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Nociception, pain, and antinociception: current concepts

Nozizeption, Schmerz und Antinozizeption

Summary The physiology of nociception involves a complex interaction of peripheral and central nervous system (CNS) structures, extending from the skin, the viscera and the musculoskeletal tissues to the cerebral cortex. The pathophysiology of chronic pain shows alterations of normal physiological pathways, giving rise to hyperalgesia or allodynia. After integration in the spinal cord, nociceptive information is transferred to thalamic structures before it reaches the somatosensory cortex. Each of these levels of the CNS contain modulatory mechanisms. The two most important systems in modulating nociception and antinociception, the N-methyl-D-aspartate (NMDA) and opioid receptor system, show a close distribution pattern in nearly all CNS regions, and activation of NMDA receptors has been found to contribute to the hyperalgesia associated with nerve injury or inflammation. Apart from substance P (SP), the major facilitatory effect in nociception is exerted by glutamate as the natural activator of NMDA receptors. Stimulation of ionotropic NMDA receptors causes intraneuronal elevation of Ca^{2+} which stimulates nitric oxide synthase (NOS) and the production of nitric oxide (NO). NO as a gaseous molecule diffuses out from the neuron and by action on guanylyl cyclase, NO stimulates in neighboring neurons the formation of cGMP. Depending on the expression of cGMP-controlled ion channels in target neurons, NO may act excitatory or inhibitory. NO has been implicated in the development of hyperexcitability, resulting in hyperalgesia or allodynia, by increasing nociceptive transmitters at their central terminals. Among the three subtypes of opioid receptors, μ- and δ-receptors either inhibit or potentiate NMDA receptor-mediated events, while κ opioids antagonize NMDA receptor-mediated activity. Recently, CRH has been found to act at all levels of the neuraxis to produce analgesia. Modulation of nociception occurs at all levels of the neuraxis, thus, eliciting the multidimensional experience of pain involving sensory-discriminative, affective-motivational, cognitive and locomotor components.

Zusammenfassung Die Physiologie der Schmerzwahrnehmung beruht auf einer komplexen Interaktion peripherer, spinaler und supraspinaler Strukturen des Zentralnervensystems (ZNS). Auf jeder Ebene des ZNS erfolgt eine Modulation nozizeptiver Information, wobei die zwei wichtigsten Transmittersysteme der Nozizeption und der Antinozizeption, das N-methyl-D-aspartate (NMDA)- und das Opioid-Receptor System, eine nahezu identische Verteilung zeigen. Glutamat, der natürliche exzitatorische Transmitter aller Neurone mit ionotropen NMDA-Rezeptoren, bewirkt durch Öffnen des Ca^{2+}-Kanals über die damit verbundene Aktivierung der intraneuronalen Stickoxidsynthase die Freisetzung von Stickoxid (NO). Diffusion des NO in Nachbarneurone erhöht deren cGMP-Synthese verbunden mit einer erhöhten neuronalen Aktivität, welche sich als Hyperalgesie oder Allodynie äußert, wenn Transmitter aus nozizeptiven Nervenendigungen freigesetzt werden. Die periphere Sensibilisierung nozizepti-

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ver Axone erfolgt meist über Serotonin, Bradykinin oder Prostaglandine. Während die μ- und δ-Opioid-Rezeptoren die NMDA-Rezeptor vermittelte Nozizeption hemmen oder verstärken, antagonisieren κ-Opioide NMDA-Rezeptor vermittelte Reaktionen vollständig. Hingegen wirkt Corticotropin-relasing-Hormon auf allen Ebenen des ZNS antinozizeptiv.

Key words Nociception – glutamate – NMDA – nitric oxide – sensitization – opioids – spinal cord – brainstem – cerebral cortex – pain – periaqueductal grey – basal ganglia – descending antinociception

Schlüsselwörter Nozizeption – Glutamat – NMDA – Stickoxid – Sensibilisierung – Opioide – Rückenmark – Hirnstamm – Kortex – Schmerz – zentrales Höhlengrau – Basalganglien – deszendierende Antinozizeption

Introduction

The integrity of all living organisms is guaranteed by interaction of two highly specialized systems: the immune system and by the ability of the brain to detect and remember danger. Whereas under physiological conditions the activities of the immune system never reach consciousness, pain immediately alerts the organism to the presence of damaging stimuli. Although both the immune and the nociceptive system appear to have been evolved separately, it is evident that during evolution mutual communication pathways have been developed by sharing common signal molecules and receptor mechanisms (9). Pain is usually defined as an „unpleasant sensory and emotional experience associated with actual or potential tissue damage. Pain is always subjective, each individual learns the application of the word through experiences related to injury in early life“ (79). Pain is not homogeneous and comprises three categories: physiological, inflammatory, and neuropathic pain. Pain is entirely a function of cerebrocortical structures composed of discriminative, affective-motivational, cognitive and locomotor components. Acute pain is mostly short-lasting because powerful antinociceptive mechanisms are simultaneously turned on by the noxious stimulus. Chronic pain is frequently associated with degenerative tissue diseases such as rheumatoid arthritis, does not spontaneously resolve and serves no obvious useful biological function (70), and it may be that for that reason genes favoring an opposing force to chronic pain have not been developed during evolution.

