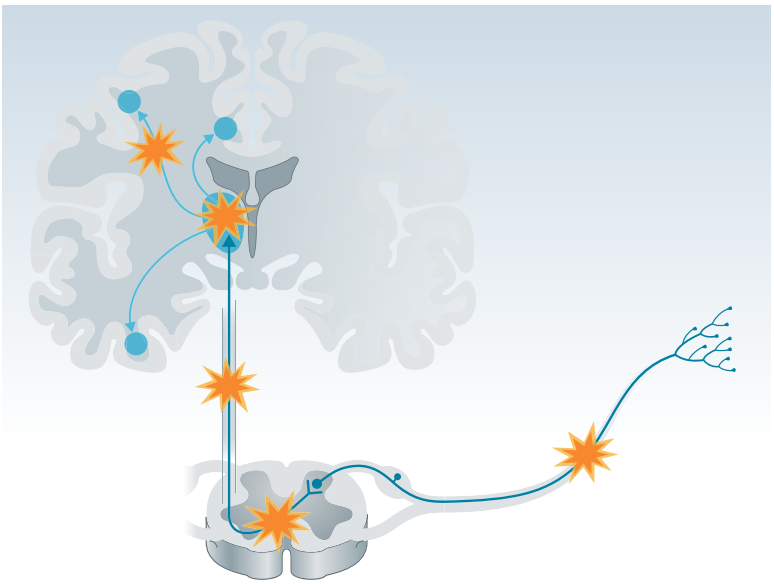
Physiological Reviews Review Article

NEUROPATHIC PAIN: FROM MECHANISMS TO TREATMENT

GRAPHICAL ABSTRACT



AUTHORS

Nanna Brix Finnerup, Rohini Kuner, Troels Staehelin Jensen

CORRESPONDENCE

finnerup@clin.au.dk

KEYWORDS

allodynia; ion channels; immune cells; neuropathic pain; pharmacology; primary neuron; spinal cord circuits

CLINICAL HIGHLIGHTS

This is a review of the recent advances in understanding neuropathic pain. It covers the clinical presentation, physiological mechanisms, and treatment of neuropathic pain. The pathophysiology involves ectopic activity in damaged nerve fibers and peripheral and central sensitization. Understanding how various neurochemical, inflammatory, and structural mechanisms are linked to specific clinical presentations of the pain may improve rational pain treatment.

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NEUROPATHIC PAIN: FROM MECHANISMS TO TREATMENT

Nanna Brix Finnerup, Rohini Kuner, and Troels Staehelin Jensen

Danish Pain Research Center, Department of Clinical Medicine, Aarhus University, Aarhus, Denmark; Department of Neurology, Aarhus University Hospital, Aarhus, Denmark; and Department of Pharmacology, Heidelberg University, Heidelberg, Germany

Finnerup NB, Kuner R, Jensen TS. Neuropathic Pain: From Mechanisms to Treatment. *Physiol Rev* 101: 259–301, 2021. First published June 25, 2020; doi:10.1152/physrev.00045.2019.—Neuropathic pain caused by a lesion or disease of the somatosensory nervous system is a common chronic pain condition with major impact on quality of life. Examples include trigeminal neuralgia, painful polyneuropathy, postherpetic neuralgia, and central post-stroke pain. Most patients complain of an ongoing or intermittent spontaneous pain of, for example, burning, pricking, squeezing quality, which may be accompanied by evoked pain, particular to light touch and cold. Ectopic activity in, for example, nerve-end neuroma, compressed nerves or nerve roots, dorsal root ganglia, and the thalamus may in different conditions underlie the spontaneous pain. Evoked pain may spread to neighboring areas, and the underlying pathophysiology involves peripheral and central sensitization. Maladaptive structural changes and a number of cell-cell interactions and molecular signaling underlie the sensitization of nociceptive pathways. These include alteration in ion channels, activation of immune cells, glial-derived mediators, and epigenetic regulation. The major classes of therapeutics include drugs acting on $\alpha_2\delta$ subunits of calcium channels, sodium channels, and descending modulatory inhibitory pathways.

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This is a review of the recent advances in understanding neuropathic pain. It covers the clinical presentation, physiological mechanisms, and treatment of neuropathic pain. The pathophysiology involves ectopic activity in damaged nerve fibers and peripheral and central sensitization. Understanding how various neurochemical, inflammatory, and structural mechanisms are linked to specific clinical presentations of the pain may improve rational pain treatment.

