Neurosurg Clin N Am 14 (2003) 445–462

NEUROSURGERY CLINICS OF NORTH AMERICA

Anatomy and physiology of chronic pain

Joshua M. Rosenow, MD*, Jaimie M. Henderson, MD

Section of Functional and Stereotactic Neurosurgery, S31, Department of Neurosurgery, The Cleveland Clinic Foundation, Cleveland, OH 44195

The modern era of understanding and managing chronic pain began with the publication of Melzack and Wall's landmark 1965 articulation of the gate control theory of pain [1]. Since that time, remarkable strides have been made in our knowledge of the mechanisms of both acute and chronic pain. This has led to the introduction of a host of neuroaugmentative therapies as well as to the demise of many destructive procedures. Newer concepts of chronic pain have allowed practitioners to target pain more precisely.

Nociceptive pain reflects ongoing tissue damage, inflammation, and noxious stimulation in intact tissues. Neuropathic pain is pathologic in that it often emanates from an anatomic region not subject to noxious stimulation. Instead, this type of pain reflects damage to and improper functioning of neural tissue. Deafferentation pain and central pain are two subtypes that fall under this rubric.

Although much has been accomplished in the past several decades, treatment of chronic pain remains imperfect. This article presents the anatomy and physiology of the pain system along with the neurobiologic changes that occur in the establishment and maintenance of chronic pain states.

Anatomy of nociception

Nociception involves the perception of certain afferent signals from sensory receptors as noxious. This begins with impulses generated by peripheral receptors. An inward transmembrane ion current (usually sodium) is produced by a receptor in response to a sensory stimulus. The cell bodies of these receptors reside in the spinal dorsal root ganglia (DRG). Mechanical stimuli result in the physical deformation of receptor transmembrane channels, thus opening them. Chemical stimuli bind directly to receptor sites. Although only a few of these have been identified (eg, that for capsaicin), it is surmised that numerous varieties exist. Although the exact mechanism for the transduction of thermal stimuli is not known, extreme thermal stimuli result in tissue damage, thus initiating current flow.

Most tissues are innervated by several different types of sensory nerve fibers. Aβ fibers are typically myelinated, larger (6–12 μm in diameter), and conduct at higher speed (30–70 m/s). They serve to transmit impulses from encapsulated sensory endings for touch, pressure, and vibration. Aδ fibers are also myelinated but smaller (1–6 μm in diameter). They conduct at slower speeds (5–30 m/s) and are believed to be responsible for the pricking pain that some refer to as "first pain." C-fibers are the smallest fibers (<1.5 μm in diameter) and conduct at the slowest speed (0.5–2 m/s). These unmyelinated fibers do not have encapsulated sensory endings. Along with the Aδ fibers, the C fibers terminate as free nerve endings in tissue. C fibers are believed to be responsible for "second pain," the slow-onset and poorly localized pain with a burning quality that begins in a slightly delayed fashion after injury [2].

When membrane depolarization caused by the summation of these excitatory currents exceeds the threshold for action potential generation, an action potential is transmitted toward the DRG and the dorsal horn of the spinal cord. The task of integrating and encoding sensory stimuli for

* Corresponding author.
E-mail address: rosenoj@ccf.org (J.M. Rosenow).

1042-3680/03/$ - see front matter
doi:10.1016/S1042-3680(03)00009-3

central transmission is accomplished at a region of the sensory axon near the receptor, which is densely populated with sodium channels. Encoding is highly specific to each sensory ending and may be altered by compounds like anticonvulsants and local anesthetics that alter sodium channel function as well as sodium channel density. This is in contrast to sensory transduction, which is not sensitive to these compounds. Lowering this threshold leads to sensitization of the receptor. Increasing it results in desensitization.

Encoded sensory impulses are transmitted centrally toward the cell body, which lies in the DRG. No synapses are made in the DRG, and the signals are then transmitted to the dorsal horn of the spinal cord. More than half of the DRG cells use the excitatory amino acid glutamate as a neurotransmitter. A substantial portion of these cells colocalize substance P, a neuropeptide with a significant facilitatory role in pain transmission as well [3–6]. Postsynaptic glutamate receptors are often colocalized with presynaptic neurons containing substance P [7]. Studies of the dorsal root itself reveal that the smaller myelinated and unmyelinated fibers cluster in the lateral aspect of the root as it approaches the dorsal horn. The larger myelinated fibers (usually those for proprioception and light touch) cluster in the medial aspect of the root and closer to the dorsal columns. The axons in the lateral root enter Lissauer's tract.

Rexed [8,9] first described the laminar organization of the spinal gray matter in the 1950s. Afferent fibers enter the dorsal horn via the dorsolateral fasciculus of Lissauer. Afferent spinothalamic axons may travel vertically several spinal segments in this superficial layer before eventually synapsing with neurons in lamina I, the posteromarginal nucleus. Cells here are nociceptive specific neurons and respond exclusively to noxious stimuli [10–12]. They contain multiple neuropeptides, such as substance P, calcitonin gene-related peptide (CGRP), enkephalin, and serotonin. Substance P and CGRP, in particular, play an important role in dorsal horn nociception [13–16]. Lamina I cells send axons contralaterally to form the lateral spinothalamic tract (STT). In addition to nociceptive-specific cells, lamina I contains a class of cells that respond to a large variety of both noxious and nonnoxious stimuli. These are known as wide dynamic range (WDR) cells, and they alter their discharge frequency substantially to reflect the input stimulus. Noxious stimuli evoke higher frequency discharges. As described below, these cells play an important role in the development of chronic pain.

Lamina II, the substantia gelatinosa, acts to modulate input from sensory receptors. Nociceptive and thermoreceptive input is concentrated in the superficial layer of this lamina (II_o), whereas mechanoreceptor input is targeted to the deeper aspect (II_i) [11,12]. Projections from substantia gelatinosa neurons terminate in lamina I and in lamina II at other spinal levels. Opiate receptors are plentiful in laminae I and II. Importantly, each sublayer of lamina II seems to contain distinct subpopulations of C fibers. Those terminating in lamina II_o are similar to those that terminate in lamina I. They express substance P and CGRP and contain the trkA receptor for nerve growth factor (NGF). In contrast, the C fibers terminating in lamina II_i do not express CGRP substance P. They express the binding site for lectin IB4, an indicator of sensitivity to glial-derived neurotrophic factor (GDNF). This lamina also contains numerous local circuit neurons whose dendritic arbors may extend into both deeper and more superficial laminae.

The Aβ fibers terminate primarily in lamina III, as do some of the Aδ mechanoreceptive fibers. Lamina IV also serves as a target zone for Aβ fibers. Some of the cells in this layer project back to layer I, aiding in integration of sensory information. Lamina V contains a large number of STT projection cells that receive input from Aδ and C fibers. A substantial proportion of the cells here are WDR neurons. These have large receptive fields whose center is responsive to both noxious and nonnoxious stimuli and a surrounding area responsive primarily to noxious stimuli only. Stimulation of the region surrounding this field causes inhibition of the WDR neuron [12].

Lamina X encompasses the gray matter surrounding the central canal of the spinal cord. The exact function of the cells here is not clear, but they are thought to play a role in visceral sensation as well as in the holospinal integration of nociceptive information. Some Aδ fibers directly terminate here, possibly carrying both visceral and cutaneous input.

The trigeminal system has an analogous anatomic arrangement. Cell bodies for facial nociceptors are located in the gasserian ganglion. The peripheral processes project via the three divisions of the trigeminal nerve, and the central processes enter the brain stem via the trigeminal sensory root. Trigeminal sensory input is then

segregated depending on the type of information. Unlike other sensory cells, those subserving proprioception have their cell bodies in the trigeminal mesencephalic nucleus. The main sensory nucleus is located in the pons and receives large myelinated Aβ afferents. Caudal to this nucleus is the spinal nucleus, which extends caudally through pons and medulla and is essentially the extension of lamina I into the brain stem. This structure is further subdivided into several subnuclei. The subnucleus oralis is located most rostrally, followed by the subnucleus interpolaris, and the large subnucleus caudalis. The subnuclei oralis and interpolaris share common tactile and pressure input with the main sensory nucleus. Nociceptive input is directed toward the subnucleus caudalis and the junction between interpolaris and caudalis.

The subnucleus caudalis has several levels of somatotopic organization. The classic model described by Déjérine [17] is the onion peel analogy. Fibers from the central portions of the face terminate in the more rostral portions of the subnucleus caudalis, whereas those in progressively more peripheral rings terminate at more caudal levels. Nociceptive fibers from other cranial nerves (VII, IX, and X) synapse in the more medial aspects of the subnucleus. Kunc [18] was able to demonstrate that a cut along the medial aspect of the spinal trigeminal nucleus could achieve analgesia in the distribution of these nerves, sparing most of the trigeminal system. His incision also interrupted nociceptive fibers from the mandibular branch of the trigeminal nerve, however. This helped to demonstrate another layer or organization. Trigeminal fibers enter the subnucleus caudalis from its dorsal and lateral aspects. Mandibular division fibers are positioned dorsally, with maxillary and ophthalmic division axons clustered dorsolaterally and laterally, respectively. Cells in the subnucleus caudalis then form the trigeminothalamic tract (TTT).

The STT and the TTT project primarily to the contralateral sensory thalamus. This is the ventrocaudal nucleus (V_c) of Hassler's nomenclature or the ventroposterior nucleus (VP) of the Anglo-American system. Once again, a definite somatotopic organization is present. Fibers from the legs and lower body project to the more lateral thalamus (VPL), whereas the trigeminal system sends axons to synapse in the more medial regions of the nucleus (VPM). Distal parts of the limbs are represented more ventrally within the nuclei, whereas inputs from the trunk and other central regions terminate more dorsally [19]. The thalamus then sends wide projections to the cerebral cortex.

Most of the STT projection cells originate in laminae I and V of the dorsal horn. Smaller contributions come from laminae VII and IX. Their axons then cross ventral to the central canal on their way to the contralateral ventrolateral region [20]. The decussation may occur either at the corresponding spinal level or one or two segments higher. This helps to account for the discrepancy between sensory level and injury level observed in spinal cord injury patients. Somatotopy is maintained within the spinothalamic tract. The first fibers to form the tract, those from the lumbosacral region, lie dorsolaterally. Fibers from successively more cranial levels then lie progressively more ventral and medial [11].

