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With 19 Figures

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List of Contents

Abbreviations

(The abbreviations apply to all figures.)

III	Third ventricle
AA	Axo-axonal terminal
ACC	Anterior cingulate cortex
AMPA	α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AP	Area postrema
BDNF	Brain-derived neurotrophic factor
Bi	Midline nucleus of Bischoff
CCI	Chronic constriction injury
CCK	Cholecystokinin
CGRP	Calcitonin gene-related peptide
CL	Nucleus centralis lateralis
Cu	Cuneate nucleus
C1, C2	Central terminals of type 1 or type 2 glomerulus
D	Dendrite
DCN	Dorsal column nuclei
DH	Dorsal horn
DT	Dome-shaped terminal
EPSP	Excitatory postsynaptic potential
EM	Electron microscopy
FB	Fast Blue
FGF-2	Fibroblast growth factor-2
fMRI	Functional magnetic resonance imaging
FRAP	Flour-resistant acid phosphatase
GABA	γ-Aminobutyric acid
GDNF	Glial cell line-derived neurotrophic factor
GluR1	AMPA receptor subunits GluR1
GluR2	AMPA receptor subunits GluR2
Gr	Gracile nucleus
HZ	Herpes zoster
IC	Insular cortex
ION	Infraorbital nerve
LCN	Lateral cervical nucleus
LM	Light microscopy

LSN	Lateral spinal nucleus
MDH	Medullary dorsal horn
MD	Mediodorsal thalamic nuclei
MDvc	Medial thalamus, ventrocaudal part
NGF	Nerve growth factor
NMDA	*N*-methyl-D-aspartate
NMDAR1	NMDA receptor subunit 1
NMDAR2	NMDA receptor subunit 2
NKA	Neurokinin A
NK1	Neurokinin 1
NO	Nitric oxide
NOS	Nitric oxide synthase
NP	Neuropathic pain
NPY	Neuropeptide Y
PA	Primary afferent (neuron)
PC	Prefrontal cortex
RF	Reticular formation
PAG	Periaquaductal gray
PET	Positron emission tomography
PHN	Postherpetic neuralgia
Po	Posterior nuclear complex
Pom	Posterior nuclear complex, medial part
PTN	Principal trigeminal nucleus
SC	Spinal cord
SG	Spinal (dorsal root) ganglia
SHT	Spinohypothalamic tract
SMT	Spinomesencephalic tract
Sol	Nucleus solitarius
SP	Substance P
SPbT	Spinoparabrachial tract
SRT	Spinoreticular tract
STN	Spinal trigeminal nucleus
STNc	Spinal trigeminal nucleus, caudal part (subnucleus caudalis)
STNi	Spinal trigeminal nucleus, interpolar part (subnucleus interpolaris)
STNo	Spinal trigeminal nucleus, oral part (subnucleus oralis)
STrT	Spinal trigeminal tract
STT	Spinothalamic tract
SI	Primary somatosensory cortex
SII	Secondary somatosensory cortex
TG	Trigeminal ganglion
THT	Trigeminohypothalamic tract
TTT	Trigeminothalamic tract
VIP	Vasoactive intestinal polypeptide
VL	Nucleus ventralis lateralis

VMpo	Nucleus ventralis medialis, posterior part
VPI	Nucleus ventralis posterior inferior
VPL	Nucleus ventralis posterior lateralis
VPLc	Nucleus ventralis posterior lateralis, caudal part
VPLo	Nucleus ventralis posterior lateralis, oral part
VPM	Ventral posteromedial thalamic nucleus
VR1, VRL1	Vanilloid receptors 1 and L1
VZV	Varicella-zoster virus

1 Introduction

Pain is defined by the International Association for the Study of Pain (IASP) as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage or both. Pain is an unpleasant but very important biological signal for danger. Nociception is necessary for survival and maintaining the integrity of the organism in a potentially hostile environment (Hunt and Mantyh 2001; Scholz and Woolf 2002). Pain is not a monolithic entity. It is both a sensory experience and a perceptual metaphor for damage (i.e., mechanically, by infection), and it is activated by noxious stimuli that act on a complex pain sensory apparatus.

However, sustained or chronic pain can result in secondary symptoms (anxiety, depression), and in a marked decrease of the quality of life. This spontaneous and exaggerated pain no longer has a protective role, but pain becomes a ruining disease itself (Basbaum 1999; Dworkin and Johnson 1999; Woolf and Mannion 1999; Dworkin et al. 2000; Hunt and Mantyh 2001; Scholz and Woolf 2002). If pain becomes the pathology, typically via damage and dysfunction of the peripheral and central nervous system, it is termed "neuropathic pain."

Here, we present an updated review of the functional anatomy of normal and neuropathic pain.

2 Functional Neuroanatomy of the Pain System

2.1 Primary Afferent Neuron

The primary afferent (PA) neuron is the pseudounipolar cell, localized in spinal (dorsal root) ganglia (SG), and in the sensory ganglia of the 5^{th}, 7^{th}, 9^{th}, and 10^{th} nerves (for reviews see Scharf 1958; Duce and Keen 1977; Brodal 1981; Willis 1985; Zenker and Neuhuber 1990; Willis and Coggeshall 1991; Hunt et al. 1992; Lawson 1992; Waite and Tracey 1995; Usunoff et al. 1997; Waite and Aschwell 2004). The perikarya of the PA neurons are round, oval, or elliptical. The neurons lack dendritic processes and generally lack direct synaptic input to the soma (Feirabend and Marani 2003). The Nissl substance is abundant but finely dispersed. In old individuals, large accumulations of lipofuscin are regularly observed. Feirabend and Marani (2003) summarized the functional aspects of the dorsal root ganglia: "It appears that the DRG cell bodies are electrically excitable, lack a blood brain barrier and some are able to fire repetitively. The first feature may be important for both propagation of impulses along the T junction and feed back regulation of sensory endings. The second aspect suggests a role as chemical sensor and the third property may be responsible for generating background sensation of

the awareness of the body scheme." The cell body emits a single process (crus commune) that bifurcates in a peripheral and central process. Frequently, and especially in the larger neurons, the crus commune is highly coiled (Ramon y Cajal 1909); this is referred to as the glomerular segment. The central process, usually thinner than the peripheral one (Rexed and Sourander 1949), enters the CNS, and the peripheral process (morphologically an axon, functionally a dendrite) runs in the peripheral nerve to its sensory innervation zone. The peripheral specialized transductive ending serves as part of a sense organ complex or as the sense organ itself as is the case with the free nerve ending.

The diameter of the pseudounipolar perikarya varies from 15 to 110 μm. Two basic types are generally recognized: large, light A cells and small, dark B cells. The cytoplasm of the large cells is rather pale and unevenly stained due to aggregations of Nissl substance interspersed with light staining regions that contain microtubules and a large amount of neurofilaments. The small cells appear dark mainly because of the densely packed cisternae of granular endoplasmic reticulum and few neurofilaments. The largest A cells are the typical proprioceptor neurons, and the small B cells are the typical nociceptor neurons (Harper and Lawson 1985; Sommer et al. 1985; LaMotte et al. 1991; Willis and Coggeshall 1991; Truong et al. 2004). The neurons in the trigeminal ganglion (TG) are similarly distinguished in light and dark cells (Capra and Dessem 1992; Waite and Tracey 1995; Usunoff et al. 1997; Waite and Ashwell 2004). Attempts have been made to classify the two populations of PA neurons further into physiological, anatomical, ultrastructural, and immunocytochemical terms (Sommer et al. 1985; Lawson et al. 1987, Lawson 1992, 2002; Schoenen and Grant 2004). Some studies suggest that a single PA neuron may give rise to more than one peripheral branch, and more than one centrally projecting branch (Langford and Coggeshal 1981; Chung and Coggeshal 1984; Alles and Dom 1985; Laurberg and Sorensen 1985; Coggeshall 1986; Nagy et al. 1995; Russo and Conte 1996; Sameda et al. 2003). This question is of interest from a clinical point of view because the possible branching of peripheral processes has bearing on the problem of referred pain (Coggeshall 1986; Schoenen and Grant 2004).

There are numerous studies on the number and size of PA neurons of the SG in various species revealing not only large species differences but also significant interindividual variations (Avendano and Lagares 1996; Mille-Hamard et al. 1999; Farel 2002; Tandrup 2004). Ball et al. (1982) examined the TG from 64 human subjects from 2 months to 81 years old; the mean neuronal count was 80,600 with no significant age or sex difference. However, they reported striking variation in individual samples (range 20,000–157,000). According to a recent investigation, the human TG comprises approximately 20,000–35,000 neurons (La Guardia et al. 2000).

The neurotransmitter of the PA cells is the amino acid glutamate, the most typical fast-acting central excitatory transmitter (Weinberg et al. 1987; De Biasi and Rustioni 1988; Rustioni and Weinberg 1989; Clements et al. 1991; Westlund et al. 1992; Broman et al. 1993; Broman 1994; Valtschanoff et al. 1994; Salt and Herrling 1995; Keast and Stephensen 2000; Meldrum 2000; Lazarov 2002; Hwang

et al. 2004; Tao et al. 2004). The glutamate acts postsynaptically on three families of ionotropic receptors, named after their preferred agonists, *N*-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and kainate. These receptors all incorporate ion channels that are permeable to cations, although the relative permeability to Na^+ and Ca^{++} varies according to the family and the subunit composition of the receptor (Hollmann et al. 1989; Yoshimura and Jessel 1990; Furuyama et al. 1993; Tölle et al. 1993, 1995; Hollmann and Heinemann 1994; Petralia et al. 1994, 1997; Tachibana et al. 1994; Popratiloff et al. 1996a, b; Ruscheweyh and Sandkühler 2002; Szekely et al. 2002). More recently, also glutamate metabotropic receptors were discovered. They are G-proteins linked and operate by releasing second messengers in the cytoplasm, or by influencing ion channels through release of G-protein subunits within the membrane (Schoepp and Conn 1993; Pin and Duvoisin 1995; Conn and Pin 1997). Glutamate is released from the peripheral terminals of PA nociceptors in the skin and joints during sensory transduction presumably as an initiating event in neurogenic inflammation (Lawand et al. 1997; Carlton and Coggeshall 1999; Carlton et al. 2001; Willis and Westlund 2004).

Especially the B cells contain, besides glutamate, various neuropeptides: substance P (SP), calcitonin gene-related peptide (CGRP), galanin, neuropeptide Y (NPY), neurokinin A (NKA), somatostatin, cholecystokinin (CCK), bombesin, vasoactive intestinal polypeptide (VIP), dynorphin, enkephalin, etc. (Rustioni and Weinberg 1989; Willis and Coggeshall 1991; Lawson 1992; Levine et al. 1993; Broman 1994; Ribeiro-da-Silva 1995; Wiesenfeld-Hallin and Xu 1998; Edvinsson et al. 1998; Todd 2002; Waite and Ashwell 2004; Willis and Westlund 2004). Two or more peptides may be colocalized in the same PA. The proportions of peptidergic SG cells that contain a particular peptide may differ depending on the type of peripheral nerve. CGRP is found in 50% of skin afferents, in 70% of muscle afferents, and in practically all visceral afferents. SP is found in 25% of skin afferents, in 50% of muscle afferents, and in more than 80% of visceral afferents. However, somatostatin is lacking in visceral afferents but is present in a small number of somatic afferents (Willis and Westlund 2004). According to Ambalavanar et al. (2003) from the cutaneous PA neurons in the rat's TG, 26% contain CGRP, 5% SP, and 1% somatostatin. In the SG, the quantity of SP-containing neurons (10%–29% of the cutaneous afferent population) is considerably higher (O'Brien et al. 1989; Hökfelt 1991; Willis and Coggeshall 1991; Perry and Lawson 1998; see also Lazarov 2002). Most cells containing SP seem to be nociceptive neurons with high thresholds (Lawson et al. 1997). In the SG (Yang et al. 1998), the percentage of CGRP-immunoreactive neurons is smaller in females that in males. In guinea pigs, the CGRP expression is detected in under half the nociceptive neurons, and is not limited to nociceptive neurons (Lawson et al. 2002). It seems likely that the peptides are neuromodulators that act in concert with the fast-acting neurotransmitter glutamate, either enhancing or diminishing its action (Levine et al. 1993; Willis et al. 1995; Besson 1999; McHugh and McHugh 2000).

The brain-derived neurotrophic factor (BDNF) meets many of the criteria to establish it as a neurotransmitter/neuromodulator in small diameter nociceptive

PA neurons, localized in dense core synaptic vesicles (McMahon and Bennett 1999; Mannion et al. 1999; Pezet et al. 2002) and is released by the PAs terminating in the superficial laminae of the dorsal horn (DH).

The gaseous transmitter nitric oxide (NO) is synthesized by the enzyme nitric oxide synthase (NOS) in some PA cells of the SG, and in the sensory ganglia of the cranial nerves (Morris et al. 1992; Aoki et al. 1993; Terenghi et al. 1993; Alm et al. 1995; Dun et al. 1995; Lazarov 2002; Thippeswamy and Morris 2001, 2002; Luo et al. 2004). NO is found mainly in the small sensory neurons (Zhang et al. 1993b; Vizzard et al. 1994; Lazarov and Dandov 1998; Rybarova et al. 2000) and coexists with CGRP, sometimes also with SP and galanin (Zhang X et al. 1993a; Majewski et al. 1995; Edvinsson et al. 1998; Rybarova et al. 2000). In the human TG, the coexistence of NO and CGRP is less pronounced (Tajti et al. 1999).

The peripheral processes of the nociceptive PA cells terminate generally as thin fibers of two types: Aδ (Group III), and C (Group IV) (Perl 1996; Bevan 1999; Basbaum and Jessel 2000; Lewin and Moshourab 2004; Willis and Westlund 2004). The Aδ-fibers are thinly myelinated, with a diameter of 1–3 μm and a conduction velocity of 5–30 m/s. More rapidly conducting nociceptive A-fibers (up to 51 m/s) have been described (Treede et al. 1995). The C-fibers are unmyelinated, with a diameter of approximately 1 μm and with a conduction velocity of 0.5–2 m/s. Goldschneider (1881) was the first to propose the existence of two pains, later universally recognized (Hassler 1960; Bowsher 1978; Craig 2003a, d). The first pain (pinprick sensation) is typical for threat of tissue damage. It is rapidly conducted to consciousness and well localized. The second pain occurs when tissue damage has already taken place. It is slowly conducted and poorly localized (Basbaum and Jessel 2000; Julius and Basbaum 2001).

Nociceptors respond maximally to overtly damaging stimuli, although they generally also respond, but less vigorously, to stimuli that are merely threatening (Willis and Westlund 2004). Stimulation of cutaneous Aδ-nociceptors leads to pricking pain, whilst stimulation of C-nociceptors leads to burning or dull pain (Campbell and Meyer 1996; Perl 1996; Willis and Westlund 1997, 2004; Millan 1999; Raja et al. 1999). The peripheral processes of nociceptive PA neurons terminate as free nerve endings (Cauna 1980; Kruger et al. 1981, 2003a, b; Halata and Munger 1986; Kruger 1988, 1996; Munger and Ide 1988; Heppelmann et al. 1995; Messlinger 1996; Petruska et al. 1997; Fricke et al. 2001). The nociceptor terminal differs from other sense organs in responding more vigorously to successive identical stimuli, a process called sensitization. This contrasts with the reduced responsiveness to successive stimuli known as adaptation—displayed by all other sensory transduction systems (Kruger et al. 2003b). Nociceptors, in contrast to modality specificity of other sense organs, are apparently responsive to mechanical, chemical and thermal perturbations, accounting for their common designation as polymodal (Kruger 1996).

The sensory endings of group III (Aδ) and group IV (C) are characterized by varicose segments, the sensory beads, described by Ramon y Cajal (1909) in the cornea. They measure 5–12 μm in length in group III and 3–8 μm in group IV

fibers (Messlinger 1996). The free nerve endings contain clusters of small clear vesicles, dense core vesicles, membranous strands of smooth endoplasmic reticulum, mitochondria, and sometimes glycogen granules (Messlinger 1996; Kruger et al. 2003a, b). The nociceptors, except the free endings, are incompletely surrounded by modified Schwann cells. In particular, their beads exhibit free areas where the axolemma is separated from the surrounding tissue by the basal lamina only. The axoplasm that underlies the bare areas of axolemma shows a faint filamentous substructure and appears more electron-dense (Messlinger 1996). A high concentration of axonal mitochondria may be correlated with energy consumption and hence the activity of the sensory endings (Heppelmann et al. 1994). Probably, the sensory beads represent the receptive sites of the sensory endings (Andres and von Düring 1973; Chouchkov 1978; Munger and Halata 1983; Messlinger 1996).

The free nerve endings contain SP, CGRP, and NKA (Gibbins et al. 1987; Dalsgaard et al. 1989; Micevych and Kruger 1992; Dray 1995; Kruger 1996; Holland et al. 1998), and the sensory endings in the cornea contain also galanin (Marfurt et al. 2001; Müller et al. 2003). However, the neuropeptides, released by the endings, do not have a neurotransmitter function (for a discussion on the noceffector concept, see Kruger 1996).

2.2 Distribution of Nociceptor Peripheral Endings

The free nerve endings are to be found throughout the body, mainly in the adventitia of small blood vessels, in outer and inner epithelia, in connective tissue capsules, and in the periosteum. They are most densely arranged in the cornea, dental pulp, skin and mucosa of the head, skin of the fingers, parietal pleura, and peritoneum.

The two main types of nociceptors in the skin are Aδ mechanical and C polymodal nociceptors (Willis and Westlund 2004), although other types of nociceptors have also been described (Davis et al. 1993). Within the dermis, the afferent fiber gives off several branches that penetrate the basal lamina and extend into the epidermis. As a rule, the myelin sheath ends within the dermis. Most large axons lose their myelin sheaths and perineurium before reaching the papillary layer of the dermis, with the exception of the axons innervating Merkel cells, although those also become unmyelinated before penetrating the epidermis (Iggo and Muir 1969; Kruger et al. 1981; Halata et al. 2003). Cauna (1973) described an elaborate cluster of unmyelinated fibers entering the papillary layer of human hairy skin as a free "penicillate ending". Terminals that penetrate the epidermis for a considerable distance (to the stratum granulosum) have been reported in studies, utilizing methylene blue or silver stainings (Woolard 1935). In the beginnings of ultrastructural examination, numerous reports on the electron microscopic image of the skin receptors appeared (Halata 1975; Andres and von Düring 1973; Cauna 1973, 1980; Chouchkov 1978; Kruger et al. 1981). Even in recent papers (Kruger 1996; Kruger and Halata 1996; Messlinger 1996; Kruger et al. 2003a, b) the authors

are careful in the description of the intraepithelial run of the free nerve endings. As the axon-Schwann cell complex approaches the basal epidermis, the thin Schwann cell basal lamina merges with the thicker epidermal basal lamina. The axon penetrating the epidermis is accompanied by thin Schwann cell processes which follow its course until a single axonal profile is completely enveloped by keratinocytes, without junctional specializations (Kruger et al. 1981, 2003b).

The Meissner corpuscles are widely regarded as low-threshold mechanoreceptors. However, Pare et al. (2001) showed that Meissner corpuscles are multiafferented receptor organs that may have also nociceptive capabilities. In the Meissner corpuscles of glabrous skin of monkey digits they found that the Aα-β-fibers are closely intertwined with endings of peptidergic C-fibers (SP and CGRP). These intertwined endings are segregated into zones containing nonpeptidergic C-fibers expressing immunoreactivity for vanilloid receptor 1.

The enormous number of free nerve endings in the cornea and the lack of any encapsulated receptors were demonstrated by Ramon y Cajal as early as 1909. The innervation density is 300–600 times that of the skin (Rozsa and Beuerman 1982). The number of PA neurons in the TG, that send their peripheral processes in the ophthalmic nerve is modest (La Vail et al. 1993); however, a single corneal sensory neuron in the rabbit support approximately 3,000 individual nerve endings (Marfurt et al. 1989; Belmonte and Gallar 1996; Müller et al. 2003). Both myelinated Aδ and unmyelinated C-fibers are present in the peripheral cornea but the central cornea is innervated by unmyelinated fibers. The latter penetrate Bowman's membrane and terminate between the epithelial cells (Müller et al. 2003; Waite and Ashwell 2004; Guthoff et al. 2005).

Human premolars receive about 2,300 axons at the root apex, and 87% of these fibers are unmyelinated. Most apical myelinated axons are fast conducting Aδ-fibers with their receptive fields located at the pulpal periphery and inner dentin. These fibers are probably activated by a hydrodynamic mechanism and conduct impulses that are perceived as a short, well-localized sharp pain. Most C-fibers are slow-conducting fine afferents with their receptive fields located in the pulp and transmit impulses that are experienced as dull, poorly localized and lingering pain (Nair 1995; Waite and Ashwell 2004). Free nerve endings in mature teeth are found in the peripheral plexus of Rashkow, the odontoblastic layer, the predentin, and the dentin. The endings are most numerous in the regions near the tip of the pulp horn, where more than 40% of the dentinal tubules can be innervated (Byers 1984). Endings can extend for up to 200 μm into the dentinal tubules in both monkey and human teeth, particularly near the cusps of the crown (Byers and Dong 1983; Waite and Ashwell 2004). The periodontal ligament is rich in free nerve endings. The periodontal pain is usually well localized and exacerbated by pressure (Waite and Ashwell 2004).

In the muscles, the free nerve endings are found in the adventitia of the blood vessels, but also between muscle fibers, in the connective tissue of the muscle and in the tendons (Andres et al. 1985). The small myelinated afferent fibers in the muscles have conduction velocities from 2.5–20 m/s, and the unmyelinated fibers less than

2.5 m/s. Of all of the small myelinated and unmyelinated fibers, approximately 40% were believed to be nociceptors (Marchettini et al. 1996; Mense 1996). Bone has a rich sensory innervation; the density of nociceptors in the periosteum is high, whereas nerve fibers in the mineralized portion of the bone are less concentrated and are associated with blood vessels in Volkman and Haversian canals (Bjurholm et al. 1988; Hill and Elde 1991; Hukkanen et al. 1992; Mach et al. 2002). Nociceptors in the joint are located in the capsule, ligaments, bone, articular fat pads, and perivascular sites, but not in the joint cartilage (Heppelmann et al. 1990; Hukkanen et al. 1992; Halata et al. 1999). The free nerve endings in the cruciate ligaments are found subsynovially, and are seen also between collagen fibers, close to blood vessels. However, at least part of the latter fibers appear to be efferent sympathetic fibers and not nociceptors (Halata et al. 1999). The branched, terminal tree of the unmyelinated fibers has a "string of beads" appearance which probably represent multiple receptive sites in the nerve ending (Heppelmann et al. 1990; Schmidt 1996).

In the healthy back, only the outer third of the annulus fibrosus of the intervertebral disk is innervated (see Coppes et al. 1990, 1997; Freemont et al. 1997). Lower back pain was studied in diseased lumbar intervertebral discs and was for the first time reported to be related to ingrowth of nociceptive fibers by Coppes et al. (1990, 1997). This finding was confirmed in 46 samples of diseased intervertebral disks (Freemont et al. 1997). Both groups characterized this ingrowth and extension of the neuronal disk network by the nociceptive neurotransmitter substance P. It is now well established that a change of the innervation of the disk is the morphological substrate for discogenic pain.

There are two classes of nociceptors in viscera (Cervero 1994). The first class is composed of "high-threshold" receptors that respond to mechanical stimuli within the noxious range. Such are found within different organs: gastrointestinal tract, lungs, ureters and urinary bladder, and heart (Cervero 1996; Gebhart 1996). The second class has a low threshold to natural stimuli and encodes the stimulus intensity in the magnitude of their discharges: "intensity-encoding" receptors. Both receptor types are concerned mainly with mechanical stimuli (stretch) and are involved in peripheral encoding of noxious stimuli in the organs (Cervero and Jänig 1992). The cardiac receptors are the peripheral processes of the pseudounipolar PA neurons, located in the SG and the ganglion inferius n. vagi. The sympathetic afferents are considered solely responsible for the conduction of pain arising in the heart. However, Meller and Gebhart (1992) suggest that afferent fibers of the vagus nerve might also contribute to the cardiac pain. The vagus nerve is largely responsible for the pain conduction arising in the lung. Klassen et al. (1951) demonstrated that the burning sensation caused by an endobronchial catheter can be abolished by vagal block. In general, solid organs are least sensitive, whereas the serous membranes, covering the viscera are most sensitive to nociceptive stimuli (Giamberardino and Vecchiet 1996).

Except for avascular structures, such as cornea, skin, and mucosa epithelia, nociceptors are adjacent to capillaries and mast cells (Kruger et al. 1985; Dalsgaard

et al. 1989; Heppelmann et al. 1995; Messlinger 1996). This triad is a functional nociceptive response unit, which is sensitive to tissue damage (Kruger 1996; McHugh and McHugh 2000). The firing of nociceptors at the site of tissue injury causes release of vesicles containing the peptides SP, NKA, and CGRP, which act in an autocrine and paracrine manner to sensitize the nociceptor and increase its rate of firing (Holzer 1992; Donnerer et al. 1993; Dray 1995; Kruger 1996; Cao et al. 1998; Holzer and Maggi 1998; Millan 1999; McHugh and McHugh 2000). Cellular damage and inflammation increase concentrations of chemical mediators such as histamine, bradykinin, and prostaglandins in the area surrounding functional pain units. These additional mediators act synergistically to augment the transmission of nociceptive impulses along sensory afferent fibers (McHugh and McHugh 2000). In addition to familiar inflammatory mediators, such as prostaglandins and bradykinin, potentially important, pronociceptive roles have been proposed for a variety of "exotic" species, including protons, purinergic transmitters, cytokines, neurotrophins (growth factors), and NO (Mannion et al. 1999; Millan 1999; Boddeke 2001; Willis 2001; Mantyh et al. 2002; Scholz and Woolf 2002). Physiological pain starts in the peripheral terminals of nociceptors with the activation of nociceptive transducer receptor/ion channel complexes inducing changes in receptor potential, which generate depolarizing currents in response to noxious stimuli (Woolf and Salter 2000). In PA neurons, the transducer proteins that respond to extrinsic or intrinsic irritant chemical stimuli are selectively expressed (McCleskey and Gold 1999; and references therein). The noxious heat transducers include the vanilloid receptors VR1 and VRL1 (Caterina et al. 1997, 1999; Tominaga et al. 1998; Guo et al. 1999; Welch et al. 2000; Caterina and Julius 2001; Michael and Priestly 1999; Valtschanoff et al. 2001; Hwang et al. 2003). VR1 are on the terminals of many unmyelinated and some finely myelinated nociceptors and respond to capsaicin, heat, and low pH (Holzer 1991; Caterina et al. 1997, 2000; Helliwell et al. 1998; Tominaga et al. 1998). On the other hand, VRL1 are on PAs with myelinated axons, have a high heat threshold, and do not respond to capsaicin and low pH (Caterina et al. 1999). mRNA for VR1 has been shown to be widely distributed in the brains of both rats and humans (Mezey et al. 2000), so that the role of these receptors in response to painful stimuli may be much more complex than previously thought.

