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The functional anatomy of neuropathic pain

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The transmission of pain from peripheral pain receptors to the brain is mediated by several ascending nociceptive pathways, including the spinothalamic, spinomesencephalic, spinoreticular, spinolimbic, spinocervical, and dorsal column pathways (for a detailed review, see the article by Willis and Westlund [1]). Nociceptive projection neurons in the spinal cord transmit information to a number of regions of the brain stem and diencephalon, including the thalamus, periaqueductal gray (PAG), parabrachial region, and bulbar reticular formation, as well as to limbic structures in the hypothalamus, amygdaloid nucleus, septal nucleus, and other sites [2,3]. Much of the nociceptive processing involving the cognitive and affective components of pain is mediated by higher centers, such as the limbic system, thalamus, and neocortex. Several central structures are also involved in the descending analgesia systems, including the neocortex, limbic system, thalamus, PAG, locus ceruleus, parabrachial area, nucleus raphe magnus (NRM), reticular formation, and anterior pretectal nucleus.

Chronic pain is related to a process of sensitization causing abnormal nociceptive processing and involving the peripheral nociceptors or the central pain pathways. Chronic pain is usually classified as inflammatory and neuropathic. Inflammatory (or nociceptive) pain is related to tissue damage, whereas neuropathic pain is produced by neural damage. Inflammatory and neuropathic pain shares a common origin at the peripheral level. In particular, the release of several neurotransmitters and neuropeptides after neural damage can induce a process of peripheral nociceptive sensitization followed by a reduced pain threshold (hyperalgesia). Central sensitization may follow, being characterized by loss of the ability of central nociceptive processing to respond selectively to noxious stimuli (allodynia), which is a characteristic feature of neuropathic pain. The dorsal horns in the spinal cord play a crucial role in linking peripheral and central sensitization as well as in originating neuropathic pain. Neuronal degeneration and subsequent sprouting after neural damage may lead to aberrant neosynaptogenesis in the dorsal horns, inducing a distortion of the sensory receptive fields as well as the confluence of sensory and nociceptive afferents onto the same neurons. A similar mechanism is probably involved in the generation of neuropathic pain not only at the level of the dorsal horns (which is by far the most common circumstance) but at higher levels (eg, thalamus). In this article, we briefly review the anatomy and physiology of the nociceptive processing and illustrate the changes involved in the initiation and maintenance of chronic pain. Special emphasis is placed on the process of peripheral and central sensitization after neural injury, which eventually leads to the generation of neuropathic pain.

Physiologic activation of the pain pathways

A large number of endogenous substances are released after tissue injury or inflammation, and these can excite or sensitize nociceptive afferents. Some of these mediators act through ligand-gated cation channels (eg, $H+$, adenosine triphosphate

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[ATP]), whereas others act via G-protein–coupled receptors (eg, calcitonin gene–related peptide [CGRP], prostaglandins, bradykinin [BK], 5-hydroxytryptamine [5HT], serotonin). Changes in the excitability of nociceptive afferent neurons may result from the downstream activation of multiple intracellular protein kinases with subsequent phosphorylation of sensory neuron–specific Na+ channels [4]. The quality of the pain sensation depends on the tissue innervated by the stimulated nociceptors (eg, stimulation of cutaneous A-δ nociceptors leads to pricking pain [5], whereas stimulation of cutaneous C nociceptors results in burning or dull pain [6]). Activation of C-fiber sensory neurons also can elicit efferent functions after antidromic stimulation, and the resulting edema and vasodilation are known as neurogenic inflammation [7].

Both substance P (SP) and CGRP are released from peripheral terminals of sensory neurons, and these neuropeptides trigger extravasation and vasodilation, respectively, and regulate secretion of inflammatory mediators (eg, histamine, prostanoids, cytokines) from mast cells and leukocytes. Nerve injury also generates antidromic impulses in C-fibers, leading to peripheral peptide release, increased blood flow, extravasation and activation of leukocytes, and neurogenic inflammation. The molecular mechanisms controlling the peripheral release of neuropeptides or neurotransmitters that mediate neurogenic inflammation involve increased intracellular Ca2+ availability, activation of multiple protein kinases, and phosphorylation of voltage- and ligand-gated channels [8].