Some of the axons from lamina I as well as those from laminae VII and IX project to sites outside the ventrocaudal thalamus [19,21]. Known as the paleospinothalamic tract, these axons synapse in the brain stem reticular formation, hypothalamus, or other thalamic nuclei. Many of the axons originating outside lamina I come from WDR cells, which tend to have a higher conduction velocity than the axons from lamina I nociceptive cells. These cells not only respond to a wide range of stimuli but have larger receptive fields than nociceptive cells. It is believed that the smaller fields of the nociceptive cells aid in pain localization and discrimination. The WDR cells may play the integrative role of the "T" cells in Melzack and Wall's original description of the gate control theory [1]. In their model, the T, or transmission, cells are the convergence point of signals from multiple peripheral afferents. These cells were depicted as being able to handle numerous types of sensory input. The signal transmitted depended on the status of the pain gate. The broader characteristics of the WDR cells are believed to be involved in the affective component of pain; hence, their projection to the reticular formation, periaqueductal gray (PAG), and medial thalamic nuclei, sites that have been implicated in modulating this [22].

Other thalamic nuclei are involved in pain processing. The intralaminar nuclei, such as the nuclei parafascicularis (Pf), centrum medianum (CM), centralis medialis, and centralis lateralis, as well as the nucleus medius dorsalis (MD) all receive higher order nociceptive inputs either directly from the STT or (more commonly) by

way of other thalamic nuclei or the brain stem nuclei [21,23–26]. These sites have served as targets for neurosurgeons treating intractable pain [27]. Antinociception may be evoked by stimulation [27] or infusion of opioids [24,28,29] into these areas.

There are many other targets for nociceptive projection axons [21]. These include the midbrain reticular formation, colliculi, hypothalamus, basal ganglia, amygdala, and limbic system. Functional imaging has disclosed activation of an extensive list of supraspinal structures in response to pain, including the medullary reticular formation; locus ceruleus; lateral parabrachial region; anterior pretectal nucleus; medial, lateral, and posterior thalamic regions; basal ganglia; and parietal, cingulate, frontal, insular. and orbital cortices [30].

The thalamus projects to the somatosensory cortex. The primary somatosensory cortex (SI, Brodmann's areas $3_{a/b}$, 2, and 1) corresponds to the postcentral gyrus and the neighboring sulci [31]. The secondary somatosensory cortex (SII) is located just posterior to SI on the medial hemisphere. Resection of the SI cortex has been attempted for control of pain without long-term success [21]. Most nociceptive afferents terminate in cortical layers III and IV [32]. The ventrobasal thalamus projects cutaneous sensation primarily to areas 3_b and 1. It has been demonstrated that anticipation of painful stimuli can lead to activation of the sensory cortex [33]. Both SI and SII cortices receive nociceptive input from the thalamus. The SI cortex is basically arranged in Penfield's classic homuncular pattern, although variations in fine organization exist. The lower extremities are represented on the medial aspect of the gyrus and even into the interhemispheric fissure. Regions like the hand and face (especially the lips) have an especially generous cortical representation. The SII cortex also is arranged somatotopically and receives some amount of bilateral input. The homunculus is reversed, however, with the face areas for SI and SII aligned [31]. Pain seems to be processed sequentially by the SI and SII cortices [34].

The insula has also been found to play a role in the higher order processing of pain. Painful stimulation can activate the insula, as seen on functional MRI (fMRI) [35]. Moreover, this effect may be noted bilaterally [36,37]. Interestingly, these pathways seem to require that a certain level of consciousness be present for them to be used. Laureys et al [38] reported that areas like the insula, SII, and cingulate cortices showed no activity when patients in a vegetative state were given a painful stimulus. The strength of insular activation is related to the magnitude of the stimulus [39]. Although some have localized insular activation to the posterior insula [40], it is clear that the anterior insula plays an important role as well [37,41,42]. In fact, Maihofner et al [43] demonstrated that the sensation of cold pain may completely bypass the SI cortex and be primarily processed in the posterior insula.

The cingulate cortex is also activated by painful sensations [41,44,45]. This region receives input from the intralaminar and medial thalamus. It is most likely responsible for the affective and motivational aspects of pain. This is partly indicated by studies [46] showing that second pain leads to anterior cingulate activation, whereas first pain only activates the SI cortex. Moreover, distracting a subject during the application of a painful stimulus attenuates the anterior cingulate activation [47]. Hofbauer et al [48] used hypnosis in an attempt to dissociate the affective and nociceptive components of pain while investigating the cortical representation of each. Although their effort was only partially successful, they did demonstrate decreases in anterior cingulate activity when the affective component was modulated. Hsieh et al [37] noted that the right anterior cingulate seemed to be dominant in that it was activated by both ipsilateral and contralateral stimulation.

Physiology of pain

A variety of peripheral nociceptors have been described [10,11,49]. These include mechanical nociceptors, heat nociceptors, mechanoheat nociceptors, and cold nociceptors. The majority of Aδ fibers are associated with mechanical or heat nociceptors. Although many sensory receptors are specific to one type of stimulus, a group of polymodal receptors exists that respond to a variety of stimuli, including neurotransmitters, neuropeptides, ions, steroids, amines, amino acids, and growth factors. Many polymodal receptors are C fibers that serve to maintain tissue homeostasis by monitoring the overall tissue environment.

For any stimulus to be converted into an action potential for transmission centrally, it must exceed a certain threshold. Many sensory receptors produce graded receptor potentials in response to stimuli of progressively increasing strength. Until that receptor potential results in

depolarization sufficient to cross the threshold level, however, no action potential is generated. In addition to the action potential threshold, some receptors have another threshold for generating repetitive action potentials.

Peripheral sensitization

Sensitization is the process by which the action potential threshold is shifted toward less intense stimuli. Peripheral sensitization may be the result of a variety of factors. Chemical mediators released during the inflammatory response, such as serotonin, histamine, bradykinins, capsaicin, glutamate, prostaglandins, and other cytokines (eg, tumor necrosis factors), may play an important role in establishing and maintaining a sensitized state. Macrophages, polymorphonuclear (PMN) leukocytes, fibroblasts, and other neurons all play a role in modulating receptor activity. A substantial proportion of nociceptors are only activated when sensitized during inflammatory states. These are not active during other states, even in the presence of strong stimuli.

Alteration in the conduction velocity and action potential duration of C and Aδ fibers may occur with prolonged tissue inflammation. Of importance to the genesis of neuropathic pain, Aβ fibers may also be sensitized by inflammatory mediators. Moreover, repetitive stimulation from ongoing injury may also result in sensitization. Peripheral sensitization is manifested clinically as hyperalgesia, an increased response to a suprathreshold noxious stimulus.

Compounds released during inflammation only alter the stimulus threshold for receptor firing. Nevertheless, injury to tissue, and thus nociceptors or free nerve endings, may evoke aberrant electric activity in nerve fibers that is perceived as pain. This is "atypical" pain, which may be referred to as neuropathic or nerve damage pain. It does not respond well to narcotic medications and is often described by patients as "burning" or "searing." Injured nerves not only develop abnormal hyperexcitability at their terminals but at previously inactive sites along the axon.

Nerve injury results in the sprouting of new terminals as part of the process of peripheral nerve regeneration. These new extensions may be hyperexcitable and exhibit ectopic electric discharges, however. Neuromas are one clinical manifestation of this process. When a neuroma has arisen at the site of a previous peripheral nerve injury, it is frequently possible to evoke paresthesias (Tinel's sign) by tapping the skin over the neuroma. When only paresthesias result, it is likely that only large Aβ fibers are involved. Stinging, shooting, burning, and aching sensations may signal the involvement of Aδ and C fibers as well, however.

England et al [50] reported that neuromas may have as many as 50% more sodium channels than normal peripheral nerve. Importantly, sodium channels were clustered at nodes of Ranvier in normal nerve, whereas injured nerves were shown to have frequently lost their myelin sheath and to have multiple dense patches of sodium channel accumulation along the axon. Accumulation was especially noted at the regenerating neurite tips. Matzner and Devor [51] selectively blocked sodium, potassium, and calcium channels in a neuroma model. Only blockade of voltage-gated sodium channels with lidocaine and tetrodotoxin (TTX) reduced neuroma firing. Moreover, impulse initiation was reduced significantly more than impulse propagation. The beneficial effects on neuropathic pain of sodium channel–blocking anticonvulsants, such as phenytoin and carbamazepine, provide further evidence of the importance of these channels in the pathophysiology of chronic pain.

Even with an excess of voltage-gated sodium channels, an adequate stimulus must be present to depolarize the cell membrane enough to open the gate and initiate an inward ion flux. The significantly reduced thresholds of injured and regenerating fibers to mechanical, thermal, and chemical irritants are likely a result of the accumulation of various other types of transmembrane channels and receptors at the fiber terminal, site of injury, or demyelinated region. The transmembrane channels present in the receptor terminal of any normal sensory fiber are synthesized in the cell soma in the DRG and then transported down the axon to the terminal receptor. Injury to the nerve (excluding the cell soma) does not necessarily slow this process. As a result, these products accumulate at the site of axotomy or demyelination. Studies show that neuromas and other damaged sensory fibers respond to the same stimuli as the undamaged nerve but at altered thresholds [52,53].

Neurotrophic growth factors have also been implicated in peripheral pain transmission and sensitization [54]. NGF, primarily produced by local fibroblasts, is a powerful neural survival factor early in development for a large group of neural subtypes, only a portion of which retain

this dependence at maturity (eg, sympathetic neurons). Specifically, sensory neurons deprived of NGF during development do not survive. This includes those neurons containing substance P, a neuromodulatory peptide important in pain transmission.