There are nociceptors that under normal circumstances are inactive and rather unresponsive. Such nociceptors were first detected in the knee joint and were called "silent" or "sleeping" by Schaible and Schmidt (1983a, b). Inflammation leads to sensitization of these fibers, they "awaken" and become much more sensitive to peripheral stimulation (Schaible and Schmidt 1985, 1988; Segond von Banchet et al. 2000). Later, "silent" nociceptors were described also in cutaneous and visceral nerves (Davis et al. 1993; McMahon and Koltzenberg 1994; Schmidt et al. 1995, 2000; Snider and McMahon 1998; Petruska et al. 2002).

2.3 Termination in the Spinal Cord and Spinal Trigeminal Nucleus

As central processes of the SG neurons approach the dorsal root entry zone, the fine, nociceptive axons become segregated in lateral portions of the rootlets and enter lateral portions of the DH, passing through fasciculus dorsolateralis Lissaueri (Ranson 1913; Kerr 1975b; Light and Perl 1979a; Brown 1981; Schoenen and Faull 1990; Willis and Coggeshall 1991; Carlstedt et al. 2004). At the junction between spinal cord (SC) and roots, there is a profound redistribution and reorganization of nerve fibers (Fraher 1992, 2000; Carlstedt et al. 2004). The transitional zone is the most proximal free part of the root, which in one and the same cross-section contains both CNS and PNS tissue. The PNS compartment contains astrocytic processes that extend from the CNS compartment forming a fringe among the nerve fibers. The CNS compartment is dominated by numerous astrocytes, while oligodendrocytes and microglia are rare. The myelinated fiber change from PNS to CNS type of organization occurs in a transitional node of Ranvier situated at the proximal end of a glial fringe cul-de-sac at the PNS-CNS borderline.

The nociceptive fibers terminate primarily in the most dorsally located laminae of Rexed (Rexed 1952, 1954, 1964). These comprise lamina I (nucleus posteromarginalis) and lamina II (substantia gelatinosa Rolandi); the Aδ-fibers terminate in laminae I and V, and C-fibers in laminae I and II. The large mechanoreceptive Aβ-axons reach laminae III–VI (Light and Perl 1979a, b; Light et al. 1979; Ralston 1979; Ralston and Ralston 1979; Perl 1996; Willis 1985; Menetrey et al. 1989; Willis and Coggeshall 1991; Hunt et al. 1992; Molander and Grant 1995; Ribeiro-da-Silva 1995; Craig 1996a; Han et al. 1998; Morris et al. 2004). Lamina I is with low neuronal density and contains small, medium-sized, and large neurons. The latter, often called marginal cells of Waldeyer are rich in granular endoplasmic reticulum and other organelles (Ralston 1979). They are usually elongated and the three main perikaryal types are fusiform, pyramidal, and multipolar (Gobel 1978a; Lima and Coimbra 1991; Lima et al. 1991; Zhang ET et al. 1996; Zhang and Craig 1997; Han et al. 1998). Based on responses to natural cutaneous stimuli, there are three major types of lamina I neurons (Craig 1996a): (a) nociceptive-specific neurons that respond only to noxious mechanical or heat stimuli, (b) polymodal nociceptive neurons that respond to noxious heat, pinch, and cold, (c) thermoreceptive-specific neurons that respond to innocuous cooling and are inhibited by warming the skin. The nociceptive-specific neurons are dominated by Aδ-fiber input and can respond tonically to a maintained noxious mechanical stimulus, so they may be important for the "first pain" (Craig 2000). The polymodal nociceptive cells are dominated by C-fiber input and are important for the "second pain." Han et al. (1998) have shown by means of intracellular labeling that the nociceptive-specific neurons are fusiform, the polymodal nociceptive neurons are multipolar, and the thermoreceptive-specific neurons are pyramidal. Later, Andrew and Craig (2001) identified "itch-specific" lamina I neurons, which are selectively sensitive to histamine. Approximately 80% of lamina I neurons express

the NK1 receptor (Todd et al. 2000). Substance P in the PAs acts on the neurokinin 1 (NK1) receptor, which is concentrated in lamina I (Marshall et al. 1996; Todd et al. 1998, 2002; Yu et al. 1999; Cheunsuang and Morris 2000; Mantyh and Hunt 2004; Morris et al. 2004).

Lamina II contains densely packed small cells, with a very low amount of perikaryal cytoplasm but relatively rich dendritic tree (Ralston 1979; Schoenen and Faull 1990, 2003; Ribeiro-da-Silva 1995). Two neuronal types called islet cells and stalked cells are to be distinguished (Gobel 1978b; Todd and Lewis 1986), and in humans, Schoenen and Faull (1990) describe four types: islet, filamentous, curly, and stellate neurons. In lamina II neurons coexist two "classical" inhibitory transmitters: the amino acids γ-aminobutyric acid (GABA) and glycine, and GABA is further co-expressed with the neuropeptides methionine enkephalin and neurotensin (Todd and Sullivan 1990; Todd et al. 1992; Todd and Spike 1993). As originally described by Rexed (1952, 1954) in the cat, lamina II might be subdivided into outer and inner zones. In the outer zone, the neurons are slightly smaller and more tightly packed than in the inner zone. In the rat, Ribeiro-da-Silva (1995) further subdivided lamina II in sublaminae A, Bd, and Bv. In humans, the separation between the outer and the inner zone is much less clear (Schoenen and Faull 1990). It has been postulated that the substantia gelatinosa may function as a controlling system modulating synaptic transmission from PA neurons to secondary sensory systems (Melzack and Wall 1965; Wall 1978; LeBars et al. 1979a, b; Light et al. 1979; Moore et al. 2000). Originally, lamina II was considered a closed system, e.g., composed exclusively of short axon interneurons. According to Ribeiro-da-Silva (1995) such a view is no longer valid, as some cells were found to project to the brain. For example, Lima and Coimbra (1991) claimed that some islet cells project to the reticular formation (RF) of the medulla oblongata. After complex local processing in the DH (Willis and Coggeshall 1991; Parent 1996; Ribeiro-da-Silva 1995) nociceptive signals are conveyed to higher brain centers through projection neurons whose axons form several ascending fiber systems.

Interestingly, after transection of sensory fibers entering the spinal DH or the descending spinal trigeminal tract, the typical substantia gelatinosa-related enzyme acid phosphatase disappeared (Rustioni et al. 1971; Coimbra et al. 1974). Moreover, in the descending spinal trigeminal tract a topographic localization for the ophthalmic, maxillary, and mandibular nerves was described using the disappearance of this enzyme (Rustioni et al. 1971). Later on, fluor-resistant acid phosphatase (FRAP) was related to the nociceptive system (see Csillik et al. 2003).

The central processes of pseudounipolar TG neurons enter the brainstem via the sensory trigeminal root. Some fibers bifurcate to give a rostral branch to the principal (pontine) trigeminal nucleus (PTN) and a caudal branch that joins the spinal trigeminal tract (STrT); some axons only descend to the spinal trigeminal nucleus (STN) (Brodal 1981; Capra and Dessem 1992; Waite and Tracey 1995; Parent 1996; Usunoff et al. 1997; Waite and Ashwell 2004). The PAs terminate somatotopically: most ventral are the ophthalmic fibers, in the middle the maxillary

fibers, and dorsally terminate the mandibular fibers. A small number of nociceptive fibers from the 7th, 9th and 10th nerves also join the spinal tract and take a position immediately dorsal to the axons of the mandibular division (Brodal 1947; Usunoff et al. 1997). Generally, the PAs emit collaterals to all three subnuclei of the STN: oralis (STNo), interpolaris (STNi), and caudalis (STNc), defined by Olszewski and Baxter (1954), and according to the classical belief, nociceptive Aδ- and C-fibers terminate almost exclusively in STNc. As suggested at the beginning of the century by Dejerine (1914), inputs from the nose and the lips reach the most rostral parts of STNc, and the posterior regions of the face reach the caudal parts of STNc (onion hypothesis). This appears to be valid from rat to human (Arvidsson 1982; Borsook et al. 2004). Terminations of trigeminal afferents are ipsilateral but some PAs with midline receptive fields terminate in the contralateral STNc (Pfaller and Arvidsson 1988; Jacquin et al. 1990; Marfurt and Rajchert 1991). Many trigeminal PAs reach the paratrigeminal nucleus and solitary nucleus (Usunoff et al. 1997); a moderate number reaches the supratrigeminal nucleus, the dorsal RF, and the cervical SC and a small number of PAs reach cuneate, trigeminal motor, and vestibular nuclei, and even the cerebellum (Marfurt and Rajchert 1991).

The structure of STNc is very similar to the spinal DH (Olszewski and Baxter 1954), and since Gobel et al. (1977) and Gobel (1978a, b), this structure is often called the medullary dorsal horn (MDH) (Craig 1992; Iwata et al. 1992; Li JL et al. 1999; Li YQ et al. 1999, 2000a, b). It has a laminar arrangement with a marginal layer (lamina I), substantia gelatinosa (lamina II), and a magnocellular layer (laminae III, IV). Lamina I is polymorphic, with few large, multipolar neurons (Gobel 1978a; Li YQ et al. 2000a, b), lamina II contains small neurons (Gobel 1978b; Li YQ et al. 1999), and the magnocellular layer actually contains predominantly medium-sized cells, also in humans (Usunoff et al. 1997). In all layers glutamate- and GABA-containing cells are present (Magnusson et al. 1986, 1987; Haring et al. 1990). The GABAergic interneurons innervate the glutamatergic projection neurons, and the latter emit collaterals to the GABA-containing cells (DiFiglia and Aronin 1990). Thus, in the STN there is a reciprocal modulation between the excitatory trigeminothalamic tract (TTT) neurons and the inhibitory interneurons. At the lateral border of the STN, especially in STNc, there are interneurons that immunoreact for NOS (Dohrn et al. 1994; Usunoff et al. 1999). These cells contact the TTT neurons, and Dohrn et al. (1994) suggest that they may indirectly influence orofacial nociceptive processing at the level of the STN via NO production.

In all probability, the MDH is the main, but not the sole part of the trigeminal nuclear complex responsive for nociception. The cornea and the tooth pulp give rise mainly to nociceptive sensations. However, the PAs of these regions reach all components of the trigeminal nuclear complex (Marfurt and Echtenkamp 1988; Barnett et al. 1995; Allen et al. 1996). The rostral parts of the STN also respond to noxious stimulation, and nociceptive responses persist in ventral posteromedial thalamic nucleus (VPM) after trigeminal tractotomy at the obex (Dallel et al. 1988), suggesting nociceptive pathways that are more complex than originally thought (Waite and Tracey 1995).

2.3.1 Types of Terminals in Substantia Gelatinosa

Two types of glomerular terminals could be identified in superficial laminae. One was scalloped, with densely packed clear vesicles of variable size, dark axoplasm, and occasional mitochondria (Figs. 1, 3A,E). These terminals, which contacted several postsynaptic dendrites, correspond to the central terminals of type 1 glomeruli (C1) described by Ribeiro-da-Silva and Coimbra (1982). They are likely to be terminals of unmyelinated PAs (Ribeiro-da-Silva 1995). Terminals of the second type were also scalloped, but with loosely packed clear vesicles of uniform size, light axoplasm and many mitochondria (Figs. 1, 3B,F). These terminals, contacting several postsynaptic profiles and involved in axo-axonic contacts with symmetric active zones, correspond to the central terminals of type 2 glomeruli (C2) described by Ribeiro-da-Silva and Coimbra (1982). These are likely to arise from thinly myelinated PAs (Alvarez et al. 1992, 1993; Light 1992). C1 terminals are concentrated in lamina IIo and dorsal IIi, whereas C2 terminals are concentrated in ventral lamina IIi (Bernardi et al. 1995). Glomeruli make only about 5% of the synapses in substantia gelatinosa (Ralston 1979). The majority of synapses in this region are axo-dendritic, and it is hard to relate them to a particular afferent input. The majority of dome-shaped terminals are believed to originate from intrinsic neurons. Axo-axonic terminals are common in lamina II. Frequently, axo-axonic terminals contain flattened or pleomorphic vesicles (Kerr 1975). Few synapses contain dense core vesicles.

Glutamate Receptors in the Superficial Laminae of the Spinal Cord The superficial laminae of the SC are of particular interest because of their role in hosting the first brain synapse involved in pain processing. This diverse region of the SC also receives other types of PA fibers. Afferents that mediate different types of stimuli (i.e., low- and high-threshold mechanoreceptors) impinge onto the same DH neurons (Willis and Coggeshall 1991). Therefore, the question persists of how spinal neurons decode the convergent inputs at the level of the first synapse. Providing a better understanding about the nature of the synaptic processing in superficial laminae of the SC will directly improve our knowledge and strategies on how to treat abnormal pain. From a pharmacological point of view, a first possibility derives from a speculation that different submodalities are mediated by different neurotransmitters. The pharmacological diversity seems to play a role since the SG neurons giving rise to C-fibers contain substance P, which was not found in cell bodies of normal SG giving rise to A-fibers. Moreover, substance P-positive axons in this area co-localize with μ-opioid receptor (Ding et al. 1995a), suggesting the role of opiates in this region. On the other hand, all PA terminals in the superficial laminae of the SC appear to contain glutamate (Rustioni and Weinberg 1989; Salt and Herrling 1995); nevertheless, the amount of glutamate available in different anatomical classes of terminals may vary (De Biasi and Rustioni 1988; Merighi et al. 1991; Tracey et al. 1991; Levine et al. 1993; Valtschanoff et al. 1994).

In general, a large variety of pre-, post-, and extrasynaptic factors may shape the timing and magnitude of glutamatergic transmission. Normally, glutamate is released by calcium-dependent mechanisms into the synaptic cleft. In the cleft, glutamate is present for brief periods of time because of the fast and highly specific uptake by specific transporters expressed by the nearby astrocytic or neuronal processes and terminals. In the synaptic cleft, glutamate is saturated by two major classes of glutamate receptors: ionotropic and metabotropic. The former are ligand-gated sodium/potassium and, under some circumstances, calcium channels that depolarize the postsynaptic membrane, whereas the latter are coupled to second messenger cascades that can impact metabolism. Three classes of ionotropic glutamate receptors are currently distinct based on their pharmacological characteristics, structure, and physiological properties: AMPA, NMDA, and kainate. AMPA receptors are pore-forming heteromers built-up of a combination of the four subunits: GluR1, GluR2, GluR3, and GluR4. A common property of native AMPA channels is their low affinity to glutamate, blocked by CNQX, and the low permeability of calcium. Local application of CNQX completely abolishes the fast component of the excitatory postsynaptic potentials (EPSP), but does not significantly alter the slower component. Each receptor subunit contributes specific pharmacological and biophysical properties to the receptor channel. For instance, partition of the edited form of the GluR2 subunit into AMPA channels renders them insensitive to internal polyamine block and impermeable to bivalent ions such as calcium.

Different groups of neurons in the brain express a wide variety of AMPA receptor subunit combinations, but not necessarily all of them. Physiological data suggest that this unique phenotyping correlates well with differences in the kinetics of corresponding EPSP. In contrast, NMDA receptors are nonsensitive to CNQX, but to NMDA, show high affinity to glutamate, high voltage dependence due to internal magnesium block, and higher conductance of bivalent ions such as calcium. They are built of an obligatory NMDAR1 subunit and several NMDAR2 subunits. NMDA receptors show lesser variability between brain regions. Finally, kainate receptors have thus far attracted attention particularly because of their presynaptic localization in the superficial laminae of the SC. Their functional significance, at least in the SC, is not clear (Hwang et al. 2001).

Among the number of postsynaptic factors that may contribute to the shape and size of the local glutamatergic depolarization events is the diversity of ionotropic glutamate receptors. Several light microscopic (LM) studies demonstrated high concentrations of AMPA receptor subunits in neurons of superficial laminae of the DH (Furuyama et al. 1993; Henley et al. 1993; Tölle et al. 1993; Tachibana et al. 1994; Kondo et al. 1995; Popratiloff et al. 1996a). However, electron microscopy (EM) was required to verify the presence of receptor subunits at synaptic sites and to explore the relations between receptor subunits and PA terminals. EM evidence for glutamate receptors subunit immunoreactivity was provided with preembedding immunocytochemistry (Liu et al. 1994; Tachibana et al. 1994; Vidnyanszky et al. 1994), suggesting accumulation of electron-dense reaction product at postsynaptic densities. Preembedding was also used in an effort to relate glutamate receptor

subunits to PA terminals (Alvarez et al. 1994). Although providing valuable qualitative data, this method was not suitable for quantitative study, both because of variable antibody penetration into the sections and because of the difficulty in quantifying the density of immunoreactions at the EM level. Postembedding immunocytochemistry with colloidal gold can in principle avoid the above technical limitations (Nusser et al. 1995a, b). However, osmic acid used in the classical EM protocols for tissue fixation abolishes or seriously impairs the antigenicity of the vast majority of the proteins, including glutamate receptor subunits. An original method that replaces osmic acid with tannic acid and uranyl salts in material fixed with glutaraldehyde yielded good structural preservation together with precise localization of multiple receptor subunits (Phend et al. 1995). With this technique, relative quantification of AMPA receptor subunits showed that these are highly concentrated at synapses and that functionally different terminals show different affinity to one or another receptor subunit.

Light Microscopic Appearance of AMPA Receptor Subunits in the Substantia Gelatinosa When the immunolabeling was revealed according to a nickel-intensified DAB-peroxidase protocol in two animals, fine granular reaction product in neuronal somata and neuropil was indicative for sites with high concentration of the antigen. Cellular staining could be identified in somata and proximal dendrites. Staining with the GluR1 antibody was concentrated in the superficial DH (Fig. 2A–C). Stained neurons in other regions except lamina X of the SC were small and sparse. Neurons immunoreactive for GluR2/3 were also concentrated in superficial laminae (Fig. 2D–F). However, this antibody also abundantly stained a number of neurons of various size and shape throughout the rest of the SC.

In lamina I, neurons stained with GluR1 were more concentrated laterally (Fig. 2B), whereas a larger population of intensely stained GluR2/3 neurons was present throughout the mediolateral extent of lamina I (Fig. 2E). Fine punctate neuropil staining was present with both antibodies, which was organized in small bundles oriented mediolaterally, especially apparent in the sections labeled with GluR1.

In lamina II, the density of neurons immunostained for GluR1 was highest near the IIo/IIi border; few stained cells were seen in the deep IIi (Fig. 2C). Neuropil staining with GluR1 overlapped the staining of somata, gradually disappearing at the ventral border of lamina II. The staining achieved with GluR2/3 antibody showed a remarkable difference: density of neuronal and neuropil staining was relatively low at the IIo/IIi border, and highest deep in lamina IIi, extending into lamina III (Fig. 2F). GluR2/3 staining is most likely due to the abundance of GluR2 subunit, because the pattern of GluR2 labeling very much resembles those achieved with the GluR2/3 antibody (not shown). Additional results showed that GluR4 antibody produces little and diffuse staining in superficial laminae of the SC. However, recent data suggest that staining with this antibody is concentrated in the presynaptic terminals and these loci are not readily distinguishable with conventional optical microscopy (Lu et al. 2002).

Electron Microscopy With both GluR1 and GluR2/3 antibodies, gold particles were sparse over cell bodies and dendrites. Gold particles were instead clustered over the postsynaptic density, postsynaptic membrane, and cleft of a large number of asymmetric synapses. A large proportion of terminals with positive synaptic zones could be recognized as originating from PAs, together with synaptic zones of many terminals lacking characteristic glomerular organization, likely to originate from intrinsic neurons. Labeling was not observed over active zones of symmetric synapses. Ninety-four percent of gold particles tallied (410/437) from a sample of 215 glomerular terminals from lamina II were in a region between 30 nm outside and 40 nm inside the postsynaptic membrane (Popratiloff et al. 1996a). The majority of gold particles were associated with the postsynaptic membrane and density. The distribution of gold particles was similar for GluR1 and GluR2/3. The very low density of gold particles away from the synaptic active zones implies that even a single gold particle at the active zone is strong evidence for immunopositivity. Examination of serial thin sections confirmed this interpretation, because synapses first identified as labeled by the presence of one gold particle on one section displayed one or more gold particles also in the adjacent sections (Fig. 3C,D). The same did not hold true for gold particles at nonsynaptic sites.

Relationship Between Types of Terminals and Different Receptor Subunits Terminals of both types were presynaptic to both GluR1 and GluR2/3, but to a different extent. C1 synapses were predominantly GluR1-positive, and synapses were predominantly positive for GluR2/3. These differences were highly significant.

Interpretation of the above-mentioned quantitative differences was complicated by the possibility that unlabeled synaptic sites might nonetheless contain receptor subunits, or that the concentration of subunits may vary at different types of synapses. To explore this issue, the number of gold particles underlying each active zone of randomly photographed PA terminals was counted. The counts were roughly Poisson-distributed, reflecting the random exposure of epitopes at the surface of a thin section. However, heterogeneity of synaptic contacts was also suggested, especially for C2 terminals immunopositive for GluR2/3. Immunolabeled C1 synapses contained a similar number of gold particles coding for GluR1, on average, as did immunopositive synapses of C2 terminals (1.88 vs 2.10), confirming that a higher proportion of C2 than of C1 synapses expressed little or no GluR1. On the other hand, immunopositive synapses of C1 terminals contained a markedly lower mean number of gold particles coding for GluR2/3 than did synapses of C2 terminals (1.92 vs 2.79). This could not be explained by differences in dimensions of active zones, because C1 and C2 had active zones of similar lengths (322.6 ± 13 vs 341.6 ± 11 nm, respectively).

Considerations The data on LM distribution of AMPA subunits are generally consistent with previous studies (Furuyama et al. 1993; Henley et al. 1993; Tölle et al. 1993, 1995; Tachibana et al. 1994; Kondo et al. 1995). The high density of AMPA receptor expression in superficial laminae of the DH is consistent with the pres-

ence of numerous glutamatergic synapses both from peripheral afferents (Broman et al. 1993; Valtschanoff et al. 1994) and from local interneurons (Rustioni and Cuenod 1982). GluR1-positive neurons are concentrated at the IIo/IIi border and are generally superficial to the GluR2/3-positive neurons. Because previous studies with in situ hybridization suggest that the GluR3 subunit is only weakly expressed in the superficial DH (Furuyama et al. 1993; Henley et al. 1993; Tölle et al. 1993, 1995; Pellegrini-Giampietro et al. 1994), our staining for GluR2/3 is likely to reveal mainly the GluR2 subunit. By extrapolation from observations in the cortex (Kharazia et al. 1996) and in the DCN (Popratiloff et al. 1997), at least a fraction of GluR1-positive neurons in superficial laminae may be GABAergic. Nitric oxide synthase (NOS) coexists with GABA in cells in these laminae (Valtschanoff et al. 1992), and NOS-positive neurons in forebrain lack GluR2 (Catania et al. 1995). However, because NO-synthesizing neurons in the SC are concentrated at the border between laminae II and III (ventral to GluR1-positive neurons), only a modest fraction of GluR1-stained neurons may synthesize NO.

Relationship of LM and EM Results The laminar distribution of staining for the two antibodies was similar at LM and EM. However, staining of somata was prominent at LM, but sparse at EM. This apparent discrepancy is presumably explained by the characteristics of the techniques: immunoperoxidase exhibits high sensitivity (because of Ni-amplification of weak signals by the DAB reaction), but is less well localized than immunogold and does not accurately reflect quantitative differences (Griffiths 1993). Alternatively, the immunogold labeling may require antigen concentration to exceed a threshold value. Craig et al. (1993) provided LM evidence for clustering of AMPA/kainate subunits at synapses in cultured neurons. This was supported by EM immunogold performed on frozen or freeze-substituted sections (Nusser et al. 1994, 1995a, b) and by the present results. The immunoglobulin bridge introduces a localization error of 20 nm for the gold particles (Kellenberger and Hayat 1991). Because staining is confined to the surface, obliquity of synaptic membranes in the section may introduce an additional error of similar magnitude. These errors do not affect the present data concerning the modal location of particles but suggest that our results documenting a strong association of AMPA receptors with the postsynaptic membrane underestimate the precision of this association. The close match between glutamate-enriched terminals and sites immunopositive for glutamate receptors (Craig et al. 1994; Phend et al. 1995) shows that the labeling is selective for excitatory synapses, a conclusion supported by the absence of gold labeling at symmetric synapses.

Number of Receptors at a Synapse The exact numerical relationship between gold particles and receptor molecules cannot yet be determined, but in other systems, one gold particle represents 20–200 molecules of antigen (Kellenberger et al. 1987; Kellenberger and Hayat 1991; Griffiths 1993). This ratio reflects various factors: (a) only antigen molecules presenting an epitope at the surface can be recognized and, even for thin (100-nm) sections, a majority of the epitopes are not

exposed; (b) many of the epitopes may be denatured by the fixation and processing; and (c) steric constraints permit only a fraction of surface epitopes to bind immunoglobulin. Thus, although even a single gold particle over a synapse is likely to indicate the presence of a receptor, its absence cannot be taken as proof of the lack of receptor. Nevertheless, because there is an approximately linear relationship between gold particles and antigen density (Ottersen 1989; Griffiths 1993), it is possible to estimate the relative densities of subunits at different synapses. This study is about subunits, not functional receptors. However, considering the high concentration of gold in the vicinity of the postsynaptic membrane, most of these subunits were presumably already in a functionally appropriate position. In cortex and hippocampus, the labeling density seen with this method corresponds well to biophysically derived estimates of functional receptors, assuming a labeling efficiency of 1%–2% (Hestrin 1992; Stern et al. 1992; Griffiths 1993). It can be argued that most subunits inserted into the synaptic membrane have been assembled into functional pentameric receptors.

Relation of Receptors to Types of Synapses C1 terminals contain a low density of mitochondria and a high density of glutamate (Broman et al. 1993; Valtschanoff et al. 1994), both features perhaps related to their lower tonic activity and the need for a larger pool of vesicular glutamate. C1 terminals are frequently presynaptic to GABAergic dendrites, whereas C2 terminals are more frequently postsynaptic to GABAergic profiles, possibly reflecting the generally lower spatiotemporal resolution of unmyelinated vs small myelinated fibers (Bernardi et al. 1995). The present quantitative data show that both types of PA terminals are associated with subtypes of AMPA receptors, but in different proportions. The preference of C1 for GluR1 contrasts with the preference of C2 terminals for GluR2/3 subunits. While the relative role of presynaptic and postsynaptic factors in establishing and maintaining these differences remains to be determined, the contrasting distribution of GluR1 and GluR2/3 immunopositivity raises the possibility that some neurons in the superficial DH may express only one of the two receptor subunits. Because AMPA receptors lacking GluR2 are calcium-permeable (presumably associated with C1 terminals, Hollman and Heinemann 1994), some neurons in the dorsal substantia gelatinosa may experience AMPA-mediated calcium transients in response to glutamatergic synaptic input, particularly that originating from unmyelinated afferents (C1), thus potentially activating second-messenger cascades. Indeed, recent work supported this possibility (Engelmann et al. 1999). Also results from primary culture demonstrate calcium-permeable AMPA channels in some neurons in the DH (Kyrozis et al. 1995). The apparent bias of terminals of unmyelinated fibers toward GluR2-poor AMPA receptors may bear on the issue of hyperalgesia. Sugimoto et al. (1990) proposed that central hyperalgesia secondary to peripheral neuropathy may involve NMDA-mediated excitotoxic damage to inhibitory interneurons. The present data raise the possibility that GABAergic interneurons in substantia gelatinosa may suffer excitotoxic damage from sustained abnormal activity in unmyelinated fibers synapsing onto calcium-permeable AMPA channels.