I. INTRODUCTION

Pain is an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage (232, 399a). The English neurologist George Riddoch in a classical paper from 1938 stated about pain: "it is experienced only intermittently in the life of the healthy, its neural mechanisms lying dormant, but vigilant, ready to be awakened if the tissues of the body are threatened" (414). As such, pain is a warning about tissue damage signaled by specific receptors and fiber systems extending from the periphery to the brain. When the normal pathways are damaged, the immediate consequence is loss or reduction of function including pain. However, in some cases as a result of the lesion, pain develops, a condition termed neuropathic pain. The International Association for the Study of Pain (IASP) defines neuropathic pain as pain caused by a lesion or disease of the somatosensory nervous system (232). This definition replaces an older definition according to which neuropathic pain was "pain initiated or caused by a primary lesion, dysfunction, or transitory perturbation of the peripheral or central nervous system" (324). Two changes are important in this change of definition: dysfunction and the neuronal lesion. In the new definition of neuropathic pain, dysfunction is no longer accepted as a criterion because it is difficult to accept symptoms and soft signs as criteria if they cannot be verified objectively. In

addition, it is now specified that the lesion needs to affect the somatosensory system meaning that lesions or diseases outside the somatosensory pathways, e.g., the cerebellum, does not qualify as neuropathic (unless future studies document that such structures are part of the somatosensory processing system) (536). The new definition means that a condition like chronic regional pain syndrome type 1 (CRPS 1) is not considered a neuropathic pain syndrome because the afferent somatosensory system is intact. Yet these patients do present with several of the positive symptoms encountered in patients with neuropathic pain. The importance to distinguish between chronic pain due to disease or lesion of the somatosensory system serves the purpose to delineate the specific characteristics and possibly mechanisms of these conditions.

When lesions of the nervous system occur peripherally or centrally, they may cause sensory loss in the innervation territory of damaged nerves or in those body parts that correspond to a spinal or brain territory that has been damaged directly or indirectly by a lesion or disease. So, an important distinguishing feature in most neuropathic types of pain is the paradoxical combination of sensory loss and pain either with or without sensory hypersensitivity phenomena in the painful area (139, 491). A large group of conditions that differ not only in their underlying etiology but also in their anatomical localization are associated with neuropathic pain (443).

II. HISTORY

Pain following injury to the nervous system has been known under different headings such as nerve injury pain, neuralgia, deafferentation pain, neurogenic pain, and central pain. However, in most instances and now also recognized by IASP, the term *neuropathic pain* is used to avoid any postulated mechanism or a specific anatomical location of the lesion. The history of neuropathic pain reports is long with contributions from many extraordinary and exceptional scientists over the last 100–150 yr. Only a few highlights from the neuropathic pain history will be mentioned.

Silas Weir Mitchell, considered the father of neurology in the United States, described in detail his experiences from examining and treating victims from the Civil War in America. In the monumental book *Injuries of Nerves and Their Consequences*, Mitchell wrote in the chapter on sensory functions of nerve injury (327): "Heightened sensibility, or that state in which agents usually felt, as touch only, become painful, is sufficiently common after many forms of injury. . .." This description by Mitchell in 1872 is probably the first example of allodynia (pain due to stimulus that usually does not produce pain). Mitchell continues: "I have never been able to discover that the tactile sense had been thus over-excited so that Weber's points could be distinguished as two, where otherwise they could have been felt as one. When, indeed, there is hyperesthesia for pain, we are apt to find it associated with lessened or lost power of tactile appreciation. . ." showing that the loss of sensibility in the painful territory is an equal important sign of neuropathic pain. Mitchell gave here also the first description of causalgia, now known as chronic regional pain syndrome type II (207, 208). Following these first descriptions of the presentation of pain syndromes after nerve injury, others followed by Foerster, Riddoch, and Livingston (151, 293, 413, 415). The structure of the nervous system was a key topic for the Spanish neuroanatomist Santiago Ramon y Cajal. In his classical book on degeneration and regeneration of the nervous system (401), Cajal described the consequences of complete and incomplete spinal nerve transections. He elaborated on this in his Noble lecture "The structure and connexions of neurons." Cajal emphasized here the "neurone doctrine," which states that neurons are individual cells with dendrites and axons and that these cells function independently of each other with gaps between them (later known as synapses) (34). Cajal used the silver nitrate stain developed by Camillo Golgi to document that nerve cells are in contiguity, while Golgi believed the nervous system more acted as a reticular system where the cells were in continuity like a spider web. Golgi and Cajal, who shared the Nobel Prize in 1906 for their studies on the nervous system, met only in Stockholm to receive the award and disagreed heavily. Golgi gave his Nobel lecture first, defending his hypothesis of "reticular" neural networks, which was strongly opposed by Cajal. Among Cajal's many groundbreaking results, he demonstrated the consequences when nerves were transected. **FIGURE 1** shows such an example, with degeneration, regeneration, and signs of reinnervation into the tissue and attempts to reach the distal end of the severed nerve end.

Henry Head, a neurologist in London, was interested in the functional consequences of nerve injury. In a remarkable study, Rivers and Head described the findings following injury to two cutaneous nerves done by the surgeon Mr. Dean on Henry Head's own forearm. The sensory findings were followed meticulously over the following 4 yr with almost weekly examination of the sensory changes on Head's forearm for various type of sensory stimuli. The findings were described by Rivers and Head in 1908 in a monumental paper of 127 published pages in *Brain* (417). In this monumental paper, Head introduced his theory of the epicritic and protopathic sensitivity of the somatosensory system. The epicritic system refers to precise well-localized touch and discriminatory thermal sensory stimuli and the protopathic sensitivity to poorly localized and painful sensations. The epicritic and protopathic systems would correspond to large and small fiber functions, respectively. Rivers and Head found that the protopathic system was the first to recover and that the protopathic sensory system could be modified by epicritic sensations. These findings were the first indication of the gate control theory, which was later to be presented by Melzack and Wall (323). Here, they gave their