Lewin's group [54–56] was instrumental in demonstrating the differential effects of NGF on pain behavior and nociceptor physiology in the neonatal, juvenile, and adult rat. They found dissociation between NGF-induced behavioral hyperalgesia and mechanical hyperalgesia as a result of peripheral sensitization of Aδ fibers. Systemic administration of NGF resulted in both behavioral and mechanical hyperalgesia in neonatal animals but only in behavioral effects in juvenile animals. Interestingly, although adult animals also developed both behavioral and mechanical phenomena, there was no mechanical hypersensitivity. This led the investigators to postulate a central mechanism for the actions of NGF in adults. Others [16] have reported that anti-NGF serum can block the increases in substance P and CGRP in the DRG usually evoked by tissue inflammation. Studies of various cells types involved in peripheral injury revealed that primary afferents and mast cells seem to mediate the effects of NGF in the periphery [57].

Attention has also been recently focused on the role of nitric oxide (NO). Originally labeled endothelial-derived relaxing factor (EDRF), this diffusible gas has been found to play multiple physiologic roles through its interaction with the guanyl cyclase second-messenger pathway. One report [58] demonstrated that endogenously as well as exogenously administered NO results in hyperalgesia, albeit via different pathways. In these experiments, endogenous NO seemed to contribute to hyperalgesia induced by prostaglandin (PG) E2 via a cyclic adenosine monophosphate (cAMP)-dependent mechanism that was independent of guanyl cyclase. This pathway was used to the same effect by exogenously administered NO. NO synthase (NOS) has been found to be upregulated in DRG after injury, and blockade of NOS inhibits neuroma-induced hyperalgesia [59]. Further evidence for the peripheral effects of NO comes from successful trials of topical NO donors as adjuvants for analgesia [60,61]. It is most likely true that release of NO by fibroblasts or vascular endothelium after tissue injury also facilitates local blood flow and healing. Thus, the hyperalgesic actions of NO may serve a protective function.

Injury also induces peripheral nociceptive fibers to increase the number of α-adrenergic receptors present. Chen et al [62] noted that α_2-adrenergic receptors were responsible for sympathetically mediated excitation in 65% of fibers that ended in neuromas. Moreover, sympathetic terminals may release substances (noradrenaline, PGE2, and PGI2) in the presence of inflammation that aid in establishing and maintaining peripheral sensitization [63]. Devor et al [64] found that sympathetic innervation of the DRG augmented abnormal activity in a majority of axotomized sciatic nerve fibers. Others [57] have produced evidence that sympathetic effects are not mediated by NGF.

Central sensitization

Pain-related changes in the peripheral nervous system can have profound central effects. Ongoing tissue damage or inflammation as well as nerve injury results in both short- and long-term changes in the central nervous system (CNS). Some of the pathways modulating these physiologic alterations have only recently been elucidated and remain the subject of much study. Clinical observations provided much of the impetus for looking to the CNS for explanations of chronic pain states. The existence of both primary and secondary hyperalgesia has long been known. Primary hyperalgesia refers to the decreased pain threshold in the area of injury. Although this appeared logical, secondary hyperalgesia, which occurs outside the original area of injury and outside the inflammatory flare region, defied definitive explanation. In addition, chronic pain states are often characterized by the development of allodynia, the misinterpretation of a nonpainful stimulus as painful. Central mechanisms can account for both of these phenomena.

Using a double thermal injury model, Raja et al [65] found that the areas of primary and secondary hyperalgesia had different response characteristics. Although the area of primary hyperalgesia displayed sensitivity to both heat and mechanical stimuli, only secondary hyperalgesia to mechanical stimuli was present. Moreover, thermal hypalgesia existed in the region between the two burns. A later report by the same group [66] found that selective blockade of C and Aδ fibers did not abolish hyperalgesia in patients with neuropathic pain. Selectively blocking Aβ fibers did serve to relieve the pain, however. This was evidence that signals from nonnociceptive

afferents could mediate chronic pain states, most likely via a central mechanism. Other investigators have published work that supports this [2,67].

Woolf [68] and others [69] found that nociceptor cutaneous receptive fields expanded in response to thermal injury in a decerebrate animal. Moreover, some of the peripheral receptors became responsive to bilateral stimulation, evidence that spinal mechanisms were involved. Other animal models have demonstrated that continued C-fiber activity can lead to a state of central excitability [70–72]. Further anatomic studies [73–75] showed that axotomy leads to substantial alterations in dorsal horn connectivity. A-fiber efferents expanded their terminal arborizations from lamina III up into lamina II, the location of most C-nociceptor terminals. Measurement of conduction velocity verified that the sprouting efferents were Aβ fibers rather than Aδ fibers.

Devor and Wall [76,77] had already demonstrated that peripheral nerve sectioning causes reorganization in the dorsal horn, with dorsal horn cells responding to new receptive fields after loss of the natural field. Further in vitro [78,79] and in vivo [78–80] studies revealed that depolarization of DRG afferents leads to the cross-excitation of neighboring neurons without obvious electric connection between the cells. Moreover, cross-depolarization resulted in a lowering of the firing threshold. A concurrent increase in membrane conductance was noted, presumably as the result of a diffusible chemical mediator. It was believed that this observation could help to explain not only the expansion of cutaneous receptive fields but allodynia, in part. This mechanism may also play a role in the "lightening pains" of trigeminal neuralgia [49].

Stimulation of the Aβ fibers in the dorsal columns is at the heart of the gate control theory and forms the basis of transcutaneous electrical nerve stimulation (TENS) and epidural spinal cord stimulation as therapies for pain. These modalities produce pain relief that is not reversible by the administration of naloxone at certain settings [12]. According to Melzack and Wall [1], activation of large myelinated afferents "closes the pain gate" in the substantia gelatinosa by enhancing the inhibitory actions of local circuit neurons in the dorsal horn on central transmission cells. They postulate that pain states are maintained by the continuous firing of unmyelinated and small myelinated efferents. A proportionately greater increase in the activation of large myelinated afferents serves to close the gate via presynaptic inhibition. This theory has held up for several decades with only empiric evidence to support it and a lack of competing theories with the experimental weight to refute it.

Molecular techniques have allowed further explanation of initiation and maintenance of chronic pain. Much of the work focuses on the central role of glutamate [81]. Glutamate is the primary excitatory neurotransmitter in the dorsal horn. Several ionotropic glutamate receptors have been cloned and named for their selective ligands, including kainate, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA), and *N*-methyl-D-aspartate (NMDA). The kainate and AMPA subtypes are stereotypic ligand-gated ion channels. Binding of a ligand (glutamate) to the extracellular binding site produces a conformational change in the receptor, allowing ions (primarily sodium) to flow down their concentration gradient into the postsynaptic terminal, thereby depolarizing the postsynaptic cell and possibly leading to action potential generation if the depolarization exceeds threshold. Metabotropic glutamate receptors have also been identified in the dorsal horn [82]. These are coupled to G-protein systems that, in turn, affect the level of phosphorylation of cytosolic proteins via protein kinases.

Although AMPA receptors have been localized to several laminae in the dorsal horn [83], it is the NMDA receptor that has garnered the most attention because of its interesting characteristics. At the cell membrane's resting potential, the ion channel of the NMDA receptor is blocked by a magnesium ion, preventing ion entry into the cell, even in the presence of a receptor agonist [84]. Membrane depolarization can remove the block, however, and allow ions to enter the cell. In addition, the NMDA receptor has another binding site for glycine, which acts as a coagonist. This is of interest, because glycine is traditionally thought of as an inhibitory neurotransmitter. Also of importance is the dual conductance of the NMDA receptor channel. Whereas sodium currents predominate through the other ionotropic glutamate channels, the opening of the NMDA receptor channel also leads to a significant influx of calcium into the cell [85]. It is calcium's significant second-messenger effects that have fueled further detailed investigation of NMDA receptors.

Calcium entry into the cytosol leads to a host of other effects and seems to be the point of intersection for the mechanisms of numerous

substances related to nociception [81]. Phospholipase C (PLC) may be activated either by substance P binding to NK-1 receptors or glutamate binding to metabotropic glutamate receptors. Substance P and glutamate may also act synergistically [86–89]. Activated PLC subsequently catalyzes the hydrolysis of phosphatidylinositol bisphosphate (PIP_2) into diacylglycerol (DAG) and inositol triphosphate (IP_3). DAG then activates protein kinase C (PKC), leading to phosphorylation of other cellular proteins and wide-ranging effects on gene expression and other processes, including the enhancement of calcium currents [90]. In addition, IP_3 causes the release of calcium from intracellular stores, such as the endoplasmic reticulum. These effects can entrain a positive feedback loop whereby more calcium enters the cell and the calcium-dependent processes are further activated [91,92]. This may be important in the development of "wind-up," the progressive increase in response that comes with repetitive C-nociceptor stimulation in neuropathic pain states. Wind-up may be prevented by NMDA receptor antagonists [93–97]. Moreover, once central sensitization has been induced by repetitive stimulation, NMDA receptor blockade may be able to return the spinal cord to its original state [95,98]. These agents also may block the expansion of nociceptor receptive fields induced by inflammation [99]. In addition, calcium entry may induce NOS. As previously stated, NO may be associated with hyperalgesia [100]. Excessive calcium entry into cells leads to excitotoxic cell damage.

Increased cellular calcium levels brought about by the combined actions of excitatory amino acids, substance P, and CGRP lead to activation of transcription factors and an increase in expression of certain genes. One in particular, the proto-oncogene *c-fos*, is significantly upregulated in dorsal horn cells in response to substance P and glutamate. The NMDA receptor-related increase in *c-fos* expression is not limited to the spinal cord [101,102]. The product of *c-fos*, Fos, then acts as a transcription factor to induce the expression of endogenous opioid peptides, such as preprodynorphin and preproenkephalin [103]. NMDA antagonists have been shown to decrease Fos expression [104,105]. Although there is a resulting increase in dynorphin levels, there is no subsequent increase in enkephalin levels. The expression of Fos with either preprodynorphin or preproenkephalin is highly related [99]. Dynorphin has been associated with the production of expanded receptive fields and facilitation of responses in a percentage of dorsal horn cells at low doses [106]. An ongoing nociceptive barrage would be expected to sustain and propagate this process, with the corelease of excitatory amino acids and peptides having rapid effects via AMPA receptors and delayed sustained effects through NMDA and metabotropic receptors leading to chronic pain states.