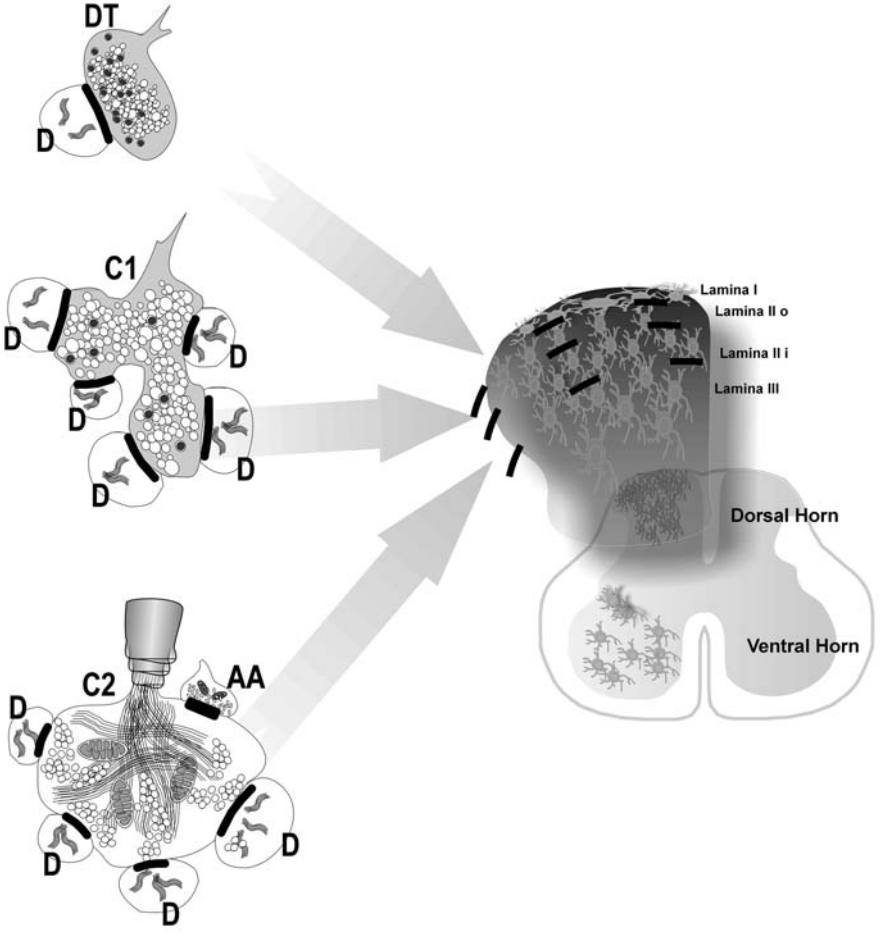
NMDAR1 and Primary Afferent Terminals in the Superficial SC With the nickel-intensified DAB-peroxidase procedure, immunostaining at the LM level produced a fine granular product in cells and neuropil. In 25-μm sections, cellular staining could be identified in somata and proximal dendritic arbors. Within the DH, staining was more prominent in the superficial laminae, especially lamina II, possibly because of its higher cellular concentration (Fig. 4A,B). Neuropil staining was densest in lamina I and IIo and tended to decrease more ventrally in the superficial dorsal horn (Fig. 4B). This was confirmed in plastic embedded, 1-μm-thick sections in which staining was denser in IIo where cells are more densely packed (Popratiloff et al. 1998b).

At the EM level, sections showed generally good structural preservation in the absence of osmium fixation (see also Feirabend et al. 1994, 1998). Myelin was poorly preserved but clear, and dense core vesicles as well as synaptic specializations were well preserved and contrasted. Gold particles were sparse over cell bodies and dendrites but more frequently encountered than in sections stained for AMPA receptors. Particles were clustered over the postsynaptic density, pre- and postsynaptic membrane, and over clefts of a large number of asymmetrical synapses. A significant fraction of terminals with positive synaptic zones could be recognized as originating from primary afferents, but synaptic zones of many terminals of uncertain origin were also immunopositive. Labeling was not observed over active zones of symmetric synapses. In addition to scalloped terminals at the center of C1 (Fig. 4C,D) and C2 (Fig. 4E) glomeruli, a third distinct group of terminals in superficial laminae are dome-shaped. They display loosely packed clear vesicles of irregular size, light axoplasm, and many dense core vesicles (DT in Fig. 1). These terminals are not involved in glomerular arrangement and contact, in the plane of transverse ultrathin section, only a single dendrite or dendritic spine. They are concentrated in lamina I, extending into IIo. Many of these terminals are of primary afferent origin.

To explore whether there is a different concentration of the receptor subunit at different classes of terminals, gold particles underlying active zones were counted for each group of terminals from random photographs. As expected, the counts were roughly Poisson-distributed, reflecting the random exposure of epitopes in a thin section. Immunopositive C1 (Fig. 4C,D) and C2 (Fig. 4E) terminals had similar counts of gold particles (2.18 ± 0.13 and 2.06 ± 0.13, respectively) and these were lower than the counts for nonglomerular terminals (2.36 ± 0.17). This difference is likely to be explained by differences in the length of active zones between glomerular and nonglomerular terminals, i.e., on one side 266 ± 26 for C1 terminals and 268 ± 18 nm for C2 terminals, respectively, and on the other side 387 ± 24 nm for nonglomerular terminals.

The apparently uniform relationship between NR1 sites and the three types of terminals considered here differs from the results of a study with AMPA subunits (Popratiloff et al. 1996a). Additional data show also that nonglomerular terminals contact postsynaptic sites with GluR2/3 subunits about twice as frequently as postsynaptic sites with the GluR1 subunit. These data show that most PA synapses in

superficial laminae express NR1; considering the limited sensitivity of immunogold. These data are also compatible with the expression of NMDA receptors at all such PA synapses. Available data generally support that, as for other regions of the CNS, synaptic potentiation requires activation of NMDA receptors, though it may be expressed mainly via AMPA receptors. The present data thus suggest that virtually all primary afferent synapses in the superficial DH may be potentiated, although in view of previously reported results, this may further strengthen expression of different AMPA subunits for different groups of synapses.



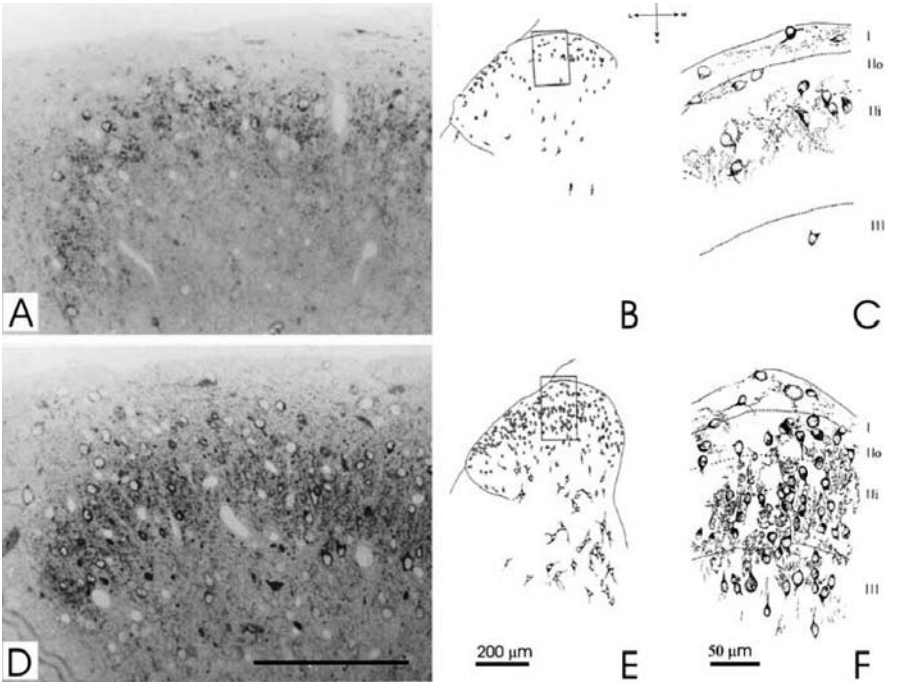


Fig. 2 A–F AMPA receptor subunits GluR1 (**A–C**) and GluR2/3 (**D–F**) in the rat substantia gelatinosa. **A** An image from semithin section labeled for GluR1. Labeling is present in neuronal cell bodies and neuropil. Labeling is denser at the border between outer lamina II (*IIo*) and inner lamina II (*IIi*), whereas in deep lamina IIi it is present as sparse punctae in the neuropil. **B** Low-power camera lucida drawing from a 50-µm-thick section labeled with GluR1 antibody, and **C** high power from the box on **B**, showing differential density of the GluR1 labeling in superficial laminae (*I–III*) of the DH. **D–F** In contrast to GluR1, GluR2/3 labeling is present in neuronal perikarya and neuropil through laminae I–III. Staining density increases from lamina I to lamina III. **D** A semithin section similar to **A** labeled for GluR2/3; **E** and **F** camera lucida drawings similar to **B** and **C** labeled for GluR2/3. Scale bar: **D** and **A**, 200 µm. (Adapted with permission from Popratiloff et al. 1996a)

Fig. 1 Schematic drawing representing the three major types of primary afferent terminals that could be distinguished by their morphology. *Upper left*, small dome shaped terminals (*DT*), which contain a few large dense core vesicles and contact a single dendrite (*D*). These terminals are more abundant in lamina I. *Central left*, a large scalloped terminal at the center of type 1 glomerulus (*C1*). These terminals have dark axoplasm, densely packed vesicles of various sizes and occasional large dense core vesicles. C1 terminals contact several dendrites and are more abundant in lamina IIo. *Bottom left*, large scalloped terminal at the center of type II glomerulus (*C2*). The terminals contain sparse clear vesicles, many neurofilaments and several mitochondria. Such terminals also contact several dendrites, but are more frequently postsynaptic to inhibitory axo-axonic terminals (*AA*). These terminals are concentrated in laminae IIi and III

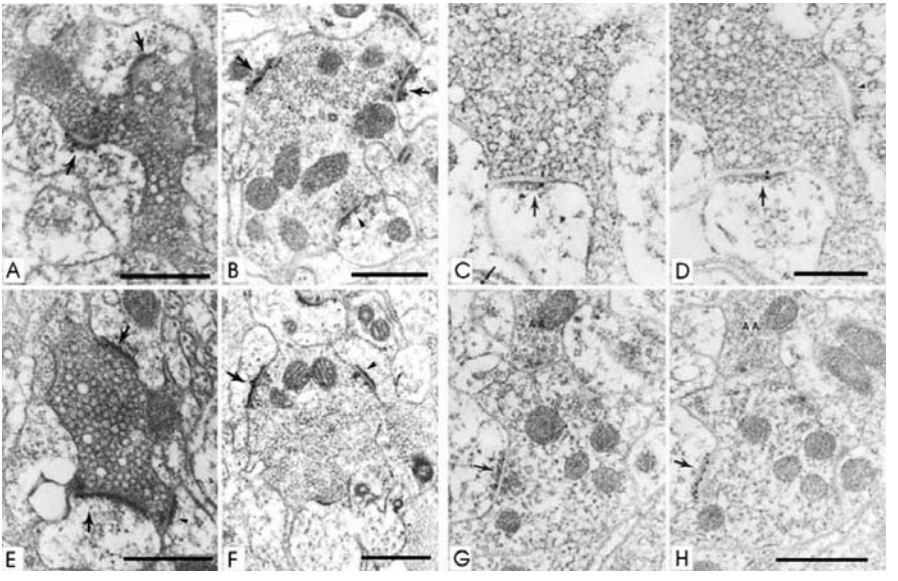
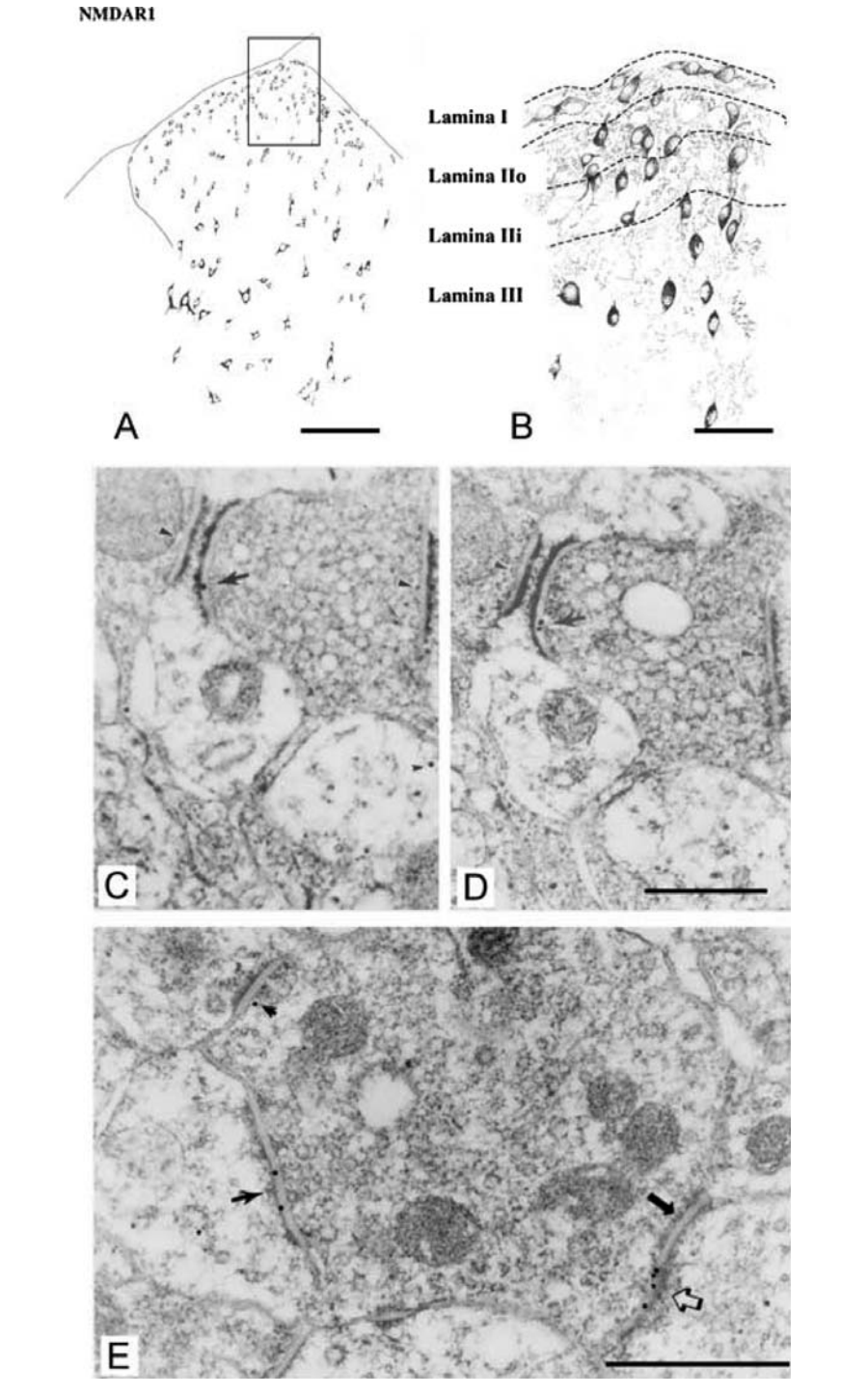


Fig. 3 A–H AMPA receptor subunits GluR1 (**A–D**) and GluR2/3 (**E–H**) at the central terminals of C1 (**A**, **C**, **D**, **E**) or C2 (**B**, **F**, **G**, **H**) in the substantia gelatinosa of the rat DH revealed with postembedding immunogold. More frequently active zones of C1 (**A**, **C**, **D**, *arrows*) than C2 (**B**, *arrows*) terminals were labeled for GluR1. However, strongly labeled active zones were present at both C1 (**A**, *left arrow*) and C2 terminals (**B**, *left arrow*). In contrast, GluR2/3 more frequently labeled terminals of C2 (**F**, **G**, **H**) than C1 (**E**) glomeruli. On average more gold particles were found at C2 active zones, compared to C1. **C**, **D** Serial sections through a same C1 terminal labeled with GluR1, and **G**, **H** serial sections through a same C2 terminal labeled with GluR2/3. *Arrows* show positive active zones, *arrowheads* (**B**, **D**, **E**, **F**) point to negative active zones. *AA* axo-axonic terminal. Scale bars: **A**, **B**, **E**, **F**, **G**, **H**, 500 nm; **D** and **C**, 250 nm. (Adapted with permission from Popratiloff et al. 1997)

Fig. 4 A Low-power camera lucida drawings from a 50-μm-thick vibratome section stained with anti-NMDAR1 antibody. **B** Higher-power camera lucida drawing from the field in box on **A**. NMDAR1 antibody stained uniformly perikarya and neuropil through laminae I–III. **C–E** NMDAR1 immunolabeling detected with postembedding immunogold in C1 **C**, **D** and C2 **E** PA terminals. Gold particles labeling was weaker than those observed for AMPA receptor subunits. **C**, **D** Consistently low labeling in serial sections through a same C1 terminal (*arrow*, positive active zone; *arrowhead*, negative active zone). **E** NMDAR1 antibody stains weakly the active zones of C2 PA terminals (*arrow*), some gold particles are present presynaptic (*arrowhead*), and a few active zones show accumulation of more than two gold particles (*open arrow*). Note that the symmetric contacts are negative for NMDAR1 (*thick arrow*). Scale bars: **A**, 200 μm; **B**, 50 μm; **D** and **C**, 250 nm; **E,** 500 nm. (Adapted with permission from Popratiloff et al. 1998b)


NMDAR1
Lamina I
Lamina IIo
Lamina IIi
Lamina III
A
B
C
D
E

2.4 Ascending Pathways of the Spinal Cord and of the STN

2.4.1 Spinothalamic Tract

In experimental animals, it was repeatedly reported that the large lamina I neurons are the source of about one-half of the spinothalamic tract (STT) (Willis et al. 1979; Apkarian and Hodge 1989a, b; Craig 1995). Recently, however, Klop et al. (2004a, b) declared that in the cat the percentage of lamina I neurons is 4.9%–14.2% of the 12,000 spinothalamic neurons in the SC. The STT in humans mediates the sensations of pain, cold, warmth, and touch (Hassler 1960; Kerr 1975a; Nathan and Smith 1979; Brodal 1981; Jones 1985, 1998; Willis 1985; Willis and Coggeshall 1991; Craig 1996a; Willis and Westlund 1997, 2004; Nathan et al. 2001). The mean conduction velocity of the STT estimated in experimental animals is approximately 8.0 m/s (Dostrovsky and Craig 1996). The modern physiological methods also allow its evaluation in humans (Rossi et al. 2000; Tran et al. 2002). The mean conduction velocity was estimated by Rossi et al. (2000) to be approximately 9.87 m/s.

The cells of origin are located mainly in laminae I and IV–VI. Few STT neurons are located in lamina X (around the central canal), and in laminae VII and VIII (in the ventral horn, dorsal to the "motoneuronal" lamina IX) (Willis et al. 1979; Granum 1986; Kemplay and Webster 1986; Apkarian and Hodge 1989a, b; Burstein et al. 1990b; Willis and Coggeshall 1991; Craig 1996b; Usunoff et al. 1999; Andrew and Craig 2001). The neurotransmitter of the STT neurons is glutamate (Ericson et al. 1995; Blomqvist et al. 1996) and the STT cells also express peptides as co-transmitters (Ju et al. 1987; Battaglia et al. 1992; Battaglia and Rustioni 1992; Todd and Spike 1993; Broman 1994). Lee et al. (1993) claimed that some STT neurons contain NOS, but for the contrary see Kayalioglu et al. (1999) and Usunoff et al. (1999). Most of the cells project to the contralateral thalamus. However, in experimental animals a fairly significant number of ipsilaterally projecting cells (approximately 10% of the total STT neuronal population) were detected (Burstein et al. 1990b). Clinical observations indicate that ipsilaterally projecting STT neurons also exist in humans (Nathan et al. 2001). The STT axons cross the midline in the commissura alba anterior transversely, rather than diagonally (Nathan et al. 2001) and ascend in the anterolateral quadrant of the SC white matter. The axons of lamina I neurons in the monkey ascend more dorsally than do the axons of neurons in the deeper laminae (Apkarian and Hodge 1989b), and in the cat the ascending fibers of the lamina I cells are scattered throughout the lateral white matter (Craig 1991). Clinical evidence from anterolateral cordotomies in patients with intractable pain indicates that the STT axons are somatotopically arranged. The axons representing the lower extremity and the caudal body parts are located more laterally, and those representing the upper extremity and the cranial body parts more anteromedially (Nathan and Smith 1979; Lahuerta et al. 1994; but see Marani and Schoen 2005 for debate). In the brainstem, the STT ascends close to the dorsolateral wedge of the medial lemniscus (Walker 1940; Bowsher 1957; Hassler

1960; Mehler et al. 1960; Mehler 1962). The axons that reach the thalamus are very few in number. In all probability, a large amount of fibers end in the brainstem. The STT starts in the spinal cord with over 10,000 axons. Glees and Bailey (1951) and Bowsher (1963) counted in the rostral midbrain approximately 1,000 axons with diameters of 2–4 μm, and only 500 axons with diameters of 4–6 μm, and the area occupied was only 0.8 mm in width. In humans and primates, the STT axons terminate in the caudal and oral parts of the nucl. ventralis posterior lateralis (VPLc and VPLo), the nucl. ventralis posterior inferior (VPI), the medial part of the posterior nuclear complex (Pom), nucl. centralis lateralis (CL), as well as in other intralaminar and medial nuclei (Walker 1940; Hassler 1960; Mehler 1966; Kerr 1975b; Boivie 1979; Mantyh 1983; Apkarian and Hodge 1989c; Cliffer et al. 1991; Ralston and Ralston 1992, 1994; Willis et al. 2001, 2003; for the delineation of the thalamic nuclei see Hassler 1959, 1982; Jones 1985, 1997a, b, 1998; Hirai and Jones 1989; Mai et al. 1997; Ralston 2003; Percheron 2004; Marani and Schoen 2005).

There is a large body of literature on the STT in subprimate species (Lund and Webster 1967b; Carstens and Trevino 1978a, b; Willis et al. 1978, 1979; Giesler et al. 1979, 1981; Kevetter and Willis 1982, 1983, 1984; Peschanski et al. 1983; Granum 1986; Craig 1987, 1991, 1995, 2003b, d; Lima and Coimbra 1988; Stevens et al. 1989; Burstein et al. 1990b; Cliffer et al. 1991; Tracey 1995; Shaw and Mitrofanis 2001; Andrew and Craig 2002; Gauriau and Bernard 2004; Klop et al. 2004a, b), but it should be interpreted with caution, since the organization of STT and thalamocortical projections related to pain is fundamentally different in primate species than in nonprimate species such as rodents and carnivores (Craig and Dostrovsky 1999; Blomqvist and Craig 2000; Marani and Schoen 2005). Percheron (2004) pointed out that there are also noticeable changes from monkeys to man: thalamic parts have disappeared, others have appeared, and some have considerably developed (see also Marani and Schoen 2005). In the cat, lamina I STT axons terminate in nucl. submedius, a significant relay nucleus for nociception (Craig 1987; Ericson et al. 1996). Craig et al. (1994) defined in the monkey clusters of nociceptive and thermoreceptive specific neurons, reached by lamina I STT axons, located in the posterior part of the nucl. ventralis medialis (VMpo). Blomqvist et al. (2000) identified VMpo also in the human thalamus; it is included in the suprageniculate/posterior complex of Hirai and Jones (1989), and corresponds to the nucleus limitans portae (located immediately caudal to the nucl. ventrocaudalis parvocellularis internus), and adjacent part of nucleus ventrocaudalis portae of Hassler (1960, 1982). The VMpo is proportionally much larger in humans than in monkeys (Blomqvist et al. 2000) and coincides with the dense zone of STT input recognized by Mehler (1966) in human posterolateral thalamus (Lenz et al. 2000). The proposal of Blomqvist et al. (2002) that STT axons do not terminate in VPL was reviewed by Willis et al. (2001, 2002). Also, Graziano and Jones (2004) questioned the existence of VMpo as an independent thalamic pain nucleus or as a specific relay in the ascending pain system in the monkey. According to Craig et al. (1994) and Craig (1998, 2000), lamina I in primates projects to three thalamic zones: (a) VMpo, (b) VPI, which receives convergent input from lamina V and the dorsal column nuclei,

and (c) to a small zone in the medial thalamus (MDvc), which receives a STT input predominantly from lamina I. The VMpo projects topographically to the fundus of the superior limiting sulcus of the insular cortex and to area 3a in the fundus of the central sulcus (Craig 1996a, 2000). MDvc projects to the fundus of the anterior cingulate cortex (field 24c) (Craig 2000). Interestingly, the termination of STT axons in the lateral habenular nucleus escaped recognition, and was only recently described by Craig (2003b) as arising in lamina I in the cat. According to Craig (2003b), the spinohabenular connection could be significant for homeostatic behaviors.

The dorsal column nuclei (DCN), consisting of nucleus gracilis (Gr) and nucleus cuneatus (Cu) are traditionally regarded as a structure primarily involved in conscious fine tactile sensation. The basis for this designation is the DCN's well-established role in relaying precise tactile information from primary dorsal column fibers to the VPL and from there to the somatosensory cortex. However, there is growing evidence that the DCN are also strongly involved in nociception. The DCN project via the medial lemniscus to VPL, Po, and zona incerta, as well as to the border zone between VPL and VL (Lund and Webster 1967a; Boivie 1978; Berkley et al. 1980, 1986; Peschanski and Ralston 1985; Kemplay and Webster 1989; Marani and Schoen 2005). The DCN-thalamic projection is glutamatergic (De Biasi et al. 1994). The connection is constantly described as completely crossed, and only Kemplay and Webster (1989) mentioned occasional ipsilaterally projecting neurons. According to Wree et al. (2005), however, about 5% of the DCN neurons project to the ipsilateral thalamus in the rat.