explanation for the dynamic activity of the nociceptive system and that activity in fast nerve fibers blocks activity in slow nerve fibers. Wall and Gutnick later showed what happened after a nerve transection with generation of abnormal spontaneous activity from regenerating nerve fibers (522). The spontaneous activity could be modulated by different types of stimuli, an indication of neuroplastic changes in the nervous system. This was further documented in other studies showing the behavioral and electrophysiological changes after nerve transection (103–105). Here they proposed a presynaptic inhibitory mechanism for a dynamic interaction between afferent input into the spinal cord. While the concept of interaction between different types of afferent input into the spinal cord still is accepted, the idea of a presynaptic inhibition has clearly been challenged by others (160, 552). Somewhat in contrast to the Melzack and Wall gate control theory, work by Christensen and Perl (69) showed that neurons in the marginal superficial zone of the dorsal horn are exclusively activated by peripheral noxious input. This and other work indicate that there is a certain specificity in processing pain. The complexity of the dorsal horn in pain processing, in particular the role of the substantia gelatinosa, remains and has been extensively reviewed (59). Although the pattern theory laid out by the gate control theory is now considered too simplistic, it raised the important issue that destroying nerve fibers or other peripheral or central areas involved in processing pain is probably not a way to cure pain, but may in fact be a paradoxical reason itself for pain. Woolf (531) found that also central mechanisms contributed to the hypersensitivity seen after peripheral injury. These studies on nerve injury represented also the start of a series of new studies on experimental models of neuropathic pain and the associated behavior. Bennett and Xie (33) described the functional changes after induction of mononeuropathy to the sciatic nerve by placing loosely constrictive ligatures around the sciatic nerve. Hypersensitivity changes to mechanical and thermal stimuli developed in the hindpaw after this sciatic nerve injury.