Although these alterations in gene expression at the central level would seem to be able to maintain central sensitization independent of peripheral input, there remains some debate as to whether continued peripheral input is required to perpetuate these central changes. Gracely et al [107] have argued that continued nociceptive input is necessary. They point to the disappearance of allodynia after applying a local anesthetic block to a separate discrete painful focus. Once the short-term local block wore off, the allodynia returned. This effect was not observed with intravenous anesthetic infusions or local blocks of other regions in the painful area. Other studies [70,95] have also shown that although allodynia may persist after the nociceptive component has been blocked, the central hypersensitivity does return to normal over time.

Large amounts of attention have been focused on testing this theory by using pre-emptive analgesia, anesthetizing an area before the application of a painful stimulus. It is hoped that by preventing the afferent barrage from reaching the dorsal horn, the myriad of changes described previously can be prevented. Excellent reviews of the numerous studies are available [108,109]. Patients who received preoperative analgesia, whether by means of local infiltration or epidural or intravenous administration, generally had a lower opioid requirement in the postoperative period. Some of the most interesting results have come from studies of phantom limb pain. Several studies of patients undergoing amputation have found that preoperative analgesic blockade of the painful limb can significantly reduce the postoperative development of phantom limb sensation and pain [110–112]. In addition, some investigators [113] have reported that those patients with preamputation pain have a higher likelihood of developing phantom limb pain.

Antinociception

The nervous system also maintains a complex system for damping nociceptive inputs. This

involves local systems in the spinal cord as well as descending supraspinal inputs. The neurotransmitters involved in this process include the endogenous opioids, gamma-aminobutyric acid (GABA), and other neuropeptides, such as neuropeptide FF, galanin, and neuropeptide Y [12].

The primary inhibitory neurotransmitter in the CNS is GABA. It exerts a potent inhibitory effect throughout the CNS via two major receptors, $GABA_a$ and $GABA_b$. The $GABA_a$ receptor is a ligand-gated chloride channel. Activation of the receptor initiates a flow of negatively charged chloride ions into the cell down their concentration gradient. This hyperpolarizes the postsynaptic cell and reduces the probability of it firing an action potential. This receptor plays several important roles in that it has binding sites not just for GABA but for benzodiazepines and barbiturates. It is believed that ethanol exerts part of its effects on the CNS via this receptor [114]. The $GABA_b$ receptor is a metabotropic receptor coupled to intracellular G-protein systems. Activation of this receptor by ligands like baclofen leads to inhibition of excitatory calcium and activation of inhibitory potassium currents. In fact, GABA receptor agonists have been shown to reduce allodynia in experimental models [115,116].

An interesting phenomenon is that of primary afferent depolarization (PAD) [12]. Some primary afferents maintain high intracellular chloride concentrations via active transport into the cell. Ligand binding to $GABA_a$ receptors then results in an outward flow of chloride, thus depolarizing the cell. Activation of this type has been hypothesized to play a role in presynaptic inhibition of neurotransmitters like substance P.

The endogenous opioid system and opioid receptors play an important role in antinociception as well. Three main types of opioid receptors have been identified, each with its own subtypes. The primary type, μ, makes up 70% of spinal opioid receptors [12]. This receptor has the highest affinity for morphine and is responsible for mediating not only the analgesic effects of morphine (via μ_1 receptors) but its respiratory depressant effects (via μ_2) [117,118]. The κ-receptor is the target of dynorphin and makes up about 6% of spinal opioid receptors. The δ-receptors bind the enkephalins with high affinity and represent about 24% of the spinal opioid receptor population.

Opioid receptors are another family of metabotropic G-protein–coupled receptors. Like the GABA receptors, they may alter the membrane conductances for inhibitory and excitatory ion currents. They may also affect the activity of PKA, leading to changes in the phosphorylation state of intracellular proteins. A host of other protein kinases have also been implicated in mediating opioid effects, including PKC, MAP kinase, and calmodulin-dependent kinase (CamK) [12]. Hori et al [119] showed that the inhibitory effects of μ-opioid agonists were likely mediated by reducing presynaptic calcium entry and neurotransmitter release from the presynaptic terminal. Postsynaptic mechanisms have also been identified, however [120]. An interesting interaction between NMDA and opioid receptors has been elucidated. Ligand binding to NMDA receptors leads to activation of PKC. This enzyme phosphorylates opioid receptors, thus inactivating them and leading to the development of opioid insensitivity or tolerance [121]. This may aid in explaining why the effects of central sensitization, such as allodynia, are so poorly responsive to opioid medications. The ability of NMDA receptor antagonists to block opioid tolerance has been demonstrated in multiple studies [122–125]. NMDA receptor antagonists may thus play a dual role in preventing opioid tolerance as well as excitotoxic damage and central sensitization.

As previously mentioned, the endogenous opioid dynorphin plays a key role in the centralization of pain. Dynorphin is cleaved from proenkephalin-B and is plentiful in the dorsal horn, primarily in laminae I and V, the origination sites for thalamic projection neurons [12]. Pain modulation sites in the brain stem, such as the PAG and the midbrain reticular formation, are also plentiful in dynorphin [126,127]. Inflammation can cause a large increase in dynorphin synthesis [128,129] that is not accompanied by a downregulation in the number of opioid receptors [130].

Neuropeptide FF is an eight–amino acid peptide found in laminae I and II of the dorsal horn [131]. The mechanism of action for this peptide's effects is not known, but it has a complex interaction with the opioid system [132]. Direct infusion may antagonize opioid analgesia indirectly, because neuropeptide FF has no significant affinity for opioid receptors [133–135]. Intrathecal administration can actually lead to antinociceptive effects, however [132,133].

Neuropeptide Y acts primarily in the superficial dorsal horn via a G-protein–coupled system. It also has both pro- and antinociceptive effects

[136,137] and may be colocalized with GABA in dorsal horn neurons [138]. Neurotensin is another small (13–amino acid) peptide found in neurons in laminae I and II of the dorsal horn. It is believed to exert antinociceptive effects by activating inhibitory interneurons [12].

In addition to NGF, brain-derived neurotrophic factor (BDNF) has been studied for its role in central sensitization. BDNF has been extensively investigated as a factor for inducing neural stem cells to proceed toward a neuronal rather than glial fate [139–142]. BDNF expression in the dorsal horn is increased after nerve injury [143,144], and inducing a state of BDNF overexpression can attenuate hyperalgesia and allodynia [145]. Although infusion of BDNF into the PAG and nucleus raphe magnus (NRM) leads to local increases only in β-endorphin, dorsal horn levels of neuropeptide Y, substance P, and β-endorphin are all dramatically elevated [146]. Despite the local increase in substance P, there was the induction of a naloxone-sensitive state of analgesia. In opposition to this, others [147] have demonstrated that intrathecal BDNF can inhibit dorsal horn release of substance P and increase local GABA release. Other recent evidence [148] that anti-BDNF serum can inhibit dorsal horn fiber sprouting in neuropathic pain and that antibodies to BDNF can block the development of thermal hyperalgesia [149] shows that BDNF's effects are most likely complex.

Supraspinal and descending systems

The existence of powerful endogenous descending antinociceptive systems was dramatically demonstrated in 1969 by Reynolds [150], who was able to perform animal surgery with analgesia provided only by stimulation of the periaqueductal region of the midbrain. Since then, this system has been extensively studied and remains a therapeutic target for deep brain stimulation for intractable pain. The two major supraspinal sites mediating antinociception are the midbrain PAG and the NRM of the rostral ventral medulla (RVM).

The PAG has been shown to have a complex set of interactions with other systems besides nociception. Stimulation of the PAG evokes both behavioral and autonomic effects in addition to antinociception. Bandler et al. [151,152] delineated two distinct cell divisions within the PAG in rats. Stimulation of the lateral column leads to behavioral responses associated with antinociception, such as tachycardia and defense behaviors. Stimulation in the ventrolateral column leads to depressor effects such as inactivity, bradycardia, and hypotension. The PAG receives input from multiple limbic structures, including the hypothalamus, insula, and amygdala [12]. Its principal descending target is the NRM, leading to speculation that the NRM is the actual mediator for the antinociceptive effects of PAG stimulation [151]. Its direct connection to the dorsal horn is considered to be of lesser importance [151].

Opioids may act directly on the PAG to cause descending inhibition of dorsal horn cells. Budai and his colleagues [153,154] reported that direct stimulation of PAG μ-opioid receptors reduced dorsal horn cell firing in response to noxious stimuli by almost two thirds. In addition, this effect may be mediated in the dorsal horn via both presynaptic and postsynaptic α_2-adrenergic receptors. In these studies, the PAG was activated using bicuculline, a $GABA_a$ antagonist, giving rise to the concept that activation of the PAG may represent blocking of inhibition. Other studies have shown similar effects [155]. The PAG is known to have cells containing endogenous opioids, and these compounds are believed to exert their influence by causing antinociceptive neurons to be released from tonic inhibition [12,155,156]. This inhibition of transmitter release is mediated by opioid-induced changes in presynaptic potassium conductance [157]. Interestingly, these opioid mechanisms are potentiated by cyclooxygenase inhibitors, helping to explain some of the beneficial effects of combination analgesic preparations.

In contrast to the PAG, the NRM has diffuse projections to the dorsal horn laminae, including laminae I, II_o, IV, and V. When injected into the NRM, opioids can cause antinociceptive effects [158,159]. These actions are modulated by serotonergic and noradrenergic systems [160] and are not always sensitive to naloxone. Electric or chemical manipulation of the NRM causes increased release of noradrenaline and serotonin in the spinal cord [161]. Evidence for the presence of both inhibitory and facilitatory systems mediating antinociception is provided by studies of the NRM, which demonstrate several distinct populations of cells [162]. "Off cells" usually fire spontaneously but exhibit a characteristic pause in firing just at the onset of the antinociceptive reflexes [12,151,163]. At the initiation of the reflexes, a second class of cells, "on cells," shows increased activity. Opioids inhibit the pain-related

inhibition of off-cells [164]. Interestingly, there is a growing body of evidence demonstrating that this effect is mediated by excitatory amino acids and the NMDA receptor [165,166].