Ralston and Ralston (1994) compared the mode of termination of STT and medial lemniscal axons and found that the thalamic synaptic relationships of these two thalamopetal systems are fundamentally different. The terminals of the medial lemniscus very often contact (46% of the synaptic contacts) the GABAergic interneurons, which in turn contact the relay neurons. In contrast, more than 85% of the spinothalamic afferents form axodendritic synapses with relay cells, and only in 4% the STT terminals contact the GABA-immunoreactive presynaptic dendrites. Ralston and Ralston (1994) pointed out that because the STT neurons predominantly transmit information about noxious stimuli, the simple axodendritic circuitry of the majority of these spinal afferents suggests that the transmission of noxious information is probably not subject to GABAergic modulation by thalamic interneurons, in contrast to the GABAergic processing of non-noxious information carried out by the medial lemniscus afferents. On another hand, Ericson et al. (1996) found that the lamina I terminations in the nucleus submedius of the cat also participate in synaptic triads, synapsing on presynaptic vesicle-containing dendrites of the interneurons. Beggs et al. (2003) investigated the termination of lamina I STT axons in VMpo in macaques. They reported that these synaptic boutons are relatively large and contain densely packed, round synaptic vesicles. The STT terminals make asymmetric synaptic contacts on low-order thalamic neurons. Similar to Ericson et al. (1996), Beggs et al. (2003) found that the STT terminals are closely associated with GABAergic presynaptic dendrites, and nearly all form classic triadic arrangements (axo-dendro-dendritic synapse).

The critical role of the STT in pain is universally acknowledged, but the relative involvement in pain sensation of lamina I neurons and the wide-dynamic-range lamina V neurons is controversial (Willis and Westlund 1997; Price et al. 2003 vs Craig 2004). According to Price et al. (2003) the wide-dynamic-range lamina V STT neurons are necessary and sufficient for all types of pain sensation and their discharge encodes pain. On the other hand, Craig (2004) reported that, in the monkey, the burning pain is signaled by modality-selective lamina I neurons and not convergent lamina V wide-dynamic-range STT cells.

Primate STT neurons that project to the lateral thalamus (VPL) have receptive fields on a restricted area. Therefore, they are well suited to a function in signaling the sensory-discriminative aspects of pain (Willis et al. 1974; Willis and Westlund 1997, 2004). Primate STT cells that project to the CL may also collateralize to the lateral thalamus, and have response properties identical to those STT neurons that project just to the lateral thalamus (Giesler et al. 1981; Willis and Westlund 1997). On the other hand, STT neurons that project only to the CL have very large receptive fields (Giesler et al. 1981; Willis and Westlund 1997).

The entire trigeminal sensory nuclear complex projects to the thalamus (Peschanski 1984; Magnusson et al. 1987; Mantle-St. John and Tracey 1987; Jacquin et al. 1989; Kemplay and Webster 1989; Dado and Giesler 1990; DiFiglia and Aronin 1990; Iwata et al. 1992; Williams et al. 1994; Barnett et al. 1995; Waite and Tracey 1995; Usunoff et al. 1997, 1999; Li 1999; Li JL et al. 1999; Zhang and Yang 1999; Hirata et al. 2000; Graziano and Jones 2004). The trigeminothalamic tract (TTT) projections are not uniform. Following unilateral horseradish peroxidase injections into the thalamus, Kemplay and Webster (1989) counted 8,683 retrogradely labeled neurons in the PTN, 524 cells in the STNo, 1,920 neurons in the STNi, and 260 labeled cells in the STNc. Generally, the projection toward the VPM and the posterior thalamic nucleus (Po) arises mainly in PTN and in STNi, while the nucl. submedius and the intralaminar nuclei are heavily innervated by the nociceptive STNc. The lamina I neurons send strong projections to the nucl. submedius, VPM, and Po. The deeper laminae moderately innervate VPM and Po, but project heavily to the ventral diencephalon (see the following section). The smallest thalamic innervation (to VPM and Po) arises in STNo. The TTT is bilateral but, especially for the STN, strongly crossed.

2.4.2 Projections to the Ventrobasal Thalamus in the Rat

We examined the projections of the trigeminal sensory nuclei, DCN, and the SC to the thalamus by means of the retrograde axonal transport fluorescent method of Kuypers et al. (1980). We injected unilaterally in the thalamus of Wistar rats ($n = 20$) 2 µl of 1% Fast Blue (FB, Sigma, dissolved in physiological saline), 0.5 µl per injection focus (Fig. 5). Two injections were placed 6 mm, and two 5 mm anterior to the interaural line. The injection foci spread to all somatosensory thalamic nuclei on the side of the injection, including the ventrobasal complex (VPL and VPM),

posterior nucleus group, and the intralaminar nuclei. Animals were transcardially perfusion fixed 5 days after injection. This fluorescent dye labels the cytoplasm silver blue, and in heavily loaded cells extends also in the dendrites. The FB injection foci are sharply demarcated (Fig. 5), and it is successfully transported over long distances. The present results are comparable with our previous data, obtained with a very effective retrograde tracer colloidal gold conjugated to the B subunit of cholera toxin (Usunoff et al. 1999).

In the brainstem, the PTN and the three subdivisions of the STN contained retrogradely labeled neurons, but to a very different extent (Figs. 6–9). The largest number of retrogradely labeled neurons was observed in the PTN, contralateral to the injection. From its rostral to its caudal pole, this nucleus was filled with densely packed labeled neurons that formed vaguely delineated clusters (Fig. 6A). The ipsilateral PTN contained a moderate number of FB-labeled neurons, mainly in its dorsal sector (Fig. 6B). The TTT neurons are multipolar, rarely exceeding 20 μm. In the ventral part of the PTN, the neurons are slightly larger. In the STNo, the labeling sharply decreases (Fig. 7). Throughout the entire rostrocaudal extent of STNo, the labeled neurons were more concentrated in the ventral part of the nucleus. The cells are slightly smaller than in the PTN, usually about 18 μm, but some neurons measure about 30 μm (Fig. 7A). There were also few ipsilaterally projecting neurons (Fig. 7B), and most of these cells measured less than 18 μm. The contralateral STNi contained a substantial number of FB-labeled neurons (Fig. 8A,B). Especially in more caudal sectors, some features of lamination were seen (Fig. 8B). The labeled neurons vary considerably in size and shape: from small, rounded to larger, heavily loaded with FB multipolar perikarya. We observed only occasional ipsilaterally projecting neurons in STNi. Throughout the contralateral STNc the retrograde labeling was moderate (Fig. 9). Toward the spinomedullary junction, the number of FB-labeled neurons gradually decreased. Most laterally in the STNc were the characteristic marginal cells (medullary lamina I) (Fig. 9A). They were usually elongated and oriented parallel to the spinal trigeminal tract. Within the latter also few labeled neurons were seen (Fig. 9A). Few labeled neurons were seen in the magnocellular layer (laminae III, IV). Actually the cells were medium-sized, with average diameters of about 20 μm. The ipsilateral projection to the thalamus from the STNc is faint but unquestionable. Almost exclusively marginal neurons were labeled (Fig. 9B).

The present experiments demonstrate a prominent crossed connection from the DCN to the thalamus, from the rostral (Fig. 10A) to the caudal pole (Fig. 10B) of the nuclear complex. The FB-labeled neurons are medium to small in size, measuring approximately 20 μm. Few neurons in the DCN ipsilateral to the injection were labeled (Fig. 10A,B), mostly one to three per section.

For cytoarchitectonic orientation in the SC, the atlas of Molander and Grant (1995) was consulted. The distribution of labeled neurons was very uneven. The highest number of STT neurons was encountered at the spinomedullary junction (Fig. 11), and in the four cranial cervical segments (C1–C4), contralateral to the thalamic injection (Fig. 12). At these levels, a prominent cell labeling was also

observed in the lateral cervical nucleus (LCN) (Figs. 11, 12). Notably, also in the first four cervical segments, there was only a moderate number of labeled marginal, lamina I neurons. Most significant labeling was found near the medial aspect of the DH, in the medial extension of lamina IV and adjacent lamina V. Scattered labeled neurons were observed in laminae V–VIII. The ipsilateral STT arising in the first four segments is substantial. Most of these neurons are located deep in the ventral horn, lamina VIII, adjacent to the motoneuronal lamina IX (Fig. 12) Only a few lamina I cells project to the ipsilateral thalamus (Fig. 12). Starting from the fifth cervical segment, the number of STT neurons sharply diminishes (Fig. 13). Very few cells were seen in lamina I, and there were few in the deeper lamina of the DH. Occasional labeled neurons were seen in lamina (area) X (Fig. 13). The ipsilateral STT from the lower cervical segments was very scant.

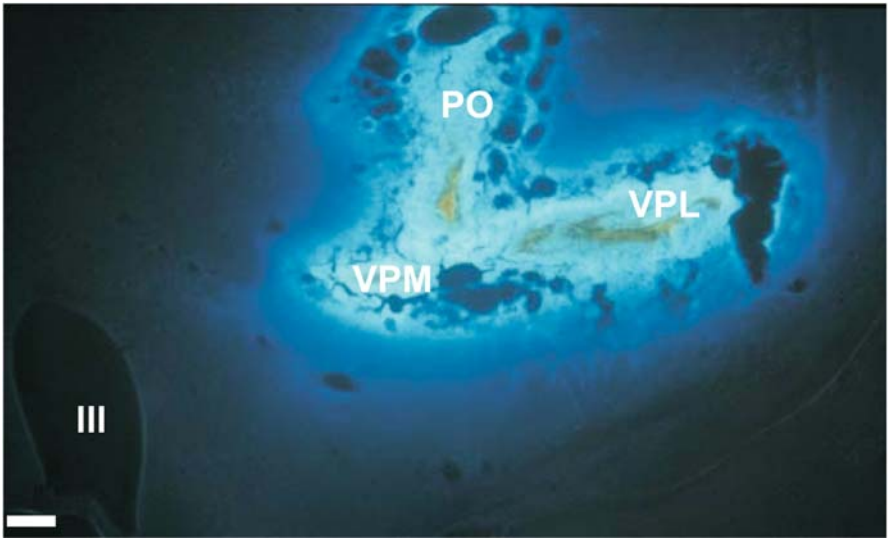
The thoracic SC of the rat contained only few STT neurons, especially in the cranial thoracic segments (Figs. 14, 15). Singly scattered cells were seen in lamina I, in the deeper laminae, as well as in lamina X. Although very few, ipsilaterally projecting neurons were seen (Fig. 14).

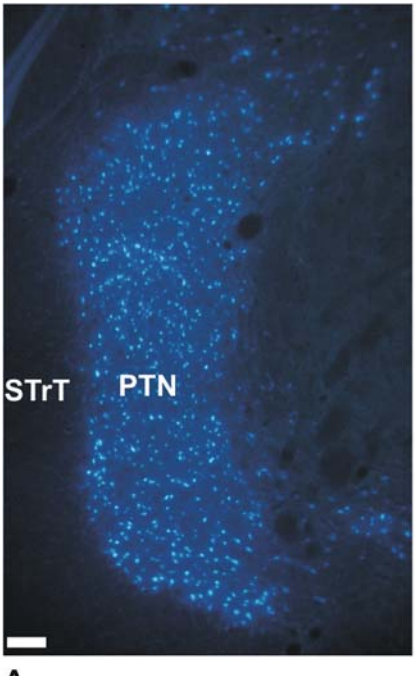
In the lumbar segments, the number of STT neurons increased (Figs. 16, 17). Labeled neurons in lamina I were very few. Scant FB-labeled neurons were seen in the lateral spinal nucleus (LSN) (Fig. 16A). More numerous were the cells in the deeper laminae (Fig. 16B), as well as in area X (Fig. 17). Some larger cells were heavily labeled and FB extended also into the dendrites. Although few, ipsilaterally projecting STT neurons were also present (Fig. 16B).

In the sacral (Fig. 18A,B) and coccygeal (Fig. 18C,D) segments only few, but heavily labeled neurons were found in the DH. STT neurons in lamina I were practically absent, but few such were seen in the LSN, and in this structure were located the occasional ipsilaterally projecting cells. Most STT neurons were found in the deep laminae of the DH, in area X, and in the dorsal laminae of the ventral horn. Some neurons are heavily loaded with FB and occasionally one was able to follow the retrogradely labeled axon (Fig. 18A,B).

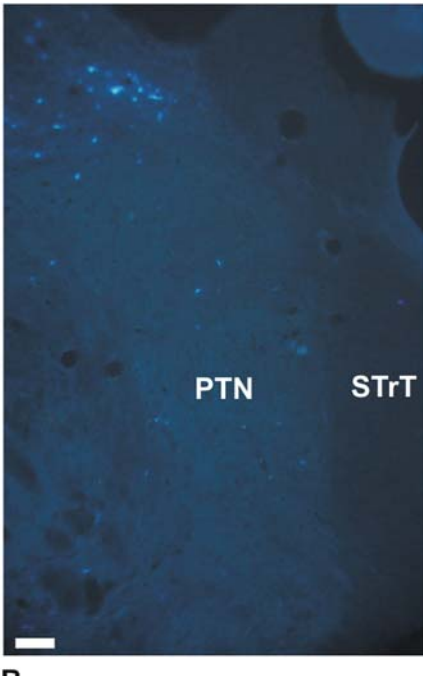
Fig. 5 (top) Low-power photograph of the maximum extent of the two rostral injection foci. By the medial focus, also the distal part of the needle tract is filled with Fast Blue. The four injection foci fused ventrally and completely engaged VPL and VPM, as well as considerable portions of Po, and the intralaminar nuclei. To the *lower left*, the dorsal part of the third ventricle (*III*). Despite the massive injection, there is no spillage of FB to the contralateral side, so that the findings below on the ipsilateral TTT and STT, as well as for the DCN-thalamic projection are reliable. Scale bar: 200 μm

Fig. 6 A (bottom) The contralateral principal trigeminal nucleus (*PTN*) is filled with regularly packed retrogradely labeled neurons, **B** while a few such cells in the ipsilateral PTN are concentrated in its dorsal part. For orientation, the laterally adjoining spinal trigeminal tract (*STrT*) is indicated. Scale bars: 100 μm





A



B

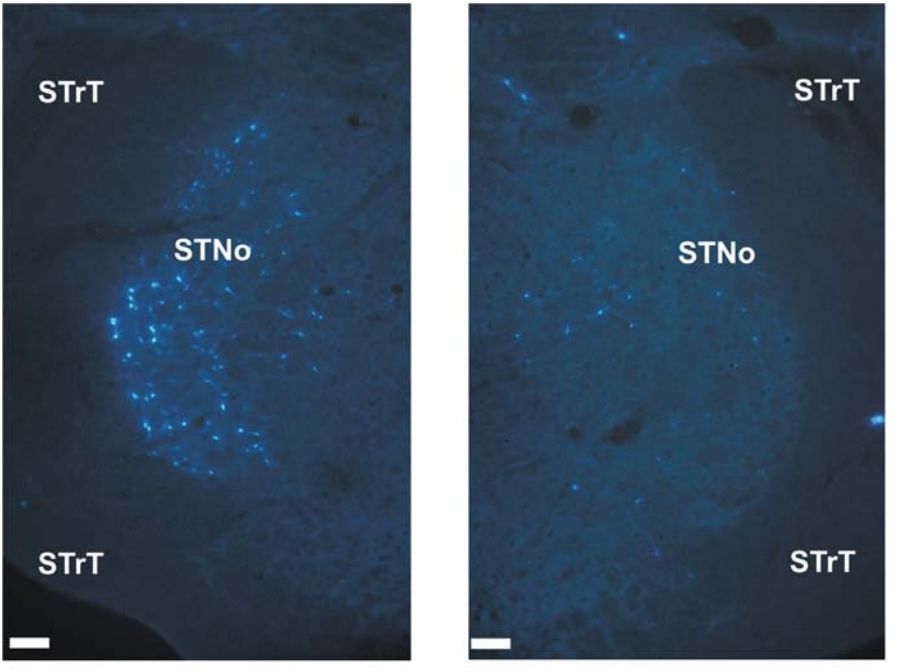
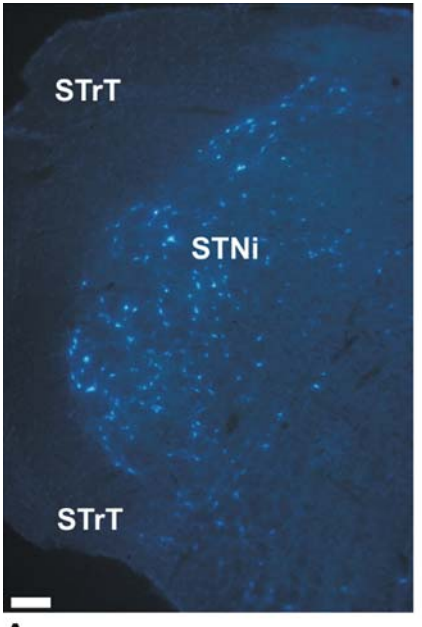


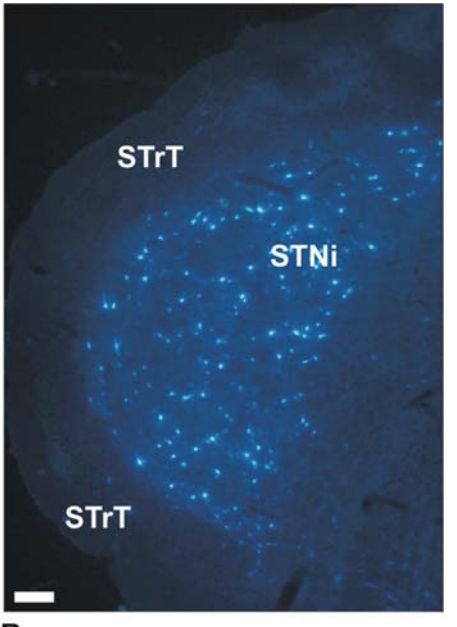
Fig. 7 A In the contralateral spinal trigeminal nucleus, oral part (*STNo*) retrogradely labeled neurons preferably are located in its ventral part, **B** while a few labeled neurons in the ipsilateral STNo are scattered throughout the nucleus. For orientation the laterally adjoining spinal trigeminal tract (*STrT*) is indicated. Scale bars: 100 μm

Fig. 8 A,B (top) A significant number of retrogradely labeled neurons are homogeneously distributed throughout the contralateral spinal trigeminal nucleus, interpolar part (*STNi*), both **A** rostrally and **B** caudally. For orientation, the laterally adjoining spinal trigeminal tract (*STrT*) is indicated. Scale bars: 100 μm

Fig. 9 A,B (bottom) Compared with the large mass of the spinal trigeminal nucleus, caudal part (*STNc*) the number of retrogradely labeled neurons in the contralateral nucleus is relatively low (**A**). There are several labeled neurons also seen in the STrT. In the ipsilateral STNc, labeled neurons are observed in lamina I, just at the border with the STrT. Scale bars: 100 μm



A



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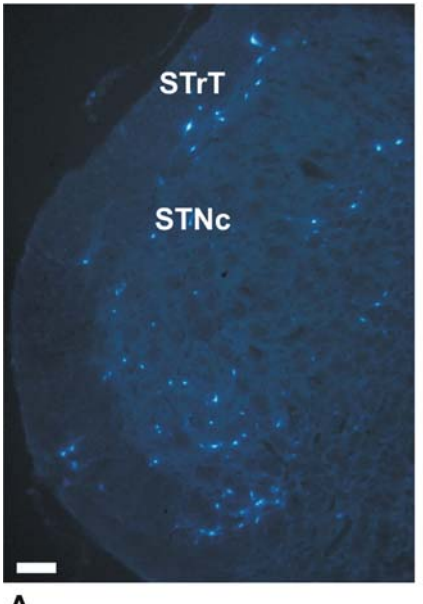
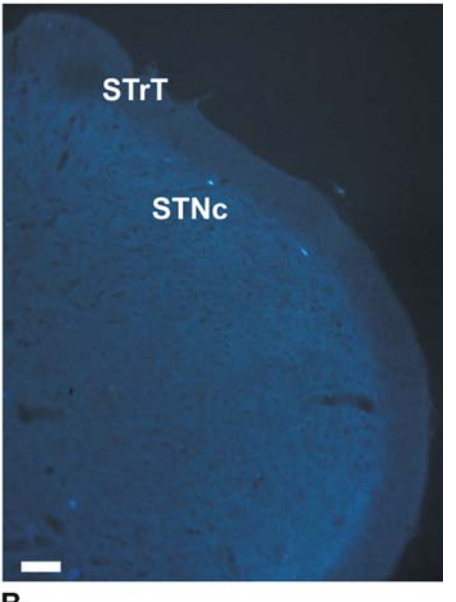


A



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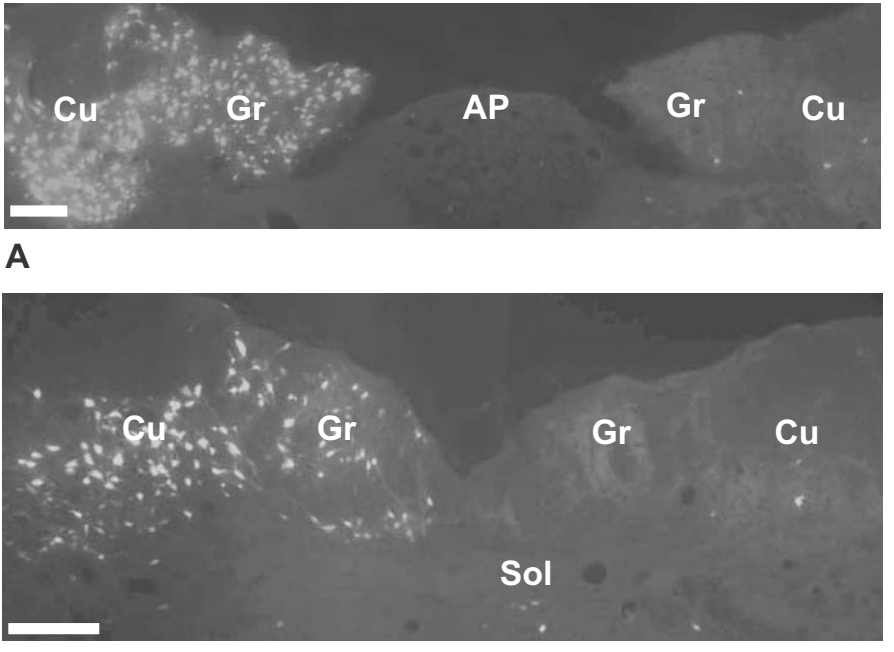


Fig. 10 A,B A large number of retrogradely labeled neurons are distributed throughout the contralateral gracile (*Gr*) and cuneate (*Cu*) nuclei (*left part of the pictures*), both rostrally **A** and caudally **B**. In the ipsilateral dorsal column nuclei, several labeled neurons are also seen. For orientation, the area postrema (*AP*) and the nucl. solitarius (*Sol*) are indicated. Scale bars: 250 μm

Fig. 11 (top) In the spinomedullary junction, a single retrogradely labeled neuron is seen in the most caudal contralateral gracile nucleus (*Gr*) and in the midline nucleus of Bischoff (*Bi*), respectively. In the spinal cord (*left half of the figure*) contralateral to the injection site distinctly retrogradely labeled neurons are seen in the lateral cervical nucleus (*LCN*) as well as in the lateral spinal nucleus (*LSN*). Within the grey matter, the retrogradely labeled neurons are scattered bilaterally. Note that in the ipsilateral cord neurons are located deep in the ventral horn (*arrowhead*). Also, two labeled cells are found within the lateral white matter (*arrow*). Scale bar: 200 μm

Fig. 12 (bottom) In the first cervical segment, the distribution of the retrogradely labeled neurons somewhat differs from that seen in the spinomedullary junction (Fig. 11). Here again, there are labeled neurons in the LCN and LSN contralateral to the injection site (*left half of the figure*). In lamina I, two labeled neurons are seen contralaterally and one ipsilaterally. In the deeper laminae distinctly retrogradely labeled neurons are found mainly in the medial grey matter, in a characteristic location of the STT cells. Bilaterally retrogradely labeled neurons are also found deep in the ventral horns. Scale bar: 200 μm

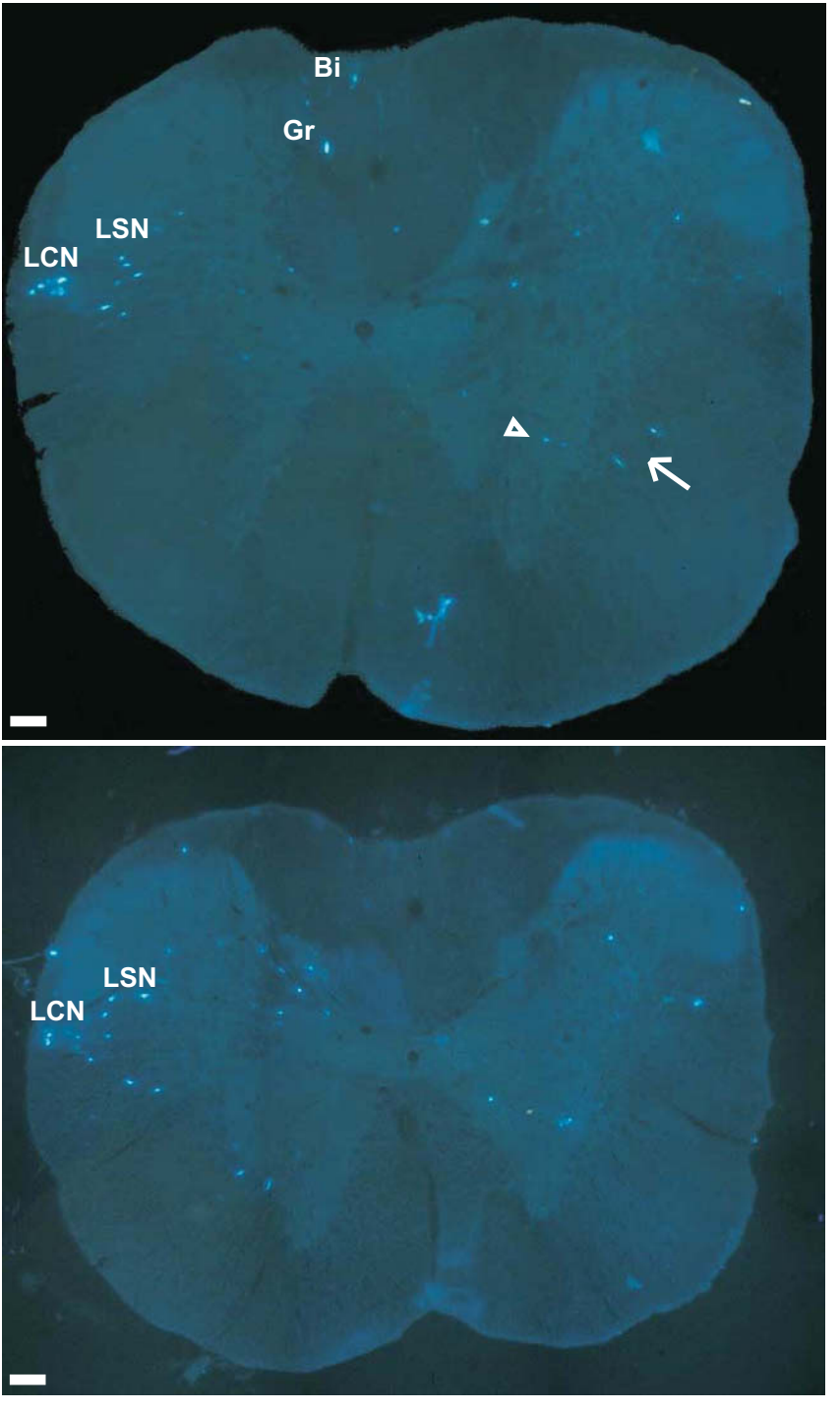

Bi
Gr
LSN
LCN
LSN
LCN

Fig. 13 Already at the level of the fifth cervical segment, the number of the retrogradely labeled neurons has drastically diminished. In the dorsal horn contralateral to the injection site (*left half of the figure*), labeled neurons are concentrated in the superficial laminae. Only one ipsilaterally projecting neuron is seen. Scale bar: 175 μm

