidine, WB 4101 and indoramin (*Peroutka* et al. 1978) as well as with yohimbine and prazosin (*Miach* et al. 1978). The differential effects of phentolamine, prazosin and yohimbine on the binding of ^{3}H-dihydroergokryptine have been used to study quantitatively α-receptor subtypes in various tissues. Only α_1-adrenoceptors were found in rat liver, only α_2-adrenoceptors in human platelets, and a mixture in rabbit uterus. Surprisingly, the affinity of a given antagonist for one receptor type varied greatly. For instance, the K_i of yohimbine at the α_2-receptor of rabbit uterus was 14 n*M*, but at the α_2-receptor of human platelets 0.8 n*M*; its K_i at the α_1-receptor of rabbit uterus was 3000 n*M*, but at the α_1-receptor of rat liver 64 n*M* (*Hoffman* et al. 1979). Species or tissue differences may be responsible, as the authors propose. Nevertheless, such large differences are disquieting when one looks for generally valid properties of α_1-adrenoceptors and α_2-adrenoceptors.

5 Synthesis and Outlook

5.1 Agonist Potencies Versus Affinities

Functional studies on sympathetic nerve-muscle junctions, functional studies in other tissues, and radioligand binding studies have converged to the hypothesis that α-adrenoceptors fall into two subclasses. A major

discrepancy between the functional and the binding experiments was pointed out earlier. For all agonists, α_1/α_2 *potency* ratios greatly exceed α_1/α_2 *affinity* ratios. The difference is about 10-fold for imidazoline agonists and about 100-fold for phenylethylamine agonists. It is suggested that two factors may explain the discrepancy: firstly, the use of nonphysiological media in binding experiments, and secondly, a particular kind of stimulus–response relationship in the case of smooth muscle α_1-adrenoceptors.

In the first place, all incubations for radioligand binding that yielded the data shown in Tables 5 and 6 were carried out in Tris buffer, sometimes supplemented with ascorbic acid, EDTA, or magnesium, but without the monovalent cations that abound in physiological media. Sodium and, less effectively, potassium ions, however, reduce the binding of ^{3}H-clonidine to brain membranes; the binding of ^{3}H-WB 4101 and ^{3}H-prazosin, on the other hand, is not changed (*Greenberg* et al. 1978; *Glossmann* and *Presek* 1979; *Hornung* et al. 1979; *Rouot* et al. 1980). In platelets, sodium ions diminish the affinity of agonists but hardly affect that of antagonists to the ^{3}H-dihydroergokryptine sites which, in these cells, are mainly α_2-receptors (*Tsai* and *Lefkowitz* 1978). These studies suggest that sodium reduces the affinity of agonists to α_2- but not α_1-adrenoceptors. Sodium may even increase the affinity of clonidine for α_1-adrenoceptors (*Glossmann* and *Hornung* 1980). If so, the use of sodium-free media will lead to a systematic overestimation of agonist affinities for the α_2-receptor and a systematic understimation of their α_1/α_2 affinity ratios (in comparison with more physiological conditions).

Secondly, in several blood vessels the contractile effect of α-adrenergic agonists seems to be an upwardly convex hyperbolic function of the stimulus generated by the agonist–receptor interaction (or of the fraction of receptors occupied, which is proportional to the stimulus; see Fig. 3 of *Johansson* et al. 1972; Fig. 3 of *Besse* and *Furchgott* 1976; and Fig. 2 of *Ruffolo* et al. 1979). Classic receptor theory states that, in such a case, an agonist with high efficacy should produce a large proportion of its maximal effect when only a small fraction of the receptors is occupied; in other words, its EC_{50} should be much lower than its dissociation constant, and the potency of the agonist should exceed its affinity. Conversely, an agonist with low efficacy even at full receptor occupation should produce only stimuli in the lower, near-linear part of the stimulus–response hyperbola; its EC_{50} should be similar to its dissociation constant, and potency similar to affinity. Indeed, noradrenaline, phenylephrine and α-methylnoradrenaline, which all have high and equal efficacies in rabbit aorta, produce 50% of their maximal effects when only 6% of the receptors are occupied (*Besse* and *Furchgott* 1976). Conversely, clonidine and naphazoline, which in rat aorta possess only 2% of the efficacy of phenylephrine, have

to occupy approximately 50% of the receptors in order to produce 50% of their maximal effect (*Ruffolo* et al. 1979). Thus, in the smooth muscle of blood vessels with classic α_1-adrenoceptors the modest affinity of phenylethylamines is translated into high potency because of the upwardly convex hyperbolic stimulus–response curve. This mechanism does not work for low-efficacy drugs such as many imidazolines.