Nociceptors are inactive and rather unresponsive under normal circumstances. Inflammation can cause the sensitization of these nerve fibers, which develop spontaneous discharges and become much more sensitive to peripheral stimulation [9,10]. Sensitization of nociceptors depends on the activation of second messenger systems by the action of inflammatory mediators released in the damaged tissue, such as BK, prostaglandins, 5HT, and histamine.

Ascending pain pathways

Noxious stimulation is transmitted to the central nervous system (CNS) by the activation of small-diameter sensory afferent nerves (eg, unmyelinated C-fibers, small-diameter myelinated A-fibers). These neurons have their cell bodies in the dorsal root ganglia (innervating the body), the trigeminal ganglia (innervating the head), and the nodose ganglia (innervating the viscera), and they project to specific laminae of the dorsal spinal cord. C-fibers with cell bodies in the dorsal root ganglia generally terminate in lamina II, whereas A-fibers terminate in laminae I and V (for a review, see the article by Millan [3]).

Dorsal horn

The central pathways for processing nociceptive information begin at the level of the spinal cord (and medullary) dorsal horn. The gray matter of the spinal cord has been divided into 10 laminae on the basis of cytoarchitectonic studies [11,12]. Dorsal horns include lamina I (marginal layer), lamina II (substantia gelatinosa), lamina III and IV (nucleus proprius), and lamina V and VI (deep layers). Different laminae are involved in specific aspects of sensory processing, including nociceptive processing. Interneuronal networks in the dorsal horn are not only responsible for the transmission of nociceptive information to neurons that project to the brain but help to modulate that information and pass it on to other spinal cord neurons, including flexor motor neurons and nociceptive projection neurons.

Spinothalamic tract

The spinothalamic tract in human beings is believed to mediate the sensations of pain, cold, warmth, and touch. This belief is mainly based on three lines of evidence: the clinical deficits related to damage of the anterolateral cord [13–16], the analgesia produced by anterolateral cordotomies performed to relieve intractable cancer-related pain [17–19], and experimental studies in primates [20–22]. Most of the cells project to the contralateral thalamus, although a small fraction project ipsilaterally. Clinical evidence from patients with anterolateral cordotomies indicates that spinothalamic axons in the anterolateral quadrant of the spinal cord are arranged somatotopically. Primate spinothalamic tract cells that project to the ventral region of the posterolateral thalamus (VPL-VPM complex) generally have receptive fields on a restricted area of the contralateral skin, whereas spinothalamic cells that project to the medial thalamus have large receptive fields, often encompassing the entire surface of the body and face [23]. This suggests that spinothalamic cells projecting to the lateral thalamus are mostly involved in signaling the sensory-discriminative aspects of

pain, whereas those projecting to the medial thalamus are involved in motivational-affective aspects of pain.

Spinomesencephalic tract

Spinomesencephalic neurons respond to noxious stimuli only or best to noxious but also innocuous stimuli [12]. A rough rostrocaudal somatotopic organization has been described; spinomesencephalic projections from more caudal parts of the body terminate caudally, and projections from more rostral parts of the body end rostrally in the midbrain [24]. Recordings from spinomesencephalic tract cells in monkeys show that these cells often have complex receptive fields on widely separated areas of the body, suggesting an analogy with spinothalamic cells projecting to the medial thalamus [25]. The PAG and pretectal nuclei are among several midbrain targets that receive projections by means of the spinomesencephalic tract.

Postsynaptic dorsal column pathway

The postsynaptic dorsal column pathway arises mostly from cells located in lamina III (nucleus proprius) in the dorsal horn. The trajectories of postsynaptic dorsal column fibers are somatotopically organized in the dorsal column [26,27]. Nociceptive activity, including responses to uterine and vaginal distension, has been demonstrated in neurons of the dorsal column nuclei [28–31]. Presumably, the visceral information is relayed together with cutaneous epicritic information in the medial lemniscus to the lateral thalamus.