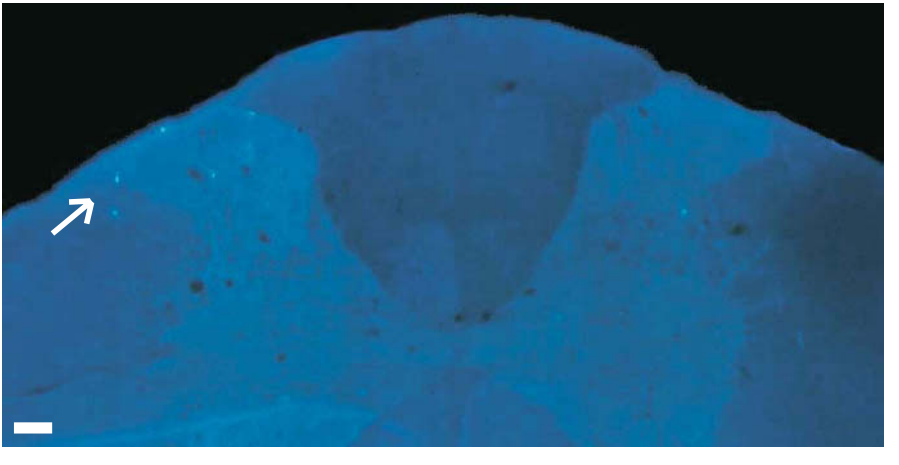


Fig. 14 In the first thoracic segment four retrogradely labeled neurons are depicted in the dorsal horn contralateral to the injection site (*left half of the figure*) and one is located in the LSN (*arrow*). There is one labeled neuron also seen in the ipsilateral DH. Scale bar: 125 μm

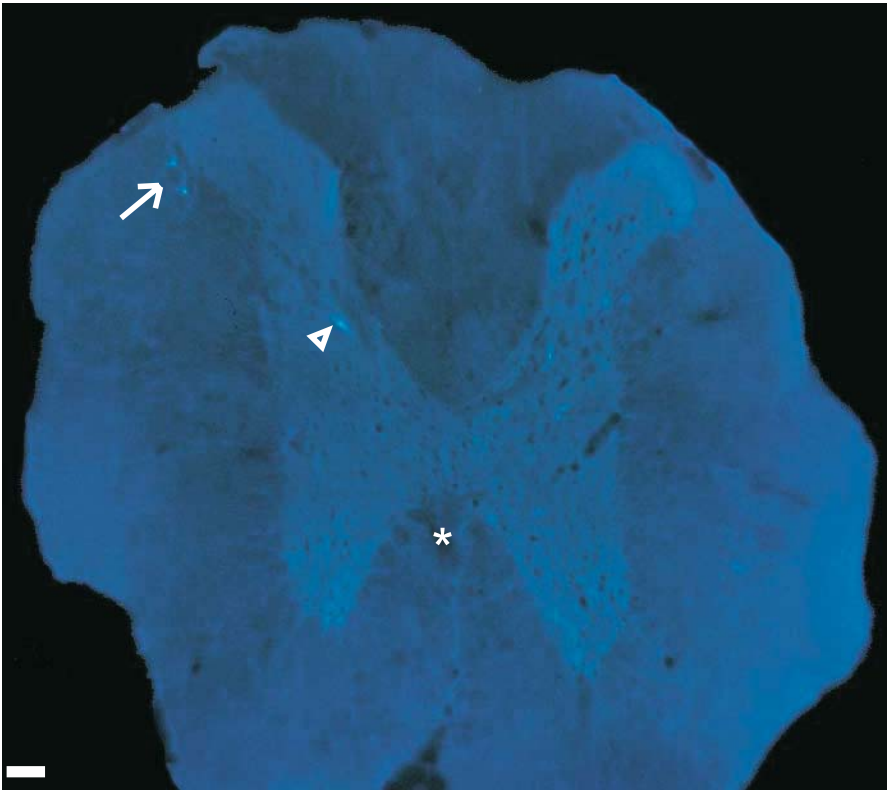


Fig. 15 At the level of fifth thoracic segment very few retrogradely labeled neurons are found. Two of them are located within the white matter contralateral to the injection site (*left half of the figure*) lateral of the DH in the LSN (*arrow*), and a large neuron is seen in the medial part of the deeper laminae (*arrowhead*). The central canal is indicated (*). Scale bar: 150 μm

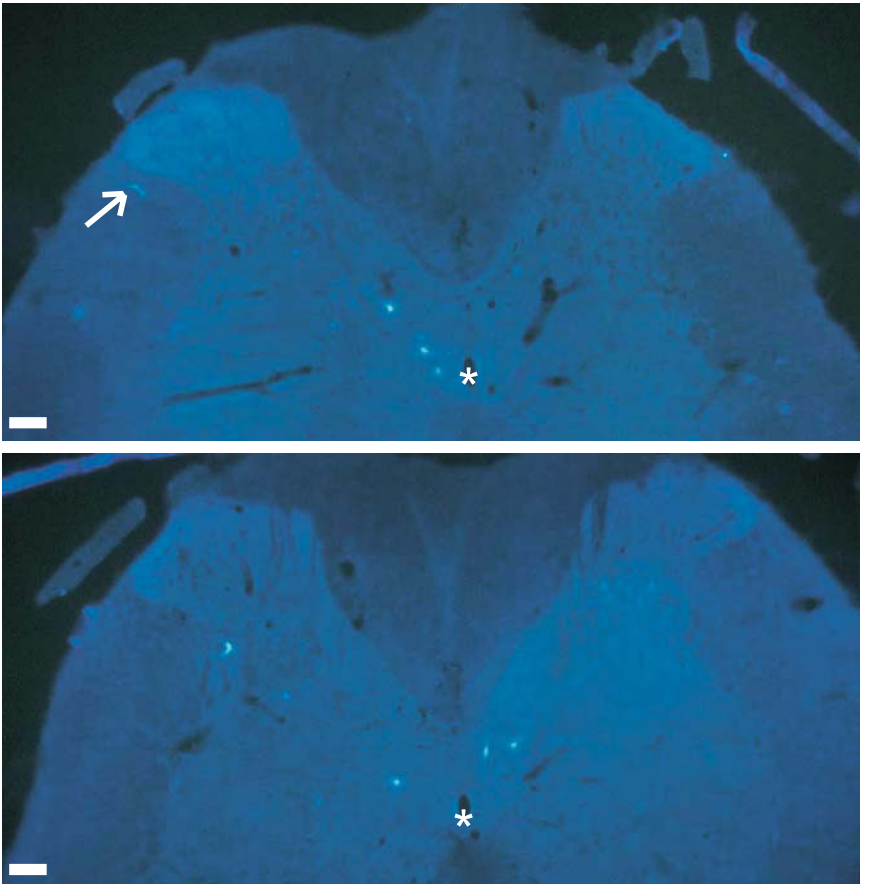
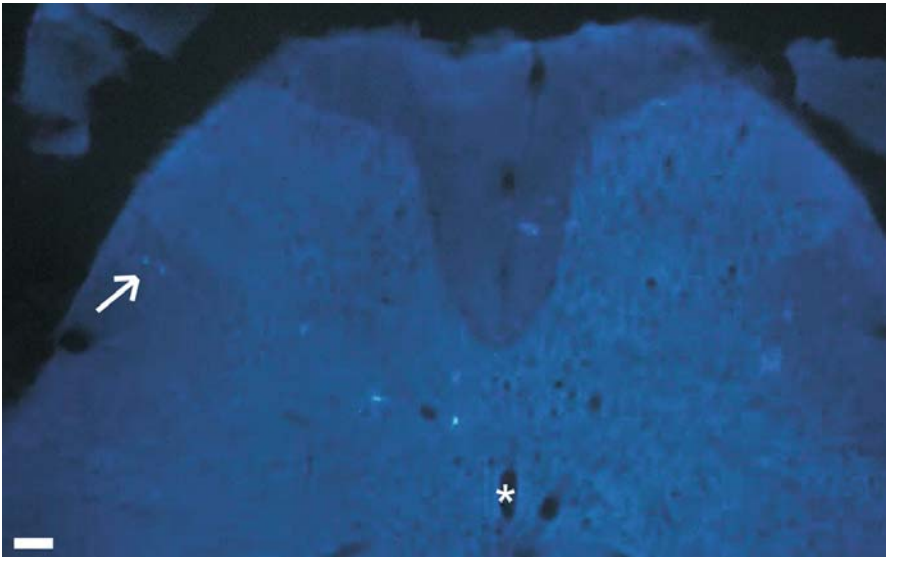
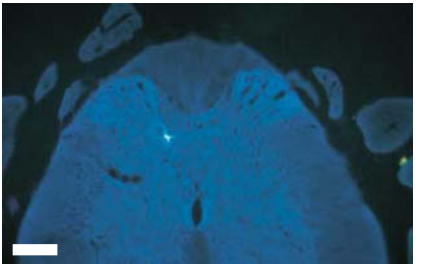


Fig. 16 A,B In the first lumbar segment the location of retrogradely labeled neurons differed between sections. **A** Contralateral to the injection site (*left half of the figure*), only labeled neurons are depicted at the base of DH, around the central canal (*) and a single one in the position of LSN (*arrow*). **B** Here, labeled neurons are seen bilaterally in the intermediate grey substance, one contralaterally in lamina III. Scale bars: 150 μm

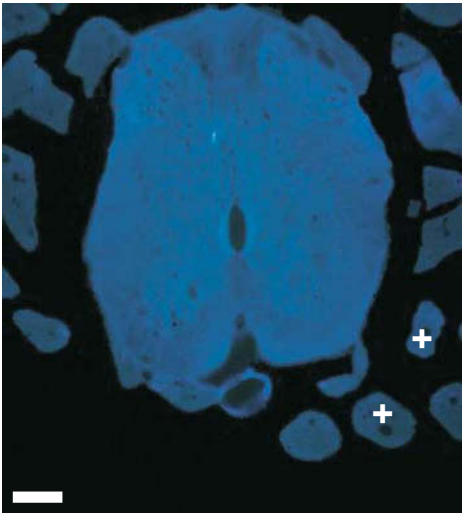
Fig. 17 (top) In the fourth lumbar segment there are few retrogradely labeled neurons only contralateral to the injection site (*left half of the figure*). Two neurons are present in the base of DH near the central canal (*) and two small STT cells are seen in LSN (*arrow*). Scale bar: 150 μm

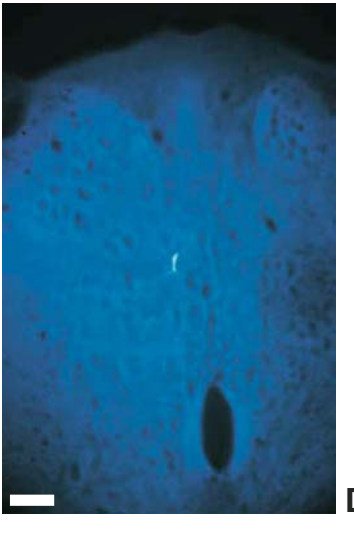
Fig. 18 A,B (bottom) In the first sacral segment, one strongly retrogradely labeled neuron is seen contralateral to the injection site (*left half of the figure*) in the deep DH. **B** In the enlargement of **A** the initial portion of the labeled axon is directed medially (*arrowheads*). **C, D** The first coccygeal segment is surrounded by the fascicles of the cauda equina (+). An elongated large neuron is seen in the medial portion of DH contralateral to the injection site (*left half of the figure*). **B** Enlargement of **A**. Scale bars: **A,C**, 250 μm; **B,D**, 500 μm





A B





C D

2.4.3 Pathways to Extrathalamic Structures

Several other pathways accompany the STT in the ventrolateral quadrant of the SC. These include the spinomesencephalic tract (SMT), the spinoparabrachial tract (SPbT), the spinoreticular tracts (SRT), and several more recently described spinolimbic tracts (Willis and Coggeshall 1991; Willis and Westlund 1997).

The SMT actually includes several projection systems that terminate in different mesencephalic areas. In primates, the neurons of origin are distributed similar to the STT neurons, e.g., in laminae I, IV–VI, and a few in the ventral horn and in lamina X (Willis et al. 1979; Mantyh 1982; Wiberg et al. 1987; Yezierski and Mendez 1991). The SMT neurons are glutamatergic (Yezierski et al. 1993; Azkue et al. 1998). Some SMT neurons emit collaterals to the lateral thalamus (Zhang D et al. 1990). The SMT projections terminate in the periaquaductal gray (PAG), nucl. of Darkschewitsch, nucl. interstitialis of Cajal, nucl. cuneiformis of the mesencephalic RF, nucl. intercollicularis, deep layers of the superior colliculus, area pretectalis, nucl. ruber, and probably in the cortical (polysensory, rather than acoustic) regions of the inferior colliculus (Bowsher 1957; Hassler 1960; Kerr 1975b; Mantyh 1982; Menetrey et al. 1982; Wiberg et al. 1987; Yezierski 1988; Blomqvist and Craig 1991; Yezierski and Mendez 1991; Bernard et al. 1995; Craig 1995). The SMT neurons project bilaterally (Wiberg et al. 1987; Blomqvist and Craig 1991; Craig 1995), and approximately 2% of the SMT cells in the rat project both ipsilaterally and contralaterally (Yezierski and Mendez 1991). According to Wiberg et al. (1987), the SMT projections from the caudal parts of the SC terminate in the caudal mesencephalon, and the projections from the cranial parts terminate more rostrally in the brainstem. The SMT is involved in nociception (Dougherty et al. 1999). However, it is not clear that it contributes to the sensory discriminative aspects of pain; instead, it seems more suited to contributing to the motivational, affective aspects of pain, as well to triggering activity in descending control systems (for details, see Willis and Westlund 1997).

There is growing evidence (at least in rodents) that the S(trigemino)PbT is a major nociceptive projection, rivaling in significance the STT (Bester et al. 1997b; Todd et al. 2000; Hunt and Mantyh 2001). This small region, surrounding the superior cerebellar peduncle at the pontomesencephalic transition, is densely innervated by ascending SC and STN axons (Hylden et al. 1985; Wiberg et al. 1987; Blomqvist et al. 1989; Bernard and Besson 1990; Craig 1992, 1995; Kitamura et al. 1993, 2001; Light et al. 1993; Slugg and Light 1994; Bernard et al. 1995; Feil and Herbert 1995; Allen et al. 1996; Yamashiro et al. 1998; Gauriau and Bernard 2002; Bourgeais et al. 2003). The cells of origin are located mainly in lamina I and many of them express the NK1 receptor (Ding et al. 1995b; Marshall et al. 1996; Yu et al. 1999; Todd et al. 2000; Bester et al. 2001), e.g., these cells receive a nociceptive input from SP-releasing PAs (Bernard et al. 1996; Craig 1996b; Hunt and Mantyh 2001, 2004; Todd et al. 2002). The SPbT is bilateral (Craig 1992; Bernard et al. 1996; Yamashiro et al. 1998; Kitamura et al. 2001). The S(trigemino)PbT is topically dis-

tributed (Bourgeais et al. 2003): parabrachial neurons excited chiefly by noxious stimulation of the face have their dendritic tree located primarily within the field of lamina I trigeminal projections, i.e., in the caudal portion of the parabrachial area, around the external medial and caudal part of the external lateral subnuclei; parabrachial neurons excited chiefly by noxious stimulation of the paw or the tail have their dendritic tree located primarily within the field of lamina I spinal projections, i.e., in parabrachial mid-extent, around the borderline between the external lateral and both the lateral crescent and the superior lateral subnuclei. The parabrachial nucleus projects heavily to the amygdala and the hypothalamus (Fulwiler and Saper 1984; Bernard and Besson 1990; Bester et al. 1997a; Gauriau and Bernard 2002). The spino-parabrachio-amygdalar/hypothalamic nocispecific multineuronal chain is probably concerned with the intensity of pain rather than its location or nature (Bernard et al. 1996; Bernard and Bandler 1998; Hunt and Mantyh 2001).

The involvement of the brainstem RF in pain conduction and modulation was studied intensively and reviewed by Hassler (1960), Bowsher (1976), Willis (1985), and Willis and Coggeshall (1991). The cells of origin of the SRT differ. Neurons in deeper laminae (V–VIII) project to the pontomedullary core: nucl. gigantocellularis, nuclei reticulares pontis oralis et caudalis (Kevetter and Willis 1982; Kevetter et al. 1982; Chaouch et al. 1983; Gauriau and Bernard 2002; for the delineation of the RF in the human brainstem see Paxinos et al. 1990; Koutcherov et al. 2004), and to nucl. reticularis lateralis (Menetrey et al. 1980, 1983). Lamina I neurons project to the dorsal central and ventrolateral reticular regions of the medulla oblongata (Craig 1995). Lamina I neurons project also to the catecholaminergic neurons of the brainstem, except for the dopaminergic group in the mesencephalon (substantia nigra and related nuclei: A8, A9, and A10 groups of Dahlström and Fuxe 1964). Craig (1992, 1995) and Westlund and Craig (1996) found that such axons project to noradrenergic and adrenergic groups in the ventrolateral medulla (A1 and C1), nucl. solitarius and the dorsomedial medullary RF (A2 and C2), the ventrolateral pons (A5), the locus coeruleus (A6), and the subcoerulear region (A7). Huber et al. (1999) encountered very few neurons in laminae II and III that project to the contralateral nucl. gigantocellularis. Nahin (1987) described several peptides in the SRT neurons. CCK-containing neurons were most common, while SP-containing cells were few. The data on the involvement of the RF in a nociceptive spino-reticulo-thalamic projection are contradictory. Bernard et al. (1990) think that the subnucl. reticularis dorsalis in the caudal medulla, which receives SRT axons and sends fibers to the parafascicular and ventromedial thalamic nuclei, could be involved in the control of pain processing. Especially Lima and Almeida (2002) argued that the subnucl. reticularis dorsalis is a prenociceptive center of the pain control system. Also, Villanueva et al. (1996, 1998) insist that the caudal RF is an important nociceptive relay to the thalamus, and the spino-reticulo-thalamic pathways may play an important role in distributing pain signals to the forebrain. On the other hand, Blomqvist and Berkley (1992) reexamined the spino-reticulo-diencephalic pathway in the cat, combining retrograde and anterograde tracing

in order to study the extent to which SRT terminations and reticulodiencephalic neuronal perikarya overlap. They found SRT terminations mainly caudolaterally, while neurons projecting to the intralaminar thalamic nuclei and subthalamus were concentrated rostromedially. Thus, information conveyed from the SC to the RF appears to have access to the thalamus only by way of a few widely scattered neurons. According to Blomqvist and Berkley (1992), these results encourage less emphasis on a putative spino-reticulo-diencephalic pathway for pain. In the transmission of nociceptive spinal signals to the forebrain, a significant involvement of the pontomedullary noradrenergic neuronal groups could be ascribed, since they profusely innervate the thalamus, the hypothalamus, the amygdala, and the cerebral cortex (Aston-Jones et al. 1995; Westlund and Craig 1996). As Hassler proposed that the pallidum externum is reached by pain-conducting axons (see Fig. 31 in Hassler, 1960), recently Gauriau and Bernard (2004) established that the deep laminae in the rat SC project substantially to the globus pallidus and the substantia innominata. In addition to the multineuronal chains that convey nociceptive information to the hypothalamus and amygdala, there is growing evidence for the existence of direct spino(trigemino)hypothalamic and spino(trigemino)limbic tracts (Burstein and Giesler 1989; Burstein et al. 1990a, 1991, 1996; Cliffer et al. 1991; Katter et al. 1991, 1996; Iwata et al. 1992; Burstein and Potrebic 1993; Dado et al. 1994a, b, c; Zhang X et al. 1995c, 1999; Newman et al. 1996; Kostarczyk et al. 1997; Li et al. 1997; Yamashiro et al. 1998; Malick et al. 2000; Gauriau and Bernard 2004). The spinohypothalamic tract (SHT), at least in lower mammals, appears to be an unexpectedly massive projection. Burstein et al. (1990a) counted more than 9,000 retrogradely labeled neurons following selective injection of the tracer in the hypothalamus of rats. They found the greatest number of SHT neurons in the deep DH, followed by the LSN, superficial DH, and around the central canal; only a small number of spinohypothalamic neurons was found in the intermediate zone and in the ventral horn. Similar location of SHT and trigeminohypothalamic (THT) neurons, displaying SP receptor-immunoreactivity was reported by Li et al. (1997): most such neurons were located in lamina I. SHT in the cat has the same cells of origin as in the rat, but the projection appears to be smaller (Katter et al. 1991). SHT is present also in the monkey (Newman et al. 1996; Zhang X et al. 1999). All studies point out that the SHT is bilateral, predominantly crossed. The SHT axons terminate in most of the hypothalamic divisions: the lateral hypothalamus, posterior, dorsal, and periventricular areas, the dorsomedial, paraventricular, and suprachiasmatic nuclei, and the lateral and medial preoptic areas (Cliffer et al. 1991). In monkeys, the axons pass through the thalamus and then enter the hypothalamus (Zhang X et al. 1999). Similarly, in rats, the SHT axons run through the Po (Kostarczyk et al. 1997). The latter authors established that the SHT axons collateralize significantly in the brainstem, innervating numerous RF nuclei, nucl. ambiguus, nucl. solitarius, and Cu. Kostarczyk et al. (1997) conclude that through its widespread collateral projections, the SHT appears to be capable of providing nociceptive input to many areas that are involved in the production of multifaceted responses to noxious stimuli. Zhang X et al. (1995c) established that some SHT

axons in the rat course through a long and complex path. After decussating in the hypothalamus, the axons descend in the ipsilateral Po, midbrain, pons, or even rostral medulla. Such axons may provide nociceptive information to a variety of nuclei throughout the diencephalon and brainstem bilaterally. Malick et al. (2000) found that most of the THT neurons are nociceptive. Their axons cross the midline and ascend until the level of supraoptic decussations in the lateral hypothalamus. More than a half of the axons recross the midline to reach the ipsilateral hypothalamus. The hypothalamic areas that receive trigeminal input are the lateral, perifornical, dorsomedial, suprachiasmatic, and supraoptic nuclei. The THT axons collateralize profusely: to the superior colliculus, substantia nigra, red nucleus, anterior pretectal nucleus, striatum, globus pallidus, and substantia innominata. According to Malick et al. (2000), the findings that non-nociceptive signals reach the hypothalamus through the direct THT route, whereas nociceptive signals reach the hypothalamus through both the direct and indirect routes, suggest that highly prioritized painful signals are transferred in parallel channels to ensure that this critical information reaches the hypothalamus, a brain area that regulates homeostasis and other humoral responses required for the survival of the organism.

Following the observation of Burstein and Giesler (1989) that the SC projects directly to the telencephalon, i.e., to the limbic structures such as nucl. accumbens and the septal nuclei, several papers confirmed and extended this unexpected finding. Cliffer et al. (1991) report a strikingly large number of structures that receive SC axons: ventral pallidum, globus pallidus, substantia innominata, basal nucleus of Meynert (cholinergic neuronal group that innervates profusely the cerebral cortex, the Ch4 group of Mesulam et al., 1984), amygdala, horizontal and vertical limbs of the diagonal band of Broca, medial and lateral septal nuclei, nucl. accumbens, and even the infralimbic and medial orbital cortex. The retrograde tracing experiments of Burstein and Potrebic (1993) indicated that the projection to the amygdala in the rat arises through the entire length of the SC. The number of spinoamygdaloid neurons is modest, and these cells are located bilaterally (mainly contralaterally) in the lateral reticulated area of the deep DH and around the central canal. These authors verified the projection to the orbital cortex but also pointed out that the number of spinocortical neurons is quite small. Newman et al. (1996) found spinal projections to the hypothalamus, ventral striatum, globus pallidus, amygdala, and the septal nuclei in rats and squirrel monkeys. They estimated that in both species the total number of terminals seen in the striatal and limbic areas was 50%–80% of the number seen within the thalamus. Following experimental tooth movement, Yamashiro et al. (1998) found in rats bilaterally Fos-expressing neurons in the periventricular hypothalamus and in the central nucleus of the amygdala. Presently, the laterocapsular part of the central amygdala is defined as the nociceptive amygdala because of its high content of nociceptive neurons (Bourgeais et al. 2001; Gauriau and Bernard 2002; Li and Neugebauer 2004).

2.5 Dorsal Column Nuclei and Nociception

Gr and Cu, their main afferent fibers traveling in the dorsal columns of the SC, and their efferent fibers traveling in the medial lemniscus, are a part of trisynaptic pathway traditionally thought to convey impulses concerned primarily with touch-pressure and kinesthesis (Foerster 1936; Willis and Coggeshall 1991; Snow and Wilson 1991; Parent 1996). It is appreciated that the PA neurons are pseudounipolar and their axons are myelinated. Giuffrida and Rustioni (1992) counted and measured thousands of retrogradely labeled SG neurons in rats that received a tracer in the DCN. They found that at every level, most labeled, i.e., projecting neurons are large.

Electrophysiological studies first addressed the role of the dorsal columns in mediating visceral pain (Amassian 1951; Rigamonti and Hancock 1978). More recently, Berkley et al. (1993) and Berkley and Hubscher (1995) have shown that the Gr neurons can be activated by distension of vagina, uterus, and colon, and half of the Gr cells that respond to cutaneous stimuli are also activated by uterine or vaginal distension. Apkarian et al. (1995) suggested that the DCN may be more important for visceral pain than is the STT. Willis and his colleagues published a series of papers that demonstrate the profound involvement of the DCN in the transmission of visceral pain (Al-Chaer et al. 1996a, b, 1997, 1998; Willis 1999; Nauta et al. 2000; Wang and Westlund 2001; Palecek et al. 2002, 2003a, b; Palecek and Willis 2003). The nociceptive inputs reach the DCN via two routes: (a) monosynaptic input from PA cells in the SG and (b) the pathway consisting of two neurons: a PA neuron and a neuron in the SC.

