43 The Pathophysiology of Neuropathic Pain: Critical Review of Models and Mechanisms

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Educational Objectives

1. Understand the definition and frontiers of neuropathic pain (NP).
2. Describe the link between NP and lesions of nociceptive systems.
3. Differentiate among the different animal models of NP.
4. Have a broad understanding of different peripheral, spinal, and supraspinal mechanisms relevant to NP.
5. Describe the difficulties in relating these mechanisms to pain in humans.
6. Translate some clinical manifestations of NP into underlying mechanisms.

Definition and Frontiers of Neuropathic Pain

The International Association for the Study of Pain (IASP) defined neuropathic pain (NP) as "pain initiated or caused by a primary lesion or dysfunction of the nervous system" [195]. However, the inclusion of the term dysfunction in the definition entails significant difficulties and was for a long time a subject of debate. Indeed, whereas pain owing to lesions of the nervous system (whether peripheral, spinal or encephalic) has comparable clinical features, shares common mechanisms, and responds to similar drugs, other types of pain, such as that in migraine, complex regional pain syndrome, fibromyalgia, or irritable bowel syndrome, while involving a clear dysfunction of the nervous system, differ from the preceding conditions in terms of pathophysiology, comorbidity, and therapeutic approaches. To avoid this and other nosological problems, an alternative definition was proposed by the IASP Neuropathic Pain Special Interest Group as "pain emerging as a direct consequence of a lesion or a disease of the somatosensory systems" [273]. We consider here the mechanisms sustaining NP in this more restricted but more homogeneous framework. Pain arising from fibromyalgia, chronic fatigue syndrome, or irritable bowel syndrome is currently considered to depend, in part, on alterations of pain control systems, which, while certainly implying a dysfunction of the nervous system, remain within a different framework than classical NP [24].

Neuropathic Pain Is Linked to Lesions of Nociceptive Systems

A general rule is that nervous system lesions giving rise to NP most commonly involve nociceptive pathways. Although this rule admits exceptions, it is generally valuable and useful. Thus, peripheral neuropathies involving selectively the large (Aα and Aβ) fibers (Charcot-Marie-Tooth disease, Friedreich ataxia), including those

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entailing virtually complete sensory deafferentation, do not commonly create pain, whereas those affecting, selectively or not, small fibers (diabetes, amyloid or arsenic neuropathies, Fabry disease, etc.) are very often painful. Also within the central nervous system (CNS), conditions associated with NP (syringomyelia, lateral medullary [Wallenberg] syndrome, dorsal horn lesions) affect in a vast majority the nociceptive systems, and the sensory abnormality most frequently found in these conditions is loss of thermoalgesic sensitivity [28,281].

Whereas lesions of nociceptive pathways appear to be necessary (or at least widely prevalent) in NP, they are not a *sufficient* condition. Thus, clinically identical thermoalgesic deficits may entail chronic pain in one subject but not another [57,77]. In addition, whereas ischemia or compression of spinothalamic tracts is frequently associated with NP [117,145], NP secondary to "clean" surgical transection of these same tracts is far less frequent [282,293]. Such differences may come, in part, from subtle pathophysiological dissimilarities among lesions, which are not yet detected by clinical examinations, and in part from genetic susceptibility. The importance of genetic factors is underscored by the differential susceptibility to NP of different breeds of mice subjected to identical experimental lesions [58,63]. On the contrary, the variable nature of pathophysiological mechanisms is supported by the existence in patients with identical anatomic lesions of different physiological responses correlated with the clinical expression of pain. Some of these subtleties may well have recognizable anatomic support. For example, the probability of pain after spinal cord injury increases when the lesion involves not only the ascending tracts, but the gray matter as well [76]. In addition, the development of NP after laterobulbar lesions has been linked to the preservation of the quintothalamic tract ipsilateral to the lesion [177]. These anatomic and physiological particularities, detected thus far with sophisticated methods, might become in the future useful landmarks to prevent the development of pain.

Animal Models of Neuropathic Pain

Peripheral Lesions

Most experimental models of NP rely on traumatic, metabolic, or toxic peripheral lesions and are meant to mimic human peripheral conditions such as neuropathies, plexopathies, and radiculopathies, which represent a considerable proportion of clinical NP. Models based on massive lesions of dorsal roots or large nerve trunks [165,285] are hardly used these days, owing to ethical and practical reasons (global deafferentation of a limb precludes the study of hyperalgesia and allodynia) and have been largely replaced by more discrete lesions that are nonetheless able to induce NP-like abnormal behaviors in experimental animals. Bennett and Xie [22] showed that placing loose ligatures around the sciatic nerve (chronic constriction injury) induced aversive behaviors similar to those provoked by human NP. It was later established that an immune reaction triggered by the suture was crucial for this effect to develop by provoking nerve edema, leading to nerve compression and axotomy. Indeed, axotomy of a variable proportion of nerve fibers has become a first-line technique for generating pain-like behaviors in animals, such as in the partial tight sciatic ligature in rodents [188,253], the spinal L5 nerve ligature [137], and the more recently described spared nerve injury model [56], in which the lesion involves two of the three terminal sciatic branches (tibial and peroneal) but spares the sural branch, and the sciatic nerve cuff model [21]. In all of these models, animals develop protective behaviors and show exaggerated (allodynic) reactions to mechanical and thermal stimuli. The most reproducible and long lasting (>6 months) NP-like behaviors appear to be induced by spared nerve injury and the sciatic cuff, whereas the results of chronic constriction injury are relatively unpredictable and might be improved by photochemical lesions of the sciatic nerve [92]. Nontraumatic models of peripheral NP have also been developed, including toxic neuropathy induced by antineoplastic drugs, such as vincristine or paclitaxel [78], and an experimental diabetes model induced by streptozotocin injection [52].

Whereas these models are relevant to the study of provoked pain (hyperalgesia, allodynia) and have contributed to our understanding of the plasticity of the nervous system after injury, the translational relevance of studies using these models remains controversial. Most studies using these models do not assess spontaneous pain, hence the problem may not be only with the model used but also with the assay method. Massive radicular lesions [165,285] are more likely to induce behaviors suggestive of continuous pain, in particular self-mutilation (autotomy). However, the interpretation of autotomy is ambiguous; some investigators consider

it a response to chronic pain in the self-mutilated limb [49,61,100,157], and others consider that it may simply be a reaction to complete limb anesthesia or to local pain created by the lesion [38,133,225]. A number of points argue in favor of an association, at least in part, between autotomy and pain, as follows: (a) a decrease in pathologically exaggerated nociceptor activity at the moment of the lesion also decreases the ensuing autotomy [96,243], while an experimental increase in nociceptive discharges enhances it [252]; (b) temporal inactivation of the cingulate gyrus by bupivacaine abolishes autotomy behavior [182]; and (c) mouse strains that develop postlesional autotomy behavior also show increased hyperalgesia relative to strains that do not develop autotomy [58]. It has been suggested that dorsal horn expression of the c-Fos protein, which increases with neuronal depolarization, is a reliable correlate of spontaneous pain [33]; however, both the c-Fos oncogene and its protein are expressed only in some types of neurons after nociceptive stimulation and may appear in other neurons in the absence of stimulation [33]. Data in rodents appear to indicate that for constant levels of pain and inflammation, the increased expression of c-Fos reflects rather the licking of the painful region [82]. There is enormous need in the field to develop "nonreflexive" measures of pain in animal models, and potentially important developments have been recently described. Based on the hypothesis that analgesic agents that are not rewarding in the absence of pain should become rewarding only when there is ongoing pain, Porreca and colleagues used conditioned place preference testing to reveal the presence of tonic pain and the efficacy of agents to relieve it [138]. However, a potential confounding factor is that most (if not all) of the drugs used to treat human NP possess psychotropic effects on mood, anxiety, and internal drive, which can also be rewarding and influence place preference [191]. To derive drug efficacy for ongoing pain in humans, this confound should be avoided with the use of appropriate controls before the routine application of this behavioral paradigm. Similar concerns might apply to novel approaches to quantify ongoing pain such as the disruption of burrowing behavior [7]. An interesting development is the measurement of spontaneous pain according to facial expressions in animals via video recordings [152], with the drawback that it works only in a subset of animal models of pain [110]. The translational relevance of the recently developed behavioral outcome measures for identifying novel "pain targets" needs further validation and is an area worthy of additional investigation.