Thalamus

The lateral region of the thalamus receives massive lower afferents from the spinal cord, cerebellum, brain stem, and basal ganglia. This region can be considered the "sensorimotor thalamus," receiving somatosensory afferents from the spinal cord and brain stem and motor afferents from the basal ganglia. The lateral region, where most stereotactic lesions or stimulations are made to treat pain or movement disorders, is also the region of greatest divergence for nomenclature and interpretation. Several classification systems have been used to subdivide the thalamus. Neurosurgeons performing stereotactic procedures maintain a worldwide predilection for the Hassler system, despite its complexity, especially regarding the organization of the motor areas of the lateral thalamus, which modern techniques have proved to be organized differently (for a thorough review, see the article by Percheron et al [32]). In particular, the caudal region of the lateral thalamus, where projections from the lemniscal and spinothalamic pathways can be found, has been assigned nomenclature differently by various investigators: ventral posterior lateral nucleus (VPL) [33–35]; caudal ventral posterior lateral nucleus (VPLc) and ventral posterior medial nucleus (VPM) [36]; subregio lateralis caudalis (LCL) and subregio lateralis medialis (LCM) [32]; nucleus ventral posterior lateral, anterior division (VPLa), nucleus ventral posterior lateral, posterior division (VPLp), and VPM [37]; nucleus zentrolateralis caudalis internus (Zci), nucleus zentrolateralis caudalis externus (Zce), nucleus ventrocaudalis anterior externus (Vcae), and nucleus ventrocaudalis posterior externus (Vcpe) [38]; and nucleus ventrocaudalis externus (Vce) [39–41].

Today, the lateral thalamus is thought to consist of four regions (from anterior to posterior): nigral, pallidal, cerebellar, and lemniscal/spinothalamic (see reviews by Percheron et al [32] and Macchi and Jones [37]). The work of Percheron et al [32] is especially remarkable, because a large number of specimens were tested and the precise location of their thalamic regions was assessed using ventriculography. In addition, this work introduced a new system of nomenclature in the thalamus, with the sensory region of the thalamus referred to as the LCL-LCM (equivalent to VPL-VPM). Because of its wider popularity and confirmed accuracy, the VPL-VPM nomenclature recently reviewed by Macchi and Jones [37] is used during the rest of this article to indicate the caudoventral region of the lateral thalamus, where somatosensory afferents have been traced.

The somatosensory region is located over the ventral tier of the posterolateral thalamus (VPL nucleus), where medial lemniscal and spinothalamic afferents can be traced. The postsynaptic dorsal column pathway projects to the dorsal column nuclei, which gives origin to the medial lemniscal pathways projecting to the VPL nucleus. Spinothalamic neurons projecting to the posteroventral thalamus belong to the ventral spinothalamic tracts [42] originating from lamina V. There is a precise spinothalamic somatotopy, except for visceral representation [43]. Electron microscopic studies have shown convergence of medial lemniscal and spinothalamic tract input onto the proximal dendritic trees of thalamocortical neurons [44]. The trigeminal afferents from the gasserian ganglion are organized in a medial

region (VPM). Recordings made in the VPL-VPM nuclei of the monkey thalamus [43–57] show that neurons located in this region are somatotopically organized with contralateral receptive fields of small size. Up to 85% of the VPL neurons respond to cutaneous and visceral stimuli [43,55], but only the cutaneous inputs are somatotopically organized [43]. A mediolateral somatotopic organization with the hind limb lateral and the forelimb medial has been described within the VPL [48]. The restricted receptive fields of the VPL nociceptive neurons are well suited to a role in the sensory-discriminative aspects of pain perception. Recent neurosurgical experience in patients with chronic pain undergoing microelectrode recordings during stereotactic procedures reveals hyperactive neurons in the sensory thalamus [58], confirming an important role of thalamic relay in the process generating and maintaining chronic pain at the central level. Although the sensory thalamus alone is probably able to localize and mediate crude pain perception, the presence of direct projections from the VPL nociceptive thalamic neurons to the somatosensory cortex [48] suggests a neocortical involvement in the higher processing of pain.