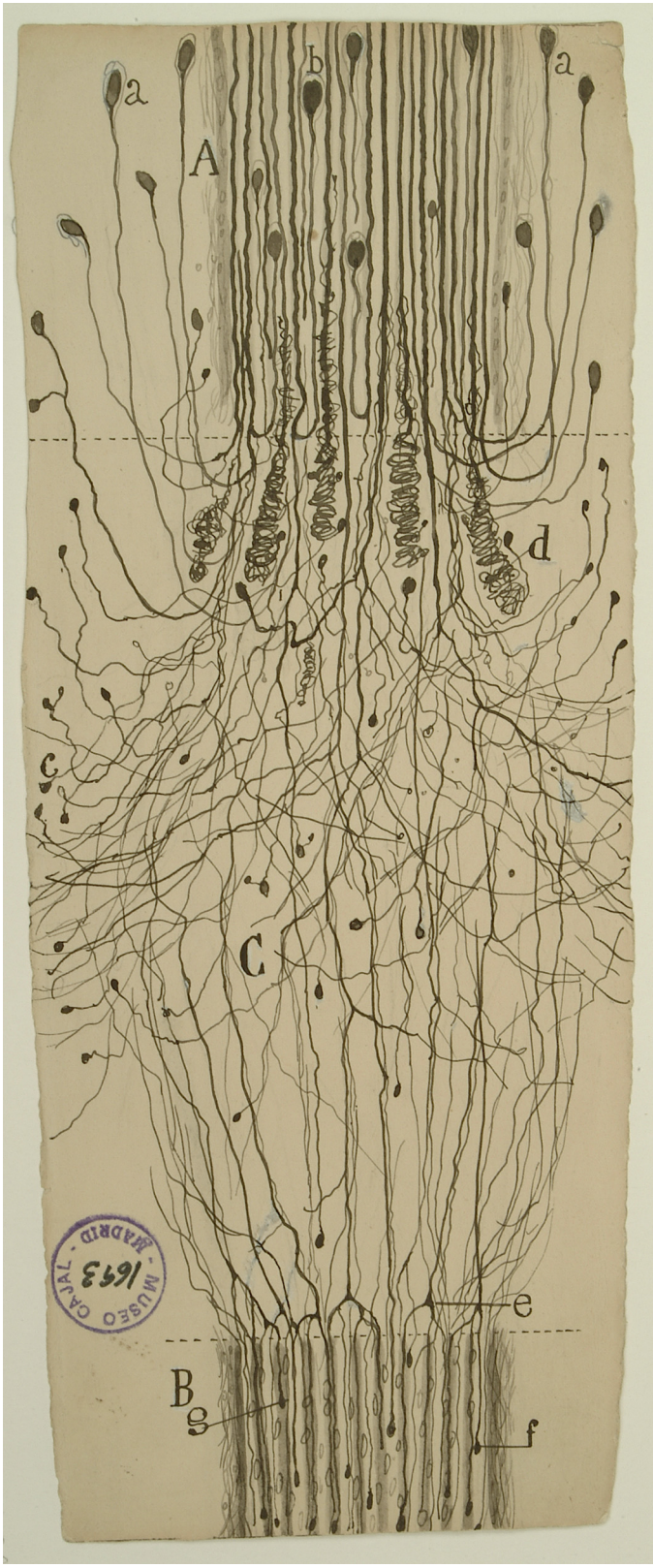

FIGURE 1. Cajal original drawing number 1693. Cajal's drawing of a complete transection of a nerve demonstrating regenerating nerve sprouts (black dots on nerve fibers) from the proximal stump of the severed nerve end (*A*). Sprouts are seen growing down into the distal stump of the nerve (*B*), marked as *f* and *g* in the figure. A chaotic reinnervation occurs at the transection site (*C*) with fibers projecting towards the distal end curving back towards the proximal end and with several fibers forming organized spirals of degenerating and regenerating fibers (401). [From Ramon y Cajal et al. (401). Courtesy of Instituto Cajal (CSIC), Cajal Legacy, Madrid.]

Lesions of the central nervous system are another well-known cause of neuropathic pain. This pain, also known as central pain, was first described by Dejerine and Egger in 1903 where they reported a case of acute stroke in a 76-yr-old woman with left-sided paralysis followed by pain and sensory abnormalities (90). Head and Holmes described cases of thalamic lesions with pain and ipsilateral sensory disturbances (217), and Riddoch concluded that central pain was not only seen in thalamic lesions, but occurred also with injury to pontine and medullar part of the brain stem but surprisingly not to the mesencephalon (414). Today it is known that stroke or other lesions damaging the somatosensory pathways from the

spinal cord to cortical structures may be accompanied by neuropathic pain (FIGURE 2).

III. DIAGNOSIS

There is no gold standard or specific set of methods or biomarkers that can document neuropathic pain. Certain neuropathic pain conditions like postherpetic neuralgia, painful diabetic neuropathy, and central poststroke pain can pose diagnostic problems, but the underlying cause is obvious. For certain mixed conditions it may be even more difficult to delineate the boundaries for neuropathic and non-neuropathic pain. With these limitations for a neuropathic classification system, what are the essential requirements for a classification? According to Woolf et al. (532), a classification should be valid (i.e., the grouping correspond to a specific pathological mechanism), reliable (i.e., correspondence