A brief recapitulation of receptor theory may illustrate this point further (see *Ariens* 1964; *Furchgott* 1964, 1972; *Waud* 1968). The equilibrium between the agonist A, the receptor R and the agonist–receptor complex AR is assumed to obey the law of mass action, from which the familiar equation

$$\frac{[RA]}{[R_t]} = \frac{[A]}{[A] + K_A} \tag{1}$$

is derived, where [RA], $[R_t]$ and [A] are the concentrations of agonist–receptor complex, total receptors, and free agonist, respectively, and K_A is the dissociation constant. *Stephenson* (1956) suggested that formation of the agonist–receptor complex generates a stimulus S which is proportional to the fraction of receptors occupied:

$$S = e\frac{[RA]}{[R_t]}$$

where e is the efficacy of the agonist. The stimulus, in turn, triggers the response of the tissue, so that the effect is some function (not necessarily linear) of S:

$$\frac{E}{E_{max}} = f(S) = f\left(e\frac{[RA]}{[R_t]}\right)$$

where E is the response at a certain concentration of a given agonist, and E_{max} the maximal response obtainable with an agonist of maximal efficacy. Let us now consider the case, exemplified by the effect of α-adrenergic agonists on vascular smooth muscle, in which E/E_{max} is a rectangular hyperbolic function of S according to

$$\frac{E}{E_{max}} = \frac{S}{S+1}$$

In Fig. 1, E/E_{max} is plotted against S, which is indicated on the abscissa in arbitrary units. Below the abscissa S is shown, for an agonist with high efficacy (e = 100) and for an agonist with low efficacy (e = 1), which fractional receptor occupation generates a certain stimulus. When the high efficacy drug occupies all receptors ($[RA]/[R_t]$ = 1), it produces the stimulus S = 100 and, hence, the effect E/E_{max} = 0.99 of the theoretical maximal effect obtainable with an agonist of maximal efficacy. The upper dashed horizontal line is drawn at the response E/E_{max} = 0.99 / 2 = 0.495, and the corresponding dashed vertical line indicates that this effect is triggered by the stimulus S = 0.98 and a fractional receptor occupation of only 0.0098. Thus, at the EC_{50} of the agonist with e = 100, only about 1% of the receptors are occupied, and from equation (1) it follows that $EC_{50} = 0.01\ K_A$. This is the type of relationship found when noradrenaline or phenylephrine acts on α_1-adrenoceptors. On the other hand, when the low-efficacy drug occupies all receptors, it produces the stimulus S = 1 and, hence the effect E/E_{max} = 0.5. The lower dashed horizontal line is drawn at the response E/E_{max} = 0.5 / 2 = 0.25, and the corresponding vertical line indicates that this effect is triggered by the stimulus S = 0.33 and a fractional receptor occupation of 0.33.

Thus, at the EC_{50} of the agonist with e = 1, about 33% of the receptors are occupied, and from equation (1) it follows that $EC_{50} = 0.5\ K_A$. This is the type of relationship found when clonidine or naphazoline acts on α_1-adrenoceptors.

One can also express the difference between high- and low-efficacy agonists using the concept of spare receptors. A calculation analogous to that described above shows that the e = 100 agonist produces 95% of its own maximal effect when only 16% of the receptors are occupied; in other words, there are unoccupied spare receptors even when the agonist produces essentially its maximal effect, and essentially the whole concentration–response curve is covered when receptor occupation is increased from 0 to only about 20%; hence the high potency in comparison with affinity. Conversely, the e = 1 agonist produces 95% of its own maximal effect when 90% of the receptors are occupied; there is no appreciable receptor reserve, and in order to cover the whole concentration–response curve, receptor occupation has to be increased from 0 to about 100%; hence the low potency in comparison with affinity.

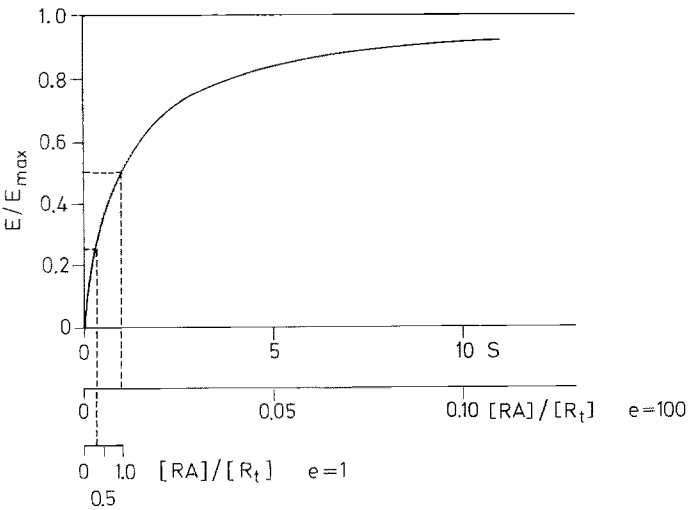

Fig. 1. Relationship between receptor occupation $[RA]/[R_t]$, stimulus S and response E/E_{max} for an agonist with high efficacy, e = 100, and an agonist with low efficacy, e = 1