Physiological pain

Physiological pain is initiated with the generation of action potentials of specialized sensory nociceptor fibers innervating peripheral tissues. The action potentials transmitting somatic pain are conducted to the CNS by forming a three-neuron chain transferring nociception to the cerebral cortex. The first-order neurons with their cell bodies in the dorsal root ganglion end in the dorsal horn of the spinal cord, the trigeminal nociceptors in the trigeminal sensory nuclei of the brainstem, and synapse there with the second-order neurons, which axons ascend in the spinothalamic tract to the thalamus. The third-order neurons project to the postcentral gyrus of the cerebral cortex, where information is somatotopically organized. Most nociceptive signals originating from visceral organs reach the CNS via afferent fibers in sympathetic nerves. Specific visceral nociceptors have been found in the heart, lungs, testes and biliary system, whereas noxious stimulation of the gastro-intestinal tract appears to be detected mainly by non-specific visceral receptors that use an inensity-encoding mechanism (23, 49). Visceral nociceptive messages are conveyed to the spinal cord by relatively few visceral afferent fibers which activate many central neurons by extensive functional divergence through polysynaptic pathways (18, 59). Impulses in visceral afferent fibers excite spinal cord neurons also driven by somatic inputs from the corresponding dermatome. Noxious intensities of visceral stimulation are needed to activate viscero-somatic neurons, most of which can also be excited by noxious stimulation of their somatic receptive fields. Thus, visceral pain is the consequence of a diffuse activation of somato-sensory nociceptive systems which prevents accurate spatial discrimination or localization of the stimuli. Although a specific ascending pathway for visceral nociception has not been found, projection of viscero-somatic neurons include the spino-reticular and spino-thalamic tracts which trigger general reactions of alertness and arousal and evoke unpleasant and poorly localized sensory experiences.

Clinical pain

Inflammatory pain is initiated by unspecific stimulation of the sensory innervation of tissues by mediators released during the interaction of the immune

system with alien matter. Neuropathic pain, caused by either peripheral or central nervous system lesions, is the most common form of opioid-poorly-responsive pain. Both forms of pain are characterized by hypersensitivity at the site of damage and in adjacent normal tissue. Allodynia, either mechanical or thermal, arises from stimuli which never normally cause pain, while greater and prolonged pain resulting from noxious stimuli manifests itself as hyperalgesia.

First-order nociceptive neurons

The sensation of pain that is experienced arrives in the CNS by mean of two pathways: a sensory discriminative system which analyzes the nature, location, intensity and duration of nociceptive stimulation, separated from a second, phylogenetically newer system which carries the affective-motivational component of pain (33, 83). The peripheral nociceptors form two classes: myelinated Aδ mechanoreceptor and unmyelinated C polymodal fibers (103). As illustrated in Fig. 1, the majority of these neurons terminates in the superficial region of the dorsal horn innervating cell bodies of laminae I and II, as distinguished by their cytoarchitecture (85), while some Aδ fibers terminate in lamina V (33, 43, 78). The nociceptive afferents terminating in the dorsal horn release numerous transmitters, of which some act directly, while some serve as modulators. Under normal conditions, high levels of the excitatory amino acids glutamate and aspartate, substance P (SP) and calcitonin gene-related peptide (CGRP) have been found in the superficial dorsal horn and are, therefore, considered as the main nociceptive transmitters under physiological conditions, while various other transmitters, colocalized and expressed in both sets of nociceptive afferents, seem to be mainly elevated under pathological conditions including their receptors.

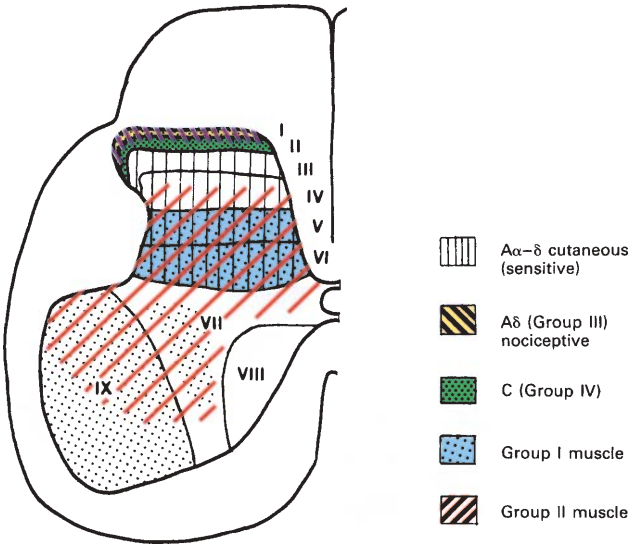

Fig. 1 Distribution of cutaneous and muscle afferent fibers to spinal grey matter