Studies of spinal serotonergic influences from the NRM have demonstrated an extensive network of serotonin-reactive processes in contact with neurons in the dorsal horn, especially in laminae I and IV [12,167]. Serotonin antagonists can reverse stimulation-induced analgesia in animals [160] that is not sensitive to naloxone, suggesting that serotonin's effects are not mediated by endogenous opioids. In addition, mice lacking serotonin reuptake transporters do not develop thermal hyperalgesia after nerve injury, even though allodynia is present [168]. Fluoxetine, an inhibitor of serotonin reuptake, also potentiates the antinociceptive effect of serotonin [169]. Serotonin infusion may accelerate the development of tolerance to opioids, an effect that may be attenuated by spinal serotonin depletion [170]. Intrathecal serotonin has been demonstrated to be effective only in certain models of local pain, however, and not in models of generalized pain [171]. Of the numerous subtypes of serotonin receptors identified, the 5-HT_3 receptors are the most likely mediators of these effects [172].

The PAG and NRM have projections to the noradrenergic system, including the nucleus subceruleus (cell group A7) [151,173–175]. These sites in the lateral pons then send diffuse projections to the ipsilateral dorsal horn [176,177]. It has been previously stated that norepinephrine is released from the spinal cord after NRM stimulation [161]. Blocking the adrenergic system leads to a reduction in opioid analgesia or the production of hyperalgesia [160,178]. Lesions of the NRM have been shown to decrease nociceptive thresholds without an effect on norepinephrine systems, demonstrating some independence between the monoaminergic projections [179]. This is not complete, however, because the administration of adrenergic blockers into the NRM has the ability to increase both serotonin and norepinephrine release in the spinal cord [180]. The spinal effects appear to be mediated by α_2-adrenergic receptors [178]. Substance P may serve as an excitatory neuromodulator for the NRM-A7 interactions [177,181].

Supraspinal plasticity

Given all the aforementioned physiologic changes at the peripheral and spinal levels accompanying chronic pain, it is logical to look at the changes in higher order structures. Kiss et al [182] and Gorecki et al [183] have demonstrated an increase in the thalamic representation of somatic regions adjacent to the denervated area in patients with deafferentation. Several animal studies have noted that cortical reorganization takes place after amputation, with the adjacent digits gaining cortical representation [184,185]. Moreover, this process can continue for extended periods of time [186] and involve shifts of greater than 10 mm in animals and greater than 30 mm in human beings [113] for various cortical representations. In fact, in some deafferented animals, the cortical representation for the deafferented area is eventually totally eliminated [186]. The shift seems to be greater in those patients with pain after deafferentation [113]. Amputees often incorrectly localize painful sensations to the phantom limb, including stimuli contralateral to the phantom limb [187,188]. It may be true that nociceptive input drives cortical reorganization in that the degree of rearrangement is directly correlated with the frequency with which a patient mislocalizes painful stimuli [188] and that pain relief can attenuate reorganization [189,190]. It may occur rapidly enough that even intense acute pain evokes some reorganization, even if only temporarily [191].

References

[1] Melzack R, Wall PD. Pain mechanisms: a new theory. Science 1965;150:971–9.
[2] Koltzenburg M, Torebjork HE, Wahren LK. Nociceptor modulated central sensitization causes mechanical hyperalgesia in acute chemogenic and chronic neuropathic pain. Brain 1994;117:579–91.
[3] Battaglia G, Rustioni A. Coexistence of glutamate and substance P in dorsal root ganglion neurons of the rat and monkey. J Comp Neurol 1988; 277:302–12.
[4] De Biasi S, Rustioni A. Glutamate and substance P coexist in primary afferent terminals in the superficial laminae of spinal cord. Proc Natl Acad Sci USA 1988;85:7820–4.
[5] Emson PC, Cuello AC, Paxinos G, et al. The origin of substance P and acetylcholine projections to the ventral tegmental area and interpeduncular nucleus in the rat. Acta Physiol Scand Suppl 1977;452:43–6.
[6] Jessell TM, Iversen LL. Opiate analgesics inhibit substance P release from rat trigeminal nucleus. Nature 1977;268:549–51.
[7] Aicher SA, Sharma S, Cheng PY, et al. The N-methyl-D-aspartate (NMDA) receptor is postsynaptic to substance P-containing axon terminals in

the rat superficial dorsal horn. Brain Res 1997; 772:71–81.
[8] Rexed B. A cytoarchitectonic atlas of the spinal cord in the cat. J Comp Neurol 1954;100: 297–400.
[9] Rexed B. The cytoarchitectonic organization of the spinal cord in the cat. J Comp Neurol 1952;96: 415–96.
[10] Byers MR, Bonica JJ. Peripheral pain mechanisms and nociceptor plasticity. In: Loeser JD, editor. Bonica's management of pain. 3rd edition. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 26–72.
[11] Carpenter MB. Spinal cord: gross anatomy and internal structure. In: Carpenter MB, editor. Core text of neuroanatomy. Baltimore: Williams & Wilkins; 1991. p. 57–82.
[12] Terman GW, Bonica JJ. Spinal mechanisms and their modulation. In: Loeser JD, editor. Bonica's management of pain. 3rd edition. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 73–152.
[13] Donnerer J, Stein C. Evidence for an increase in the release of CGRP from sensory nerves during inflammation. Ann NY Acad Sci 1992;657: 505–6.
[14] Donnerer J, Amann R. Time course of capsaicin-evoked release of CGRP from rat spinal cord in vitro. Effect of concentration and modulations by ruthenium red. Ann NY Acad Sci 1992;657:491–2.
[15] Donnerer J, Schuligoi R, Amann R. Time-course of capsaicin-evoked release of calcitonin gene-related peptide from rat spinal cord in vitro. Effect of concentration and modulation by Ruthenium Red. Regul Pept 1992;37:27–37.
[16] Donnerer J, Schuligoi R, Stein C. Increased content and transport of substance P and calcitonin gene- related peptide in sensory nerves innervating inflamed tissue: evidence for a regulatory function of nerve growth factor in vivo. Neuroscience 1992;49:693–8.
[17] Dejerine JJ. Semiologie des affections du système nerveux. Paris: Masterson; 1914.
[18] Kunc Z. Significance of fresh anatomic data on spinal trigeminal tract for possibility of selective tractotomies. In: Knighton RS, Dumke PR, editors. Pain. Boston: Little, Brown, and Company; 1996. p. 351–66.
[19] Carpenter MB. The diencephalon. In: Carpenter MB, editor. Core text of neuroanatomy. 4th edition. Baltimore: Williams & Wilkins; 1991. p. 250–97.
[20] Carpenter MB. Tracts of the spinal cord. In: Carpenter MB, editors. Core text of neuroanatomy. Baltimore: Williams & Wilkins; 1991. p. 83–114.
[21] Chudler EH, Bonica JJ. Supraspinal mechanisms of pain and nociception. In: Loeser JD, editor. Bonica's management of pain. 3rd edition. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 153–79.
[22] Willis WD, Westlund KN. Neuroanatomy of the pain system and of the pathways that modulate pain. J Clin Neurophysiol 1997;14:2–31.
[23] Bowsher D, Mallart A, Petit D, et al. A bulbar relay to the centre median. J Neurophysiol 1968; 31:288–300.
[24] Mao J, Price DD, Mayer DJ, et al. Pain-related increases in spinal cord membrane-bound protein kinase C following peripheral nerve injury. Brain Res 1992;588:144–9.
[25] Reyes-Vazquez C, Prieto-Gomez B, Dafny N. Noxious and non-noxious responses in the medial thalamus of the rat. Neurol Res 1989;11:177–80.
[26] Krout KE, Belzer RE, Loewy AD. Brainstem projections to midline and intralaminar thalamic nuclei of the rat. J Comp Neurol 2002;448:53–101.
[27] Richardson DE, Akil H. Pain reduction by electrical brain stimulation in man. Part 1: acute administration in periaqueductal and periventricular sites. J Neurosurg 1977;47:178–83.
[28] Harte SE, Lagman AL, Borszcz GS. Antinociceptive effects of morphine injected into the nucleus parafascicularis thalami of the rat. Brain Res 2000;874:78–86.
[29] Reyes-Vazquez C, Qiao JT, Dafny N. Nociceptive responses in nucleus parafascicularis thalami are modulated by dorsal raphe stimulation and microiontophoretic application of morphine and serotonin. Brain Res Bull 1989;23:405–11.
[30] Porro CA, Cavazzuti M, Baraldi P, et al. CNS pattern of metabolic activity during tonic pain: evidence for modulation by beta-endorphin. Eur J Neurosci 1999;11:874–88.
[31] Carpenter MB. The cerebral cortex. In: Carpenter MB, editor. Core text of neuroanatomy. 4th edition. Baltimore: Williams & Wilkins; 1991. p. 390–433.
[32] Chudler EH, Anton F, Dubner R, et al. Responses of nociceptive SI neurons in monkeys and pain sensation in humans elicited by noxious thermal stimulation: effect of interstimulus interval. J Neurophysiol 1990;63:559–69.
[33] Porro CA, Baraldi P, Pagnoni G, et al. Does anticipation of pain affect cortical nociceptive systems? J Neurosci 2002;22:3206–14.
[34] Tran TD, Inui K, Hoshiyama M, et al. Cerebral activation by the signals ascending through unmyelinated C- fibers in humans: a magnetoencephalographic study. Neuroscience 2002;113: 375–86.
[35] Niddam DM, Yeh TC, Wu YT, et al. Event-related functional MRI study on central representation of acute muscle pain induced by electrical stimulation. Neuroimage 2002;17:1437–50.
[36] Frot M, Mauguiere F. Dual representation of pain in the operculo-insular cortex in humans. Brain 2003;126:438–50.
[37] Hsieh JC, Belfrage M, Stone-Elander S, et al. Central representation of chronic ongoing