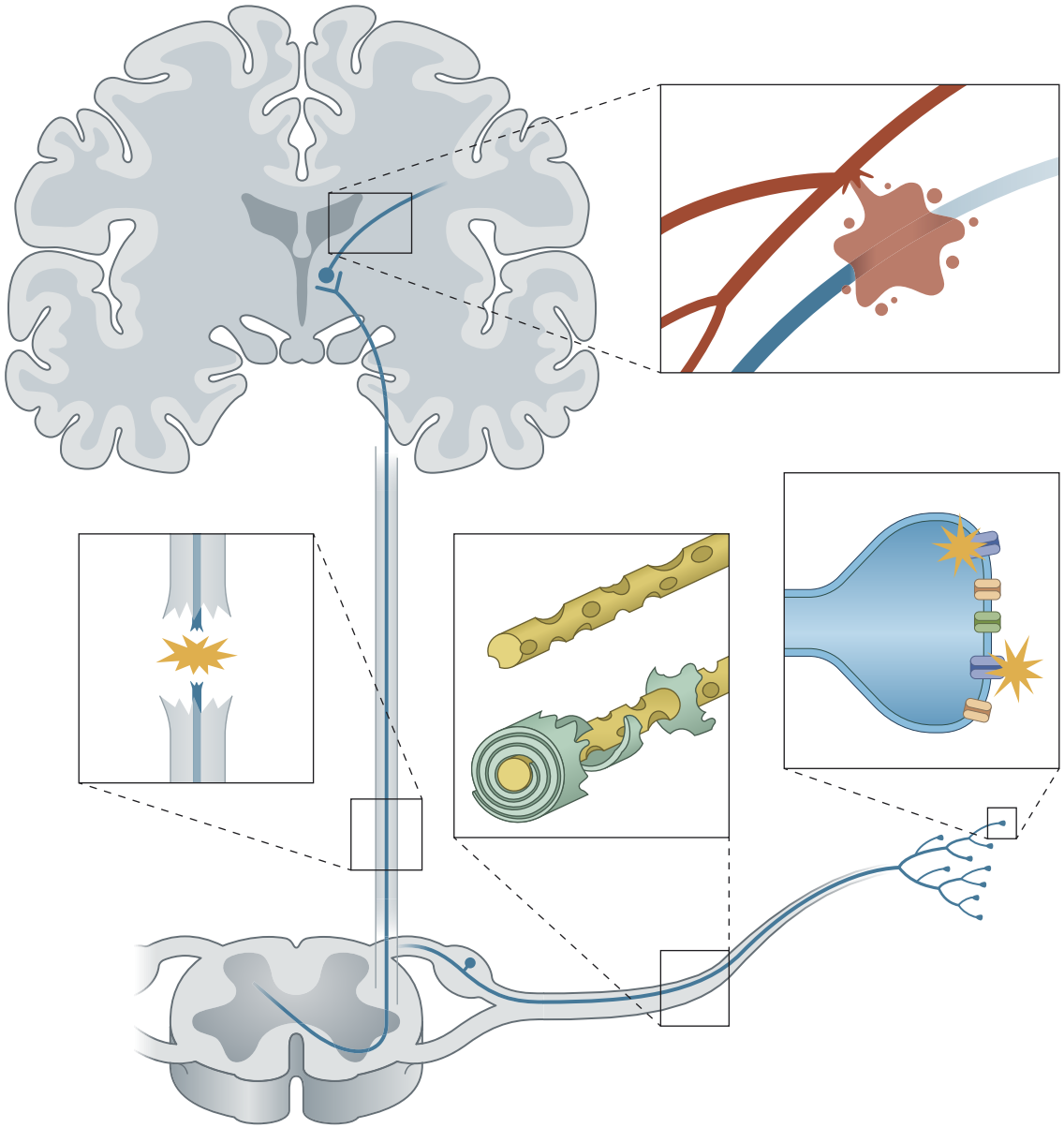

FIGURE 2. Lesions of the nervous system from the peripheral nociceptor to the cortical brain may give rise to neuropathic pain. The figure illustrates four typical examples of lesions. In the periphery at the receptor level, mutation in genes may give rise to changes of receptors and ion channels that underlie certain rare neuropathic conditions such as erythromelalgia and paroxysmal extreme pain disorder. Along the peripheral nerve, different types of lesions may damage either the entire nerve or selectively the axons or myelin causing axonal or demyelinating neuropathies, respectively. In the central nervous system, lesions of the spinal cord as seen for example following traumatic injury or in multiple sclerosis may lead to central neuropathic pain. In particular, lesion of the spinothalamic tract is critical for the development of central pain. In the brain, lesions such as ischemic stroke, hemorrhages, or multiple sclerosis plaques in the brain stem, thalamus, or subcortical structures are examples of diseases that may lead to central neuropathic pain.

between examiners and between results from one time point to the next), and finally, generalizable (i.e., applicable to all conditions, mild as well as severe). The dynamic nature of the nociceptive system especially under abnormal conditions may be an obstacle for finding such universal classification. When diseases and disorders are dominated by symptoms, which are merely subjective, and the associated clinical signs are few or nonexistent, the requirement for validity and reliability becomes even more demanding. Different scales and questionnaires have during the years been developed in an attempt to demonstrate discriminative features between neuropathic and non-neuropathic pain states. But, at this point, no studies have provided a classification of symptoms and signs and a scoring system, where the above requirements are fulfilled. For that reason, a hierarchical system has been developed, which is based on a grading of evidence for the presence of neuropathic pain. This grading system was presented in 2008 (491) and has recently been updated (139). According to this grading system, neuropathic pain is divided into three classes: possible, probable, and definite neuropathic pain **(FIGURE 3)**. The different levels are determined on the basis of neurological history, the distribution of pain, the presence and location of sensory signs, and finally on a confirmatory test.

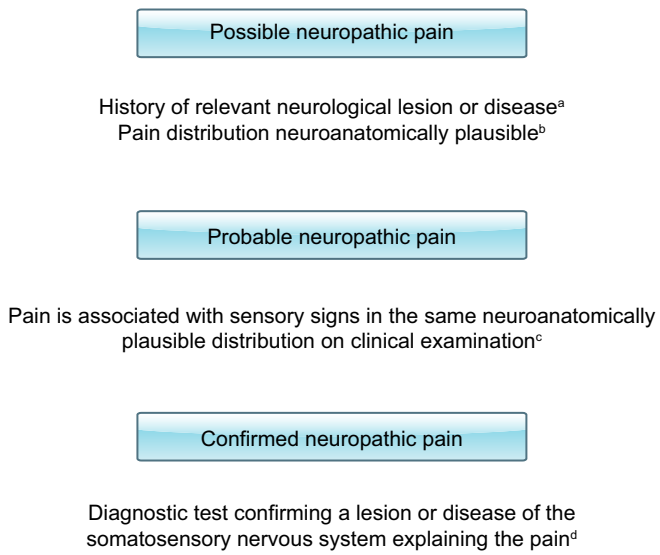

FIGURE 3. Grading system for neuropathic pain. [a]History, including pain descriptors and the presence of nonpainful sensory symptoms compatible with a lesion in the nervous system and not an inflammatory or non-neurological condition. [b]The pain distribution reported by the patient is consistent with the suspected lesion or disease. [c]The area of sensory changes may extend beyond, be within, or overlap the area of pain. Sensory loss is generally required, but touch-evoked or thermal allodynia may sometimes be the only finding at bedside examination. [d]The term "definite" means "probable neuropathic pain with confirmatory tests" because the location and nature of the lesion or disease have been confirmed to be able to explain the pain. A definite diagnosis of neuropathic pain requires that other types of pain are excluded or highly unlikely to entirely explain the pain condition. The grading system is fully described previously (139).