The classic monosynaptic nociceptive input was described repeatedly (Patterson et al. 1989, 1990; Garrett et al. 1992). According to Conti et al. (1990), the nociceptive input to the DCN may be mediated, though to a very limited extent, directly by way of small, substance P-containing PA neurons.

More important is the second route: via the so-called postsynaptic fibers traveling in the dorsal column. By this bisynaptic pathway, the central process of the PA neuron terminates upon a second-order projection neuron, located in the gray matter of the SC. The axons of these neurons—the postsynaptic fibers—reach the DCN (Rustioni 1973, 1974; Rustioni and Kaufman 1977; Cliffer and Giesler 1989; Cliffer and Willis 1994; Hirschberg et al. 1996; Wang et al. 1999). Rustioni (1977) and Rustioni et al. (1979) investigated the cells of origin of postsynaptic fibers in monkeys. The found that the fibers originate mainly from ipsilateral DH, particularly from its medial part at upper cervical levels and from a band of gray matter throughout the SC, largely corresponding to lamina IV and adjacent laminae. Large neurons along the lateral border of the ventral horn at lumbar levels may also contribute nonprimary afferents to the ipsilateral DCN. In the cat (Rustioni and Kaufman 1977), the cells of origin are numerous in the upper cervical, brachial, and lumbosacral SC, but are sparse in the thoracic segments. In the brachial and lumbosacral cord, the neurons of origin are mainly localized in lamina IV and more ventrally. According to Giesler et al. (1984), in the rat the postsynaptic dorsal

column neurons constitute over 38% of the neurons that project to Cu, and approximately 30% that project to the Gr. In the lumbar segments, the cells of origin are located within a narrow band extending across the ipsilateral DH, subjacent to substantia gelatinosa. Hirschberg et al. (1996) reported a population of cells originating in lamina X and overlying dorsal commissural region at the sacral level of the rat SC. Similarly, Wang et al. (1999) found out that in the rat, neurons in the area adjacent to the central canal of the midthoracic or lumbosacral level of the SC send ascending projections to the dorsal, lateral rim of the Gr and the medial rim of Cu or the dorsomedial rim of the Gr, respectively. The non-PAs to the DCN ascend mainly in the dorsal columns and, to a lesser extent, in the dorsal part of the lateral funiculus both in monkeys (Rustioni et al. 1979) and in the rat (Giesler et al. 1984). The data on the role of the postsynaptic fibers in somatosensory processing are contradictory. Brown and Fyffe (1981) and Brown et al. (1983) indicated that this fiber system transmits cutaneous nociceptive and tactile information to the brain. On the other hand, Giesler and Cliffer (1985) remained skeptical that the postsynaptic fibers are involved in nociception. Also, according to Al-Chaer et al. (1996a, 1997) the dorsal columns play a minor role in relaying excitatory noxious cutaneous input to the VPL thalamic nucleus.

2.6 Cerebellum and Nociception

The cerebellum is regarded as a part of the CNS that is implicated mainly in motor behavior and its coordination. However, numerous studies showed a broad diversity of its functions (reviewed by Saab and Willis 2003). Data indicating that the cerebellum is also involved in nociception has been abundant in recent years, although Chambers and Sprague (1955a, b) described an analgesic effect following cerebellar cortical lesions. Siegel and Wepsic (1974) observed antinociceptive effects following electrical stimulation of the superior cerebellar peduncle in the monkey. Spiegel (1982) speculated that impulses generated by posterior column stimulation may lead to relief of pain and spasticity by activating the cerebellum.

The first reliable evidence that nociceptive stimulation evokes activity in pathways and neurons of the cerebellum was provided by Ekerot et al. (1987a, b). They reported that climbing fiber-evoked responses were recorded in Purkinje cells and as field potentials from the surface of the cerebellum upon stimulation of the ipsilateral superficial branch of the radial nerve. Similar data were reported by Wu and Chen (1990) following stimulation of C-fibers in the saphenous nerve. Ekerot et al. (1991) proposed that the cutaneous nociceptive input may be transmitted to the inferior olive by the postsynaptic dorsal column nuclei. McGonigle et al. (1996) found out that fibers containing substance P terminate upon neurokinin-1 receptor-immunoreactive neurons of the dorsal spinocerebellar tract that project to paravermal areas. Saab et al. (2001) examined the influence of cerebellar cortical stimulation on spinal nociceptive neurons that responded to noxious visceral and somatic stimuli. The stimulation increased the responses of all isolated cells to vis-

ceral stimuli (colorectal distension), while the effect on the responses to somatic stimuli was less clear. In addition, Saab and Willis (2001) found that Purkinje cells in the caudal vermis respond to nociceptive visceral stimulation in the form of early and delayed changes in activity, and proposed a negative feedback circuitry involving the cerebellum for the modulation of peripheral nociceptive events.

Recently, imaging studies on the nociceptive input to the cerebellum have also appeared. In positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies, increases in blood volume or flow in the vermis and paravermal areas were reported during the perception of acute heat pain (Casey et al. 1994), deep cold pain (Casey et al. 1996), muscle pain (Svensson et al. 1997), and capsaicin-evoked pain and allodynia (Iadarola et al. 1998). Saab and Willis (2003) concluded that "... one central pillar (of pain research) is missing to confirm a role for the 'little brain' in pain: clinical data.... Whereas the 'little brain' may influence nociception, its grip on pain remains pliable."

2.7 Cortices Involved in Pain Perception and Thalamocortical Projections

There is a multiregional organization of supraspinal pain processing (Bromm and Lorenz 1998; Coghill et al. 1999; Treede et al. 1999; Hudson 2000; Peyron et al. 2000) and cortical areas involved in pain perception are the primary somatosensory cortex (SI), the secondary somatosensory cortex (SII), the insular (IC), the anterior cingulate (ACC), and the prefrontal (PC) cortices. The respective cortical areas differ functionally, as seen in electrophysiological and functional imaging studies: the sensory-discriminative aspect of pain (localization, intensity, duration, quality) is presented in SI and SII, receiving thalamic input from lateral thalamic nuclei, the motivational-affective aspect (subjective suffering, unpleasantness, aversive emotions), and the cognitive-evaluative aspects of pain are presented in the IC, ACC, and PC, receiving thalamic input from medial thalamic nuclei.

Primary Somatosensory Cortex The role of SI (located in the postcentral gyrus, Brodmann's areas 3, 1, 2) in pain perception has been a matter of dispute for decades. The early findings were largely negative. Head and Holmes (1911) reported that patients with long-standing cortical lesions did not show deficits in pain perception, which lead to an erroneous suggestion that the pain sensation takes place in the thalamus. During epilepsy surgery, Penfield and Boldrey (1937) performed electrical stimulation of patients' exposed SI and encountered only very few cases (11 out of more than 800 responses) that reported a sensation of pain. Single-cell recording in monkeys (Kenshalo et al. 1988) revealed only very few nociceptive neurons, and the authors concluded that their functional significance was uncertain. Also, the findings from human brain imaging studies have produced rather inconsistent results concerning the role of SI in pain perception (Bushnell et al. 1999; Craig 2003a). Despite certain controversies, an increasing number of PET and fMRI studies found an activation of SI during painful stimuli (Casey et

al. 1994; Coghill et al. 1994; Andersson et al. 1997; Torebjörk 1997; Derbyshire and Jones 1998; Porro et al. 1998; Davis 2000; Wiech et al. 2001), also corroborating electrophysiological findings (Drushky et al. 2000; Kanda et al. 2000). According to Craig (2003a, d), nociceptive activation near the central sulcus in humans probably occurs in area 3a (where the thalamic VMpo projects), but its location is below the level of PET resolution. Bushnell et al. (1999) suggest that in SI primarily the sensory-discriminative aspect of pain is presented. Two classes of neurons are activated in SI: neurons with a wide dynamic range react already to stimuli that are not painful; however, they show the highest activity to painful stimuli (Chudler et al. 1990). They have large receptive fields and probably code pain intensity. Specific nociceptive neurons only react to painful stimuli. They have small receptive fields, are somatotopically located in the postcentral gyrus and enable the determination of the localization, intensity, and temporal attributes of the painful stimuli. The SI neurons get their afferents from the lateral thalamic nuclei (VPL, VPM, VPI; in primates and humans also from VMpo; Willis 1997), and also heavily project back to these nuclei. The thalamocortical projections are excitatory glutamatergic (Kharazia and Weinberg 1994). Lesions of the respective thalamic nuclei, the thalamocortical connections or of SI result (besides loss of somatosensory function) in a dramatic decrease in temperature and pain perception (Bassetti et al. 1993; Leijon et al. 1989). But there is no complete analgesia. Nevertheless, pain is still interpreted as uncomfortable and unpleasant (Ploner et al. 1999).

Secondary Somatosensory Cortex SII is located just lateral and slightly anterior to the lateral end of the central fissure in the human brain, roughly occupying Brodmann's area 43 and parts of area 40. In contrast to SI, SII neurons do not seem to be involved in discrimination of location and/or intensity of painful stimuli, but seem to have an important role in recognition, learning, and memory of painful events (Schnitzler and Ploner 2000). A number of studies found significant pain-related activation of SII with functional imaging and electrophysiological methods (Talbot et al. 1991; Casey et al. 1994; Coghill et al. 1994; Oshiro et al. 1998; Xu et al. 1997; Davis 2000; Druschky et al. 2000; Kanda et al. 2000; Treede et al. 2000), mostly bilaterally. The SII neurons get their mostly bilateral afferences from the lateral thalamic nuclei partly different from those projecting to SI, namely from the VPI and the dorsal part of the Po, thus indicating an anatomical and functional segregation of the SI- and the SII-nociceptive pathways. Additionally, SII is reciprocally connected to SI. Nevertheless, the function of SII in pain processing is still unclear. Lenz et al. (1997) proposed that SII may play a key role in relaying nociceptive information to the IC and the temporal lobe limbic structures, providing fast access to pain-related learning and memory.

Insular Cortex Functional imaging studies showed increased blood flow of the insular cortex during painful stimuli, either contralaterally or bilaterally (Casey et al. 1994; Coghill et al. 1994; Andersson et al. 1997; Derbyshire and Jones 1998; Treede et al. 1999, 2000; Davis 2000; Sawamoto et al. 2000). It is not yet clear whether

the anterior (Brodmann's area 13) or posterior insular cortices (Brodmann's areas 14–16) are mainly involved in pain perception (Craig 2003c, d). Moreover, patients with lesions of the IC had an elevated pain tolerance and loss of or inadequate emotional reactions to painful stimuli although recognizing pain (asymbolia for pain; Bertier et al. 1988, Greenspan et al. 1999). The IC gets thalamic afferents from the VMpo, the mediodorsal (MD), and intralaminar thalamic nuclei (Craig et al. 1994; Craig 1996a) and from SII, and projects to limbic structures such as the amygdala and the perirhinal cortex. Also, these connections speak in favor of the importance of the IC in the motivational-affective aspect of pain and in autonomic reactions to noxious stimuli.

Anterior Cingulate Cortex The cingulated cortex is involved in cognition and emotion. Both functions are located in different anatomical subareas. The subarea involved in the motivational-affective aspect of pain is most probably located in the rostral part of Brodmann's area 24 and the adjoining area 32. Patients with lesions of the ACC lost the emotional reactions to painful stimuli although pain could be further correctly localized. In the ACC, pain-receptive neurons were found with large, often bilateral receptive fields not allowing localizing information. Significantly increased functional activity of the ACC was robustly found in many imaging studies (Casey et al. 1994, 1996; Coghill et al. 1994; Derbyshire and Jones 1998; Bromm et al. 2000; Casey 2000; Davis 2000; Hudson 2000) mostly described in the hemisphere contralateral to the painful stimulus. The ACC gets thalamic afferents from the VMpo, the MD, and intralaminar nuclei, from the IC and PC, and projects to the amygdala, the mediodorsal thalamic nuclei, the PAG, motor nuclei of the brainstem, and the IC thus being involved in motivational-affective aspects of pain and in conditioned fear reaction. As the ACC can modulate the affective aspect of sensory perception by pain expectation it is also involved in mediating the affective components associated with attention and anticipation of upcoming noxious stimulation (Sawamoto et al. 2000). In this respect, it is interesting to note that hypnotic suggestion can selectively alter the unpleasantness of noxious stimuli in parallel with reduced pain-evoked activity within the ACC (Rainville et al. 1997). Thus the ACC may have a pivotal role in interrelating attentional functions with that of establishing emotional valence and response properties (Price 2000).

Prefrontal Cortex There are still some doubts with respect to the function of the PC in pain perception. The PC is rather believed to function as a supervisory attention system (Andersson et al. 1997) and to be correlated with the cognitive-evaluative aspect of pain. Functional imaging studies, however, described activation of parts of the PC (probably Brodmann's areas 9 and 10) during the painful stimuli. Interestingly, mostly the right hemisphere showed increased activity irrespective of the side of stimulation (Derbyshire and Jones 1998). Patients with unilateral lesions of the PC show changes in both the sensory-discriminative and the motivational-affective aspects of pain. The PC gets thalamic afferents from the VMpo, the MD and intralaminar nuclei, and projects to the MD and the ACC.

Sewards and Sewards (2002) proposed that separate sensory and hedonic representations exist in each of the primary structures of the somatosensory system, including brain stem, thalamic, and cortical components. They think that in rodent primary somatosensory cortex, a hedonic representation can be found in laminae Vb and VI. In carnivore and primate primary and secondary somatosensory cortical areas no hedonic representation exists, and the activities of neurons in both areas represent the sensory aspect exclusively. However, there is a hedonic representation in the posterior part of the insular cortex, bordering on the retroinsular cortex, that receives projections from the thalamic areas in which hedonics are represented. According to Sewards and Sewards (2002), these segregated components are related to the subjective awareness of pain.

Motor Cortex Interestingly, motor cortex stimulation has been shown to be benevolent for chronic pain suppression. Nearly 300 cases of motor cortex stimulation have been published. Although the results were variable, it was applied successfully in central post-stroke pain and in trigeminal neuralgia. The electrode is placed epidurally over the precentral gyrus. By stimulating the precentral cortex, increased neuronal activity was found in the ventroanterior and ventrolateral nuclei of the thalamus. Computer modeling can predict the immediate bioelectrical effects of the motor cortex stimulation (see Manola et al. 2005 for overview and modeling).

2.8 Descending Modulatory Pathways

The communication of Reynolds (1969) that he was able to perform abdominal surgery in rats without chemical anesthesia, but instead stimulation of the midbrain PAG, was followed by a veritable boom of investigations on the descending analgesia systems. The considerable body of literature was reviewed by Basbaum and Fields (1984), Willis (1984), Besson and Chaouch (1987), Willis and Coggeshall (1991), Light (1992), Wang and Nakai (1994), Beitz (1995), Stamford (1995), Willis et al. (1995), Willis and Westlund (1997), Fields and Basbaum (1999), Fields (2000), Lima and Almeida (2002), and Suzuki et al. (2002). Therefore, only a concise review will be presented here.

The efferent connections of the PAG to the SC are indirect. The PAG neurons project to the serotoninergic raphe nuclei of the medulla oblongata and to the noradrenergic nuclei in the dorsolateral pons (Van Bockstaele et al. 1991; Bajic and Proudfit 1999). Both the catecholaminergic and indolaminergic neuronal groups project heavily to the SC and to the STN.

From the serotoninergic groups, the largest contribution of raphespinal connections is provided by nucl. raphe magnus, followed by the pallidus, obscurus and pontis raphe nuclei (Bowker et al. 1981, 1983; Steinbusch 1981; Willis 1984; Kwiat and Basbaum 1990; Jones and Light 1990, 1992; Jones et al. 1991; for the topography of the raphe nuclei in the human brainstem, see Törk and Hornung 1990). The serotoninergic nucl. raphe dorsalis, located in the midbrain, also participates in

antinociception, however not with a direct raphespinal connection; it is rather involved both in ascending and descending pain inhibitory systems (Wang and Nakai 1994). Polgar et al. (2002) showed that the serotonin-containing axons in the SC selectively innervate the lamina I projection neurons that possess the NK1 receptor.

The noradrenergic connections to the SC arise in the locus coeruleus, subcoeruleus nucleus, and nucleus of Kölliker-Fuse (Westlund and Coulter 1980; Holstege and Kuypers 1982; Stevens et al. 1982; Westlund et al. 1983, 1984; Kwiat and Basbaum 1990; Clark and Proudfit 1991; Yeomans and Prodfit 1992; West et al. 1993; Zhang C et al. 1997; Tsuruoka et al. 2003). The projections are bilateral, predominantly crossed, and mainly laminae I, II, and V are innervated. Zhang C et al. (1997) stated that there is a predominantly inhibitory role on nociceptive transmission at the SC level by descending noradrenergic fibers, and a facilitatory role on the responsiveness of the thalamic parafascicular nucleus to noxious inputs by ascending locus coeruleus axons. Tsuruoka et al. (2003) found out that a unilateral inflammation of the hind paw in rats results in bilateral activation of locus coeruleus, followed by descending modulation.

The neurochemistry of the transmitters and receptors in the multineuronal antinociceptive pathway arising in the PAG is very complex (Bowker et al. 1983; Cui et al. 1999). Along with serotonin and noradrenaline, also endogenous opiates and the amino acids glutamate, GABA, and glycine are clearly involved (Willis 1985; Willis and Coggeshall 1991; Stamford 1995; Willis and Westlund 1997; Lima and Almeida 2002).

The pretectal area is regarded as a part of the visual system. However, the connections of the anterior pretectal nucleus suggest that it is a part of the somatosensory system (Berkley et al. 1986; Wiberg et al. 1987; Foster et al. 1989; Yoshida et al. 1992; Terenzi et al. 1995). Stimulation in the anterior pretectal nucleus results in long-lasting antinociception without aversive side effects (Rees and Roberts 1993). Again, the antinociceptive impulses, arising in the anterior pretectal nucleus, are mediated via descending multineuronal chains, involving the deep mesencephalic nucleus, the pedunculopontine tegmental nucleus (the cholinergic Ch5 group of Mesulam et al. 1984, 1989), and the noradrenergic and serotoninergic neurons in the pons and medulla (Terenzi et al. 1991, 1992, 1995; Wang et al. 1992; Zagon et al. 1995).

In human patients, stimulation of the VPM and VPL thalamic nuclei is followed by a reduction in pain in postherpetic neuralgia (PHN), thalamic syndrome, and facial anesthesia dolorosa (Turnbull et al. 1980). Gerhart et al. (1983) found that stimulation in the VPL causes an inhibition of primate STT neurons. Such inhibition might result from antidromic activation of STT axons that emit collaterals to nucl. raphe magnus and to the PAG. Also, the stimulation of the SI region of the monkey cerebral cortex causes the inhibition of STT neurons (Yezierski et al. 1983). However, the cortical inhibition acts mainly on the responses to innocuous mechanical stimulation, rather reducing nociceptive responses (Yezierski et al. 1983; Zhang D et al. 1991).

Although the focus of investigation has been on the inhibitory modulation of spinal nociceptive processes, data are accumulating that brain stem stimulation can also enhance spinal nociceptive processes (Porreca et al. 2002). Fields (1992) suggested that descending facilitatory influences could contribute to chronic pain states. Later, Urban and Gebhart (1999) stated that such influences were important to the development and maintenance of hyperalgesia. Several studies indicate that the rostroventromedial medulla is a crucial relay in the persistence of descending facilitation of noxious stimuli (Porreca et al. 2002).

The spinal neurons that express the NK1 receptor appear to play a pivotal role in regulating descending systems that modulate activity of nociceptive dorsal horn neurons (Mantyh and Hunt 2004; Khasabov et al. 2005).

3 Neuropathic Pain

While the acute nociceptive pain is a necessary defense mechanism that warns against damage to the organism, chronic pain can be so deleterious that patients not rarely prefer death. The nociceptive ("good") pain is essential for survival but the chronic ("bad") pain serves no defensive, helpful function. There is no biological advantage but only suffering and distress. Acute pain is produced by the physiological functioning of the normal nervous system. The chronic, maladaptive pain typically results from damage to the nervous system (peripheral nerve, PA neuron, CNS) and is known as neuropathic pain (Basbaum 1999; Dworkin and Johnson 1999; Woolf and Salter 2000; Bridges et al. 2001; Hunt and Mantyh 2001; Zimmermann 2001; Scholz and Woolf 2002; Woolf 2004; Tsuda et al. 2005).

The spectrum of NP covers a variety of disease states and presents in the clinic with a variety of symptoms (Woolf and Mannion 1999; Bridges et al. 2001). Several etiologies of peripheral nerve injury might result in NP: PHN (Dworkin et al. 1997; Dworkin and Johnson 1999), traumatic injury (Schwartzman and Maleki 1999; Rodriguez-Filho et al. 2003), phantom limb pain (Nicholajsen and Jensen 2001), diabetes (Boulton and Ward 1986; Calcutt 2002; Khan et al. 2002; Simmons and Feldman 2002; Kapur 2003; Spruce et al. 2003), and malignancy (Schwei et al. 1999; Regan and Peng 2000; Cain et al. 2001; Farrar and Portenoy 2001; Clohisy and Mantyh 2003; Sabino et al. 2003). Despite its varied etiologies, NP conditions share certain clinical characteristics: spontaneous, continuous pain, usually of a burning character; paroxysmal (shooting, lancinating) pain; evoked pain to various mechanical or thermal stimuli such as allodynia and hyperalgesia. Hyperalgesia is an increased pain response to a suprathreshold noxious stimulus and is a result of abnormal processing of nociceptor input. Allodynia is the sensation of pain elicited by a non-noxious stimulus and can be produced in two ways: by the action of low threshold myelinated Aβ-fibers on an altered CNS, and by a reduction in the threshold of nociceptive fibers in the periphery. The fact that pain is often located in hypoesthetic or anesthetic areas may appear paradoxical and implies that NP

not only depends on the genesis of nociceptive messages from nociceptors, but may depend on other mechanisms as well, in contrast to nociceptive pain (Attal and Bouhassira 1999).

That terminals of uninjured PA neurons terminating in the DH can collaterally sprout was first suggested by Liu and Chambers (1958), but was disputed by numerous investigators (Mannion et al. 1996; Wilson and Kitchener 1996). Woolf and colleagues presented a series of reports on the topographic reorganization of the SC PAs following chronic NP (Fitzgerald et al. 1990; Woolf et al. 1992, 1995; Coggeshall et al. 1997, 2001; Doubell et al. 1997, 1999; Mannion et al. 1998; Mannion and Woolf 2000; Tandrup et al. 2000; Woolf and Salter 2000; Decosterd et al. 2002; Sabino et al. 2003). Peripheral nerve injury results in a rearrangement of the highly ordered laminar termination of PAs within somatotopically appropriate regions of the DH. As described above, large myelinated mechanoceptive Aβ-axons normally terminate in laminae III–VI, thin myelinated nociceptive Aδ-fibers in laminae I and V, and the thinnest, unmyelinated C-axons in lamina II. Peripheral axotomy causes long-lasting sprouting of A-fibers into lamina II, an area in which they do not normally terminate. Intracellular injections of tracers show that at least some of these fibers are Aβ-afferents from lamina III. This A-fiber sprouting into lamina II appears to be a result of at least two phenomena. The first is the presence of vacant synaptic sites within the superficial laminae following the transganglionic degeneration of C-axons; the second is the induction of a regenerative capacity in the injured neurons (Mannion et al. 1996). Intrathecally supplied neurotrophic factors, which may act as C-fiber "therapy," can prevent A-fiber sprouting (Bennett 1994). The functional importance of A-fiber sprouting is that lamina II begins to receive information about non-noxious stimuli. This information may be misinterpreted by the CNS as noxious: an anatomical substrate for mechanical allodynia (Woolf and Doubell 1994; Attal and Bouhassira 1999; Woolf and Mannion 1999; Bester et al. 2000). The findings of Woolf and colleagues concerning sprouting of A-axons in the superficial laminae were confirmed by others (Koerber et al. 1999; Nakamura and Myers 1999; Kohama et al. 2000), and several reports on regenerative sprouting following nerve injury also appeared (McMahon and Kett-White 1991; Cameron et al. 1992; Florence et al. 1993; LaMotte and Kapadia 1993; Florence and Kaas 1995; Darian-Smith and Brown 2000; Darian-Smith 2004). On the other hand, Tong et al. (1999) demonstrated that in monkey and rat, a subpopulation of mainly small PA neurons acquires the capacity to take up certain tracers (cholera toxin) after axotomy, a capacity normally not associated with these SG neurons. Thus, after peripheral axotomy, cholera toxin is a marker not only for large but also for small (nociceptive) neurons, thus possibly also for both myelinated and unmyelinated PAs. According to Blomqvist and Craig (2000), such phenotypic changes mean that axonal sprouting may be less pronounced than originally assumed. It is clear that both peripheral and central pathophysiological mechanisms contribute to PHN pain. Some PHN patients have abnormal sensitization of unmyelinated cutaneous nociceptors (irritable nociceptors) and minimal sensory loss. Other patients have

pain associated with small fiber deafferentation. In such patients, pain and temperature sensations are profoundly impaired but mechanical stimuli can produce severe pain (allodynia). In these patients, allodynia may be due to the formation of new connections between non-nociceptive, thick (Aβ) PAs and central pain transmission neurons. The third class of patients complain of severe spontaneous pain without hyperalgesia or allodynia, and according to Fields et al. (1998), such patients presumably have lost both large- and small-diameter fibers, and the pain is likely due to increased spontaneous activity in deafferented central neurons and/or reorganization of central connections. The central sensitization is an activity-dependent functional plasticity that results from activation of different intracellular kinase cascades leading to the phosphorylation of key membrane receptors and channels, increasing synaptic efficacy (Woolf and Mannion 1999; Ji and Woolf 2001).

The experiments with animal models of NP (Bennett and Xie 1988; Seltzer et al. 1990; Kim and Chung 1992; Chacur et al. 2001; Decosterd and Woolf 2000; Khan et al. 2002; Mantyh et al. 2002; Rodriguez-Filho et al. 2003) have considerably increased our knowledge on the neuroanatomical and neurochemical plasticity in the CNS. Sugimoto et al. (1989) reported that following a ligature around the ischiadic nerve in rats, there was a bilateral increase in the number of neurons in the lumbar region of the SC showing signs of degeneration (pyknosis and hyperchromatosis); however, the ipsilateral increase was significantly greater. They also noted that daily doses of strychnine in neuropathic animals significantly increased the incidence of degenerative neurons, suggesting that excessive excitation, which can be exacerbated by strychnine-induced disinhibition, is one mechanism underlying the appearance of such cells. Further, Sugimoto et al. (1990) observed massive transsynaptic degeneration of interneurons in lamina II, and suggested that these neurons die through an excitotoxic mechanism.