neuropathic pain studied by positron emission tomography. Pain 1995;63:225–36.
[38] Laureys S, Faymonville ME, Peigneux P, et al. Cortical processing of noxious somatosensory stimuli in the persistent vegetative state. Neuroimage 2002;17:732–41.
[39] Bornhovd K, Quante M, Glauche V, et al. Painful stimuli evoke different stimulus-response functions in the amygdala, prefrontal, insula and somatosensory cortex: a single-trial fMRI study. Brain 2002;125:1326–36.
[40] Ostrowsky K, Magnin M, Ryvlin P, et al. Representation of pain and somatic sensation in the human insula: a study of responses to direct electrical cortical stimulation. Cereb Cortex 2002; 12:376–85.
[41] Peyron R, Laurent B, Garcia-Larrea L. Functional imaging of brain responses to pain. A review and meta-analysis. Neurophysiol Clin 2000;30: 263–88.
[42] Treede RD, Apkarian AV, Bromm B, et al. Cortical representation of pain: functional characterization of nociceptive areas near the lateral sulcus. Pain 2000;87:113–9.
[43] Maihofner C, Kaltenhauser M, Neundorfer B, et al. Temporo-spatial analysis of cortical activation by phasic innocuous and noxious cold stimuli—a magnetoencephalographic study. Pain 2002;100:281–90.
[44] Rolls ET, O'Doherty J, Kringelbach ML, et al. Representations of pleasant and painful touch in the human orbitofrontal and cingulate cortices. Cereb Cortex 2003;13:308–17.
[45] Schnitzler A, Ploner M. Neurophysiology and functional neuroanatomy of pain perception. J Clin Neurophysiol 2000;17:592–603.
[46] Ploner M, Gross J, Timmermann L, et al. Cortical representation of first and second pain sensation in humans. Proc Natl Acad Sci USA 2002;99: 12444–8.
[47] Frankenstein UN, Richter W, McIntyre MC, et al. Distraction modulates anterior cingulate gyrus activations during the cold pressor test. Neuroimage 2001;14:827–36.
[48] Hofbauer RK, Rainville P, Duncan GH, et al. Cortical representation of the sensory dimension of pain. J Neurophysiol 2001;86:402–11.
[49] Devor M. Neurobiology of normal and pathophysiological pain. In: Aronoff MD, editor. Evaluation and treatment of chronic pain. 3rd edition. Baltimore: Williams & Wilkins; 1999. p. 11–25.
[50] England JD, Happel LT, Kline DG, Gamboni F, Thouron CL, Liu ZP, et al. Sodium channel accumulation in humans with painful neuromas. Neurology 1996;47(1):272–6.
[51] Matzner O, Devor M. Hyperexcitability at sites of nerve injury depends on voltage-sensitive Na+ channels. J Neurophysiol 1994;72:349–59.
[52] Welk E, Leah JD, Zimmermann M. Characteristics of A- and C-fibers ending in a sensory nerve neuroma in the rat. J Neurophysiol 1990;63: 759–66.
[53] Devor M, Keller CH, Ellisman MH. Spontaneous discharge of afferents in a neuroma reflects original receptor tuning. Brain Res 1990;517:245–50.
[54] Lewin GR, Mendell LM. Nerve growth factor and nociception. Trends Neurosci 1993;16:353–9.
[55] Lewin GR, Ritter AM, Mendell LM. Nerve growth factor-induced hyperalgesia in the neonatal and adult rat. J Neurosci 1993;13:2136–48.
[56] Ritter AM, Lewin GR, Mendell LM. Regulation of myelinated nociceptor function by nerve growth factor in neonatal and adult rats. Brain Res Bull 1993;30:245–9.
[57] Woolf CJ, Ma QP, Allchorne A, et al. Peripheral cell types contributing to the hyperalgesic action of nerve growth factor in inflammation. J Neurosci 1996;16:2716–23.
[58] Aley KO, McCarter G, Levine JD. Nitric oxide signaling in pain and nociceptor sensitization in the rat. J Neurosci 1998;18:7008–14.
[59] Wiesenfeld-Hallin Z, Hao JX, Xu XJ, et al. Nitric oxide mediates ongoing discharges in dorsal root ganglion cells after peripheral nerve injury. J Neurophysiol 1993;70:2350–3.
[60] Lauretti GR, Perez MV, Reis MP, et al. Double-blind evaluation of transdermal nitroglycerine as adjuvant to oral morphine for cancer pain management. J Clin Anesth 2002;14:83–6.
[61] Yuen KC, Baker NR, Rayman G. Treatment of chronic painful diabetic neuropathy with isosorbide dinitrate spray: a double-blind placebo-controlled cross-over study. Diabetes Care 2002; 25:1699–703.
[62] Chen Y, Michaelis M, Janig W, et al. Adrenoreceptor subtype mediating sympathetic-sensory coupling in injured sensory neurons. J Neurophysiol 1996;76:3721–30.
[63] Janig W, Levine JD, Michaelis M. Interactions of sympathetic and primary afferent neurons following nerve injury and tissue trauma. Prog Brain Res 1996;113:161–84.
[64] Devor M, Janig W, Michaelis M. Modulation of activity in dorsal root ganglion neurons by sympathetic activation in nerve-injured rats. J Neurophysiol 1994;71:38–47.
[65] Raja SN, Campbell JN, Meyer RA. Evidence for different mechanisms of primary and secondary hyperalgesia following heat injury to the glabrous skin. Brain 1984;107:1179–88.
[66] Campbell JN, Raja SN, Meyer RA, et al. Myelinated afferents signal the hyperalgesia associated with nerve injury. Pain 1988;32:89–94.
[67] Price DD, Long S, Huitt C. Sensory testing of pathophysiological mechanisms of pain in patients with reflex sympathetic dystrophy. Pain 1992; 49:163–73.

[68] Woolf CJ. Evidence for a central component of post-injury pain hypersensitivity. Nature 1983; 306:686–8.
[69] Hylden JL, Nahin RL, Traub RJ, et al. Expansion of receptive fields of spinal lamina I projection neurons in rats with unilateral adjuvant-induced inflammation: the contribution of dorsal horn mechanisms. Pain 1989;37:229–43.
[70] Woolf CJ, Wall PD. Relative effectiveness of C primary afferent fibers of different origins in evoking a prolonged facilitation of the flexor reflex in the rat. J Neurosci 1986;6:1433–42.
[71] Cook AJ, Woolf CJ, Wall PD, et al. Dynamic receptive field plasticity in rat spinal cord dorsal horn following C-primary afferent input. Nature 1987;325:151–3.
[72] Cook AJ, Woolf CJ, Wall PD. Prolonged C-fibre mediated facilitation of the flexion reflex in the rat is not due to changes in afferent terminal or motoneurone excitability. Neurosci Lett 1986;70: 91–6.
[73] Woolf CJ, Shortland P, Coggeshall RE. Peripheral nerve injury triggers central sprouting of myelinated afferents. Nature 1992;355:75–8.
[74] Mannion RJ, Doubell TP, Coggeshall RE, et al. Collateral sprouting of uninjured primary afferent A-fibers into the superficial dorsal horn of the adult rat spinal cord after topical capsaicin treatment to the sciatic nerve. J Neurosci 1996;16: 5189–95.
[75] Markus H, Pomeranz B, Krushelnycky D. Spread of saphenous somatotopic projection map in spinal cord and hypersensitivity of the foot after chronic sciatic denervation in adult rat. Brain Res 1984;296:27–39.
[76] Devor M, Wall PD. Plasticity in the spinal cord sensory map following peripheral nerve injury in rats. J Neurosci 1981;1:679–84.
[77] Devor M, Wall PD. Effect of peripheral nerve injury on receptive fields of cells in the cat spinal cord. J Comp Neurol 1981;199:277–91.
[78] Devor M, Wall PD. Cross-excitation in dorsal root ganglia of nerve-injured and intact rats. J Neurophysiol 1990;64:1733–46.
[79] Amir R, Devor M. Chemically mediated cross-excitation in rat dorsal root ganglia. J Neurosci 1996;16:4733–41.
[80] Utzschneider D, Kocsis J, Devor M. Mutual excitation among dorsal root ganglion neurons in the rat. Neurosci Lett 1992;146:53–6.
[81] Coderre TJ, Katz J, Vaccarino AL, et al. Contribution of central neuroplasticity to pathological pain: review of clinical and experimental evidence. Pain 1993;52:259–85.
[82] Kawai F, Sterling P. AMPA receptor activates a G-protein that suppresses a cGMP-gated current. J Neurosci 1999;19:2954–9.
[83] Willcockson WS, Chung JM, Hori Y, et al. Effects of iontophoretically released amino acids and amines on primate spinothalamic tract cells. J Neurosci 1984;4:732–40.
[84] Mayer ML, Westbrook GL, Guthrie PB. Voltage-dependent block by Mg2+ of NMDA responses in spinal cord neurones. Nature 1984;309:261–3.
[85] Chen N, Murphy TH, Raymond LA. Competitive inhibition of NMDA receptor-mediated currents by extracellular calcium chelators. J Neurophysiol 2000;84:693–7.
[86] Dougherty PM, Willis WD, Enhancement of spinothalamic neuron responses to chemical and mechanical stimuli following combined micro-iontophoretic application of N-methyl-D-aspartic acid and substance P. Pain 1991;47:85–93.
[87] Murase K, Ryu PD, Randic M. Excitatory and inhibitory amino acids and peptide-induced responses in acutely isolated rat spinal dorsal horn neurons. Neurosci Lett 1989;103:56–63.
[88] Randic M, Hecimovic H, Ryu PD, Substance P. modulates glutamate-induced currents in acutely isolated rat spinal dorsal horn neurones. Neurosci Lett 1990;117:74–80.
[89] Dougherty PM, Palecek J, Zorn S, et al. Combined application of excitatory amino acids and substance P produces long-lasting changes in responses of primate spinothalamic tract neurons. Brain Res Brain Res Rev 1993;18:227–46.
[90] DeRiemer SA, Strong JA, Albert KA, et al, Enhancement of calcium current in aplysia neurones by phorbol ester and protein kinase C. Nature 1985;313:313–6.
[91] Chen L, Huang LY. Protein kinase C reduces Mg2+ block of NMDA-receptor channels as a mechanism of modulation. Nature 1992;356: 521–3.
[92] Chen L, Huang LY. Sustained potentiation of NMDA receptor-mediated glutamate responses through activation of protein kinase C by a mu opioid. Neuron 1991;7:319–26.
[93] Davies SN, Lodge D. Evidence for involvement of N-methylaspartate receptors in 'wind-up' of class 2 neurones in the dorsal horn of the rat. Brain Res 1987;424:402–6.
[94] Thompson SW, King AE, Woolf CJ. Activity-dependent changes in rat ventral horn neurons in vitro; summation of prolonged afferent evoked postsynaptic depolarizations produce a d-2-amino-5-phosphonovaleric acid sensitive windup. Eur J Neurosci 1990;2:638–49.
[95] Woolf CJ, Thompson SW. The induction and maintenance of central sensitization is dependent on N-methyl-D-aspartic acid receptor activation; implications for the treatment of post-injury pain hypersensitivity states. Pain 1991;44:293–9.
[96] Dickenson AH, Sullivan AF. Evidence for a role of the NMDA receptor in the frequency dependent potentiation of deep rat dorsal horn nociceptive neurones following C fibre stimulation. Neuropharmacology 1987;26:1235–8.