IV. CLINICAL MANIFESTATIONS

Most patients with neuropathic pain complain of an ongoing or intermittent spontaneous pain. Although any pain descriptor may apply, neuropathic pain is often described as a burning, shooting, pricking, pins and needles, squeezing, or freezing pain (24, 45). The spontaneous pain is sometimes dominated by intermittent electric-shock-like pain paroxysms either alone or in addition to an ongoing pain. As a consequence of the nervous system lesion, there may be nonpainful abnormal sensations. These include dysesthesia, which are unpleasant abnormal sensations, and paresthesia, which are abnormal sensations that are not unpleasant (232). Both may occur spontaneously or evoked. Evoked types of pain may occur in addition to spontaneous pain and rarely as the only pain manifestation (14). Patients most often complain of touch-evoked or cold-evoked pain. On examination, allodynia (pain due to a stimulus that does not normally provoke pain) and hyperalgesia (increased pain from a stimulus that normally provokes pain) to mechanical or thermal stimuli can be found in addition to sensory loss (232). There may be aftersensations, which is pain continuing after a stimulation has ceased (188); hyperpathia, an abnormal and often explosive painful reaction to a stimulus, especially a repetitive stimulus in addition to an increased threshold (221, 232, 346); and referred sensations with referral of pain or nonpainful sensations to denervated areas elicited by stimulation of adjacent body areas (143, 251). A poor association between self-reported evoked pain and gain on quantitative sensory testing is well-known (173), and discrepancy is also documented between findings on bedside and quantitative sensory testing (283). The reasons for this may be that the tests are inadequate to capture allodynia and that the symptoms sometimes occur intermittently and therefore may not be present at examination.

Spontaneous pain often occurs without any evoked pain, e.g., in painful polyneuropathy (PPN) and complete spinal cord injury, and evoked pain may rarely occur without any spontaneous pain. This suggests that evoked and spontaneous pain are caused by different mechanisms, or alternatively, by overlapping mechanisms, but preservation or loss of specific afferent fibers determines the presence or absence of evoked pain. Several studies in postsurgical pain, postherpetic neuralgia (PHN), and central neuropathic pain suggest that early evoked pain or hypersensitivity predicts the later development of neuropathic pain (144, 200, 264, 317, 420, 546), suggesting that there may be shared underlying mechanisms.

A. Spontaneous Pain

Spontaneous neuropathic pain may be generated by ectopic impulse generation in somatosensory pathways or by a summation of evoked pain due to stimuli of daily activities in the presence of peripheral and central sensitization (31, 99,

224, 533). An ectopic pacemaker may discharge spontaneously or in response to other depolarizing stimuli such as circulating catecholamines, temperature changes, ischemia, hypoglycemia, and mechanical stimulation (99, 102) and thus be involved in both spontaneous and evoked pain. It is logical to assume that the quality of pain depends on the type of fiber generating ectopic evoked or spontaneous discharges according to the labeled line theory. The labeled line theory postulates that the sensory quality corresponds to activity in a specific sense organ and ascending pathway (354, 383). Although the labeled line theory has been challenged (131), there is often a link between afferent fiber type and perceived quality. Tingling, pulsating, prickling pain, or unpleasant sensations are evoked by sea anemone toxin activation of large Aδ and Aβ fibers (261), and ectopic nerve impulses in large fast-conducting myelinated mechanoreceptive fibers are found in neurological disorders and suggested to be associated with tingling or buzzing sensations (56, 353). Burning pain can be elicited by intraneural microstimulation of C nociceptive fibers (362), and the burning pain elicited by capsaicin (305, 439) or cowhage (191) is likely mediated by activation of C-fibers, although some role of myelinated afferents is also suggested (416). Burning pain elicited by methylglyoxal (121) and sinusoidal electrical stimulation (244) predominantly involves mechano-insensitive C-fibers. In diabetic PPN, the GAP43-stained intraepidermal nerve fiber density was higher in those with burning pain, suggesting a role for regenerating C-fibers in burning neuropathic pain (166). Hyperexcitability and spontaneous activity in C-fibers have been found in patients with different types of PPN (44, 363, 366, 450), and although not all C-fiber discharges are capable of producing pain (31), ectopic activity, in particular mechano-insensitive or sleeping C-nociceptors, is suggested to be linked to pain (259, 367, 440). Possible sources of ectopic activity involved in neuropathic pain include nerve-end neuroma and regenerating sprouts (50, 67, 164), neighboring uninjured neurons (535), compressed nerves or nerve roots (356), dorsal root ganglia (DRG) (302, 355, 509), the spinal dorsal root entry zone (2, 123, 130, 295), and deafferented neurons in the thalamus (223, 284, 482).

B. Evoked Pain

Evoked pain requires preservation of afferent pathways, and deafferentation protects against evoked pain (120, 168, 189, 192, 215, 425, 494). Evoked pain may spread slightly beyond the innervation territory of the affected nervous structure (135, 187, 205, 533). The prevalence of evoked pain in neuropathic pain depends on the underlying condition (241). In a large study using quantitative sensory testing in patients with mixed neuropathic pain conditions, dynamic mechanical allodynia was present on average in 19.7%, most common in PHN (49%), and least common in PPN (12%); pinprick hyperalgesia was present in 36% in PHN, 30% in peripheral nerve injury, 22% in central pain, and 9% in PPN; and cold and warm allodynia was present in 21% in PHN, 25–27% in peripheral nerve injury, 6–10% in central pain, and 2–7% in PPN (307). With the use of patient-reported outcomes from the Neuropathic Pain Symptom Inventory, 55% had brush-evoked allodynia, 31% pain evoked by contact with cold objects, and 52% pressure-evoked pain, and evoked pain to any of these three ranged from 44% in painful radiculopathy to 51–64% in PPN and 92% in PHN (16). Similar findings were found using the painDETECT questionnaire, where 47% of patients with PHN and 18% of patients with PPN reported clinically relevant touch-evoked allodynia, and 31 and 14%, respectively, reported allodynia to cold or warmth (24).