Central Lesions

The armamentarium of animal models of central pain is much less profuse than that of peripheral lesions. Although a number of spinal injury models have been described, they have been analyzed mostly in terms of motor deficits. Animal models of brainstem, thalamic, or cortical lesions inducing NP remain exceptional.

Contusive Models

Most spinal injuries in humans result from fracture-dislocations inducing compressive contusions [209]. Spinal trauma models are consequently the most relevant to study clinical phenomena. Reginald Allen was the first to describe a spinal contusion model in 1911, whereby a weight was dropped onto dog spinal cords uncovered via laminectomy [249]. More than 15 different models of contusion have been developed since, most using predefined weight drops from a fixed height to produce a rapid and localized displacement of cord tissue (for a review, see [99]). Novel "impactor devices" have been conceived, which use force rather than tissue displacement as a user-defined variable to minimize potential errors that may arise from tissue movement occurring during the impact event, and other models have been conceived to induce slow-compression ischemic lesions using forceps, clips, or a balloon [131].

Excitotoxic Models

Contusion models give rise to nonselective spinal lesions affecting to various degrees the spinal gray and white matter. More specific excitotoxic models have been developed recently using glutamate analogs (kainate or quisqualate); these allow for selective gray matter lesions (similar to those induced by the sudden increase of excitatory amino acids in spinal injury) while sparing passing fibers. However, whereas motor deficits are almost constant after lumbar-level kainate injections, NP-like behaviors are obtained in less than half of injected rats [181]. More promising are spinal quisqualate injections, giving rise to a cavitation with lesion of the dorsal horn. Yezierski and colleagues [205,304] have developed injection parameters (volume and depth) to induce licking as well as behaviors suggesting mechanical allodynia and thermal hyperalgesia in a majority of rats. Reproducible spinal lesions can also be induced by photochemical lesions [288];

however, these reflect to a lesser extent lesions observed in humans.

As expected, the experimental lesions that most closely mimic the pain-generating injuries in humans are also the most efficacious in generating NP-like behaviors in animals. This includes excitotoxic lesions of the gray mater [305], surgical lesions of the spinothalamic tract and adjacent gray matter [282], and calibrated contusions with impactors (e.g., the NYU impactor [114], a cylinder of 2 mm diameter and 10 g mass dropped from a height of 12.5 mm). It has been estimated that mechanical hyperalgesia develops only if spinal concussion affects at least 90% of the white matter at the lesion level [140]. Models inducing "clean" spinal lesions such as "pure" anterolateral cordotomies or some photochemical lesions, are the least efficacious in inducing pain behaviors [167,282].

Peripheral Mechanisms of Neuropathic Pain

The following broad types of pathological changes have been described in peripheral axons and dorsal root ganglia after nerve lesions and have been postulated to play a role in the mechanisms of NP:

1. Ectopic discharges in lesioned fibers and their corresponding ganglia.
2. Abnormal activity in axons undamaged by the lesion.
3. Alterations in the expression and regulation of intracellular Ca^{2+} ion and modulatory receptors on primary afferent terminals.
4. Neuroimmune interactions resulting in enhanced and/or altered production of inflammatory signaling molecules.
5. Sensory-sympathetic coupling and other alterations in receptor signaling.

Each of the above mechanisms is described below. Additional details of the cellular mechanisms of ectopic impulse generation, including alterations in gene expression, regulation and trafficking of proteins such as ion channels, and alterations in behavior of ion channels and receptor molecules, are discussed in the chapter by Devor et al. The roles of peripheral neuroimmune interactions, including the roles of immune cells and mediators released by these cells, are discussed in further detail in the chapter by Bennett et al.

Ectopic Discharges in Injured Fibers

This refers to the spontaneous production of action potentials, in general within sites of axonal demyelination owing to altered distribution of voltage-dependent Na^+ channels in the demyelinated segments of the membrane. This can be seen as a mechanism of repair that enhances the probability of action potential transmission through the demyelinated segment. The newly inserted channels include $Na_V1.7$, a channel linked to hereditary pain syndromes (if excessive activity) and to insensitivity to pain (if loss of function), and $Na_V1.3$, a channel normally expressed only in sensory neurons during embryonic development, as well as a β subunit, all of which have biophysical properties that result in nerves that are particularly prone to trigger action potentials (for a review, see [62]). Combined with a decrease in K^+ channels and an increase in nonselective hyperpolarization- and cyclic nucleotide–modulated (HCN) channels, these changes can result in membrane instability sufficient for the emergence of spontaneous activity. In addition, there is evidence of ectopic expression of mechano-, thermo-, and chemotransducers along axons or in neuromas, which can serve as aberrant points of action potential initiation. For example, mechanical pressure to which nerves are generally insensitive is often sufficient to trigger ectopic discharges [64]. Together, these changes are thought to underlie Tinel and Phalen clinical signs. Tingling and paresthesiae after gentle tapping (Tinel sign) or mechanical compression (Phalen sign) of a peripheral nerve are indicative of an underlying nerve lesion, for example in carpal tunnel syndrome. Other hypotheses, such as the ectopic expression of mechanoelectric transduction proteins on axonal lesion sites, have also been put forward to explain these phenomena [38].

Eliminating the points where lesioned nerves are stretched or mechanically activated is therefore useful for lessening pain when this mechanism appears prevalent, such as in peripheral neuroma or trigeminal neuralgia [23,34]. The modified kinetics of sodium channels, and the low conduction velocity within the demyelinated segment, may enable membrane depolarization to last longer than the refractory period of adjacent Na^+ channels, giving rise to antidromic propagation of action potentials (proximal to distal)—so-called mirror discharges that are in turn reflected back by distal segments. A single action potential generated by a

distal receptor may thus generate a high-frequency barrage of impulses toward the dorsal horn.

Changes in the expression of Na^+ channels also operate at the ganglion level. The principal Na^+ channels studied thus far ($Na_V1.3$, 1.7, 1.8, and 1.9) are expressed mainly in small root ganglion cells and might be at the origin of abnormal action potentials in nociceptors. The tetrodotoxin-sensitive $Na_V1.3$ receptor has been found to be overexpressed in spinal ganglia of lesioned fibers, whereas the $Na_V1.8$ receptor tends to be underexpressed in these same fibers and could have a pronociceptive role in fibers preserved by the lesion ([95], see below). The necessary role of these channels has been challenged in recent studies from King's College London, showing that allodynia-like behavior and ectopic discharges can be produced by nerve lesions in knockout mice for $Na_V1.7$, 1.8, and even 1.3 [205,206]. Although of potential significance, these results should be viewed with caution, given the compensatory changes that are known to occur in knockout animals.

Given that ectopic impulses are triggered mostly in myelinated fibers [62], most of which are not engaged in nociception, one might wonder how they can be related to the origin of abnormal pain. High-frequency stimulation of small myelinated fibers (Aδ) generates pain [257], and a great deal of data favor the implication of large Aβ fibers in touch allodynia and secondary hyperalgesia. In addition, the temporal dynamics of tactile allodynia after nerve section closely follow those of ectopic discharges in myelinated A fibers—while such discharges are not observed in amyelinic C axons [161]. Microneurography has shown that secondary allodynia after capsaicin injection depends on activity in Aβ fibers that normally evoke tactile sensations [271], and mechanical dynamic hyperalgesia after nerve lesions disappears when Aβ activity is eliminated by compression block [39,212]. The mechanisms enabling normally nonnociceptive (Aβ) input to engage nociceptive circuitry may rely on both pre- and postsynaptic mechanisms. A presynaptic action was proposed by Cervero and Laird, who suggested that Aβ activity after nerve injury could induce crossed depolarization of afferent C terminals in the dorsal horn via collateral axoaxonal synapses (Aβ to C) or interneurons [6,44]. This hypothesis, based on the existence of C fiber–dependent vasodilation in response to peripheral Aβ activity, has not been consistently reproduced (compare [286] and [90]). As will be described below, a postsynaptic decrease in γ-aminobutyric acid (GABA)-ergic/glycinergic tone in the dorsal horn is also a probable mechanism of nociceptive engagement by activity in Aβ fibers after nerve injury [51,197]. Further to these putative mechanisms, a number of Aβ fibers may, in the case of nerve lesion, undergo phenotypic changes and express neurotransmitters, such as calcitonin gene-related peptide (CGRP) and substance P, typical of nociceptive neurons [60,208,226]. This might provide a further mechanism of nociceptive activation contributing to sensitize dorsal horn neurons, although controversial data on such phenotypic changes also exist [113].