In the definition proposed in Table 1 it was necessary to distinguish between the high affinity and the low potency of clonidine, relative to phenylephrine, *at α_1-adrenoceptors*. We can now explain this by the low efficacy of clonidine coupled with a hyperbolic stimulus–response curve at the α_1-receptors so far studied. Interestingly, published data show no analogous difference between the potency and the affinity of clonidine, relative to phenylephrine, *at α_2-adrenoceptors* (see Table 1). Agreement between relative potencies and relative affinities at α_2-receptors is also found when other imidazolines and phenylethylamines are compared. Since the agonists do have different efficacies in eliciting α_2-adrenergic effects (see Chap. 2 and *Wikberg* 1978b), the agreement suggests that for the α_2-adrenergic mechanisms studied so far the stimulus–response function is approximately linear.

In conclusion, factor 1 (the monovalent cation effect) holds good for all agonists. Factor 2 (the hyperbolic stimulus-response function) introduces a difference between the effects of high and the effects of low efficacy agonists at α_1- but not at α_2-adrenoceptors. Taken together, the factors may explain why the α_1/α_2 potency ratio is about 10 times higher than the α_1/α_2 affinity ratio for the imidazolines, and about 100 times higher for the phenylethylamines, for the α-adrenergic mechanisms studied so far. α_1/α_2 Affinity ratios of phenylephrine, noradrenaline and α-methylnoradrenaline are 0.10, 0.017 and 0.0028, respectively (*U'Prichard* et al. 1977). The 100-fold increase results in phenylephrine becoming α_1-selective, noradrenaline being equipotent, and α-methylnoradrenaline remaining α_2-selective in functional experiments.

Wikberg (1978b) proposed the following definition of α-receptor subtypes: "When the relative affinities of phenylephrine and noradrenaline are greater than those of tramazoline, xylazine and clonidine, α_1 receptors are present, and when these orders are reversed, the receptors are of the α_2 type". *Ruffolo* et al. (1979) criticized this definition since "ED50 values . . . may be poor estimates of agonist affinity". They pointed out that in rat aorta clonidine had 14 times higher affinity than phenylephrine for the smooth muscle α-receptor, so that, according to *Wikberg* (1978b), "the postsynaptic *alpha* receptors of the rat aorta would have to be termed presynaptic which is clearly incorrect". The somewhat misleading terminology in these statements (presynaptic/postsynaptic; affinity/potency) should not detract from the fact that the scientific messages of these authors can be reconciled when affinity and potency are distinguished as in Table 1 and when possible reasons for the apparent discrepancy are recognized. *Wikberg* (1978b) determined relative potencies only, and the *potency* of phenylephrine does exceed, or is about as high as, that of clonidine at all α_1-receptors studied including those of rat aorta (*Ruffolo* et al. 1979).

5.2 Some Open Questions

Questions, not least those concerning discrepant findings, have been raised throughout this review. Some of a more general nature will be added here.

Receptor classes, once established, tend to divide, and it is stressed that the α_1/α_2 subclasses may not be homogeneous. Some divergent results may be due to the existence of sub-subclasses. A given receptor may also change its behaviour when its environment changes. Therefore, descriptions and distinctions should refer to a defined, preferably the physiological, environment. Although differences between receptors were defined here as differences in their recognition sites, receptors may differ elsewhere

in their molecules as well. We know too little, however, about components outside the recognition site to make them the basis for classification.

There may be many more α_2-receptors than those discussed in Chaps. 2 and 3, such as in frog skin melanocytes (*Berthelsen* and *Pettinger* 1977), fat cells (*Berthelsen* and *Pettinger* 1977; *Aktories* et al. 1980), and the kidney, where they may inhibit renin release (*Berthelsen* and *Pettinger* 1977; see however, *Morris* et al. 1979). These various possibilities deserve further study.