Peripheral sensitization

Nociceptor sensitization underlies the phenomenon of peripheral hyperalgesia that results in an increase in the perception of and response to pain. Several mechanisms have been proposed to account for hyperalgesia including direct activation of nociceptors as well as sensitization of nociceptors through the production of prostanoids or the release of various mediators during tissue injury, inflammation or anoxia and low pH (37). Especially kallidin and bradykinin (BK), derived from kininogen precursors following activation of tissue and plasma kallikreins by pathophysiological stimuli, appear to be implicated in the etiology of a number of pain conditions, associated with inflammation and rheumatoid diseases. Most actions of BK, including the acute activation of pain, are mediated through the membrane-bound B_2 receptor, coupled with a G protein. B_2 receptors have been localized to nociceptive nerve terminals in skin, skeletal muscle, joints and visceral organs (42, 48, 55, 60, 75, 76). Via the G protein BK activates intraneuronally phospholipase C to generate diacylglycerol, which, in turn, activates protein kinase C (PKC), which regulates ion channels and thereby neuronal excitability. Via diacylglycerol, BK stimulates the production of arachidonic acid. Prostanoids, especially prostaglandin E_2 and I_2, act on nociceptors to induce sensitization of the neuronal membrane (57). The activation of sensory fibers by BK also causes the release of neuropeptides such as SP, neurokinin A (NKA) and CGRP (6). In a reciprocal fashion, however, prostaglandins can sensitize nociceptors, Aδ as well as C fibers, to the action of BK, as well as several other stimuli, including serotonin (1, 88).

The dorsal horn of the spinal cord

In addition to the transmitters involved in pain sensation derived from the primary afferent fibers, the dorsal horn contains various other neuropeptides originating from neurons intrisic to the dorsal horn,

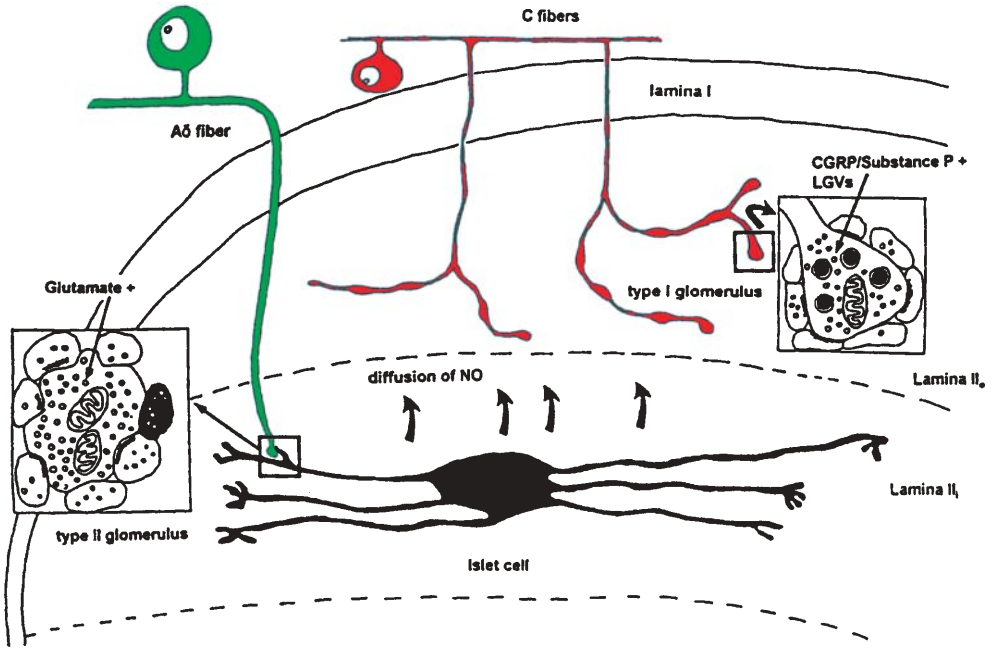

Fig. 2 Hypothetical mechanism of action of NO on peptide-containing primary afferent C fibers involved in central sensitization. Stimulation of Aδ fibers activates via glutamate in islet cells the NMDA-NO cascade. NO diffuses throughout lamina II and enhances the release of SP or CGRP form C fibers. From (2), with permission