Several other medial thalamic nuclei, including the center median (CM) and parafascicular (Pf) nuclei, have been shown to be involved in aspects of nociceptive processing; however, as distinct from the VPL-VPM complex, these regions do not seem to be related to tasks involving topographic pain discrimination. Nociceptive neurons located in the medial thalamus are characterized by large and usually bilateral receptive fields and are able to discriminate stimulus intensities. Therefore, the contribution of medial thalamic neurons to sensory discrimination is probably related to the appreciation of pain intensity and to the motivational-affective response to pain [59].

Cerebral cortex

Evidence that the human cerebral cortex participates in nociception derives from imaging studies [60–63] showing functional activation of specific regions of the cortex in relation to pain. Cortical areas most prominently involved include the somatosensory cortex, anterior insula, and anterior cingulate gyrus (for a review, see the article by Schnitzler and Ploner [64]). There is evidence that the primary somatosensory cortex is involved in the processing of tactile sensations and sensory-discriminative aspects of pain. Within the somatosensory cortex, pain processing seems to be less hierarchically organized than tactile processing. Cognitive factors can alter the perceived intensity of pain and, accordingly, can modulate the activity of somatosensory cortex in functional imaging studies. Further cognitive processing of pain is likely to be directed from the primary somatosensory cortex to the secondary somatosensory cortex, the anterior cingulate cortex, and the anterior insular cortex, which are involved in the recognition of the nature of the noxious stimulus and the processing of pain memories. In particular, the epicritic versus cognitive components of pain have been differentially traced to the somatosensory and cingulate cortex. The "first pain," which is characterized by a discriminative-epicritic component carried by the fast-conducting A-δ fibers, has been shown to induce an early activation of the primary and secondary somatosensory cortex. Conversely, the "second pain," which is characterized by a strong cognitive component and carried by slow-conducting C-fibers, induces a later activation of the anterior cingulate cortex [65].

The direct involvement of the cingulate cortex in the cognitive processing of pain as well as its strict relation to the somatosensory cortex suggests a central role in linking the ascending sensory pain pathways and the descending modulatory pathways.

Descending modulatory pathways

Cerebral cortex

Stimulation of the somatosensory cortex in monkeys causes inhibition of spinothalamic tract cells [66,67]. This cortical inhibition acts mainly on responses to innocuous mechanical stimulation, whereas the inhibition produced by stimulation in the PAG or NRM exerts a powerful analgesic effect acting on nociceptive processing [68]. Chronic stimulation of the motor cortex in human beings produces relief of neuropathic pain in a somatotopy-specific fashion, suggesting an important role of the motor cortex in the descending modulation of pain [69]. Another cortical region exerting a descending modulatory role on pain is the anterior cingulate gyrus, which, as indicated previously, is strategically placed to link the ascending and descending pathways. Increased metabolic activity of the anterior cingulate gyrus has been described in chronic pain patients after thalamic deep brain stimulation [70],

suggesting an active role of this cortical area in the neural mechanisms producing pain relief.

Thalamus

Thalamic VPL stimulation induces analgesia in monkeys through direct inhibition of the spinothalamic tract neurons [71]. The inhibition was suggested to result from antidromic activation of the axons of spinothalamic tract neurons sending collaterals to brain stem nuclei involved in the descending modulatory pathways, such as the PAG and NRM. Recordings from neurons in the NRM show an excitatory response after stimulation of the VPL nucleus [72,73], followed by serotonin release in the spinal cord [74]. Another possible explanation is that the spinal cord inhibition resulting from stimulation in the VPL nucleus occurs through a cortical loop involving the somatosensory or anterior cingulate cortex. In human patients, stimulation of VPL or VPM thalamic nuclei has been described as effective in producing pain relief in cases of medically refractory facial pain caused by anesthesia dolorosa, postherpetic neuralgia, and thalamic syndrome [75–78].

Brain stem

The "descending analgesia systems" exert a powerful modulating role on ascending pain pathways [79–82]. This modulatory network is spread over wide regions of the brain stem, including several nuclei of the bulbar reticular formation, the NRM, the PAG, the locus ceruleus, the subceruleus, the Kölliker-Fuse nucleus, and the anterior pretectal nucleus.