Pinprick (punctate) hyperalgesia is thought to be caused by central sensitization with decreased threshold or increased response to nociceptor input (253, 266), but microneurography studies also suggest a role of mechano-insensitive C-fibers in pinprick hyperalgesia in the secondary hyperalgesia area following capsaicin injection (434, 451). Dynamic mechanical allodynia (DMA) or touch-evoked allodynia is a specific type of allodynia, because the evoking stimulus is under normal conditions not capable of activating nociceptors, and it is therefore not a result of a change in threshold or a response to suprathreshold stimuli (294). DMA in neuropathic pain shares features with DMA in the secondary hyperalgesia area in experimental pain models, like capsaicin, suggesting that they may have similar underlying mechanisms (54, 188, 190, 267, 364, 431). Most studies support that DMA is mediated by central sensitization to input from low-threshold Aβ fibers (60, 253, 266, 279, 364, 489), and the presence in neuropathic pain requires intact large fiber innervation (192, 517). The exact mechanism how large fiber input gains access to the nociceptive pathways in the presence of central sensitization is unclear, but may involve sprouting of Aβ fibers into lamina II of the spinal cord (303, 534), phenotypic switch of Aβ fibers (352), disinhibition of pre-existing pathways (442, 489), loss of inhibition from low-threshold mechanoreceptive C tactile afferents (290), disrupted chloride-mediated spinal inhibition (73, 311, 412, 489), and disturbed supraspinal coding of the balance between altered Aβ fiber firing frequency and nociceptive input (296). Preclinical studies suggest a role for unmyelinated low-threshold mechanoreceptors (446), and clinical studies also suggest that DMA is mediated through low-threshold C-fibers that signal the pleasantness of gentle skin stroking, although the role of these fibers in neuropathic pain is still unsettled (289, 446).

Hyperalgesia and allodynia to blunt pressure are suggested to be mediated mainly by peripheral sensitization of C-fibers (250, 253, 266, 364). Mechano-insensitive C-fibers have been shown to be able to encode pressure-induced pain and may play a role in pressure hyperalgesia (441). In diabetic PPN, patients carrying rare variants in the voltage-gated sodium channel $Na_v1.7$, a key determinant for neuronal excitability, had lower pressure pain thresholds than those not

carrying the variant, consistent with peripheral mechanisms (41). Decreased pressure pain thresholds are, however, also found in patients with central pain (475), suggesting that pressure pain allodynia can also be caused by central mechanisms.

Neuropathic pain patients complain more often of cold than warm allodynia, although both signs are found on examination (307). Cold allodynia is particularly common in central pain (144, 264, 514), small fiber neuropathy due to non-freezing cold injury (344, 504), the acute phase after treatment with the chemotherapeutic agent oxaliplatin (13, 219, 511, 512), and Ciguatera, which is a neurological disorder caused by ciguatoxins found in tropical fish (551). In peripheral neuropathic pain, sensitization of different types of primary afferents may cause cold allodynia depending on the cause. A differential compression blockade of A-fibers abolished cold allodynia induced by oxaliplatin, suggesting that it is mediated by A-fibers (153), consistent with the fact that the evoked sensation is described as a pricking dysesthesia or pain (219, 512). Studies using nerve excitability testing indicate that it is caused at least partly by slowing of sodium channel inactivation (219, 376). Spontaneous generation of action potentials and sensitization to cold and menthol responsiveness of C-nociceptors have been identified using microneurography in a patient with small fiber neuropathy and cold allodynia, and it is likely that C-fibers are involved in cases where cold allodynia is perceived as a deep aching and burning sensation (452). Abnormal expression of transient receptor potential (TRP) melastatin 8 (TRPM8) channel or disinhibition by loss of Aδ fibers may underlie this sensitization (55). In addition to sensitization of peripheral nerve fibers, central sensitization of spinothalamic pathways or central disinhibition may play a role, particular in central pain conditions (76, 320). Heat allodynia and hyperalgesia are characteristic of inherited erythromelalgia, which is a painful condition with severe burning pain in the feet and hands with vasodilatation and reddening of the skin (111, 112). The condition is linked to a missense mutation in the $Na_v1.7$ channel (111) and spontaneously active and sensitized mechano-insensitive C-fibers (257, 367), but also to alterations in peripheral axonal membrane function in large fibers possible due to $Na_v1.7$-mediated disturbances in vascular regulation (132). Heat allodynia in other neuropathic pain conditions is not well-understood but may involve both peripheral and central sensitization, altered TRP vanilloid 1 (TRPV1) function (39), and disinhibition (168, 537).