The sympathetic nervous system probably plays a role in a relatively low subset of patients with PHN (Nurmicco et al. 1991; Sato and Perl 1991; Jänig 1996; Attal and Bouhassira 1999; Wu et al. 2000; Kress and Fickenscher 2001). The normal PA pseudounipolar neurons (except for the mesencephalic nucleus of the trigeminal nerve) receive no synaptic input (Zenker and Neuhuber 1990; Willis and Coggeshall 1991). However, following peripheral nerve lesion a sprouting of sympathetic noradrenergic fibers takes place (McLachlan et al. 1993; Chung et al. 1996, 1997; McLachlan and Hu 1998; Ramer et al. 1999). The sympathetic fibers, which normally innervate the blood vessels in the ganglia, now form basket-like structures around PA somata without establishing synaptic contacts with them, as is usual in normal tissues (autonomic nonsynaptic terminals). Zhou et al. (1999) suggest that satellite cell-derived nerve growth factor and neurotrophin-3 are involved in the induction of the sympathetic sprouting. However, the sympathetic sprouts predominantly form pericellular baskets around the large SG neurons that do not transmit pain information (Ramer et al. 1998; Zhou et al. 1999), and the density of sympathetic sprouts in the SG does not correlate with NP intensity (Baron et al. 1999). Sympathectomy has been shown to alleviate allodynia in an-

imal models, some patients with causalgia respond positively to sympathicolytic procedures, and injection of epinephrine in a stump neuroma may induce intense pain (Chabal et al. 1992; Choi and Rowbotham 1997; Attal and Bouhassira 1999). Similarly, intracutaneous applications of adrenaline and phenylephrine have been shown to increase spontaneous pain and allodynia in the affected area of PHN patients (Choi and Rowbotham 1997). However, most of the patients do not demonstrate significant benefit from various sympathicolytic procedures (Nurmikko et al. 1991; Kingery 1997; Attal and Bouhassira 1999; Ochoa 1999; Ochoa and Verdugo 2001; Mailis and Furlan 2003), suggesting that the role of the sympathetic nervous system may have been overemphasized. Moreover, Mailis and Furlan (2003) point out that the complications of the sympathicolytic procedure may be significant, in terms of both worsening the pain or producing a new pain syndrome.

Along with neuroanatomical plasticity, the NP is accompanied with sometimes profound neurochemical plasticity, especially in the PAs. Experimental studies (Abbadie et al. 1996; Basbaum 1999; Schwei et al. 1999; Hunt and Mantyh 2001; Gardell et al. 2003; Hains et al. 2003a, b) strongly suggested that often there are distinct differences in the neurochemical changes that occur in the PA neurons and in the SC in neuropathic, inflammatory, and cancer pain states. In NP models (injuring the spinal nerve by means of cutting, crushing, or ligating) in the PA neurons there is a down-regulation of CGRP, SP, isolectin B4, and fluoride-resistant acid phosphatase, combined with up-regulation of glutamate, galanin, NPY, VIP, dynorphin, and GAP-43 (Jessel et al. 1979; Bennett et al. 1989; Noguchi et al. 1990; Cameron et al. 1991; Villar et al. 1991; Donnerer and Stein 1992; Al-Ghoul et al. 1993; Zhang X et al. 1993a, 1995a, b; Hökfelt et al. 1994; Ma and Bisby 1998; Miki et al. 1998; Honore et al. 2000b; Blakeman et al. 2003). On the other hand, in a model of persistent inflammatory pain, Honore et al. (2000b) encountered increases in SP and CGRP, and Segond von Banchet et al. (2002) showed increased up-regulation of neurokinin 1 and bradykinin 2 receptors in DRG neurons subsequent to antigen-induced arthritis.

In animal models of NP, a significant up-regulation of NOS was found in the PA neurons (Verge et al. 1992; Zhang X et al. 1993b; Steel et al. 1994; Choi et al. 1996; Shi et al. 1998; Luo et al. 1999). In addition, Gordh et al. (1998) encountered NOS up-regulation also in the SC gray matter, ipsilateral to the ligated spinal nerve. In all probability, also carbon monoxide plays a role in nociceptive processes, since Gordh et al. (2000) found an up-regulation of its synthesizing enzyme, the heme oxygenase. Zhang X et al. (1998) suggested that one factor underlying the insensitivity of NP to opioid analgesics could be due to a marked reduction in the number of mu-opioid receptors both in the axotomized primary sensory neurons and in the lamina II interneurons. Furthermore, after sciatic nerve ligation in the mouse Narita's group (Narita et al. 2000, 2004) demonstrated an up-regulation of various protein kinase C isoforms in the superficial layers of the DH, hypothesizing that these molecules are implicated in the sensitization of synaptic transmission associated with persistent pain.

Actual studies in neuropathic rats using the chronic constriction injury (CCI) model of the sciatic nerve reveal that important changes also take place in the respective muscles (Gradl et al. 2005). Muscles with impaired innervation react with apoptosis of their fibers. However, at present it is unclear how apoptosis of the muscle tissue contributes to neuropathic pain.

Furthermore, in the CCI model the invasion of T lymphocytes into the injured nerve was found to be correlated with neuropathic pain, whereas athymic nude rats, which lack mature lymphocytes, develop a significantly reduced allodynia and thermal hyperalgesia compared to normal rats (Moalem et al. 2004). Transfer of cytokine-producing T lymphocytes from CCI rats into nude rats enhanced pain hypersensitivity in the recipients, speaking in favor of the T cell immune response as a potential and important target for the treatment of NP (Moalem et al. 2004).

3.1 Central Changes Consequent to Peripheral Nerve Injury

Peripheral nerve injury in humans may result in clinical pain, including enhanced responsiveness to noxious stimuli (hyperalgesia) and the sensation of pain in response to innocuous stimuli (allodynia, Willis 1992). The two phenomena may involve different mechanisms, but an injury-triggered discharge in small-caliber PA fibers leading to hypersensitivity of DH neurons may occur at least at initial stages of both (McMahon et al. 1993; Thompson et al. 1993; Woolf and Doubell 1994). This increased excitability can be blocked by glutamate antagonists (Woolf and Thompson 1991; Liu and Sandkühler 1995), supporting release of glutamate by these fibers and a primary role for glutamatergic transmission in hypersensitivity (Willis 2001, 2002). Thus, better understanding of the mechanisms of hypersensitivity may be gained by studying the effects of peripheral injury on glutamate and its receptors. Glutamate receptors in the SC are down-regulated bilaterally following unilateral inflammation of the paw in rats, possibly as a result of indirect effects of the lesion (Pellegrini-Giampietro et al. 1994; Kus et al. 1995). On the other hand, immunocytochemical evidence suggests ipsilateral up-regulation of AMPA receptors in superficial laminae of the DH following chronic nerve ligation (Harris et al. 1996). While these apparent discrepancies may be explained on the basis of differences in the experimental models, none of these studies provides direct evidence that changes in glutamate receptors occur at synapses of PA terminals. Recent advances in postembedding immunocytochemistry made it possible to address this question at the first brain synapse (Phend et al. 1995; Kharazia et al. 1996; Matsubara et al. 1996; Popratiloff et al. 1996a). The present study is focused on the lamina II, because this is the region where the basic mechanisms responsible for the processing of nociceptive stimuli reside and where peripheral fibers involved in central sensitization after injury terminate (Woolf and Doubell 1994). Section of a peripheral nerve was chosen as the experimental model, because this procedure is known to result in hyperexcitability of DH cells, perhaps triggered by ectopic discharge at the neuroma or in SG (Devor 1994), and because it is highly reproducible from animal to animal.

Changes in AMPA Receptor Expression in Substantia Gelatinosa After Sciatic Nerve Lesion Sections reacted for FRAP exhibited a dense band of reaction product in the superficial dorsal horn on the control side (Popratiloff et al. 1998a). A portion of this band, corresponding to the representation of the sciatic nerve, was attenuated or absent on the lesioned side. In contrast to this prominent effect, only modest changes were seen in immunoreactivity for GluR2/3 on the two sides using conventional confocal microscopy. These included weakly increased staining intensity for somata, dendrites and poorly defined neuropil on the lesioned side. The mean intensity of immunofluorescence over lamina II on the lesioned side (as measured in ten 25-μm-thick sections from two rats) was only 7% greater than that on the control side. However, more detailed image analysis revealed significant changes in staining, especially a substantial increase in the number of very bright pixels on the lesioned side (Popratiloff et al. 1998a). Though consistent with an up-regulation of glutamate receptor protein, it was not possible from LM data to establish whether the increase was primarily in somata (perhaps reflecting increased biosynthesis), dendrites (reflecting increased transport), or at the postsynaptic membrane (reflecting functional glutamate receptors). At the EM, structural details were clearly visible even in the absence of osmium, allowing identification of glomerular terminals at the end of PA fibers. Myelin whorls and glycogen particles were observed on the lesioned side, but not on the control side (Kapadia and LaMotte 1987; Zhang X et al. 1995a). Another change apparent on the lesioned side involved glomerular terminals that in control material have dark axoplasm, few mitochondria and clear vesicles of irregular size. These terminals correspond to the central element of type C1 glomeruli (Figs. 1, 3A; Ribeiro-da-Silva and Coimbra 1982, 1984). After peripheral nerve lesion, these terminals can no longer be identified (Castro-Lopes et al. 1990). Other glomerular terminals in superficial DH with clear axoplasm, numerous mitochondria, and clear vesicles of regular size, corresponding to the central element of type C2 glomeruli (Figs. 1, 19C,D; Ribeiro-da-Silva and Coimbra 1982), are likely to originate from small-caliber myelinated PA fibers. Quantitative analysis was performed on these terminals, since they were recognizable on the operated side as easily as on the control side. A larger number of particles coding for AMPA receptor subunits was evident at glomerular synapses on the lesioned (Fig. 19C) as compared to the control side (Fig. 19D). To verify these qualitative observations, we counted gold particles at synapses made by C2 terminals on the two sides in the three animals used for EM. In each of the animals, labeling at synapses of C2 terminals was significantly increased on the injured side, with ratios ranging from 1.35 to 1.72. A slight (7%–8%) increase in the length of the synaptic active zone may have contributed to this increase, but most of the increased labeling could be attributed to increased receptor density, as indicated by the density of gold particles per micrometer of synaptic contact. Nonparametric analysis confirmed that receptor density was significantly elevated on the injured side ($p \leq 0.01$, Mann-Whitney U-test). These data established AMPA receptor up-regulation at synapses of PAs ipsilateral to the lesion in each of the animals studied. Might this result arise from intra-animal variability? To address this issue, we further analyzed the data

with a paired *t*-test, comparing the mean number of gold particles/synapse on the lesioned and unlesioned sides for the three animals. Notwithstanding inevitable variations in tissue processing, the mean labeling on lesioned and control sides for each animal was very consistent in our material, thus making it possible to reject the null hypothesis that the observed effect might arise from random variations among animals ($p>0.05$, two-sided *t*-statistic).

We took advantage of the characteristic morphology of different types of synapses in superficial laminae to address whether changes in glutamate receptors after peripheral injury are confined to synapses of PAs. Besides glomerular terminals, superficial laminae contain nonglomerular, dome-shaped terminals filled with clear, round vesicles, and making single asymmetric synaptic contacts. Most of these are glutamatergic terminals originating from interneurons or descending fibers (Rustioni and Weinberg 1989). We counted gold particles associated with synapses made by dome-shaped terminals (Figs. 19A,B) randomly selected from lamina II in the same grids used for counts of synapses at C2 terminals. The mean number of gold particles was not significantly changed: synapses made by dome-shaped terminals on the injured side had an average of 0.94 times as much labeling as synapses made by dome-shaped terminals on the control side. These results imply that the increase in GluR2/3 is selective for terminals of PAs.

Considerations The effects of nerve injury upon the first synaptic link in the SC have been studied in many experimental models, and reported in a vast literature. The reaction to peripheral injury consists in part of trophic changes related to attempts at regeneration (Sebert and Shooter 1993; Hökfelt et al. 1994); however, the altered sensations associated with injury are likely to involve neurotransmitter mechanisms. The present results are of special interest, as glutamate is the main transmitter released at synaptic sites of PA terminals in the spinal DH (Jessell et al. 1986; Valtschanoff et al. 1994). Relatively little information from microscopic evidence has been published on glutamate and its receptors after peripheral nerve injury. A modest increase in immunocytochemical staining for glutamate has been reported in the DH, 7–14 days after chronic constriction injury of the sciatic nerve (Al-Ghoul et al. 1993). This is in contrast with the decrease in staining, after the same type of injury or after nerve section, of neuropeptides released by PA fibers, e.g., substance P and CGRP (Bennett et al. 1989; Al-Ghoul et al. 1993; Hökfelt et al. 1994; Kajander and Xu 1995). LM evidence suggests that neuropeptide receptors are up-regulated in the postsynaptic target after peripheral injury (Schäfer et al. 1993; McCarson and Krause 1994; Croul et al. 1995; Abbadie et al. 1996), whereas the literature on glutamate receptors is equivocal (Pellegrini-Giampietro et al. 1994; Croul et al. 1995; Kus et al. 1995; Harris et al. 1996; LaMotte et al. 1996). A modest increase in mean LM staining was observed in the present study; image analysis revealed more substantial increases within strongly fluorescent spots. Some of these were somata, perhaps reflecting increased biosynthesis, and others were within the neuropil, suggesting increased staining at synapses. The latter possibility was confirmed by our EM evidence that peripheral nerve injury induced an increase in

the number of glutamate receptors at synapses of small-caliber PAs terminating in the substantia gelatinosa. Because negative synapses were not included, it may be argued that the increased counts of gold particles shown here may have resulted in one or two gold particles at synapses that might otherwise be negative on the side of the lesion. As the results, however, demonstrate increased counts in strongly immunopositive synapses, the exclusion of negative synapses from the counts would be expected to reduce rather than increase the difference in gold particle counts between the control and operated sides. Though our data indicate that the increase was mainly in receptor density, we also detected a modest increase in active zone length. Even if this increase was confirmed in a larger group of animals, both increased length and density would lead to a greater number of postsynaptic receptors. The results are unlikely to reflect selective survival of those synapses that normally express receptors at high density, because, at variance with C1 terminals, we did not see signs of loss of C2 terminals. We chose to use material stained for an antibody that recognizes both GluR2 and GluR3, because this antibody gives intense staining in lamina II. Moreover, C2 terminals, clearly recognizable by their morphology and well preserved after peripheral injury, have a distinct affinity to label with GluR2/3 (Popratiloff et al. 1996a). In the superficial laminae, the antibody for GluR2/3 appears to stain primarily the GluR2 subunit (Popratiloff et al. 1996a), since the GluR3 subunit is only sparsely present there (Furuyama et al. 1993; Henley et al. 1993; Tölle et al. 1993, 1995; Pellegrini-Giampietro et al. 1994). LM evidence suggests that peripheral injury may result in up-regulation of GluR1 in superficial laminae of the DH (Harris et al. 1996; Popratiloff et al. 1996b). However, changes in glutamate receptors may be limited to those of the AMPA type. Binding density for ligands selective for NMDA receptors was virtually unchanged after dorsal rhizotomy (Croul et al. 1995). Although we show here that glutamate receptors at synapses of intrinsic origin in superficial laminae are not up-regulated, we cannot exclude changes in receptors at terminals that are not glutamatergic. For instance, the number of neurons that are immunopositive for GABA in the DH decreases 2 weeks after sciatic nerve section. Concomitant changes in GABA receptors may occur at synapses upon PA terminals (Castro-Lopes et al. 1993, 1995). Increased efficacy of excitatory synaptic transmission is supported by an increase in synaptic field potentials recorded from the DH ipsilateral to peripheral neuropathy (Colvin et al. 1996), and the similarity in the time course of hyperalgesia and up-regulation of AMPA receptors in the superficial laminae after chronic constriction injury (Harris et al. 1996). Up-regulation of AMPA receptors has been implicated as a mechanism for increased synaptic efficacy (Maren et al. 1993; Isaac et al. 1995). The present report provides the first direct evidence for increased receptor protein at the synapse. Because AMPA receptors in substantia gelatinosa are mainly of the high-efficiency "flip" type (Tölle et al. 1995), an increase in their concentration postsynaptic to PA terminals may be the main mechanism available for increasing synaptic efficacy in this system. This increase may contribute to central sensitization and neuropathic pain in humans.

This monograph also shows up-regulation of AMPA receptor proteins at the synapses. The concentration increase at primary afferent synapses is presumably the explanation for increased synaptic efficacy in this system.

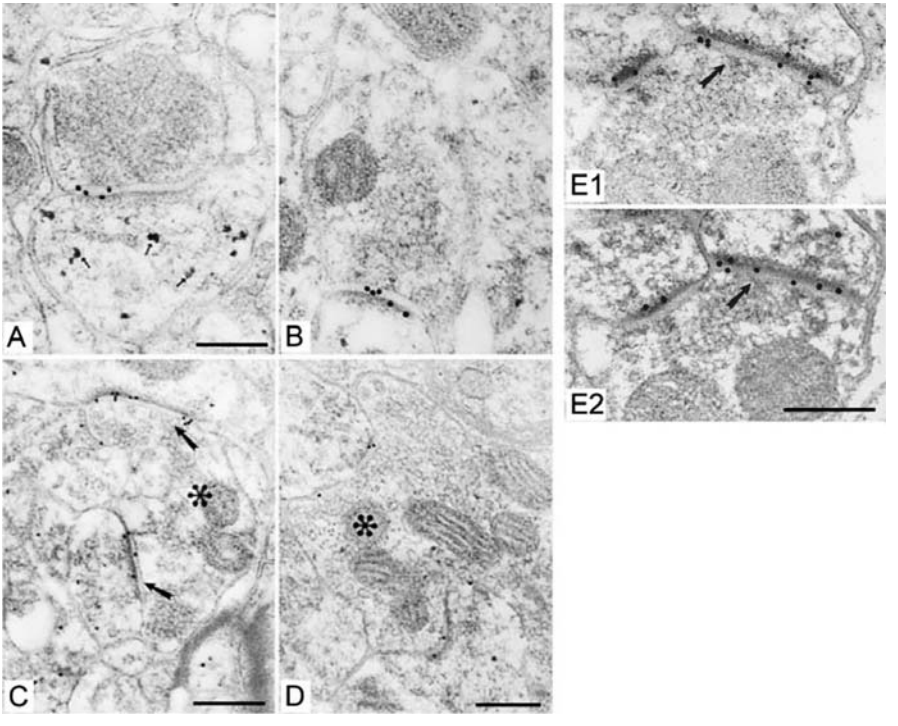


Fig. 19 A–E AMPA receptor subunits GluR2/3 labeling in PA terminals of the substantia gelatinosa of rat DH 2 weeks after sciatic nerve section. On the operated side, average labeling density does not change in the active zones sampled from small terminals likely originating from neurons in the spinal cord **A** compared to control side **B**. Average number of gold particles coding GluR2/3 increases at the active zones of C2 glomeruli, which is due to more frequently observed active zones with more gold particles on operated side **E1**, **E2**, and **C**, compared to the control side **D**. *Small arrows*—glycogen granules on injured side, *arrows*—strongly labeled active zones. Scale bars: **A** and **B**, 200 nm; **C**, 300 nm; **D**, **E2** and **E1**, 250 nm (Adapted with permission from Popratiloff et al. 1998a)

3.2 The Role of Glial Cells

There is growing evidence that both in the periphery and in the CNS, the glial cells play a modulatory role in the response to inflammation and injury, and in processes modifying nociception (Millan 1999; Watkins et al. 2001, 2003; Wieseler-Frank et al. 2004). The microglia is activated by NP (Eriksson et al. 1993; Honore et al. 2000; Tsuda et al. 2005). The substances derived from glial cells exert autocrine and paracrine effects and are able to globally effect activity in the SC (Aldskogius and Kozlova 1998; Minghetti and Levi 1998, Milligan et al. 2003, 2004; Watkins et al. 2003; Verge et al. 2004). According to Watkins et al. (2001) and to Watkins and Maier (2002b), the findings on the glial function—particularly that the glia express characteristics in common with immune cells—suggest a new, dramatically different approach to pain control, as all clinical therapies are focused exclusively on altering neuronal, rather than glial function.

Glia came to attention following the observations of Garrison et al. (1991) that following constriction of the sciatic nerves, the astrocytes in the lumbar SC display an increased staining for glial fibrillary acidic protein. The microgliocytes and astrocytes in the DH are presently known to show up-regulated expression of activation markers in response to different conditions that produce hyperalgesia, such as injury of the peripheral nerve (Colburn et al. 1999; DeLeo and Colburn 1999; Hashizume et al. 2000; Stuesse et al. 2000; Inoue et al. 2004; Ji and Strichartz 2004; Tsuda et al. 2005), subcutaneous formalin injection (Fu et al. 1999), experimental peritonitis (Watkins and Maier 2002a), experimental bone cancer (Schwei et al. 1999), SC injury (Popovich et al. 1997), and immune SC activation (Milligan et al. 2001). Increases in NGF and BDNF mRNA occur in Schwann cells and satellite cells in SG during inflammation of peripheral tissues (Cho et al. 1997), suggesting that by altering the expression and release of trophic factors, the Schwann cells and SG satellite cells may modulate nociceptive signaling. Peripheral axotomy induces a significant increase in NGF mRNA in the SG satellite cells, enhancing the pathologic sympathetic sprouting (Zhou et al. 1999). Other satellite cell-derived substances that might have demonstrable effects consistent with enhanced pain include glial cell-derived neurotrophic factor (GDNF), BDNF, neurotrophin-3, and proinflammatory cytokines (Watkins and Maier 2002a). The endothelins are peptides that have a diverse array of functions mediated by two receptor subtypes, the endothelin A and B receptors (Pomonis et al. 2001). Endothelin A receptor expression may play a role in signaling acute pain or NP, whereas endothelin B receptor expression may be involved in the transmission of chronic inflammatory pain. Pomonis et al. (2001) found the A receptor in a subset of small PA cells; however, the endothelin B receptor was not seen in the PA neurons but rather in the satellite cells and in nonmyelinating Schwann cells. These data indicate that the endothelins can have direct, nociceptive effects on the peripheral sensory nervous system and that peripheral glia may be directly involved in signaling nociceptive events in peripheral tissues. Madiai et al. (2002) examined the expression of fi-

broblast growth factor-2 (FGF-2) following ligation of lumbar spinal nerves. They found that FGF-2 was up-regulated both in PA neurons and in the SC astrocytes, suggesting neurotrophic functions of this growth factor following peripheral nerve lesion and possibly in astrocyte-related maintenance of pain states.

Watkins et al. (2001) recall the strange observation in the AIDS clinical literature that most patients suffer from chronic pain, a high percentage of which is of unknown bodily origin. This suggests that spinal viral invasion, causing glial activation and proinflammatory cytokine release, might potentially explain such pain.

3.3 Neuropathology of Herpes Zoster and of Postherpetic Neuralgia

Varicella-zoster virus (VZV) is an alpha herpes virus that is found exclusively in humans. VZV can cause a wide spectrum of disorders throughout life (Gilden et al. 2000; Kleinschmidt-DeMasters and Gilden 2001). This highly contagious virus causes a relatively benign disease in childhood: varicella (chickenpox). CNS complications are estimated to occur in less than 1% of chickenpox cases, and even this low number may be an overestimate (Kleinschmidt-DeMasters and Gilden 2001). Children have mild meningitic symptoms. The most common abnormality is cerebellar ataxia; very rarely, transverse myelitis has been reported.

After varicella resolves, VZV becomes latent in the SG and in the sensory ganglia of the cranial nerves and persists throughout the life of the host (Esiri and Tomlinson 1972; Gilden et al. 1983, 1987, 2000; Hyman et al. 1983; Croen et al. 1988; Mahalingam et al. 1990, 1999; Dueland et al. 1995; Esiri and Kennedy 1997; Kennedy et al. 1998; Cohrs et al. 2000; Kleinschmidt-DeMasters and Gilden 2001; Gilden et al. 2003). The data on the cellular localization of the latent VZV are contradictory. Croen et al. (1988) and Meier et al. (1993) opposed the common belief that VZV is localized in neurons, and declared that VZV is localized exclusively in the perineuronal satellite cells in latently infected human TG. Recent publications indicate that the virus is located predominantly in the pseudounipolar PA neurons, but the satellite cells are also implicated as a potential reservoir of latent VZV (Lungu et al. 1995, 1998; Kennedy et al. 1998; Mahalingam et al. 1999). During latency, VZV is not infectious and does not transcribe most of its genetic material, thereby escaping detection and clearance of the virus by the immune system.

The likelihood of viral reactivation to HZ increases with each advancing decade of age. HZ usually develops in elderly individuals and is eight to ten times more frequent after the age of 60 years than before (Kost and Straus 1996; Bowsher 1999c). Immunocompromised patients are at especially high risk (Kleinschmidt-DeMasters and Gilden 2001). With reactivation, the virus spreads transaxonally to the skin, causing a rash with a dermatomal distribution, and is associated with severe radicular pain. Any level of the neuraxis might be involved, but thoracic HZ is the most common one, affecting one to two, rarely more dermatomes, followed by the ophthalmic division of the 5th nerve (Hope-Simpson 1965; Portenoy et al. 1986; Zaal et al. 2000; Kleinschmidt-DeMasters and Gilden 2001; Devulder 2002).

HZ ophthalmicus may be associated with keratitis, a potential cause of blindness of the affected eye. The involvement of the facial nerve results in HZ oticus, often combined with paresis of the ipsilateral muscles of facial expression: geniculate neuralgia, described as early as 1907 by Ramsay Hunt (Hunt 1907, 1937; Brodal 1981). Similar combination of painful dermatomal rash with myotomal motor weakness might be observed also in the spinal nerve HZ (Yaszay et al. 2000). In the majority of patients, a prodrome of dermatomal pain starts before the appearance of the characteristic rash (Dworkin and Portenoy 1996; Dworkin and Johnson 1999). Dermatomal pain without a rash (zoster sine herpete) occurs rarely (Lewis 1958; Gilden et al. 1992). HZ is monophasic with recurrence occurring in less than 5% of immunocompetent patients. In contrast, in immunocompromised patients (especially in AIDS patients) HZ is recurrent, protracted, and often accompanied with severe neurological complications (De La Blanchardiere et al. 2000; Gilden et al. 2000, 2003).