Are these mechanisms relevant to clinical pain? A positive response is suggested by the analgesic efficacy of drugs, such as carbamazepine and its derivatives, phenytoin, lamotrigine, and lidocaine-like anesthetics, for which the main action is to stabilize Na^+ channels by binding selectively to their inactive form. All of these drugs are efficacious in the treatment of certain forms of NP, although side effects often limit their use. In certain types of NP, such as trigeminal neuralgia, Na^+ channel blockers are even a first-line treatment. Channel blocker properties have been recently reported for other drugs, such as tramadol and fentanyl, used in the treatment of NP [102]. However, the fact that Na^+ channel blockers are not universally useful, even in conditions with clear cut peripheral lesions, suggests that overexpression of Na^+ channels and ectopic discharges are just one of a number of different processes leading to NP.

Abnormal Activity in Axons not Damaged by Lesions

Lesions distal to dorsal root ganglia lead to Wallerian degeneration, with the development of inflammatory phenomena, edema, and macrophage activation in the axonal segment disconnected from the soma. The timing of this process parallels that of hyperalgesia in rat models of chronic sciatic constriction [259], and Wallerian degeneration may favor the development of abnormal activity, including neurochemical abnormalities in the contiguous intact root ganglion, with overexpression of transient receptor potential vanilloid receptor 1 (TRPV1), neurotrophic factors such as brain-derived neurotrophic factor (BDNF), and mRNA for nociceptive neurotransmitters such as CGRP, in fibers spared by the lesion [84]. Noninjured C fibers that share a portion of their trajectory with lesioned axons develop abnormal discharges [5,302], may exhibit sensitivity to catecholamines, and even overexpress certain

Na^+ channels such as $Na_V1.8$—a channel that is downregulated, at least at early time points, in injured fibers [5,95]. All of these abnormalities are dependent on the existence of a lesion distal to the root ganglion and do not appear in the case of a proximal lesion [211]. It is consequently thought that products of degradation linked to Wallerian degeneration alter the properties of adjacent noninjured C fibers sharing a same nerve (or same Remak bundle) with axotomized fibers [143].

The efficacy of topical capsaicin in certain cases of peripheral NP supports some functional alteration of noninjured C fibers because capsaicin action can only be exerted on intact nociceptors (discussion in [38]). Experiments with animal models point to similar conclusions [255]. Local application of a Ca^{2+} blocker or a glutamate receptor antagonist diminishes hyperalgesia signs only if they are applied ipsilateral to the nerve lesion [67]. In one patient with NP owing to nerve lesion, Cline and colleagues [48] documented sensitization (exaggerated responses and postdischarges) in C fibers in which electrical stimulation also reproduced clinical symptoms. However, it was not shown whether sensitization applied to injured or noninjured C axons.

Alterations in the Expression and Regulation of Intracellular Ca^{2+} and Modulatory Receptors on Primary Afferent Terminals

Neurotransmitter release by nociceptive terminals is triggered by Ca^{2+} entry and therefore depends on voltage-dependent channels (for a review, see [41]). Spinal nerve ligation in rats induces overexpression of the α2/δ Ca^{2+} channel subunit in the corresponding dorsal ganglia [170], which might entail an enhanced neurotransmitter release (in particular glutamate) by these terminals. This phenomenon, also demonstrated in the dorsal horn [158], may be at the basis of the clinical efficacy of drugs, such as gabapentin (Neurontin) and pregabalin (Lyrica), that selectively block the α2/δ subunit, given that most data suggest that these drugs may decrease neurotransmitter release by linking specifically to the α2/δ Ca^{2+} channel subunit [24]. However, Ca^{2+} receptor blockade by itself cannot completely explain the pain-relieving effect of these drugs because other substances with equivalent affinity for the same subunit, such as m-chlorophenylglycine and 3-exo-aminobicyclo(2.2.1) heptane-2-exo-carboxylic acid (ABHCA), show no anti-allodynic effect in rat spinal nerve ligation models [171].

Glutamate liberation by nociceptive terminals is inhibited presynaptically by metabotropic receptors for opioids and adenosine and the $GABA_B$ receptor, as well as by the ionotropic $GABA_A$ receptor. It is likely that nerve lesions induce a downregulation of all or some of these receptors [142], which could contribute to enhanced glutamate release and sensitization of spinal neurons. Decreased activation of presynaptic opioid receptors on injured primary afferent central terminals may minimize any reduction by opioids of the spontaneous pain mediated by ectopic input from lesioned afferents, and thus underlie the resistance of NP to opioid therapy.

Neuroimmune Interactions Resulting in Enhanced and/or Altered Production of Inflammatory Signaling Molecules

There is increasing evidence that nerve injury–induced activation of peripheral immune cells, and the factors that they produce, can alter sensory processing and play critical roles in the development and maintenance of NP. Cytokines and chemokines released by immune cells, such as tumor necrosis factor-a (TNF-α), interleukins (ILs), nerve growth factor (NGF), and CC chemokine ligands, can cause sensitization of channels, such as TRPV1, and result in firing of nociceptors at normal body temperature. The role of peripheral immune mechanisms in chronic pain is discussed in detail in the chapter by Bennett et al.

Sensory-Sympathetic Coupling and Other Alterations in Receptor Signaling

Nerve growth factor plays an important biological role in the development and maintenance of small-diameter somatic and sympathetic neurons. Increased production of NGF, both locally and within the corresponding dorsal root ganglia, has been demonstrated in different models of NP [106,232]. In rodents, endoneurial administration of NGF induces neuronal sprouting and behavioral signs of thermal hyperalgesia [240]. In humans, local injection of NGF has been shown to decrease thermal pain thresholds and induce pressure allodynia [74]. Increased production of NGF (and possibly of other products including IL-6 [236]) induces sympathetic neurons innervating blood vessels in the dorsal root ganglia to send new sprouting branches toward the ganglion neurons themselves [192]. Such arborizations have been described since the end of the 19th century, and Ramón y Cajal was the first in 1899 to suggest their sympathetic origin [91]. Norepinephrine release in these sprouting fibers produces abnormal discharges of

polymodal nociceptors [64], which themselves express abnormally elevated levels of α-adrenoceptors in their axon and soma. Adrenergic receptor–bearing neurons become so sensitive that they may respond to circulating norepinephrine, and this mechanism might contribute to a number of "sympathetically maintained" or complex regional pain syndromes. In models of sciatic section, nerve block performed immediately after lesion considerably lessens both the spontaneous activity of injured fibers and the sympathetic neoarborization. This beneficial effect persists up to 4 to 5 weeks after block [303,309], involves inhibition of NGF via tyrosine kinase activation [267], and underscores the therapeutic interest of early nerve anesthetic blocks to prevent the development of NP after nerve trauma. Although these data also support the therapeutic use of sympathetic block to treat complex regional pain syndromes, such an approach has not proved useful in controlled studies (meta-analysis [139]).