or from descending axon terminals of neurons with cell bodies located in the brainstem (11, 12). The laminae I, II, V, VI and X of the grey matter of the spinal cord, and with a similar role the medullary caudalis nucleus of the trigeminal system, are those regions predominantly involved in the reception, processing and rostral transmission of nociceptive information (24, 75, 76, 90, 91). Within the dorsal horn, all neurons possess receptive fields which are organized in a somatotopic manner (93). Tissue damage as well as peripheral nerve injury may cause an expansion of dorsal horn receptor fields, thereby mimicking an increase in peripheral input. Based on the existence of inhibitory and excitatory intrinsic neurons, with either inter- or intralaminar, inter- or intrasegmental distribution, the dorsal horn constitutes a major station for the integration and modulation of all peripheral afferent signals, noxious and innocuous, and, depending of the profile of the latter, amplification or attenuation of nociceptive information may occur. Particular projection neurons transfer the processed sensory information to supraspinal destinations. Glutamate or aspartate has been considered being the main transmitter of excitatory interneurons, but also vasoactive intestinal peptide (VIP), SP, cholecystokinin (CCK) and neurotensin have been identiefied in enhancing nociceptive nervous traffic (29). To the contrary, inhibitory interneurons importantly counteract the flow of nociceptive signals. Gamma-amino-butyric acid (GABA), a major inhibitory transmitter in the CNS, is localized in high concentration in interneurons of laminae I–III, among others also in islet cells (Fig. 2), and has been implicated in the inhibition of acute and persistent pain (64, 89). However, because NO also acts as a crucial transmitter in models for persisting pain, co-localization of GABA with NOS, as it occurs in islet cells, may suggest even opposite functions for these neurons (2). Colocalization of GABA with acetylcholine, enkaphalin, or glycine in different subpopulations of dorsal horn interneurons constitute a further modulatory principle of nociception. In addition, an antinociceptive role has been attributed to cholinergic interneurons, acting via muscarinic and nicotinic receptors, and to opioidergic interneurons containing enkephalins or dynorphin, which exert their actions via μ-, δ- and κ-opioid receptors (29, 41, 77).

NMDA receptors, NO, and opioid receptors

The NMDA and opioid receptor systems are regarded as the most important structures in nociception and antinociception; in addition, by comparison of their distribution patterns a close relationship between opioid receptors and NMDA receptors in

many regions of the CNS has been found (67). Opioid receptors are synthesized within peripheral nociceptive neurons and transported to both the peripheral and central endings of these fibers. Both, opioid and NMDA receptors have a major representation in the dorsal horn, particularly within lamina II, suggesting a close functional relationship between these two classes of transmitters. Evidence for a colocalization of μ-opioid and NMDA receptors in both pre- and postsynaptic sites supports such a conclusion (47). Numerous studies have shown that opioids directly or indirectly modulate NMDA receptor-mediated electrophysiological events within the CNS. Among the three subtypes of opioid receptors, μ and δ have either inhibited or potentiated NMDA receptor-mediated electrophysiological events (25, 97, 106, 112), while κ opioids by directly interacting with the NMDA receptor per se antagonized NMDA receptor-mediated currents (14, 26). However, although upregulation of the κ opioid peptide dynorphin in the dorsal horn has been detected in inflammation, it was associated with either enhancement or reduction of nociceptive transmission at the spinal levels. A key factor in determining the potency of spinal opioid receptors, particularly of the μ subtype, appears to be the spinal level of CCK, which potently reduces spinal μ opioid actions (100). The inhibition of opioids on Ca^{2+} channel activity of the NMDA receptor suggests that they may act rather by regulating intracellular events following NMDA receptor activation. Besides PKC (7, 68), this affects two other calcium-calmodulin dependent targets, NOS with NO, and phosholipase A_2 with mobilization of arachidonic acid and prostaglandin formation (13, 30). Evidence that NO might be formed also in the brain is a recent finding (45). Although only a few percent of the neurons of the brain stain for NOS, their neuronal processes ramify so extensively that it is likely that nearly every neuron in the brain is exposed to NO. In 1989, Bredt and Snyder discovered that the excitatory transmitter glutamate acting at the NMDA subtype of glutamate receptor generates NO formation (16, 17). This is achieved in that glutamate opens the Ca^{2+} ion channel of this NMDA receptor and the elevation of intracellular calcium activates NOS (94). NO as a gaseous molecule easily diffuses out from the neuron to act on neighboring nerve endings and astrocyte processes, and functions such as a neurotransmitter (98). Because of its high affinity to guanylyl cyclase, NO stimulates the formation of cGMP in neurons. Most of the physiological effects of cGMP are mediated by its intrinsic target molecule, the cyclic GMP-dependent protein kinase (PKG), which plays a central role in regulating cGMP signaling in neurons, including such functions as modulation of neurotransmitter release, gene expression, learning and memory (92, 107). Though NO, on the one hand, amplifies neuronal activities via cGMP pathways, it acts, on the other, as a negative feedback regulator of NMDA receptor activity, providing, thus, a subtle control on NOS-containing neurons to prevent overstimulation by glutamate. The structure involved is the so-called redox-modulatory site of the NMDA receptor which contains vicinal sulfhydryl (thiol) groups which in their reduced state allow Ca^{2+} influx, but prevent Ca^{2+} influx after their oxidation to disulfides (3, 63, 96, 99). NO may, however, exert its inhibitory effect on NMDA responses not only via the thiol redox site but may also modify intraneuronal Ca^{2+} homeostasis directly (53). The redox-modulatory site of the NMDA receptors has been successfully modified with thiol reductants like dithiothreitol (63), dihydrolipoic acid or cysteine (56, 87), while oxygen-derived radicals and oxidized glutathione depressed NMDA-induced responses (101, 102). In the superficial dorsal horn, NO synthesis linked to NMDA receptor activation has been implicated in the maintenance of hyperalgesia in several models of persistent pain (73). Numerous studies have demonstrated that the release of CGRP and SP is increased in the dorsal horn during hyperalgesia, and that the NMDA-NO cascade is initiated by prolonged release of SP and glutamate from primary afferents (72, 84). Sodium nitroprusside, a NO donor, evokes the release of CGRP and SP from dorsal horn slices (44), while thermal hyperalgesia can be blocked by the NO inhibitor N^{ω}-nitro-L-arginine methyl ester, L-NAME (84). Both, the development and expression of thermal hyperalgesia are mediated through activation of NMDA receptors (69). It has been hypothesized, therefore, that NO, released from islet cells upon activation by Aδ fibers, diffuses throughout lamina II and enhances the release of SP and CGRP from C-fiber terminals (2), representing such one mechanism of central sensitization (Fig. 2). However, because of coexistence of GABA in large islet cells, an inhibitory counteraction on nociceptive traffic and, hence, on the development of spinal hyperexcitability, has to be considered. There is general agreement that hyperalgesia and allodynia are induced, at least in part, by the development of spinal hyperexcitability. This phenomenon was first described by Mendell and Wall (74) as „windup“ and it is most likely that it develops selectively by increased C fiber activity with concomitant release of their co-transmitters NK and SP in the dorsal horn, which qualitatively alter the postsynaptic effects of glutamate or aspartate (105). The amplitude and duration of the windup is depressed by NMDA and NK receptor antagonists. Thus, under conditions of chronic hyperalgesis, the interaction between NK, especially NK_1 and NMDA