The neuropathological investigation of HZ was started by the monograph of Head and Campbell (1900), reviewed by Oaklander (1999). Also quite early, von Bokay (1909) postulated an infectious agent common to varicella and HZ. The basic pathologic substrate for HZ is ganglionic hemorrhage, necrosis, and inflammation (Ghatak and Zimmerman 1973; Nagashima et al. 1975; Kleinschmidt-DeMasters and Gilden 2001). The histopathologic features include mononuclear and lymphocytic infiltration, neuronal degeneration, neuronal phagocytosis by satellite cells, empty neuronal cell beds, and fibrous scarring of the ganglia (Kleinschmidt-DeMasters et al. 1996; Esiri and Kennedy 1997). Vasculitis in the adjacent nerve results in damage of the axons (Gilden et al. 1996; Kleinschmidt-DeMasters et al. 1996), and especially destroyed are the myelin sheaths (Fabian et al. 1997). Rarely, VZV spreads in the CNS. The virus might spread both in centripetal and centrifugal directions (Schmidbauer et al. 1992; Kleinschmidt-DeMasters and Gilden 2001) causing myelitis (Hogan and Krigman 1973; Esiri and Kennedy 1997). In patients with HZ ophthalmicus, the virus might spread via trigeminal afferent fibers to the large blood vessels at the base of the brain, with resultant vessel thrombosis, vessel wall inflammation, and large, ipsilateral brain infarctions (Reshef et al. 1985; Gilden et al. 1996).

Most HZ in immunocompetent patients resolves without sequelae. However, many elderly patients have prolonged, debilitating pain, known as PHN. The increased incidence with increasing age is well known (Kost and Straus 1996; Bowsher 1999c; Dworkin and Johnson 1999; Helgason et al. 2000; Jung et al. 2004). The incidence of PHN has also been found to be much higher in adults with cancer (Lojeski and Stevens 2000) and in patients experiencing psychologic and physiologic stress (Livengood 2000). Jung et al. (2004) examined 965 HZ patients. They found out that older age, female sex, presence of a prodrome, greater rash severity, and greater acute pain severity made independent contributions to identifying which patients developed PHN.

According to Dworkin et al. (1997), five different types of pain may characterize PHN: throbbing pain, steady burning pain, intermittent sharp or shooting pain,

allodynia, and hyperpathia (see below). Chronic pain causes suffering and distress. Here, pain became a disease itself, and it is a ruining disease (Portenoy et al. 1986; Nurmikko et al. 1991; Watson et al. 1991; Dworkin and Portenoy 1996; Attal and Bouhassira 1999; Dworkin and Johnson 1999; Dworkin et al. 2000; Gilden et al. 2000; Kanazi et al. 2000; Dworkin 2002). Dworkin and Johnson (1999) start their handbook article with an impressive phrase: The Norwegians have an admirable name for zoster (which like shingles means belt): "a belt of roses from hell", while the Danes call it "hell-fire."

Unfortunately, pharmacotherapy of NP is limited. Patients with PHN do not respond to nonsteroidal and anti-inflammatory drugs, and resistance or insensitivity to opiates is common (Bowsher 1997; Ossipov et al. 2000; Kanazi et al. 2000; Panlilio et al. 2002; Dworkin and Schmader 2003; Pappagallo and Haldey 2003; Harden 2005). Recent research (Panlilio et al. 2002; Dworkin and Schmader 2003; Lilie and Wassilew 2003) has shown that antiviral therapy can significantly reduce the risk and duration of postherpetic neuralgia in elderly patients, provided that treatment is started early in the course of disease (Jung et al. 2004).

The pathology of PHN is just beginning to be understood, and much less morphologic information is available for this condition than for HZ (Kleinschmidt-DeMasters and Gilden 2001). Along with the investigation of human material (Smith 1978; Watson et al. 1991; Rowbotham and Fields 1996; Rowbotham et al. 1996; Oaklander et al. 1998; Gilden et al. 2003), more or less successful animal models of NP conditions were developed (Willis et al. 1995; Attal and Bouhassira 1999; Honore et al. 2000b). Smith (1978), utilizing both LM and EM, described cystic distortion of thoracic SG removed 2.5 months after the onset of HZ, and persistent chronic inflammatory cells. He found "ghost cells" in a patient with removed SG 2 years after the onset of PHN, and hypothesized that the altered structure of surviving cells might contribute to the pathophysiology of the intractable pain. Watson et al. (1991) reported findings in the SG and adjacent portions of the nerve and of the rootlets in three cases with severe PHN and in two cases with no persistent pain. The findings of DH atrophy and cell, axon, and myelin loss were encountered only in patients with persistent pain. Marked loss of myelin and axons in the nerve and/or sensory roots were found in cases with and without pain. Not unexpectedly, Rowbotham et al. (1996) and Oaklander et al. (1998) demonstrated a greater loss of small cutaneous nerve endings in skin biopsies obtained from patients with HZ who developed PHN than in those who developed no neurologic sequelae.

3.4
Diabetic Neuropathic Pain

The diabetic neuropathy is a severe late complication of diabetes mellitus, and is the most common cause of neuropathy in the Western world (Simmons and Feldman 2002). Its pathogenesis is multifactorial, involving both metabolic and vascular factors (Feldman et al. 1999; Eaton et al. 2001). Diabetic neuropathy has been extensively studied in experimental animals exposed to the hyperglycemic agent strepto-

zocin (Fox et al. 1999). The NP involves predominantly the distal portions of the extremities (Vrethem et al. 2002). It has been suggested that diabetic NP results from hyperactivity of damaged C-fibers (Chen and Levine 2001; Kapur 2003; McHugh and McHugh 2004). In addition, the electrophysiological data of Khan et al. (2002) provide evidence that an abnormal sensory input not only from C- and Aδ-fibers, but also from Aβ-fibers may play an important role in diabetic NP. Heavy alterations of the myelinated axons (onion-bulb formation) in patients with diabetic neuropathy were first described by Thomas and Lascelles (1966). Severe damage of the myelin sheaths in the dorsal and ventral lumbar roots of rats after 8 months of streptozotocin-induced diabetes was reported by Tamura and Parry (1994). Mizisin et al. (1998) examined biopsies from cats with spontaneously occurring diabetes with the electron microscope, and Kalichman et al. (1998) observed biopsy samples from the sural nerve of patients with diabetic neuropathy. In both studies, the most evident finding was a heavy myelin defect characterized by splitting and ballooning of the sheath, while the axons were relatively spared. Schwann cell injury was significant. The reactive changes included accumulations of Pi granules of Reich, lipid droplets and intermediate cytoplasmic filaments. Degenerative changes ranged from dissolution of Schwann cell cytoplasm at the inner glial loop associated with periaxonal swelling and axonal shrinkage to demyelination. According to Eckersley (2002), hypoxia, hyperglycemia, and increased oxidative stress contribute directly or indirectly to Schwann cell dysfunction in diabetic neuropathy. The results include impaired paranodal barrier function, damaged myelin sheaths, reduced antioxidative capacity, and decreased neurotrophic support for axons.

There are few data on the central mechanisms of diabetic NP, although DeJong (1977) found that lesions of the SC are not uncommon and may result in pain syndromes.

3.5 Cancer Neuropathic Pain

For many patients, pain is the first sign of cancer, and 30%–50% of all cancer patients will experience moderate to severe pain; the frequency and intensity of pain tend to increase during the advanced stages, so that 75%–95% of patients with metastatic or advanced-stage cancer will experience severe pain (Portenoy 1992; Portenoy et al. 1999; Regan and Peng 2000; Mantyh et al. 2002). In the cancer population, NP is often related to compression, direct neoplastic invasion of the peripheral nerves and/or the SC, or to a neuropathy caused by chemotherapy (Farrar and Portenoy 2001). Manfredi et al. (2003) examined 187 patients with cancer and pain, and the pain was categorized as neuropathic in 103 patients. The most frequent sites of neurological injury were nerve roots, SC and cauda equina, brachial and lumbosacral plexus, and peripheral nerves. There were no patients with pain caused by injury to the brain.

Strangely enough, although not significantly, some tumors might be innervated by sensory neurons (O'Connell et al. 1998; Seifert and Spitznas 2001; Terada

and Matsunaga 2001), but this is not the main reason for the cancer pain. Far more importantly, the tumor frequently entraps and injures the nerves by compression, ischemia, or proteolysis. The proteolytic enzymes injure the sensory and sympathetic nerve fibers, causing NP (Mantyh et al. 2002). Along the tumor cells, the tumor contains immune-system cells (macrophages, neutrophils, T cells). Both tumor and inflammatory cells secrete numerous factors that sensitize or directly excite PA neurons: prostaglandins, tumor necrosis factor-α, endothelins, interleukin-1 and -6, epidermal growth factor, transforming growth factor-β, and platelet-derived growth factor (Mantyh et al. 2002).

The most comprehensive studies on cancer NP concern bone cancer (Mantyh et al. 2002; Clohisy and Mantyh 2003; Sabino et al. 2003, 2005), since there is a reliable experimental animal model (Honore et al. 2000a, b; Mantyh and Hunt 2004). It appears that bone cancer pain represents a unique pain state (Clohisy and Mantyh 2003). In the persistent inflammatory pain state induced by subcutaneous injection of capsaicin, there is besides massive functional and electrophysiological changes an up-regulation of SP and CGRP, while a down-regulation of these neuropeptides takes place in the NP state following nerve transection or ligation (Noguchi et al. 1989; Villar et al. 1991; Donnerer et al. 1993; Garrison et al. 1993; Safieh-Garabedian et al. 1995; Cho et al. 1996, 1997). However, Honore et al. (2000b) found no significant changes in the expression of these neurotransmitters in the murine bone cancer model. These authors encountered large differences that occur with each pain state in the SC: inflammation induced an increase in SP and CGRP in laminae I and II, neuropathy induced down-regulation of these transmitters, while bone cancer had no effect. In the murine model of bone cancer pain, Schwei et al. (1999) observed a dramatic up-regulation of glial fibrillary acidic protein in the SC, indicating massive astrogliosis. Again, this phenomenon is not observed in the inflammatory and neuropathic pain models.

3.6 Central Neuropathic Pain

3.6.1 Spinal Cord Injury

Chronic NP occurs in approximately 50% (varying from 42% to 77%) of patients with SC injury (Bonica 1991; Anke et al. 1995; Levi et al. 1995; Eide et al. 1996; Christensen and Hulsebusch 1997; Bowsher 1999a; Siddall et al. 1999; Siddall and Loeser 2001; Finnerup et al. 2001; Finnerup and Jensen 2004). Syringomyelia is a rare disease but with a very high incidence of central pain (Boivie 1999). In 22 patients, he found that all had pain.

There are two varieties of NP following SC injury: (a) at-level pain (in segments corresponding to the level of SC injury), (b) below-level pain (in parts of the body corresponding to segments caudal to the injury) (Siddal et al. 2000). According to Siddal et al. (1997), the below-level NP should be considered as a central pain

condition caused by the SC injury, while at-level pain may have peripheral and central components that are difficult to separate.

Eide et al. (1996) compared somatosensory abnormalities in painful and non-painful denervated areas at or below injury in patients with SC injuries. They observed that allodynia was more common in painful areas, and suggested that in the pathogenesis of NP a major role is played by the hyperexcitability of STT neurons. Bouhassira et al. (2000) investigated patients with painful and painless syringomyelia. They observed no significant differences in thermal or mechanical sensory function between patients with or without pain. Similarly, Defrin et al. (2001) found no differences between thermal and tactile sensations in patients with or without pain, but allodynia was only elicited in pain patients. Finnerup et al. (2003) compared clinical examination, quantitative sensory testing and somatosensory evoked potentials in patients with traumatic SC injury with and without pain below spinal lesion level. The patients with central pain more frequently had sensory hypersensitivity in dermatomes corresponding to the level of the injury. They found a significant correlation between the disesthesia at the level of the lesion and spontaneous pain caudal to the injury level. Finnerup et al. (2003) think that STT damage may be a necessary but not sufficient condition for developing below the level pain, since deficits of STT functions were equally severely affected in patients without pain. They propose that pain in body segments below the level of injury should be linked to the presence of abnormal evoked sensations in segments at the level of injury. Finnerup et al. (2003) suggest that neuronal hyperexcitability in second- or third-order neurons, which have lost their normal afferent input, is an important mechanism for pain below spinal injury.

3.6.2 Brain Injury

According to Boivie (1999), historically central pain appears to have been first described as early as 1883 by Greiff in a patient who, following cerebrovascular lesions including the thalamus, developed *reissende Schmerzen* (tearing pain). The term "thalamic syndrome" was introduced by Dejerine and Roussy (1906), who described three cases of a condition in which spontaneous pain followed a stroke, and the autopsies showed the infarct to be in the thalamus. Presently, the condition is known as central post-stroke pain (Leijon et al. 1989; Bowsher 1999b). Vestergaard et al. (1995) reported that approximately 8% of all stroke patients develop central post-stroke pain. Lesions at any level along the neuraxis can cause central pain. Thus lesions at the first synapse in the DH of the SC or trigeminal nuclei, along the ascending pathways, in the thalamus, in the subcortical white and probably in the cerebral cortex have all been reported to cause central pain (Riddoch 1938; Garcin 1968; Cassinari and Pagni 1969; Leijon et al. 1989; Tasker 1990; Bowsher 1996, 1999a; Pagni 1998). The highest prevalence has been noticed after lesions of the SC, lower brainstem and ventroposterior part of the thalamus (Bonica 1991; Boivie 1992, 1999). The importance of the location of the thalamic

lesion was repeatedly evaluated. According to Bogoussslavsky et al. (1988), only patients with lesions including the ventroposterior thalamus develop central pain. Also in studies carried out by Leijon et al. (1989) and Bowsher et al. (1998), all thalamic lesions included part of the ventroposterior thalamic nuclei. Boivie (1999) recalls that this is in accordance with Hassler's idea that the V.c.p.c. thalamic nucleus (an important site of STT termination in humans), is the crucial location for thalamic lesions causing central pain (Hassler 1960).

The lesions that cause central pain vary enormously in location, size, and structure. There is no study indicating that a small lesion in the DH of the SC carries less risk for central pain than a huge infarct involving much of the thalamus and large parts of the white matter lateral and superior to the thalamus (Boivie 1999). There are several hypotheses concerning the mechanisms involved in the pathophysiology of central pain. Head and Holmes (1911) proposed a disinhibition of the STT-thalamocortical system, triggered by lesions of the DCN-medial lemniscus system. Foerster's hypothesis (1936) was similar: he thought that epicritic sensitivity (touch, pressure, vibration) normally exerts control over protopathic sensitivity (pain and temperature). According to Foerster's hypothesis, central pain can only occur when there is a loss of epicritic sensitivity, e.g., destruction of the lemniscal system. More recently, indications were repeatedly found that the STT system is affected in the majority of patients with central pain (Boivie et al. 1989; Tasker 1990; Bowsher et al. 1998; Pagni 1998). Central pain patients have abnormal temperature and pain sensibility, but they may have normal threshold to joint movements, vibration, and touch (Boivie et al. 1989; Bowsher et al. 1998). Low brainstem infarcts (Wallenberg syndrome) and cordotomies, in which the STT but not the medial lemniscus is interrupted, may cause central pain (Boivie et al. 1989; Bowsher 1996; Bowsher et al. 1998; Pagni 1998; Boivie 1999). Probably, the crucial lesions affect the neo-STT, e.g., the projection to the ventroposterior thalamic region (Garcin 1968; Bowsher 1996; Pagni 1998). This kind of lesion leave the more medially and inferiorly terminating paleo-STT projections intact (Boivie 1999).

Another hypothesis focuses on the role of the reticular thalamic nucleus, and the medial and intralaminar zones receiving STT fibers. The reticular nucleus is the only thalamic nucleus built by GABAergic, inhibitory projection neurons that do not give rise to thalamocortical fibers but heavily innervate the remaining thalamic nuclei (Gonzalo-Ruiz and Lieberman 1995; Guillery et al. 1998; Jones 2002a, b; Guillery and Harting 2003). According to this hypothesis, the lesion removes the suppressing activity exerted by the reticular thalamic nucleus on intralaminar and medial thalamic nuclei, thereby releasing abnormal activity in this region, which in turn leads to pain and hypersensitivity (Cesaro et al. 1991). In accordance with this hypothesis, Edgar et al. (1993) pointed out that most thalamic lesions that cause central pain might involve part of the reticular nucleus, as well as parts of the ventroposterior nuclei.

Recently Craig (1998, 2003d) put forward a new hypothesis about the mechanisms of central pain. His hypothesis builds on the classical insights of Head and Holmes (1911). Central pain is due to the disruption of thermosensory integra-

tion and the loss of cold inhibition of burning pain. This disruption is caused by a lesion along the STT to the nuclei VPI, VMpo, and MDvc. These projections tonically inhibit nociceptive thalamocortical neurons, which by the lesion increase their firing and produce pain. The pathway is activated by cold receptors in the periphery, which in turn activate cold-specific and polymodal lamina I cells in the DH. According to Boivie (1999), this hypothesis might be applicable in some patients, but not in others, because of the location of the lesions and the character of the pain (roughly 40%–60% of all central pain has a burning character).

3.6.3 Changes in Cortical Networks Due to Chronic Pain

Persistent pain causes suffering and distress, and pain can become a disease in itself. Chronic pain or NP can result from damage of the nervous system at different levels of pain processing: peripheral nerve, SG, dorsal root, CNS. Chronic syndromes mostly show positive symptoms such as pain, dysesthesia, and paresthesia, often in combination with negative symptoms such as sensory deficits. Unfortunately, pharmacotherapy of NP is limited, perhaps because the etiology, the mechanisms, and the symptoms of NP may differ considerably between patients. In patients with PHN pain, mainly peripheral mechanisms are discussed as being involved, but central changes might also be involved. Peripheral neuropathic pain is a spontaneous pain (stimulus-independent pain) or a hypersensitivity pain caused by a stimulus following damage of sensory neurons (stimulus-evoked pain). Inflammation in the DG can sensitize neurons to respond to normal innocuous thermal or mechanical stimuli and loss of DG perikarya can induce changes in surrounding surviving neurons. Thus, loss of sensory dendrites in the epidermis of patients suffering from PHN was positively correlated with both sensory deficits and with pain (Baron and Saguer 1993; Koltzenburg et al. 1994; Woolf and Doubell 1994; Rowbotham et al. 1996; Oaklander et al. 1998). Changes caused by alterations of peripheral input, followed by altered spinal processing can be forwarded to the cortex via thalamic nuclei (Coderre et al. 1993; Hsieh et al. 1995). Neurons in the somatosensory thalamus of patients with NP showed various electrophysiological abnormalities: responses to stimuli of body regions not normally driving those cells, high spontaneous firing rates, and abnormal bursting activities. Thus, besides peripheral and spinal changes there is massive cortical plasticity contributing to the development of pathological pain.

Neuropathic pain has been studied using CT, EEG, PET, and fMRI. Substantial plastic changes were found in the cortex using these techniques. Functional reorganization in SI and SII were described. In NP, a change related to chronicity and amount of pain was reported (Flor 2003). Moreover, using ^{1}H-MRS chemical changes were noted in the dorsolateral prefrontal cortex in chronic back pain for N-acetyl aspartate and glucose, which could be related to measures of pain and anxiety (Grachev et al. 2000).

One of the thoroughly investigated topics in this field is the processing of ongoing phantom limb pain (Flor et al. 1995, 1997). In humans, it could be shown that there is a takeover of SI representation fields, no longer "used" because of limb amputation, by directly adjoining cortical fields representing adjacent areas of the body surface (Birbaumer et al. 1997): in SI the representation of the lower lip of the side of amputation was found in the position that should have been occupied by the contralateral (amputated) upper extremity. Changes in the cortical presentation are intimately correlated with phantom limb pain (Flor et al. 1995, Birbaumer et al. 1997): larger amounts of cortical reorganization are correlated with increased pain impression (Montoya et al. 1998). In patients suffering from pain due to traumatic upper limb loss, pharmacological blockade of the respective brachial plexus could reverse the "pathological" cortical map in those patients that showed a pain reduction (Birbaumer et al. 1997).

That chronic ongoing NP (painful mononeuropathy) altered cortical activity was shown by a positron emission topography study comparing patients' habitual pain state with that of a pain-alleviated state induced by regional nerve block with lidocaine (Hsieh et al. 1995). Although activities of SI and SII were not significantly altered during both states in the patients, there was a clear state difference in the activities of the IC, the posterior parietal, and the inferior lateral prefrontal cortices, indicating an involvement of those areas in NP processing. Most interestingly, the ACC of the right hemisphere was found activated irrespective of the body side of the painful nerve. The noninvolvement of SI in chronic pain corroborates the observation that surgical extirpation of SI and SII provided little or no relief from chronic pain. The cerebral activation pattern in neuropathic patients found by Hsieh et al. (1995) shows the importance of the motivational-affective dimension of pain in this illness. These findings are also in accordance with reports (Craig et al. 1996a) that the ACC is activated in models demonstrating illusion of pain.

4
Concluding Remarks

The neuroanatomy of pain is complex, as many ascending systems in parallel are involved in pain processing. Even more complex is the neuropathology of PHN as far as it is understood to date. Damage of the nervous system at the level of SG results in a rearrangement of the highly ordered laminar termination of PAs within the appropriate regions of the DH. Normally, unmyelinated C-fibers terminate in lamina II, myelinated mechanoceptive Aβ-axons in laminae III–VI of the SC. Following the virus-induced transganglionic degeneration of C-axons, long-lasting sprouting of A-fibers into lamina II occurs. The functional importance of A-fiber sprouting is that lamina II begins to receive information about non-noxious stimuli. This information may be misinterpreted by the CNS as noxious. Thus PHN can be interpreted firstly as a result of a massive sprouting on the level of the SC, secondly leading to abnormal ascending projection that thirdly are

pathologically further processed in the brainstem, the thalamus, and the cortical areas involved in pain perception.

5 Summary

Pain is an unpleasant but very important biological signal for danger. Nociception is necessary for survival and maintaining the integrity of the organism in a potentially hostile environment. Pain is both a sensory experience and a perceptual metaphor for damage and it is activated by noxious stimuli that act on a complex pain sensory apparatus. However, chronic pain no longer having a protective role can become a ruining disease itself, termed neuropathic pain.

From periphery to cortex, the neuroanatomical chain of pain consists of the primary afferent (PA), the perikarya localized in spinal ganglia (SG) and in the sensory ganglia of the 5^{th}, 7^{th}, 9^{th} and 10^{th} nerves. The largest A cells are typical proprioceptor, and the small B cells are typical nociceptor neurons. The peripheral processes of the nociceptive PA cells are thin fibers of two types: Aδ- and C-fibers, the Aδ-fibers being responsible for the "first pain" (pinprick sensation), and C-fibers for the "second pain" (burning or dull pain). The free nerve endings are to be found throughout the body, mainly in the adventitia of small blood vessels, in outer and inner epithelia, in connective tissue capsules, and in the periosteum.

As central processes of SG neurons, the nociceptive fibers terminate primarily in laminae I and II; the Aδ-fibers terminate in laminae I and V, and C-fibers in laminae I and II. The nociceptive-specific neurons are dominated by Aδ-fiber input. The polymodal nociceptive cells are dominated by C-fiber input and are important for the second pain. The central processes of pseudounipolar TG neurons mostly descend especially to the caudal part of the spinal trigeminal nucleus, with a structure similar to the spinal dorsal horn. Two types of glomerular terminals could be identified in superficial laminae resembling terminals of unmyelinated or from thinly myelinated PAs. In the superficial laminae of the SC, especially glutamate receptors and their relation to types of synapses play a crucial role for decoding the convergent inputs at the level of the first brain synapse and for the understanding of abnormal pain.

A distribution of GluR1 and GluR2/3 for AMPA receptors is described in the superficial dorsal horn of the spinal cord. GluR1 showed a lateral localization, while GluR2 was localized over the mediolateral extent of the superficial dorsal horn. Electron microscopic results revealed that GluR1 antibody was related to C1 synapses, while GluR2/3 antibodies were localized on C2 synapses.

Ascending pathways of the spinal cord (SC) and of the spinal trigeminal nucleus, the spino- and the trigeminothalamic tracts, mediate the sensations of pain, cold, warmth, and touch. The cells of origin are located mainly in laminae I and IV–VI, their mostly crossing axons reaching various nuclei of the thalamus. Also, the dorsal column nuclei (DCN) are highly involved in nociception, projecting via the

medial lemniscus to thalamic nuclei. Furthermore, the entire trigeminal sensory nuclear complex projects to the thalamus.

Our retrograde axonal transport studies revealed the projections to the ventrobasal thalamus in the rat. In the brainstem, the contralateral principal sensory and all subdivisions of the spinal trigeminal nucleus contained retrogradely labeled neurons, but to a different extent. The ipsilateral projection to the thalamus is faint but unquestionable. The experiments also demonstrated a prominent crossed connection from the DCN to the thalamus. Only a few neurons in the DCN ipsilateral to the injection were labeled. In the SC, the distribution of labeled neurons was uneven. The highest number of labeled neurons was encountered at the spinomedullary junction and in the four cranial cervical segments, mostly contralateral to the thalamic injection. In the more caudal segments, the number of labeled neurons decreased.

There is a multiregional organization of supraspinal pain processing, and the cortical areas involved in pain perception are the primary (SI) and secondary (SII) somatosensory cortex, the insular (IC), the anterior cingulate (ACC), and the prefrontal (PC) cortices. The sensory-discriminative aspect of pain (localization, intensity, duration, quality) is presented in SI and SII, the motivational-affective aspect (subjective suffering, unpleasantness, aversive emotions) and the cognitive-evaluative aspects of pain are presented in IC, ACC, and PC.

Pain processing is controlled by descending modulatory pathways. Neurons from the periaqueductal grey (PAG) project to the serotoninergic raphe nuclei of the medulla oblongata and to the noradrenergic nuclei in the dorsolateral pons. Both the catecholaminergic and indolaminergic neuronal groups project heavily to the SC and to the spinal trigeminal nucleus. Along with serotonin and noradrenaline, also endogenous opiates and the amino acids glutamate, GABA, and glycine are clearly involved. It was suggested that descending facilitatory influences could contribute to chronic pain states, and such influences were important to the development and maintenance of hyperalgesia.

Chronic, maladaptive neuropathic pain typically results from damage to the nervous system. Several etiologies of peripheral nerve injury might result in neuropathic pain: postherpetic neuralgia (PHN), traumatic injury, phantom limb pain, diabetes, and malignancy. Neuropathic pain conditions share certain clinical characteristics: spontaneous, continuous pain, usually of a burning character; paroxysmal (shooting, lancinating) pain; and evoked pain to various mechanical or thermal stimuli, such as allodynia and hyperalgesia.

As the result of neuroanatomical and neurochemical plasticity in the CNS, peripheral nerve injury results in transsynaptic degeneration and a rearrangement of the highly ordered laminar termination of PAs within appropriate regions of the dorsal horn.

Chronic neuropathic pain occurs in approximately 50% of patients with SC injury and following various brain injuries, i.e., central post-stroke pain in approximately 8% of all stroke patients and lesions at any level along the neuraxis. Chronic pain seems to be the result of changes in cortical networks.

PHN can be interpreted firstly as a result of a massive sprouting on the level of the SC, secondly leading to abnormal ascending projection that thirdly are pathologically further processed in the brainstem, the thalamus, and the cortical areas involved in pain perception.

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Subject Index