Novel mechanisms potentially able to create pain after peripheral nerve lesions are being continuously described. Among the most recent, we should include overexpression of TRPV1 noxious heat receptors, both in injured fibers [25] and the contiguous noninjured axons [84]. Correction of NP-like signs has been described after blockade of these receptors [46]. The overexpression of bradykinin and purinergic receptors, and downregulation of substance P, bradykinin-2, and mu-opioid receptors, has also been described, but it remains currently impossible to determine their actual relevance to the development of NP in humans [276a,302a].

Spinal Mechanisms

Hyperexcitability of second-order neurons, selective neuronal loss, failure of inhibitory mechanisms, and structural reorganization have each been suggested or experimentally demonstrated after lesions inducing NP. Spinal lesions are associated with neuroinflammatory processes, with formation of a glial scar limiting axonal regeneration, and degeneration of ascending and descending tracts entailing supraspinal reactive phenomena. Although all of these processes are imbricated and interdependent, we shall present them here separately for didactic reasons.

At the heart of central processes of NP lies the phenomenon of central sensitization, defined as an abnormal increase of spontaneous and evoked activity of CNS nociceptive neurons. This phenomenon is not exclusive to NP and also develops in inflammatory states; however, it is self-limited in these states and disappears with resolution of the primary cause, whereas such sensitization persists beyond the acute episode in NP. Central sensitization exists at both the spinal and supraspinal levels, but the best-studied phenomena concern the spinal dorsal horn. Two abnormal phenomena develop after an inflammatory lesion of cutaneous tissues: primary hyperalgesia to mechanothermal stimuli at the level of the lesion, and secondary hyperalgesia to mechanical stimuli over nonaffected sites around the lesion. These two types of hyperalgesia are dependent on the initial increase of peripheral nociceptive input because blockade of this input by local anesthetics can eliminate them completely [151]. However, whereas primary hyperalgesia depends on C-nociceptor hyperexcitability, secondary hyperalgesia does not involve any response modification of peripheral C fibers [17], is reversed by selective block of Aβ fibers [151,271], and appears therefore to depend on sensitization of second-order (i.e., central) nociceptive neurons to input from nonnociceptive fibers. Within this framework, tactile allodynia is thought to depend on exaggerated central responses to Aβ fiber activation, whereas hyperalgesia to punctiform stimuli (e.g., Von Frey filaments) would be vehiculated by non-capsaicin-sensitive Aδ fibers [178]. Alternatively, some investigators have proposed that secondary hyperalgesia might, at least in some cases, result from sensitization of peripheral C fibers [48,302]. However, these alternative views have thus far not received much experimental support.

The mechanism whereby nociceptive peripheral signals (mainly from C fibers) result in exaggerated spinal responses is defined as homosynaptic central sensitization, whereas the term heterosynaptic sensitization is applied to spinal noxious responses to nonnociceptive input [179]. Within the conceptual framework described above, homo- and heterosynaptic sensitization are at the basis of primary and secondary hyperalgesia, respectively. Homosynaptic sensitization reveals itself in the wind-up phenomenon, whereby repetitive stimulation of nociceptive C fibers leads to a disproportionate enhancement of dorsal horn noxious responses. Evidence of this in humans is the progressive enhancement of nociceptive spinal reflexes and pain sensations in response to repeated painful stimuli at frequencies greater than 1 Hz [247]. Whereas homosynaptic sensitization is present in the intact nervous system,

heterosynaptic sensitization implies an abnormal, acquired capacity of Aβ mechanoreceptors to evoke central nociceptive responses, including in the dorsal horn, and therefore induce tactile allodynia. The peripheral changes described in previous sections provide a number of plausible mechanisms leading to sensitization including abnormal ectopic discharges in injured fibers, abnormal hyperexcitability of noninjured C fibers, and C fibers classified as silent or mechanoinsensitive. In addition, downregulation of opioid and nonopioid inhibitory presynaptic receptors tend to increase the nociceptive barrage onto dorsal horn neurons, therefore contributing to homosynaptic sensitization. Furthermore, crossed depolarization of C fibers and phenotypic changes making Aβ fibers express nociceptive neurotransmitters provide mechanisms whereby second-order nociceptive neurons may become activated by stimulation of nonnociceptive afferents (heterosynaptic sensitization).

Repeated and exaggerated discharge of spinal nociceptive neurons via the mechanisms described above gives rise to phenomenon termed long-term potentiation (LTP), defined as an increase in synaptic efficacy (i.e., increased probability of firing) resulting from coincident activity of pre- and postsynaptic elements. This phenomenon brings about a facilitation of chemical transmission that lasts for hours in vitro and that can persist for periods of weeks or months in vivo. Long-term potentiation was first described in the hippocampus and is considered a synaptic model of learning and memory. The existence of similar mechanisms in the spinal cord was described only much later [237], and their relevance for nociceptive transmission has largely benefited from the work of J. Sandkühler in Austria. Powerful and repeated nociceptive input is a premise for LTP to develop, and it has been suggested that LTP might be one of the mechanisms ensuring the transition from acute to chronic pain [241,245,246].

This section will review different spinal processes likely to contribute to central sensitization and LTP. The conceptual implications of LTP in the phenomenon of pain learning are important but beyond the scope of this refresher course.

Connectivity Changes of Non-nociceptive Aβ Terminals

The excessive production of growth factors and other neuroactive substances is thought to induce collateral sprouting of nonnociceptive Aβ fibers. An early and attractive theory postulates that such axons develop synaptic boutons in dorsal horn layers usually receiving C-fiber terminals [190,301]. Activation of large myelinated fibers would therefore evoke responses in nociceptive second-order neurons, providing support for tactile allodynia. However, experimental data in favor of this hypothesis remain controversial (e.g., [12,112] versus [292]). One reason for disagreement concerns the marker for Aβ fibers used in arborization studies (cholera toxin B subunit). Although considered specific for myelinated fibers, this marker may also tag unmyelinated fibers after nerve section [12]. Another reason not to consider abnormal sprouting as the sole mechanism for tactile allodynia is the temporal dynamics of the latter, which can develop as early as 1 day after partial nerve lesion in both rats and mice [188]—a timing hardly compatible with the development of sprouting and reconnection processes. Therefore, aberrant arborization—if it is confirmed—could rather participate in the long-term persistence of the allodynic state.

A variant of the misconnection hypothesis postulates the existence of subliminal local circuits connecting middle and superficial dorsal horn laminae, which can be unmasked in the presence of glycine/GABA disinhibition. This circuit could turn touch into pain by unmasking innocuous inputs to superficial dorsal horn nociceptive-specific neurons via a local, excitatory, N-methyl-D-aspartate (NMDA)-dependent neural circuit involving neurons expressing the γ isoform of protein kinase C (PKC-γ) and lamina I nociceptive-specific neurons [197,198].

Whereas models of tactile allodynia stemming from these hypotheses are founded on the concept of some abnormal wiring of nonnociceptive input, other investigators have suggested that tactile allodynia may be signaled by large myelinated fibers ascending through the dorsal column system, without the need for altered processes in the dorsal horn. Thus, nerve injury–induced tactile allodynia (but not thermal hyperalgesia) may be prevented by ipsilateral lesions of the dorsal columns or by lidocaine microinjection into the nucleus gracilis [215,263] and may therefore result exclusively from abnormal supraspinal integration. In support of this view, neuropeptide Y, normally not detected in the dorsal root ganglia or nucleus gracilis in rats, is upregulated at both sites after spinal nerve injury in animals expressing tactile hyperresponsiveness, and the administration of neuropeptide Y antiserum

abates this behavior [215]. Similar results have been obtained with the use of glutamate receptor antagonists [144], supporting the possibility that tactile hyperresponsiveness after nerve injury may be selectively mediated via a low-threshold, myelinated-fiber pathway to the nucleus gracilis. Possible phenotypic changes whereby large fibers may express neurotransmitters commonly restricted to nociceptive fibers in nerve-lesioned animals [208,310] also support this view.