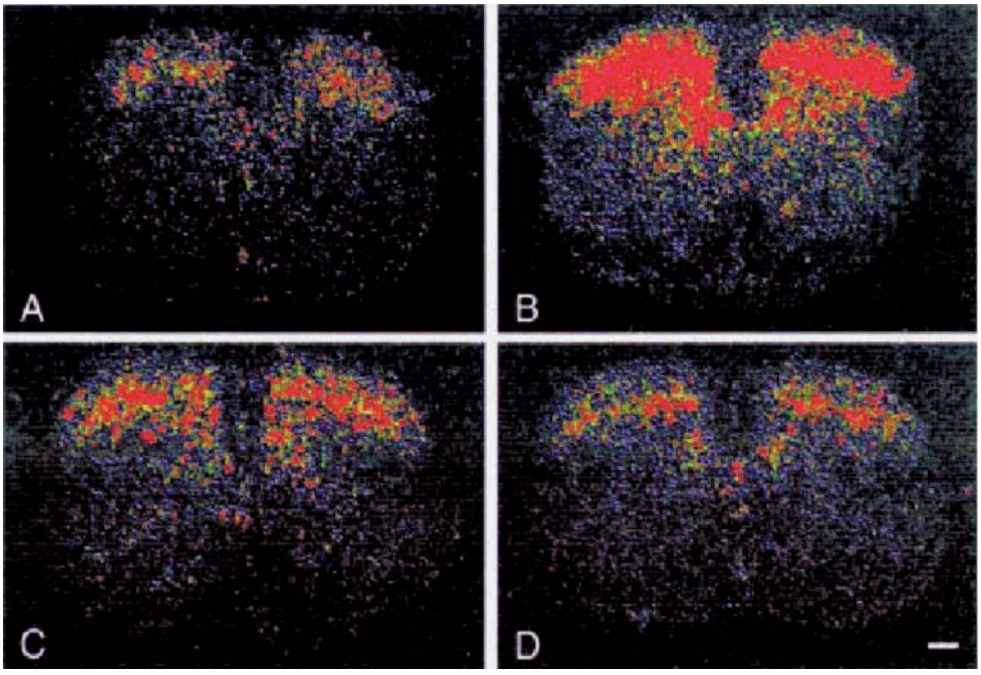

Fig. 3 Image analysis of changes in mGluR3 mRNA expression during the course of UV-induced hyperalgesia in rats. **A**: control, **B**: one day, **C**: two days, **D**: three days after UV irradiation. The pseudocolors cover all grey values representing significant expression (red-yellow: maximum, green-blue: minimum). Scale bar = 200 µm. From (15), with permission