[97] Dougherty PM, Willis WD. Modification of the responses of primate spinothalamic neurons to mechanical stimulation by excitatory amino acids and an N-methyl-D-aspartate antagonist. Brain Res 1991;542:15–22.
[98] Haley JE, Sullivan AF, Dickenson AH. Evidence for spinal N-methyl-D-aspartate receptor involvement in prolonged chemical nociception in the rat. Brain Res 1990;518:218–26.
[99] Dubner R, Ruda MA. Activity-dependent neuronal plasticity following tissue injury and inflammation. Trends Neurosci 1992;15:96–103.
[100] Grzybicki D, Gebhart GF, Murphy S. Expression of nitric oxide synthase type II in the spinal cord under conditions producing thermal hyperalgesia. J Chem Neuroanat 1996;10:221–9.
[101] Szekely AM, Barbaccia ML, Alho H, et al. In primary cultures of cerebellar granule cells the activation of N-methyl-D-aspartate-sensitive glutamate receptors induces c-fos mRNA expression. Mol Pharmacol 1989;35:401–8.
[102] Lerea LS, Butler LS, McNamara JO. NMDA and non-NMDA receptor-mediated increase of c-fos mRNA in dentate gyrus neurons involves calcium influx via different routes. J Neurosci 1992;12: 2973–81.
[103] Iadarola MJ, Douglass J, Civelli O, et al. Differential activation of spinal cord dynorphin and enkephalin neurons during hyperalgesia: evidence using cDNA hybridization. Brain Res 1988;455:205–12.
[104] Hudspith MJ, Harrisson S, Smith G, et al. Effect of post-injury NMDA antagonist treatment on long-term Fos expression and hyperalgesia in a model of chronic neuropathic pain. Brain Res 1999;822:220–7.
[105] Munglani R, Hudspith MJ, Fleming B, et al. Effect of pre-emptive NMDA antagonist treatment on long-term Fos expression and hyperalgesia in a model of chronic neuropathic pain. Brain Res 1999;822:210–9.
[106] Hylden JL, Nahin RL, Traub RJ, et al. Effects of spinal kappa-opioid receptor agonists on the responsiveness of nociceptive superficial dorsal horn neurons. Pain 1991;44:187–93.
[107] Gracely RH, Lynch SA, Bennett GJ. Painful neuropathy: altered central processing maintained dynamically by peripheral input. Pain 1992;51:175–94.
[108] Niv D, Devor M. Transition from acute to chronic pain. In: Aronoff MD, editor. Evaluation and treatment of chronic pain. 3rd edition. Baltimore: Williams & Wilkins; 1999. p. 27–45.
[109] Collins JG, Kendig JJ, Mason P. Anesthetic actions within the spinal cord: contributions to the state of general anesthesia. Trends Neurosci 1995;18:549–53.
[110] Schug SA, Burrell R, Payne J, et al. Pre-emptive epidural analgesia may prevent phantom limb pain. Reg Anesth 1995;20:256.
[111] Jahangiri M, Jayatunga AP, Bradley JW, et al. Prevention of phantom pain after major lower limb amputation by epidural infusion of diamorphine, clonidine and bupivacaine. Ann R Coll Surg Engl 1994;76:324–6.
[112] Bach S, Noreng MF, Tjellden NU. Phantom limb pain in amputees during the first 12 months following limb amputation, after preoperative lumbar epidural blockade. Pain 1988;33:297–301.
[113] Flor H, Elbert T, Knecht S, et al. Phantom-limb pain as a perceptual correlate of cortical reorganization following arm amputation. Nature 1995; 375:482–4.
[114] Aguayo LG, Peoples RW, Yeh HH, et al. GABA(A) receptors as molecular sites of ethanol action. Direct or indirect actions? Curr Top Med Chem 2002;2:869–85.
[115] Wiesenfeld-Hallin Z, Aldskogius H, Grant G, et al. Central inhibitory dysfunctions: mechanisms and clinical implications. Behav Brain Sci 1997; 20:420–5.
[116] Hwang JH, Yaksh TL. The effect of spinal GABA receptor agonists on tactile allodynia in a surgically-induced neuropathic pain model in the rat. Pain 1997;70:15–22.
[117] Pasternak GW, Childers SR, Snyder SH. Naloxazone, a long-acting opiate antagonist: effects on analgesia in intact animals and on opiate receptor binding in vitro. J Pharmacol Exp Ther 1980;214: 455–62.
[118] Pasternak GW, Childers SR, Snyder SH. Opiate analgesia: evidence for mediation by a subpopulation of opiate receptors. Science 1980;208:514–6.
[119] Hori Y, Endo K, Takahashi T. Presynaptic inhibitory action of enkephalin on excitatory transmission in superficial dorsal horn of rat spinal cord. J Physiol 1992;450:673–85.
[120] Schneider SP, Eckert WA III, Light AR. Opioid-activated postsynaptic, inward rectifying potassium currents in whole cell recordings in substantia gelatinosa neurons. J Neurophysiol 1998;80: 2954–62.
[121] Mayer DJ, Mao J, Price DD. The development of morphine tolerance and dependence is associated with translocation of protein kinase C. Pain 1995;61:365–74.
[122] Mao J, Price DD, Lu J, et al. Antinociceptive tolerance to the mu-opioid agonist DAMGO is dose- dependently reduced by MK-801 in rats. Neurosci Lett 1998;250:193–6.
[123] Mao J, Price DD, Mayer DJ. Mechanisms of hyperalgesia and morphine tolerance: a current view of their possible interactions. Pain 1995; 62:259–74.
[124] Manning BH, Mao J, Frenk H, et al. Continuous co-administration of dextromethorphan or MK-801 with morphine: attenuation of morphine dependence and naloxone-reversible attenuation of morphine tolerance. Pain 1996;67:79–88.

[125] Price DD, Mayer DJ, Mao J, et al. NMDA-receptor antagonists and opioid receptor interactions as related to analgesia and tolerance. J Pain Symptom Manage 2000;19(Suppl):S7–11.
[126] Cruz L, Basbaum AI. Multiple opioid peptides and the modulation of pain: immunohistochemical analysis of dynorphin and enkephalin in the trigeminal nucleus caudalis and spinal cord of the cat. J Comp Neurol 1985;240:331–48.
[127] Basbaum AI, Cruz L, Weber E. Immunoreactive dynorphin B in sacral primary afferent fibers of the cat. J Neurosci 1986;6:127–33.
[128] Draisci G, Iadarola MJ. Temporal analysis of increases in c-fos, preprodynorphin and preproenkephalin mRNAs in rat spinal cord. Brain Res Mol Brain Res 1989;6:31–7.
[129] Draisci G, Kajander KC, Dubner R, et al. Up-regulation of opioid gene expression in spinal cord evoked by experimental nerve injuries and inflammation. Brain Res 1991;560:186–92.
[130] Iadarola MJ, Brady LS, Draisci G, et al. Enhancement of dynorphin gene expression in spinal cord following experimental inflammation: stimulus specificity, behavioral parameters and opioid receptor binding. Pain 1988;35:313–26.
[131] Gouarderes C, Roumy M, Advokat C, et al. Dual localization of neuropeptide FF receptors in the rat dorsal horn. Synapse 2000;35:45–52.
[132] Dupouy V, Zajac JM, Neuropeptide FF. receptors control morphine-induced analgesia in the parafascicular nucleus and the dorsal raphe nucleus. Eur J Pharmacol 1997;330:129–37.
[133] Courteix C, Coudore-Civiale MA, Privat AM, et al. Spinal effect of a neuropeptide FF analogue on hyperalgesia and morphine-induced analgesia in mononeuropathic and diabetic rats. Br J Pharmacol 1999;127:1454–62.
[134] Roumy M, Zajac JM. Neuropeptide FF, pain and analgesia. Eur J Pharmacol 1998;345:1–11.
[135] Dupouy V, Zajac JM. Effects of neuropeptide FF analogs on morphine analgesia in the nucleus raphe dorsalis. Regul Pept 1995;59:349–56.
[136] White DM. Intrathecal neuropeptide Y exacerbates nerve injury-induced mechanical hyperalgesia. Brain Res 1997;750:141–6.
[137] Munglani R, Hudspith MJ, Hunt SP. The therapeutic potential of neuropeptide Y. Analgesic, anxiolytic and antihypertensive. Drugs 1996; 52:371–89.
[138] Rowan S, Todd AJ, Spike RC. Evidence that neuropeptide Y is present in GABAergic neurons in the superficial dorsal horn of the rat spinal cord. Neuroscience 1993;53:537–45.
[139] Louissaint A Jr, Rao S, Leventhal C, et al. Coordinated interaction of neurogenesis and angiogenesis in the adult songbird brain. Neuron 2002;34:945–60.
[140] Benraiss A, Chmielnicki E, Lerner K, et al. Adenoviral brain-derived neurotrophic factor induces both neostriatal and olfactory neuronal recruitment from endogenous progenitor cells in the adult forebrain. J Neurosci 2001;21:6718–31.
[141] Goldman SA. Adult neurogenesis: from canaries to the clinic. J Neurobiol 1998;36:267–86.
[142] Pincus DW, Keyoung HM, Harrison-Restelli C, et al. Fibroblast growth factor-2/brain-derived neurotrophic factor-associated maturation of new neurons generated from adult human subependymal cells. Ann Neurol 1998;43:576–85.
[143] Michael GJ, Averill S, Shortland PJ, et al. Axotomy results in major changes in BDNF expression by dorsal root ganglion cells: BDNF expression in large trkB and trkC cells, in pericellular baskets, and in projections to deep dorsal horn and dorsal column nuclei. Eur J Neurosci 1999;11:3539–51.
[144] Miletic G, Miletic V. Increases in the concentration of brain derived neurotrophic factor in the lumbar spinal dorsal horn are associated with pain behavior following chronic constriction injury in rats. Neurosci Lett 2002;319:137–40.
[145] Eaton MJ, Blits B, Ruitenberg MJ, et al. Amelioration of chronic neuropathic pain after partial nerve injury by adeno-associated viral (AAV) vector-mediated over-expression of BDNF in the rat spinal cord. Gene Ther 2002;9:1387–95.
[146] Siuciak JA, Wong V, Pearsall D, et al. BDNF produces analgesia in the formalin test and modifies neuropeptide levels in rat brain and spinal cord areas associated with nociception. Eur J Neurosci 1995;7:663–70.
[147] Pezet S, Cunningham J, Patel J, et al. BDNF modulates sensory neuron synaptic activity by a facilitation of GABA transmission in the dorsal horn. Mol Cell Neurosci 2002;21:51–62.
[148] Deng YS, Zhong JH, Zhou XF. Effects of endogenous neurotrophins on sympathetic sprouting in the dorsal root ganglia and allodynia following spinal nerve injury. Exp Neurol 2000; 164:344–50.
[149] Yajima Y, Narita M, Matsumoto N, et al. Involvement of a spinal brain-derived neurotrophic factor/full-length TrkB pathway in the development of nerve injury-induced thermal hyperalgesia in mice. Brain Res 2002;958:338–46.
[150] Reynolds DV. Surgery in the rat during electrical analgesia induced by focal brain stimulation. Science 1969;164(878):444–5.
[151] Bandler R, Keay KA. Columnar organization in the midbrain periaqueductal gray and the integration of emotional expression. Prog Brain Res 1996;107:285–300.
[152] Bandler R, Shipley MT. Columnar organization in the midbrain periaqueductal gray: modules for emotional expression? Trends Neurosci 1994;17: 379–89.
[153] Budai D, Fields HL. Endogenous opioid peptides acting at mu-opioid receptors in the dorsal