Sensitivity Changes in Postsynaptic Receptors

Peripheral nerve injury also results in receptor changes in second-order neurons. Central nociceptive transmission is supported mainly by ionotropic glutamatergic receptors, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/kainate receptors (which depolarize the postsynaptic neuron) and NMDA receptors (activation of which prompts the entry of Ca^{2+} into the neuron). An abnormal increase of nociceptive messages to the cord triggers an increase in the number of AMPA receptors associated with facilitation of central glutamatergic synapses [160], and an increase in mRNA coding for AMPA and NMDA receptors has been described in a model of experimental diabetes prone to diabetic neuropathy [270]. The link between these changes in receptor expression and density and behavioral pain-related changes is supported by the fact that after sciatic ligation in rats, the timing of AMPA receptor overexpression in the outer layers of the dorsal horn closely parallels that of mechanical hyperalgesia induced by the lesion [104].

Both homo- and heterosynaptic sensitization in rats are largely dependent on hypersensitivity of glutamate receptors and can be blocked by their antagonists [141,172]. In humans, blocking of NMDA receptors by ketamine does not modify the immediate burning sensation created by capsaicin injection, but it significantly attenuates the mechanical and thermal hyperalgesia that follows [231]. This underscores the specific role of glutamate receptors in central sensitization and opens possible therapeutic lines. In addition to the dorsal horn, the role of glutamate receptors may also be relevant at projection nuclei of the dorsal column system (nuclei gracilis and cuneatus), where postdischarges of wide-dynamic-range neurons are decreased by the selective block of AMPA receptors [144]. However, alteration in sensitivity of ionotropic glutamate receptors after a nerve lesion may render nociceptive neurons less sensitive to exogenous modulation, and this may explain why agonists and antagonists of glutamate receptors, which have pro- and antinociceptive effects in control animals, respectively, fail to exert these effects after sciatic ligation in rats [307]. This effect may limit the therapeutic efficacy of NMDA blockers such as ketamine and dextromethorphan.

Nonglutamatergic postsynaptic receptors that may also be relevant to NP development are those for tachykinins, of which the best studied are CGRP and substance P. The substance P receptor NK-1 is a G protein-coupled receptor, is postsynaptic and distributed almost exclusively within the most superficial dorsal horn layer (layer I), and mostly receives nociceptive-specific afferents. Data from rodent models suggest that tachykinins (notably substance P) are only released under conditions that would entail very severe pain, whereas glutamate release occurs under conditions of lesser stimulus intensity [15]. Partial or total nerve lesions in rats and mice enhance NK-1 expression in the dorsal horn [1], and there is a correlation between the timing of expression changes and that of thermal (not mechanical) allodynia and hyperalgesia behaviors [37,188].

The same nociceptive (especially nonmyelinated) terminals cosynthesize glutamate and substance P, and interactions between receptors for glutamate and neuropeptides are highly likely. For example, the slow depolarization induced by substance P and other neuropeptides is able to open NMDA channels [71,307], and it has been postulated that any excitotoxic lesion in the dorsal horn could give rise, via activation of a kinase signaling cascade (e.g., extracellular signal-regulated kinase [ERK]1/2), to exaggerated expression of both NK-1 (for substance P) and NMDA receptor subunits [308]. This overexpression would be further enhanced by simultaneous downregulation of pre- and postsynaptic opioid receptors, which under normal conditions inhibit the ERK kinase cascade [142].

Lesion-induced changes in nonglutamatergic, non-neuropeptide neurons in layer II of the rodent dorsal horn have been the subject of multiple studies, and results suggest that a C-type protein kinase (e.g., PKC-γ) may be essential for the development of NP in mice. Transgenic mice not expressing PKC-γ show normal responses to acute pain but are extremely resistant to NP after sciatic lesions and do not develop neurochemical changes commonly associated these lesions such as overexpression of NK-1 and neuropeptide Y receptors in the dorsal horn [189]. The localization of

PKC-γ is in a very restricted region of the dorsal horn (IIi layer) [15], and lesion of its afferents may trigger activation of PKC-γ and an ensuing biological cascade, the mastering of which might be therapeutically useful. Unfortunately, neither the exact type of afferents nor the corresponding postsynaptic neurons have been characterized. A newly identified nociceptive pathway originating in a population of nonpeptidergic nociceptors has been described, involving IIi layer interneurons projecting toward projection neurons in deeper horn layers (layer V) and to the amygdala, hippocampus, and globus pallidus [31]. However, this pathway does not appear to involve PKC-γ–containing interneurons.

Attenuation of Spinal Inhibition and Selective Neuronal Loss

The most relevant inhibitory transmitter in the CNS, including within layers I and II of the dorsal horn, where most specific nociceptive fibers project, is GABA. It is an essential regulator of spinal sensory neuron sensitivity, and substantial evidence suggests that alteration of GABA inhibition within the dorsal horn contributes to NP. For example, a decrease in GABA-related postsynaptic inhibitory potentials in superficial dorsal horn layers has been described after partial nerve lesion in rats [201]. Intrathecal instillation of the $GABA_A$ antagonist bicuculline in rodents entails behavioral signs of tactile allodynia and enhances nociceptive reflexes [187,258]. Alteration of GABAergic intraspinal inhibition is generally proposed as a contributing mechanism to NP [262,300], but the relative contribution of functional alterations of inhibitory neurons, neuronal death, and decreased efficacy of GABA on nociceptive neurons remains unknown.

After nerve lesion, hyperactivity of both myelinated and nonmyelinated fibers increases the amount of excitatory amino acids and neuropeptides in the synaptic cleft, setting the stage for excitotoxicity, leading to neuronal death [269]. The final actors of such death include nitric oxide, toxic increases in intracellular Ca^{2+}, and possibly the translocation of certain molecules, such as histone deacetylase 4, from the cytoplasm to the cellular nucleus [29]. Such translocation and ensuing apoptosis can be prevented by the action of BDNF, which is intriguing, taking into account that BDNF appears to contribute to neuronal hyperexcitability too. A relatively simple explanation may account for this. Like other neurotrophins (e.g., NGF and neurotrophins 3–6), BDNF exerts its protective role by inhibiting neuronal death (for a review, see [69]), thus explaining its antiapoptotic action. At the same time, BDNF has strong effects on synaptic plasticity and enhances the release of neurotransmitters such as glutamate and GABA [69]. Liberation of glutamate obviously bolsters neurotoxicity, and that of GABA could also paradoxically contribute to it via the pathological reversal of GABA activity after nerve lesion, which transforms this amino acid into an excitatory, rather than inhibitory, transmitter (see below).

Any disinhibiting mechanism based on neuronal loss implies a lesion of dorsal horn gray matter. Intrinsic cord lesions simultaneously affect the white and gray matter, and it is difficult to distinguish their respective roles in pain generation. Lesion of ascending fibers in the white matter should play a role via deafferentation of supraspinal targets (see below), but we also know that isolated injury to the spinal gray matter, for example in excitotoxic models, can give rise to pain behaviors similar to those observed after traumatic lesions affecting both gray and white matter [181]. In humans, spinal cavitary lesions, such as syringomyelia or hematomyelia, can give rise to pain despite little loss of ascending fibers. In rodents, selective neuronal loss in the dorsal horn after quisqualate injection triggers pain behaviors, such as excessive grooming, mechanical allodynia, and thermal hyperalgesia [305], with intensity directly correlated with the spread of gray matter loss [97]. In contrast, spinal lesions restricted to the white matter ascending funiculus, such as in anterolateral cordotomy, do not generate pain behaviors in rodents unless the lesion also entails damage to the gray matter [282]. In accordance with this, a significantly greater involvement of gray matter is observed in patients with partial spinal lesions and with pain compared to those without pain [77]. All of these data support the notion that the probability of developing pain after a spinal lesion increases with involvement of the dorsal horn gray matter.

A number of other points further indicate that the algogenic effect of gray matter lesions is linked to a loss of GABAergic inhibitory neurons. In rodents, mechanical allodynia after traumatic spinal lesion is associated with a decrease in GABA inhibition adjacent to the lesion [68]. In excitotoxic models of pain, neuronal loss is concentrated in deep dorsal horn layers, where inhibitory interneurons are predominant, whereas the superficial layers, where nociceptive afferents project and where neurons expressing NK-1 and responsible

for segmental nociceptive behavior lie, are selectively spared [305,306].