receptors would play the major role in determining hyperexcitability in the spinal cord. Boxall et al. (15) recently reported an early gene expression in spinal cord during ultraviolet irradiation induced peripheral inflammation. As shown by the image analysis of changes in metabotropic glutamate receptor 3 (mGluR3) mRNA in Fig. 3, there is an increase in mGluR3 mRNA expression at least for two days post unilateral hindpaw irradiation almost exclusively in the dorsal horn of the appropriate lumbar segments of the spinal cord, with the highest density in lamina II and III, however, on both sides of the spinal cord. There was a strong coincidence of the upregulation of mGluR3 mRNA with the development of mechanical hyperalgesia and allodynia. Although the precise role of changes in mGluR3 mRNA expression during hyperalgesis is not known, Boxall et al. (15) considered that mGluR activation, in general, could enhance the activity of the ionotropic excitatory amino acid receptors, which are the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, kainat and NMDA receptors.

Second-order nociceptive neurons

The second-order nociceptive neurons, with their cell bodies in the dorsal horn and their axon termination in the thalamus, are mainly of two types: those that respond to gentle stimuli and increase their responses when the stimuli become intense are classified as wide-dynamic-range neurons, and those that respond exclusively to noxious stimuli are classified as nociceptive-specific neurons (10). Although many transmitters, including SP and CCK, are involved in carrying nociceptive information from the spinothalamic tract to the thalamus, and from the spinomesencephalic tract to the periaqueductal grey, numerous studies have shown that the most powerful system in nociception is the NMDA receptor system. Recent studies have shown, however, that besides the classic spinothalamic tract of nociception multiple other ascending pathways innervate not only the thalamus, but also the amygdala, the striatum, nucleus accumbens, hypothalamus and septum, as well as the frontal, orbital cingulate, and infralimbic cortex may also be directly accessed by spinal nociceptive neurons (19, 46, 54, 82). Although there is no absolute clear anatomical separation in the ascending nociceptive transfer systems to the supraspinal targets by which the global sensation of pain is finally modulated and experienced, two dimensions of pain can be distinguished: the sensory-discriminative, and the affective-cognitive component. The former deals with the perception and detection of noxious stimuli per se depending on their intensity, location, duration, temporal pattern and quality, the

latter comprises the relationship between pain and mood, the attention to and memory of pain, the capacity to cope with and tolerate pain and its rationalization (31, 78). The thalamus, subdivided in various nuclei, is still considered as the crucial relay for the reception and processing of nociceptive information en route to the cortex (20). Whereas integration of sensory-discriminative nociceptive input can be allocated mainly to posterior thalamic nuclei, input from visceral tissues to the thalamus is, in general, not topographically organized (23).

Third-order nociceptive neurons

Various approaches are used to investigate the pathway of nociceptive information from the thalamus to the cortex. Particularly metabolic and cerebral blood flow imaging techniques have revealed that the somatosensory area (S-I) is only one among many other circumscribed cortical areas which are implicated in the global experience of pain. Recently, the somatosensory area II (S-II), several regions of the inferior and anterior parietal cortex, the insular cortex, the anterior cingulate cortex and the medial prefrontal cortex have been identified as being consistently activated by cutaneous and intramuscular noxious stimulation (21, 22, 34, 71). It is possible that apart from a direct thalamocortical projection some of the cortical areas, constituting a complex pattern of connections among themselves, may be also indirectly activated via various limbic structures. Whereas activation of area S-I is almost exclusively contralaterally detected following noxious stimulation, in line with a pain-localizing and discriminative-sensory function of this area, the affective-cognitive aspects of pain have been attributed to area S-II, the cingulate, inferior parietal, prefrontal and insular cortex. As illustrated in Fig. 4, females, exhibit-