horn contribute to midbrain modulation of spinal nociceptive neurons. J Neurophysiol 1998; 79:677–87.
[154] Budai D, Harasawa I, Fields HL. Midbrain periaqueductal gray (PAG) inhibits nociceptive inputs to sacral dorsal horn nociceptive neurons through alpha2-adrenergic receptors. J Neurophysiol 1998;80:2244–54.
[155] Depaulis A, Morgan MM, Liebeskind JC. GABAergic modulation of the analgesic effects of morphine microinjected in the ventral periaqueductal gray matter of the rat. Brain Res 1987; 436:223–8.
[156] Vaughan CW, Christie MJ. Presynaptic inhibitory action of opioids on synaptic transmission in the rat periaqueductal grey in vitro. J Physiol 1997; 498:463–72.
[157] Vaughan CW, Ingram SL, Connor MA, et al. How opioids inhibit GABA-mediated neurotransmission. Nature 1997;390:611–4.
[158] Jensen TS, Yaksh TL. Comparison of antinociceptive action of morphine in the periaqueductal gray, medial and paramedial medulla in rat. Brain Res 1986;363:99–113.
[159] Yaksh TL, Plant RL, Rudy TA. Studies on the antagonism by raphe lesions of the antinociceptive action of systemic morphine. Eur J Pharmacol 1977;41:399–408.
[160] Hammond DL, Yaksh TL. Antagonism of stimulation-produced antinociception by intrathecal administration of methysergide or phentolamine. Brain Res 1984;298:329–37.
[161] Hammond DL, Tyce GM, Yaksh TL. Efflux of 5-hydroxytryptamine and noradrenaline into spinal cord superfusates during stimulation of the rat medulla. J Physiol 1985;359:151–62.
[162] Fields HL, Heinricher MM. Anatomy and physiology of a nociceptive modulatory system. Philos Trans R Soc Lond B Biol Sci 1985;308:361–74.
[163] Barbaro NM, Heinricher MM, Fields HL. Putative pain modulating neurons in the rostral ventral medulla: reflex- related activity predicts effects of morphine. Brain Res 1986;366:203–10.
[164] Heinricher MM, Morgan MM, Tortorici V, et al. Disinhibition of off-cells and antinociception produced by an opioid action within the rostral ventromedial medulla. Neuroscience 1994;63:279–88.
[165] Heinricher MM, McGaraughty S, Farr DA. The role of excitatory amino acid transmission within the rostral ventromedial medulla in the antinociceptive actions of systemically administered morphine. Pain 1999;81:57–65.
[166] Heinricher MM, Schouten JC, Jobst EE. Activation of brainstem N-methyl-D-aspartate receptors is required for the analgesic actions of morphine given systemically. Pain 2001;92:129–38.
[167] Polgar E, Puskar Z, Watt C, et al. Selective innervation of lamina I projection neurones that possess the neurokinin 1 receptor by serotonin-containing axons in the rat spinal cord. Neuroscience 2002;109:799–809.
[168] Vogel C, Mossner R, Gerlach M, et al. Absence of thermal hyperalgesia in serotonin transporter-deficient mice. J Neurosci 2003;23:708–15.
[169] Singh VP, Jain NK, Kulkarni SK. On the antinociceptive effect of fluoxetine, a selective serotonin reuptake inhibitor. Brain Res 2001; 915:218–26.
[170] Li JY, Wong CH, Huang EY, et al. Modulations of spinal serotonin activity affect the development of morphine tolerance. Anesth Analg 2001;92:1563–8.
[171] Bardin L, Schmidt J, Alloui A, et al. Effect of intrathecal administration of serotonin in chronic pain models in rats. Eur J Pharmacol 2000;409: 37–43.
[172] Bardin L, Lavarenne J, Eschalier A. Serotonin receptor subtypes involved in the spinal antinociceptive effect of 5-HT in rats. Pain 2000;86: 11–8.
[173] Clark FM, Proudfit HK. Projections of neurons in the ventromedial medulla to pontine catecholamine cell groups involved in the modulation of nociception. Brain Res 1991;540:105–15.
[174] Bajic D, Proudfit HK, Van Bockstaele EJ. Periaqueductal gray neurons monosynaptically innervate extranuclear noradrenergic dendrites in the rat pericoerulear region. J Comp Neurol 2000; 427:649–62.
[175] Bajic D, Proudfit HK. Projections of neurons in the periaqueductal gray to pontine and medullary catecholamine cell groups involved in the modulation of nociception. J Comp Neurol 1999;405: 359–79.
[176] Clark FM, Proudfit HK. The projection of noradrenergic neurons in the A7 catecholamine cell group to the spinal cord in the rat demonstrated by anterograde tracing combined with immunocytochemistry. Brain Res 1991;547:279–88.
[177] Yeomans DC, Proudfit HK. Antinociception induced by microinjection of substance P into the A7 catecholamine cell group in the rat. Neuroscience 1992;49:681–91.
[178] Sagen J, Proudfit HK. Effect of intrathecally administered noradrenergic antagonists on nociception in the rat. Brain Res 1984;310:295–301.
[179] Proudfit HK. Effects of raphe magnus and raphe pallidus lesions on morphine-induced analgesia and spinal cord monoamines. Pharmacol Biochem Behav 1980;13:705–14.
[180] Sagen J, Proudfit HK. Release of endogenous monoamines into spinal cord superfusates following the microinjection of phentolamine into the nucleus raphe magnus. Brain Res 1987;406: 246–54.
[181] Proudfit HK, Monsen M. Ultrastructural evidence that substance P neurons form synapses with noradrenergic neurons in the A7 catecholamine

cell group that modulate nociception. Neuroscience 1999;91:1499–513.
[182] Kiss ZH, Dostrovsky JO, Tasker RR. Plasticity in human somatosensory thalamus as a result of deafferentation. Stereotact Funct Neurosurg 1994;62:153–63.
[183] Gorecki J, Hirayama T, Dostrovsky JO, et al. Thalamic stimulation and recording in patients with deafferentation and central pain. Stereotact Funct Neurosurg 1989;52:219–26.
[184] Merzenich MM, Nelson RJ, Stryker MP, et al. Somatosensory cortical map changes following digit amputation in adult monkeys. J Comp Neurol 1984;224:591–605.
[185] Jenkins WM, Merzenich MM, Ochs MT, et al. Functional reorganization of primary somatosensory cortex in adult owl monkeys after behaviorally controlled tactile stimulation. J Neurophysiol 1990;63:82–104.
[186] Pons TP, Garraghty PE, Ommaya AK, et al. Massive cortical reorganization after sensory deafferentation in adult macaques. Science 1991;252: 1857–60.
[187] Knecht S, Henningsen H, Elbert T, et al. Cortical reorganization in human amputees and mislocalization of painful stimuli to the phantom limb. Neurosci Lett 1995;201:262–4.
[188] Knecht S, Henningsen H, Elbert T, et al. Reorganizational and perceptional changes after amputation. Brain 1996;119:1213–9.
[189] Huse E, Larbig W, Flor H, et al. The effect of opioids on phantom limb pain and cortical reorganization. Pain 2001;90:47–55.
[190] Birbaumer N, Lutzenberger W, Montoya P, et al. Effects of regional anesthesia on phantom limb pain are mirrored in changes in cortical reorganization. J Neurosci 1997;17:5503–8.
[191] Soros P, Knecht S, Bantel C, et al. Functional reorganization of the human primary somatosensory cortex after acute pain demonstrated by magnetoencephalography. Neurosci Lett 2001; 298:195–8.