However, GABAergic neuronal loss might not be necessary for the development of pain in peripheral models of NP [228,230]. Indeed, given that the intrinsic excitability of GABAergic neurons might not be substantially modified by pain-inducing peripheral lesions [250], the decrease of GABA inhibition may not depend on neuronal death but rather on a decrease of GABA synthesis/release or of its efficacy on nociceptive neurons. A possible mechanism likely to decrease the inhibitory efficacy of GABA without modifying the activity of GABAergic neurons has recently been put forward. It stands on the fact that downregulation of the K^+/Cl^- transporter KCC2 in the postsynaptic dorsal horn by peripheral lesions can invert the Cl^- equilibrium potential and increase the intracellular Cl^- concentration, with the result that the opening of Cl^- channels by the action of GABA induces cell depolarization (by exit of Cl^- anions) instead of hyperpolarization [51]. The action of GABA becomes therefore excitatory, as is the case during embryonic development, when GABA is the main excitatory neurotransmitter [20]. Initially described in peripheral lesions, this KCC2-mediated reversal of GABA action has also been shown to be operational in intrinsic spinal injury [169]. The next section will show that neuroinflammation and glial activation are critical for producing such an inversion of GABA action.

Albeit less studied than GABA, glycine is also a major inhibitory transmitter in the spinal cord, and its dysregulation can also contribute to NP. Receptors for both glycine and GABA are often colocalized in dorsal horn neurons [134], and increasing glycinergic activity by intrathecal nicotine administration (via activation of acetylcholine receptors) can decrease tactile allodynia after nerve section in rats [2]. This effect is blocked by glycinergic antagonists, such as strychnine, but resistant to GABAergic blockers, such as bicuculline, indicating that, at least in certain instances, the inhibitory action of glycine can be decisive even in isolation [2]. Miraucourt and colleagues [197,198] have suggested that removal of segmental glycine inhibition with strychnine selectively induces dynamic mechanical allodynia via a low-threshold Aβ input to lamina I neurons. A local dorsal horn circuit may exist, which operates via lamina II neurons expressing PKC-γ and superficial lamina I NK-1 nociceptive-specific neurons. This normally inactive circuit might convert touch into pain provided that, in addition to glycinergic disinhibition, PKC-γ and NMDA receptors are activated [197,198]. Interestingly, the KCC2-mediated reversal of GABA action also affects glycinergic inhibition [129].

Inflammation, Cytokines, and Glial Cells

All types of central and peripheral neural lesions, whether ischemic, traumatic, infectious, or immune mediated, entail an inflammatory reaction, with increased activity of neutrophils and macrophages that rapidly invade the injured axons and dorsal root ganglion. Whereas there may be invasion of the dorsal horn by circulating macrophages, the immune cells primarily activated in the dorsal horn appear to be resident microglial cells (at least at first). Such neuroinflammation has neurotrophic and neuroprotective effects but may be associated with neuronal damage that contributes to NP [81,202]. The main molecular actors in this cascade that affect neuronal function are cytokines, immunoreactive substances secreted by neutrophils and macrophages as well as by activated glial cells. Interleukin-1β (IL-1β), IL-6, and TNF-α are among the most studied proinflammatory cytokines.

The spinal astrocyte and microglial activation observed after peripheral nerve injury is associated with an increased production of intracellular markers such as acidic fibrillary protein. Glial activation can be induced by multiple pathways, including liberation of substance P and glutamate by C-fiber terminals, or of nitric oxide and prostaglandins by superficial dorsal horn layers. Activated glia liberate, in turn, nitric oxide, prostaglandins, and proinflammatory cytokines (IL-1, IL-6, and TNF-α), receptors for which are expressed in both neurons and glial cells. In animal models, glial activation is linked to the development of pain behaviors, and allodynic behavior after spinal lesions in rats is associated with enhanced expression of glial activation-related genes [199].

Understanding of the molecular effects of glial activation is at its beginnings. Expression of an ionotropic purinergic receptor ($P2X_4$) by activated microglia appears to lead to spinal hyperexcitability, given that blocking of the receptor attenuates allodynic behavior after nerve lesion in rats, whereas injection of activated microglia expressing $P2X_4$ can trigger allodynic behavior in intact animals [276]. Activation of $P2X_4$ on microglia results in BDNF secretion, which would support glia-neuron interactions leading to hyperexcitability [272]. The mechanism whereby BDNF can enhance

neuronal excitability would in turn depend on an inversion of the GABA/glycine effect on interneurons, as described above; BDNF drives a decrease in KCC2, which results in an increase in intracellular Cl^- and hence a depolarizing shift in the anionic equilibrium potential, therefore reducing, if not inverting, the effects of Cl^- channel opening by glycine and GABA [50].

Although clear clinical correlates are still lacking, these discoveries provide a potential basis for the development of new analgesic therapies. For example, inhibition of glial metabolic activity or of BDNF also decreases hyperalgesia and allodynia in animal models [50], including those similar to actual clinical conditions such as brachial plexus avulsion [232]. In addition, procedures that counteract the action of proinflammatory cytokines, such as blockade of their spinal receptors [196,213], injection of specific antibodies [260], or administration of anti-inflammatory cytokines such as IL-10 [227], can lessen allodynic behavior triggered by nerve or spinal lesions. Closer to everyday clinic findings, administration of a common nonsteroidal anti-inflammatory drug (ketorolac) was found to decrease NP behavior just after nerve injury [173], which may open interesting and perhaps practical therapeutic avenues.

The Brainstem

Projections of the nociceptive dorsal horn to brainstem and thalamic structures trigger descending loops back to the dorsal horn, which modulate the spinal transfer of nociceptive transmission. A number of arguments suggest that some of these loops involving the brainstem participate in NP maintenance. Postlesional tactile allodynia in rodents can be abolished not only by destruction of the dorsal columns and dorsal column nuclei; [215,263,264]) but also by selective damage to dorsolateral pathways in the spinal cord [214], suggesting that it may depend not only on ascending input but that it can be maintained by descending influx from the brainstem.

In rodents, thermal hyperalgesia is not abolished by dorsal column ablation, but it can be blocked by injection of lidocaine or cholecystokinin receptor antagonists in the ventromedial medulla (nucleus raphe magnus). Given that this region is the source of abundant descending projections to the spinal cord, it is thought that enhanced ascending input secondary to a peripheral or spinal lesion can trigger descending facilitation phenomena integrated in the medulla and involving cholecystokinin receptors (for a review, see [279]). Such facilitatory activity would not operate in the initial development of allodynia but rather contribute to its maintenance. For example, sectioning descending projections before ligating a peripheral nerve does not block mechanical or thermal allodynia but considerably decreases their duration [35]. McMahon and Wall [193] also described a pathway between layer I neurons and the caudal mesencephalon, with positive retroaction toward the nociceptive neurons initiating the loop. Bulbospinal input can also activate postsynaptic sympathetic neurons, which might therefore contribute to the maintenance of NP [121]. All of these results support a relatively new concept broadly supported by results from Porreca's group, namely that once initiated, maintenance of central sensitization in the dorsal horn needs the contribution of descending facilitation from the brainstem, in particular from the ventrolateral medulla [280], such descending input being likely fueled by serotonin (5-HT) acting via 5-HT3 receptors [265,266].

Of course, not all bulbospinal loops are facilitatory to pain. Neural lesions inducing NP also trigger inhibitory descending inputs through spinobulbospinal loops, activation of which delays or inhibits autotomy behavior [242]. Feedback systems controlling pain and involving the brainstem have been known for many years [45]; they involve descending serotonergic and noradrenergic input from the lower brainstem through the dorsolateral funiculus and are considered to underlie the pain-relieving effects of tricyclic antidepressants (for a review, see [65]) and in part that of peripheral or spinal neurostimulation [13,162]. Other ascending-descending loops, such as the diffuse noxious inhibitory controls, involve integration in the dorsal reticularis medullary nucleus [283].