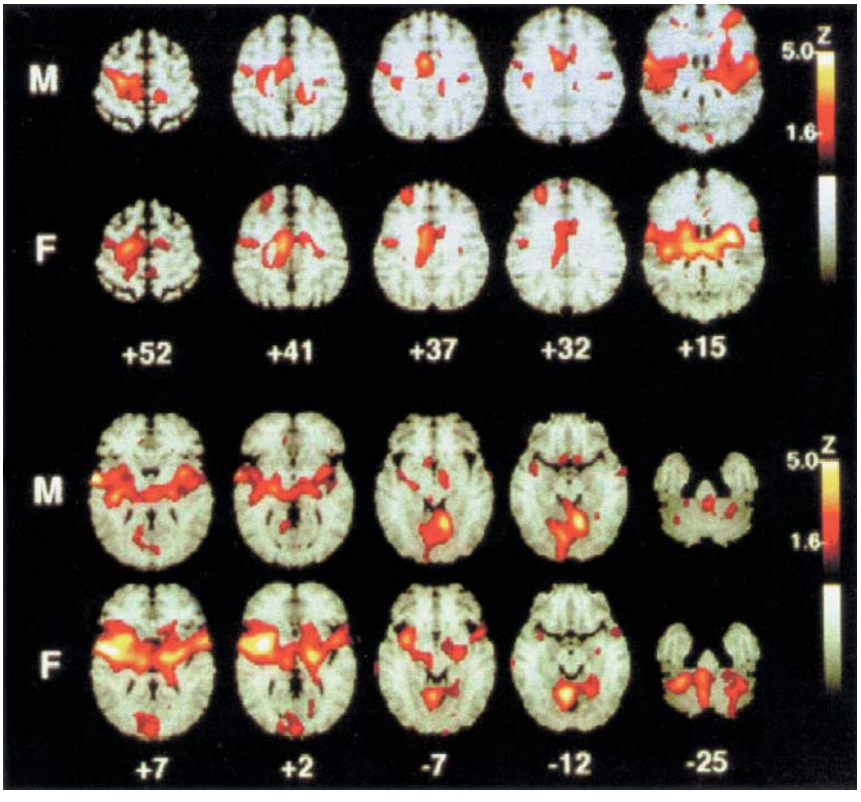

Fig. 4 Statistical map of regional cerebral blood flow responses of 10 males (M) and 10 females (F) to repetitive noxious heat stimulation (50 °C) of the left volar forearm. Color coding of Z scores as indicated by flame bar at right. The right hemisphere of the MRI stereotactic template is on the reader's left. The numbers below columns of images indicate millimeters above a plane connecting the anterior and posterior commissures. Significant activations occur in the contralateral cingulate cortext (+41, +37), premotor, and insular cortex (+15, +7), ipsilateral insula (+7, +15), and bilateral cerebellar vermis (–12). Structures significantly activated in males were contralateral prefrontal cortex (+52), anterior insula (+2), thalamus (+15), ipsilateral lenticular nucleus (+2), contralateral cerebellum (–25). Structures significantly activated in females were contralateral prefrontal cortex (+32), anterior insula (+2), thalamus (+15), ipsilateral lenticular nucleus (+2), contralateral cerebellum (–25). Significant differences between males and females occurred in contralateral thalamus, anterior insula and prefrontal cortex. From (21), with permission

ing no difference in pain thresholds, react to noxious cutaneous stimulation with a distinctly different pattern of cortical activation and a significantly greater activation of the contralateral prefrontal cortex compared with males (21). Whether this gender difference can be related to diseases with musculoskeletal pain of undefined origin, like fibromyalgia and which occurs mainly in females, awaits further elucidation.

Antinociception

It is a generally accepted view that noxious stimuli signal tissue injury or, in a broader sense, the loss of homeostasis, either locally or systemically. It seems, therefore, plausible to consider the restoration of homeostasis and the induction of analgesia as a main function of the nociceptive system, besides of the obvious importance of pain in survival. Nociceptive signals have been found to be modulated at any level of the brain giving the impression of the existence of a hierarchically organized antinociceptive system (8, 50). Pain modulation is a behaviorally significant physiological process, using a discrete CNS network involving release of opioid peptides, biogenic amines and other transmitters.

It appears from many studies that the strongest antinociception occurs at that the level where the primary nociceptors end, which is the dorsal horn of the spinal cord. Activation of GABAergic interneurons, or mimicking their activity by $GABA_B$ receptor agonist baclofen reduces the release of glutamate, SP and CGRP from nociceptive afferents (64). The concentration of GABA is the highest in the dorsal horn of the spinal cord. The dense distribution within the dorsal horn, especially lamina I and II, of benzodiazepine (GABA-A_{1a}) and opioid receptors underlines the capacity of these regions in modulating nociception leading to total spinal analgesia in response to strong nociceptive input (43, 64, 65). The intraspinal antinociceptive circuits only extend a few segments from the level at which they are engaged.

Less intense noxious stimuli can activate these spinal antinociceptive circuits via serotonergic and noradrenergic projections descending from the nuclei in the rostral ventro-medial medulla (50, 108–111). The extent to which antinociceptive mechanisms in the dorsal horn are activated may depend critically on environmental events which are considered as aversive or stressful, or are elicited by innate danger signals (39, 40).