The reticular formation is characterized by the multimodality processing of a wide variety of sensory inputs. A single center for nociceptive processing in the reticular formation has not been defined, but it is known that many reticular neurons respond preferentially to noxious stimuli [83–87]. Ascending projections have been reported from the reticular formation to the medial thalamus, hypothalamus, and limbic structures and are likely involved in the activation of the endogenous analgesia systems and the relay of information that triggers motivational-affective responses to pain [88–96].

The raphe nuclei are another rather diffuse complex spread over the brain stem and are involved in the modulation of nociceptive processing. As distinct from the reticular formation, which is organized in a loose network, specific nuclei located near the midline of the medulla, pons, and midbrain can be identified (reviewed in the article by Willis [97]). The serotonergic projections from the raphe nuclei to the spinal cord [98,99] are the major source of serotonin in the spinal cord. The antinociceptive effects of stimulation in the NRM have been attributed to the inhibition of nociceptive dorsal horn neurons [80,100], including spinothalamic tract cells [101–104]. Stimulation in the ventrolateral PAG and NRM can induce a strong analgesic effect related to the inhibition of nociceptive dorsal horn neurons, including spinothalamic tract cells [68,103–106].

Other midbrain structures known to project to the dorsal horns are the locus ceruleus and the subceruleus, which have been shown to produce contralateral projections to laminae I, II, and V [107,108]. Another dense input to the dorsal horn originates from the ipsilateral Kölliker-Fuse nucleus [109–112]. Physiologic studies have suggested that the subceruleus and Kölliker-Fuse nuclei are primary antinociceptive regions affecting spinal transmission [113] and are able to inhibit the responses of dorsal horn neurons, including spinothalamic tract neurons.

Stimulation in the anterior pretectal nucleus results in long-lasting antinociception without adverse side effects in contrast to stimulation in many other brain stem sites, including the PAG [114–117]. Nociceptive dorsal horn neurons are affected in different ways after stimulation in the anterior pretectal nucleus depending on the laminar position of the neurons. Nociception-specific neurons in the superficial dorsal horn are excited by anterior pretectal stimulation, whereas nociceptive neurons in the deeper layers of the dorsal horn are inhibited [118]. Excitation of lamina I neurons has been proposed to activate a positive feedback loop whose inhibitory output to the deep dorsal horn neurons results in analgesia [117].

Factors involved in the generation of neuropathic pain: peripheral and central sensitization

Neuropathic pain is a pathologic process characterized by abnormal nociception induced by a process of sensitization after neural damage (either at a peripheral or central level). There are two main types of sensitization: peripheral sensitization, which acts on the nociceptors, and central sensitization, which can take place at various levels ranging from the dorsal horns to the brain. Both peripheral and central sensitization plays a crucial

role in the generation of neuropathic pain. As we have seen, the initial step in pain transmission is activation of nociceptors located on small-diameter afferent nerves that transmit noxious signals to the superficial layers of the dorsal spinal cord and within the brain stem. This information is subsequently relayed to the thalamus, limbic system, and neocortex, which produce pain perception and integration. Injuries to the neural pathways carrying pain can cause the release of chemical mediators enhancing neural transmission and thus sensitizing the pain fibers. In particular, peripheral nerve damage can cause changes in the concentrations of several neurotransmitters and peptides in the dorsal root ganglia and in the dorsal horn of the spinal cord, followed by transitory or permanent enhancement of the nociceptive processing. In addition to peripheral and central sensitization, abnormal interactions between the sympathetic and sensory pathways and decreased intrinsic and descending inhibition contribute to mechanisms mediating neuropathic pain.