It is indeed puzzling that all of these systems, facilitatory and inhibitory, may be simultaneously activated by noxious ascending impulses and share the same anatomic pathways, at least at the macroscopic level. It appears clear that the respective contributions and interactions of the facilitatory and inhibitory mechanisms will be important factors in the (eventual) development of clinically relevant NP. Given that the effects of neurotransmitters depend on the specific receptors that they activate, it is important to note that serotonin receptors may be either pro- (5-HT3) or antinociceptive (5-HT1/5-HT2) [14], whereas all noradrenergic central receptors are antinociceptive, hence proposing a possible explanation for the well-known superiority of mixed

antidepressants (involving both norepinephrine and 5-HT) relative to selective inhibitors of serotonin reuptake.

Thalamocortical Mechanisms

Thalamocortical structures not only change their activity in response to abnormal ascending input [194], but they can also generate NP after intrinsic lesions [59,85,87]. Given that validated models of central NP owing to pure thalamic or cortical lesions are scarce (but see [287]), most available data concerning these lesions come from studies conducted in humans, with the inherent limitations linked to the impossibility of inducing controlled lesions and correlating molecular and cellular changes with behavior. Nonetheless, studies in humans have the nontrivial advantage of allowing for immediate verbal responses concerning the pain experience, including the important distinction between spontaneous and evoked pain, instead of the inherently ambiguous behavioral responses of animals.

Thalamic Changes in Neuropathic Pain

Increased neural thalamic excitability, marked by enhanced spontaneous and evoked somatosensory thalamic activity and increased receptive fields, has been shown in animal models of partial nerve or spinal lesion [94,101,284,291]. Signs of abnormally increased activity in the somatic lateral thalamus, as indexed by an enhanced concentration of K^+, have also been described after rhizotomy in rats [146]. Work on rat models of spinal lesions suggest that such hyperexcitability may depend on overexpression of embryonic $Na_V1.3$ Na^+ channels [289,311], and indeed injection of oligodeoxynucleotides blocking the expression of $Na_V1.3$ channels decreases both neural hyperactivity and hyperalgesic behavior [103]. These data suggest that intrinsic changes in the thalamus can yield additional amplification of abnormal ascending signals, which persists even after suppression of the abnormal ascending input [103], in line with hypotheses put forward by Albe-Fessard and Rampin [4]. However, channel overexpression may not be a necessary condition for the development of NP, which can also be generated by nerve lesion in mice with genetically absent $Na_V1.3$ channels [205].

A different type of abnormal thalamic activity after deafferentation has been described in rats [166,277] and in humans with deafferentation NP [118,119,154,155,164,199,238]. Such activity is formed by high-frequency action potential bursts (400–600 Hz intrinsic frequency) repeating at 8 to 10 Hz in rodents or 3 to 4 Hz in humans, that have sometimes been termed epileptoid [4]. The intrinsic features of these bursts are quite stereotypical and consistent with the well-known low-threshold Ca^{2+} spike bursts (LTS), which are exceedingly rare in awake intact animals [235,254] but typical of tonically hyperpolarized neurons during slow-wave sleep [163,261]. In patients with NP, this activity might be the result of chronic hyperpolarization, owing to thalamic deafferentation with loss of excitatory input, and it has been proposed that it might contribute to generate and/or perpetuate NP [119]. Suppression of this activity by therapeutic lesions of the medial thalamic nuclei has been used with some success to treat NP [120]. However, neither this procedure, nor its replacement by rapid activity via thalamic electrical stimulation, can achieve pain control in more than 40% to 60% of patients [27,120]. This, together with the observation that NP can arise in the absence of a functional sensory thalamus [217] and that similar LTS thalamic bursting can occur in other nonpainful situations [180,233], indicates that the above abnormalities are not necessary conditions for NP to develop.

In accordance with the above data, functional imaging in humans, both of glucose metabolism [55,107,116] and regional blood flow [36,66,111,147,216,219], has repeatedly shown signs of metabolic depression in the thalamus contralateral to the site of NP. It has been shown that such hypoactivity does not merely reflect lesion or deafferentation [86,111], and a direct link between thalamic hypometabolism and thalamic rhythmic LTS-like bursting was suggested in patients with central poststroke pain by Hirato and colleagues [108]. The link between thalamic hypoactivity and NP is supported by its reversibility in response to pharmacologic analgesia [36,111], ablative therapeutic procedures [66,216], or therapeutic neurostimulation [54,83,86,132,219]. However, as is the case with LTS bursting, whereas thalamic hypoactivity appears to be robustly associated with NP, its reversibility (i.e., increased blood flow) does not guarantee pain relief. Peyron and colleagues [219] were the first to describe an increase in thalamic blood flow in two patients who underwent motor cortex stimulation (MCS), only one of whom was effectively relieved of pain. Other instances of dissociation between reversal of thalamic

hypoactivity and reversal of pain have been described [73,147], and in a series of patients with NP undergoing trigeminal or cortical stimulation, the increase in thalamic activity was not associated with the clinical effect, whereas that in other cortical structures was [88,294]. Taken together, these results support several conclusions, namely (a) thalamic metabolic depression appears to be significantly linked to NP pathophysiology; (b) this abnormality can be related to the electrophysiological activities typical of hypoactive states also demonstrated in the NP thalamus, including LTS-like rhythmic bursts; and (c) such phenomena can be reverted by different therapeutic actions but such reversibility does not ensure successful analgesia.

Microglial activation comparable to that described in the spinal cord can also occur in the brainstem and thalamus, either from direct lesions [287] or transsynaptically as a result of retrograde or anterograde projection from the primary lesion focus [11], as occurs after limb amputation. As in the spinal cord, microglia activation may lead to the emergence of functional compartments in which ILs and other signaling molecules may change cell-cell communication, including by altering the properties of normally inhibitory neurotransmitters (see above), and therefore may be related to the emergence of central sensitization and plasticity phenomena in the cerebral cortex [11].

Cortical Functional Abnormalities in Neuropathic Pain

Thalamic abnormalities can be translated to the cortical stage. In cats, a small percentage (~10%) of cortical cells are able to develop LTS-like activity when hyperpolarized [210]. An increase in the number of bursting cells has been described in cats after peripheral nerve section [75,290]. Although the possible role of these activities in relation to NP development remains unknown, it has been proposed that rhythmic activity in the cortex might reflect that previously described in the thalamus and perhaps support abnormal pain perception [164,248]. These results have not yet been reproduced. Three functional abnormalities in cortical responses have been consistently reported in patients with NP, as described below.

Functional Depression of Ventromedial Prefrontal Regions in Neuropathic Pain

Although local metabolic or blood flow increases in patients with NP have been reported in numerous subregions of the insular, posterior parietal, prefrontal, and cingulate cortices (for reviews, see [8,148,222]), these are mostly anecdotal reports which have not been consistently reproduced. A notable exception to this is the dampened responses of the perigenual cingulate and orbitofrontal cortices (i.e., ventromedial prefrontal cortex [PFC]), which have been consistently described in patients with NP. A conspicuous feature of neuropathic (relative to experimental) allodynia is indeed lack of activation of the ventromedial cortices, and a recent grouped survey of 39 published reports showed that the incidence of ventromedial frontal activation is significantly less in neuropathic than in experimental allodynia, whereas the middle and anterior cingulate cortex sections (MCC and ACC, brain areas 24–32) were equally activated in both instances [89]. The response shortfall of the ventromedial PFC in human neuropathic allodynia has been reproduced by many independent groups and in different pain models, including central poststroke pain [220,221], syringomyelia [70], peripheral neuropathy [185,218,251], trigeminal or postherpetic neuralgia [19,93], and complex regional pain syndrome (CRPS) [183]. Incidental dampened perigenual responses have also been reported during ongoing NP [111]. Some reports underscore the large variability of perigenual activation, which could be present in individual patients yet absent by group analysis, and suggest that high preactivation levels owing to background pain might prevent further increases in neuropathic allodynia [298]. However, such a ceiling effect appears unlikely; ventromedial frontal activity in NP can even decrease during allodynic pain [149,220] or be negatively correlated with pain intensity [93], and in healthy subjects, significant ongoing pain owing to previous capsaicin injection does not prevent ventromedial activation during experimental allodynia [150,184,297].