Several studies have provided evidence that such conditionally antinociceptive responses are mediated by opioid and GABAergic mechanisms in the periaqueductal grey, which projects via glutamatergic descending pathways to the rostral ventro-medial medulla and activates there the descending antinociceptive serotonergic and noradrenergic pathways to the spinal dorsal horn (51). The periaqueductal grey is pivotally located to transmit cortical and diencephalic inputs to the lower brainstem. Retrograde studies have established that the periaqueductal grey receives significant inputs from the frontal and insular cortex, the amygdala, and the hypothalamus (5, 8). Learned or innate danger signals mediated via the amygdala to the periaqueductal grey with its intrinsic GABAergic and opioid receptors seems to constitute a neuronal network engaged in the central sensitization of antinociception. Recent studies have disclosed for the periaqueductal grey a high degree of anatomical and functional organization with longitudinal subdivisions in a lateral and a ventrolateral column. Coordinated patterns of skeletal, autonomic and antinociceptive adjustments have been elicited which appear to be triggered by discrete cortical inputs, the medial preoptic area, and the central nucleus of the amygdala (5). It was found that deep somatic noxious stimuli from muscle, joints or the viscera preferentially activated the ventrolateral periaqueductal grey, whereas cutaneous noxious stimulation activated the lateral column. Experimental excitation of the ventrolateral column evoked cessation of spontaneous activity, hyporeactivity, hypotension, bradycardia, associated with opiod analgesia, resembling the reaction pattern following injury, or after defeat in a social encounter. Activation of the lateral column produced a confrontational defensive reaction, either a fight or a flight response, hypertension, tachycardia, associated with non-opioid analgesia via activation in the lower brainstem of the descending serotonergic and noradrenergic antinociceptive pathways. The medial preoptic area is strongly implicated in temperature regulation and sleep receiving thermal signals from the body core (86) and the skin (52) and projects predominantly to the ventrolateral column of the periaqueductal grey (5). It has been shown that inescapable shock which functionally paralleles the experimental activation of the ventrolateral periaqueductal grey is associated with hyperthermia resembling fever (35). Whether the rise of body temperature which almost always accompanies pain rests on these pathways has to be elucidated.

Pain, and any kind of stress, whether psychological, infectious or traumatic, activates corticotropin-releasing hormone (CRH) neurons (27, 32). Since stress induced activation of the hypothalamic-pituitary axis has been shown to produce analgesia (4), the analgesia induced was considered to be due pri-

marily to the release of β-endorphin (38). Recently, however, it was shown that CRH can act at all levels of the neuraxis to produce analgesia, which is not dependent on the release of β-endorphin (61). Interestingly, inflammation must be present for local CRH to evoke analgesia. The specificity of the effects of CRH on tonic pain suggests that CRH may preferentially play a role in prolonged clinical pain. Recent experiments performed by Timpl et al. (104) have confirmed that the absence of the CRH receptor 1 (Crhr1) in specific areas of the brain distinctly diminishes the physiological response of the organism to a stressful stimulus. These results imply strongly that Crhr1 is the receptor that mediates the response to stress.

The precise role of the cortex and its projection to structures involved in antinociception is less clear. It is evident that the area S-I, thalamus and other higher centers do not merely behave as passive recipients and relayers of information from the dorsal horn. Rather, they are themselves involved in the further integration of adaptive, neuronal changes in acute and chronic painful states due to either inflammation or peripheral nerve damage (95). Cortical areas have been found to undergo a considerable reorganization of their receptive fields in patients suffering from phantom limb pain, showing shifts of the cortical areas adjacent to the amputation zone towards the representation of the deafferented body part (80). Stimulation of area S-II has been found to produced a weak antinociceptive behavioral response, which was remarkably potentiated by systemic administration of an NOS blocker (58). All three opioid receptor types have been identified in such regions as the deep layers of the parietal, temporal and occipital cortex, and particularly activation of opioid receptors in the anterior cingulate cortex can produce powerful antinociception (62, 66).

Pain as a multidimensional experience comprises not only motivational, affective and cognitive components, but also most often a locomotor response. Nociceptive information has been found to reach the basal ganglia through several afferent sources including the cerebral cortex, from area S-II, the prefrontal cortex, and the anterior cingulate cortex (28). Multiple neuronal loops transmitting nociceptive information connected with the cerebral cortex, the basal ganglia and thalamus may provide a mechanism that regulates ascending nociceptive signals. Opioids produce markedly different effects on locomotion, with μ- and δ-receptor agonists increasing locomotion, and κ-receptor agonists decreasing locomotion. These pharmacological differences appear to correlate with the effects of opioids on nigrostriatal release of dopamine, where μ- and δ-receptor agonists increase, and κ-receptor agonists decrease, striatal release of dopamine (36, 81). The basal ganglia do not participate in the spatial localization of pain. Patients with basal ganglia disease (Parkinson's disease, Huntington's disease) complain of pain that involves large areas of their body and that is difficult to localize in punctate areas. What can be deduced from the expression of the various patterns of pain experience is that pain develops not along rigid pathways from a defined peripheral location to defined areas of the cortex, but merely discloses the plasticity of the nervous system or the wisdom of the body to preserve homeostasis in a noxious environment.

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