The occurrence of α_2-like receptors in smooth muscle makes reconsideration of previous investigations necessary. α_2-Receptors should be sought in tissues which have been used for the definition of α_1-receptors, such as the rabbit pulmonary artery. It has been reported that high concentrations of oxymetazoline desensitize the smooth muscle of rat vas deferens to oxymetazoline and other imidazoline agonists but not to noradrenaline, methoxamine, and phenylephrine (*Ruffolo* et al. 1977). Is this because the imidazolines, in contrast to the phenylethylamines, act mainly via smooth muscle α_2-receptors [in spite of the fact that under different experimental conditions *Docherty* et al. (1979) did not find postsynaptic α_2-receptors in this organ]? In some tissues the response to sympathetic nerve stimulation is reduced only slightly or not at all by clonidine (e.g. in the cat hindlimb: *Haeusler* 1976). Postsynaptic α_2-receptors might account for such findings. It may be that some reports on tissue or species differences in smooth muscle α-receptors (see *Harper* et al. 1979) which have not been discussed here can also be partly explained in the light of the existence of smooth muscle α_2-receptors. Generally speaking, the possibility that both α_1- and α_2-receptors mediate smooth muscle contraction, and in particular vasoconstriction, opens up a wide field for research (e.g., *Constantine* and *Lebel* 1980; *Langer* et al. 1980).

Studies of radioligand binding to α-adrenoceptors have led to many discrepancies, such as the wide variation in K_i values of antagonists for inhibiton of ^{3}H-dihydroergokryptine binding to what one would assume to be the same receptor. It is important to discover the reason. The binding of ligands to α-receptors is influenced not only by monovalent but also by divalent cations and nucleotides (*U'Prichard* and *Snyder* 1978; *Glossmann* and *Presek* 1979; *Tsai* and *Lefkowitz* 1979; *Rouot* et al. 1980), and this may be relevant for the physiological implications of binding studies. The binding of selective radioligands has been used to visualize α_1- and α_2-receptors in rat brain autoradiographically (*Young* and *Kuhar* 1979). This method may help to localize the receptors not only in terms of brain nuclei but also in terms of cell regions, such as the pre- and postsynaptic sides of synapses.

^{3}H-Dihydroergokryptine is assumed to bind with about equal affinity to α_1- and α_2-adrenoceptors. Surprisingly, the effects of dihydroergokryptine on the subtypes have not been compared functionally.

A final question that can only be mentioned briefly is whether part of the binding of radioligands is to presynaptic or soma-dendritic α-receptors of noradrenergic neurones. So far, such autoreceptor binding has been demonstrated only in rat heart (*Story* et al. 1979), and has been sought in vain in several other tissues (e.g., *U'Prichard* et al. 1977; *Tanaka* and *Starke* 1979; for possible reasons, see *Taube* et al. 1977).

5.3 Therapeutic Implications

The existence of two α-adrenoceptor subclasses has therapeutic significance. As mentioned in Chap. 3.3 clonidine-like drugs and α-methylnoradrenaline probably owe their antihypertensive effect to their α_2-adrenergic properties. The same holds good for some side effects such as sedation and dry mouth (inhibition of cholinergic transmission). Imidazolines used as nasal decongestants may cause sedation; this may also be an α_2-adrenergic effect. Clonidine suppresses symptoms of opiate withdrawal (*Gold* et al. 1978) possibly by acting at α_2-autoreceptors of the noradrenaline neurones of the locus ceruleus, which are also endowed with opiate receptors (*Montel* et al. 1974). If depression involves diminished transmission through central noradrenergic synapses, α_2-selective antagonists might have a salutary effect by facilitating transmission. This has in fact been reported (*Puech* et al. 1979). On the other hand, the view that mianserin acts as an antidepressant by blockade of central α_2-autoreceptors is questionable since the drug is not selective (see Chap. 2).

Selectivity for α_1-adrenoceptors may also be important. Sympathomimetic drugs used as vasoconstrictors should have a marked α_1 component. From this point of view, phenylephrine and methoxamine would have an advantage over the imidazolines. α_1-Selective antagonists such as prazosin appear to be useful, peripherally acting antihypertensive drugs. At low doses they should not interrupt the α-adrenergic feedback inhibition of noradrenaline release and hence should cause less tachycardia and hyperreninaemia than nonspecific α-adrenolytic drugs like phentolamine. Other factors, however, must contribute to the lack of reflex tachycardia after hypotensive doses of prazosin (*Hardey* and *Lokhandwala* 1979). α_1-Selective antagonists also cause less gastrointestinal stimulation than does phentolamine, possibly because they do not interfere with the noradrenergic inhibition of intestinal cholinergic neurones.

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