In support of a relevant role of perigenual depression in NP, all types of analgesic procedures in humans (pharmacological, stimulative, and placebo) enhance perigenual and orbitofrontal activity, hence compensating for their functional depression [3,43,54,111,244,278,294; reviewed in 88]. Whether lack of activity in the ventromedial cortices is causal or consequential with regard to NP remains debated. The perigenual and orbitofrontal cortices integrate cognitive and emotional information [130], are crucial to adapt to physiological challenges, and support production and regulation of affective states [156,224]. This region is also the source of descending connections triggering opioid-mediated inhibition of pain signals

via the periaqueductal gray [16], and pain relief in human NP has been associated with enhanced functional connectivity between the perigenual and periaqueductal gray regions [88].

Chronic stressors entail morphological changes in the ventromedial PFC; prolonged immobilization simplifies the branching and shortens apical dendrites of rat ACC neurons—damage reversible by a stress-free period [234]. Such structural changes lead to functional depression and may result from a release of glucocorticoids and excitatory amino acids via PFC glutamate neurotransmission (for a review, see [200]). As a chronic stressor, NP might also trigger the above cascades and lead to decreased responsiveness of the ventromedial PFC as a consequence rather than a cause of chronic NP. This is consistent with the fact that similar ventromedial depression has been reported in patients with chronic nonneuropathic pain [125]. In turn, weakening of ventromedial PFC function may decrease descending pain-inhibitory signals, with relative unleashing of ascending noxious input and therefore still increased pain. As a maladaptive consequence of persistent pain, lack of ventromedial responsiveness would not only change the subjective appraisal of the pain experience but also limit the system's capacity to react adaptively to ascending pain signals.

Changes in Interhemispheric Activation Balance

Hemodynamic activation of the contralateral operculoinsular (OI) cortex in experimental pain is more frequently reported than that of its ipsilateral counterpart, whereas ipsilateral activation has been reported to predominate in neuropathic allodynia. Such paradoxical lateralization has been described both in patients with cortical damage and in peripheral neuropathy and spinal injury [70,218,221,223,251,298]. In accordance with these data, a recent meta-analysis of functional imaging data showed the insula activated bilaterally in experimental hyperalgesia but ipsilaterally in patients with NP [153]. This ipsilateral overreaction might be mechanistically related to painful symptoms and possibly supported by disinhibition of ipsilateral thermoalgesic pathways. It has been estimated that approximately 17% of primate spinothalamic axons project to the ipsilateral thalamus [9,47], and abundant clinical data indicate that ipsilateral transmission, normally suppressed when both spinothalamic pathways are intact, may become functional after a unilateral lesion [30,42,135,203,204]. Poststroke allodynia can be abolished by a new lesion involving OI areas ipsilateral to the pain [53,105]. Under physiological conditions, OI activity contralateral to the stimulus is thought to tonically inhibit its ipsilateral counterpart [30,135,203]. Such inhibition is overcome only at intensely noxious levels [115,186,297], and therefore any enhancement of ipsilateral OI responses might be physiologically encoded as a signal specifically associated with very strong nociceptive input. Disinhibition of ipsilateral responses after a neuropathic lesion might also be interpreted by perceptive networks as a signal that the magnitude of the stimulus is abnormally high. According to this perspective, overactivation of the ipsilateral OI region would directly contribute to a perceptive bias sustaining the subjectively enhanced sensation [89].

Changes in Cortical Opioid Receptors in Human Neuropathic Pain

The distribution of opioid receptors in the human brain was first shown in vivo in the early 1990s via the use of specific radiotracers and positron emission tomography and is now well characterized [18,122,123]. Different groups have reported significant decreases in tracer fixation both at the thalamocortical and brainstem levels in patients with peripheral or central NP. In peripheral NP, such a decrease appeared to be bilateral and symmetrical and was interpreted as the reflection of endogenous opioid release secondary to chronic pain [175]. A more important decrease in opioid binding was observed in patients with central pain secondary to stroke, which was lateralized toward the hemisphere bearing the lesion and contralateral to the pain [124,175,295,296]. Such lateralized abnormalities suggest specific opioid receptor loss or inactivation in receptor-bearing neurons. Decreased opioid binding could not be explained by tissue necrosis because it was much more extensive than the brain anatomic lesions and was not colocalized with them. Metabolic depression (diaschisis), degeneration of receptor-bearing neurons, or receptor internalization therefore appears to be a more likely pathophysiological explanation.

The relation between abnormalities in opioid receptor density and the development of NP is far from clear, especially because no study has yet compared opioid receptor density in patients with similar lesions, having or not developed NP, and because central NP is often refractory to opioid therapy. However, data from neurostimulation procedures suggest some

link between the functional state of the brain opioid system and pain relief. For example, analgesic stimulation of the motor cortex in patients with NP triggers changes consistent with enhanced occupancy of opioid receptors in the anterior cingulate and periaqueductal gray by endogenous endorphins, and this effect is related to analgesic efficacy [176]. In accordance with this, the level of remaining functional opioid receptors in patients with NP has been recently shown to be a significant predictor of subsequent MCS efficacy [174].

Cortical Plasticity and Neuropathic Pain

Injuries to subthalamic somatosensory structures can trigger deep anatomical and functional changes at both the thalamic and cortical levels [126,128] including topographic modifications of somatotopic sensorimotor representations, which may change very rapidly, just minutes after a peripheral lesion [32,239]. In the long term, this phenomenon can result in drastic changes in somatotopic thalamic and cortical maps [128,299]. Mechanisms underlying these maladaptive plastic changes are related to a loss of GABAergic inhibition, glutamate-mediated long-term potentiation, and structural alterations such as axonal sprouting [79], and some investigators have proposed a link between the importance of this particular type of plasticity in the S1 cortex and the emergence of postamputation phantom pain [79,80]. Given that such reorganization has been reported to regress after successful pain-relieving therapies [26,168], it has been suggested that interventions designed to reverse these maladaptive changes may be beneficial for the prevention and treatment of phantom limb pain [79]. Despite the attractiveness of these hypotheses, establishing a direct link between plasticity in S1 networks and NP is challenging for several reasons. The primary somatosensory cortex is not a crucial region for the processing of nociceptive afferents; less than 10% of spinothalamic system projections may reach S1 in primates, whereas >70% project to the posterior OI cortices [72]. In accordance, selective lesions of S1 rarely entail deficits in pain perception in humans [136], whereas OI injury consistently attenuates pain perception [87,98]. Identical plastic changes in S1 representations after amputation have recently been described in patients with or without postamputation pain [256], and direct stimulation of the somatosensory cortex can expand the sensory hand representation [268] but does not attenuate pain perception [109] and may even exacerbate it [274,275]. Functional changes within the S1 in patients with NP might then be viewed as a simple indication of the capacity of somatosensory lesions at any level to exert influences over cortical networks more directly related to cortical integration of the pain experience [89].

Conclusions

In response to injury, the nervous system undergoes changes in an attempt to re-establish synaptic transmission. These changes entail functional modifications not only at the injury site but also at all levels rostral to it, and NP is just one epiphenomenon resulting from these changes. The data reviewed here should underscore the importance of preventing long-term changes that result from persistent injury, as well as the importance of animal models to understand subtle mechanisms but also their inability to fully account for the complex phenomenon of NP in humans. The pain experience is a cortical phenomenon, and relevant data on its underlying cortical networks can be obtained in humans by the use of minimally invasive procedures. Whereas molecular phenomena remain inaccessible to direct investigation in humans, no particular level of explanation is of greater importance than another to explain the phenomenon in its entirety. Only the simultaneous access to macro- and microscopic levels, from molecules to those cortical networks, will allow for understanding of the phenomena of aberrant learning giving rise to NP.

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