Peripheral sensitization

Sensitization of nociceptive afferents after traumatic or inflammatory damage has recently been found to be strictly linked to the induction of neuropathic pain. Damage to a peripheral nerve can cause the upregulation of several neuropeptides, including galanin and vasoactive intestinal polypeptide (VIP) in dorsal root ganglion cells and their central branches [119]. Also, an increased release of CGRP has been found in complex regional pain syndromes [120]. The upregulation of such neuromodulators after nerve injury can induce long-term changes in the nociceptive afferents, which become hypersensitive to stimuli, developing enlarged receptive fields, an enhanced response to stimuli, and loss of stimulus selectivity. Abnormal features of sensitized nociceptive afferents include sensitivity to innocuous stimuli, exaggerated responses to nociceptive stimuli, increased spontaneous discharges, and abnormal sympathetic sensitivity [121]. Further changes in the pain pathways are characterized by sprouting and reorganization of the dorsal horn network. After nerve injury, larger diameter afferent A-fibers, which normally innervate the deeper laminae in the dorsal horns [122], may start to grow in more superficial layers and to express membrane components that are characteristic of C-fibers, such as the vanilloid receptor (VR-1) receptors [123] or SP [124] and sensory neuron–specific $Na+$ channels [125]. The sprouting of A-fibers and sympathetic fibers entering the dorsal horn is probably stimulated by the release of neuropeptides and growth factors after nerve injury. In particular, the growth of large myelinated afferents, which are usually involved in proprioception, into lamina II after peripheral nerve injury [126,127] and the generation of abnormal connections with the nociceptive neurons of the dorsal horn are likely to be the central players in the process inducing neuropathic pain and allodynia [128].

Central sensitization

After strong or damaging stimuli, nociceptive neurons in the dorsal horn develop an enhanced responsiveness to peripheral stimuli applied to undamaged regions of the skin [129–134]. Sensitization of neurons in the dorsal horn has been attributed to the combined effects of excitatory amino acids (eg, glutamate, aspartate) and peptides (eg, SP, CGRP) released into the dorsal horn [132,133,135–145]. Sensitization can be blocked by antagonists of glutamate receptors [132,133] or neurokinin 1 (NK1 [SP]) receptors [140]. As for peripheral nociceptors, sensitization of dorsal horn nociceptive neurons seems to result from the activation of second messenger systems, such as the protein kinase C system [145–147]. Within the spinal cord, release of excitatory amino acids, SP, neurokinin, and CGRP from the central terminals of C-fibers plays a significant role in the initial steps involved in the central signaling of pain by activating receptors (DL-α-NH2,3-dihydro-5-methyl-3OXO-4-isoxazolepropanoic acid [AMPA], NK1) localized on postsynaptic transmission neurons [3]. Intensive or persistent noxious stimulation produces increased or prolonged release of excitatory neurotransmitters and results in cumulative depolarization of postsynaptic transmission neurons, which leads to removal of an $Mg2+$ block and activation of N-methyl-D-aspartate (NMDA)–gated channels. Activation of NMDA receptors induces $Ca2+$ influx, and the increase in intracellular $Ca2+$ levels activates a cascade of changes, including activation of multiple protein kinases, which results in phosphorylation of ion channels and membrane receptors and further increases the excitability of spinal transmission neurons [4]. Increased intracellular $Ca2+$ also can activate transcriptional or translational pathways and lead to expression of new proteins or receptors, which leads to long-term plastic changes in spinal cord sensory transmission [4], likely linked to the

induction of allodynia. A further step in the generation of chronic pain, especially after peripheral or central lesions causing neural injury or denervation, is the reorganization of the sensory body maps, which has been described in the spinal cord [148,149], brain stem [150–153], thalamus [154,155], and somatosensory cortex [155–157]. This process is characterized by a sequential spread of body map reorganization starting from the dorsal horns all the way up to the somatosensory cortex (for a comprehensive review, see the article by Wall et al [158]).

Summary

The generation of neuropathic pain is a complex phenomenon involving a process of peripheral and central sensitization producing enhanced transmission of nociceptive inputs to the brain associated with the loss of discriminatory processing of noxious and innocuous stimuli. This increased flow of abnormally processed nociceptive inputs to the brain may overcome the ability of descending modulatory pathways to produce analgesia, causing further worsening of the pain. Several crucial locations involved in the physiologic generation of pain inputs (eg, peripheral nociceptors, dorsal horns, thalamus, cortex) show evidence of functional reorganization and altered nociceptive processing in association with chronic pain. These locations present the best targets for therapeutic intervention, including systemic administration of drugs able to counteract the chemical storm induced by neural injuries in the nociceptive afferents and dorsal horns, or for more focused intervention, such as neuroablative procedures; intrathecal drug delivery; and spinal cord, deep brain, or motor cortex stimulation.

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