C. Aftersensations, Hyperpathia, and Referred Pain

Aftersensations are common in different types of neuropathic pain states (188). Ephaptic, or "electrical" crosstalk and crossed afterdischarges, as well as central sensitization, including decreased inhibition and facilitated excitation, are suggested to be involved in temporal summation and aftersensations (100, 188, 280, 506). Hyperpathia is defined by IASP as "a painful syndrome characterized by an abnormally painful reaction to a stimulus, especially a repetitive stimulus, as well as an increased threshold" (232). It was first described by Foerster in 1927 as an intense, explosive pain to stimuli right above threshold and with spread of pain and aftersensations in patients who recovered after nerve injury (151, 221). He found that it was present during recovery of pain sensation until recovery of large fiber function and suggested it is caused by disinhibition from loss of large fiber functions in combination with regenerative and repair processes (151). It is likely to involve both peripheral and central sensitization. Referred pain and referred sensations to denervated or missing limbs by stimulation of adjacent body areas are reported in, e.g., plexus avulsion (143, 227), amputation (200a, 396, 400), and spinal cord injury (333), but also to areas of neuropathic pain with preserved sensation as described in a patient with PHN (154). Early brain imaging studies have linked referred pain to cortical reorganization and invasion of the deafferented cortex by neighboring representations (195, 400). The causal role of cortical reorganization for referred pain has been questioned because pain may be referred to areas with preserved sensation (154), to the contralateral side (265, 346), and to areas which have segregated cortical activation (143, 154, 333), and thus cannot be explained by a simple S1 remapping but rather point to a subcortical mechanism. The cortical changes are thus suggested to represent a relay of subcortical change (150). A spinal or brain stem mechanism of referred sensations is compatible with the elicitation of referred pain from dermatomes adjacent to deafferented areas (143, 154, 333), short latency of evoked referred muscle jerks and late compound muscle axonal potentials occurring simultaneous with the referred sensations (143), and abolishment of trigger zones and referred pain associated with root avulsions with dorsal root entry zone lesions (345, 374). The mechanisms are unclear, but one study suggested that it involves a shift from inhibitory towards facilitatory descending activation because of increased functional magnetic resonance imaging (MRI) signal activity in supraspinal structures (e.g., periaqueductal gray and subnucleus reticularis dorsalis) after capsaicin application in a patient with referred pain (154). Other proposed mechanisms involve increased receptive fields of second-order neurons and sprouting and unmasking of normally ineffective connections due to central sensitization in addition to a rostral and caudal spread of neuronal hyperexcitability in the spinal cord and brain stem (115, 150, 295, 521). It is also suggested to involve loss of presynaptic inhibition of propriospinal multisynaptic pathways in the deep dorsal horn with disinhibition of dual perceptions with referral to the deafferented area (142, 342, 346).

V. DISEASE-BASED CLASSIFICATION

Neuropathic pain is traditionally classified based on underlying disease. In the newly released ICD11 classification,

neuropathic pain is first organized into peripheral and central neuropathic pain based on the location of the lesion or disease in the peripheral or central somatosensory nervous system (443). Within each of these categories, pain is classified into different neuropathic pain conditions based on the underlying disease **(FIGURE 4)** (443). In this review, the focus will on the most common neuropathic pain conditions, but other conditions, e.g., carpal tunnel syndrome and other mononeuropathies, painful plexopathy, inherited erythromelalgia, and other gain-of-function mutations (30), are not described in detail.

A. Trigeminal Neuralgia

Trigeminal neuralgia is a specific type of orofacial pain affecting one or more divisions of the trigeminal nerve (79). The diagnosis depends on the patient's description of characteristic electric shock-like pain attacks that are abrupt in onset and termination, last a few seconds to less than 2 min, and occur spontaneously or evoked by innocuous stimuli at trigger zones (79, 303a). The trigger zones are within cutaneous or mucous trigeminal areas, and chewing, touch, tooth brushing, or washing may provoke a paroxysm. It is debated whether the spontaneous attacks are truly spontaneous or in fact stimulus-depended attacks triggered by subclinical stimuli (109). The frequency of attacks varies (304, 543). There is often a remission period lasting weeks to years where patients are pain free (109, 544). Despite being classified as a peripheral neuropathic pain, the lesion is often within the root entry zone, where the myelin is primarily produced by central nervous system oligodendrocytes that extent beyond the pons and transits into myelin produced by peripheral Schwann cells, and the lesion may also be in the brain stem within the central nervous system, and trigeminal neuralgia is thus sometimes a central pain condition (96, 197, 229, 297, 299, 382, 460).

The underlying cause of classical trigeminal neuralgia is thought to be a vascular compression of the trigeminal nerve root in the cisternal segment, the root entry zone, or the pontine segment resulting in morphological changes and atrophy in the nerve (10, 197, 229, 304a, 356), and case series suggest that the effect of microsurgical decompression or radiosurgery is related to more severe compression of the nerve (22, 228, 433, 461). Electron-microscopic and immunohistochemical examinations of nerve biopsies taken during surgery for microvascular decompression have shown

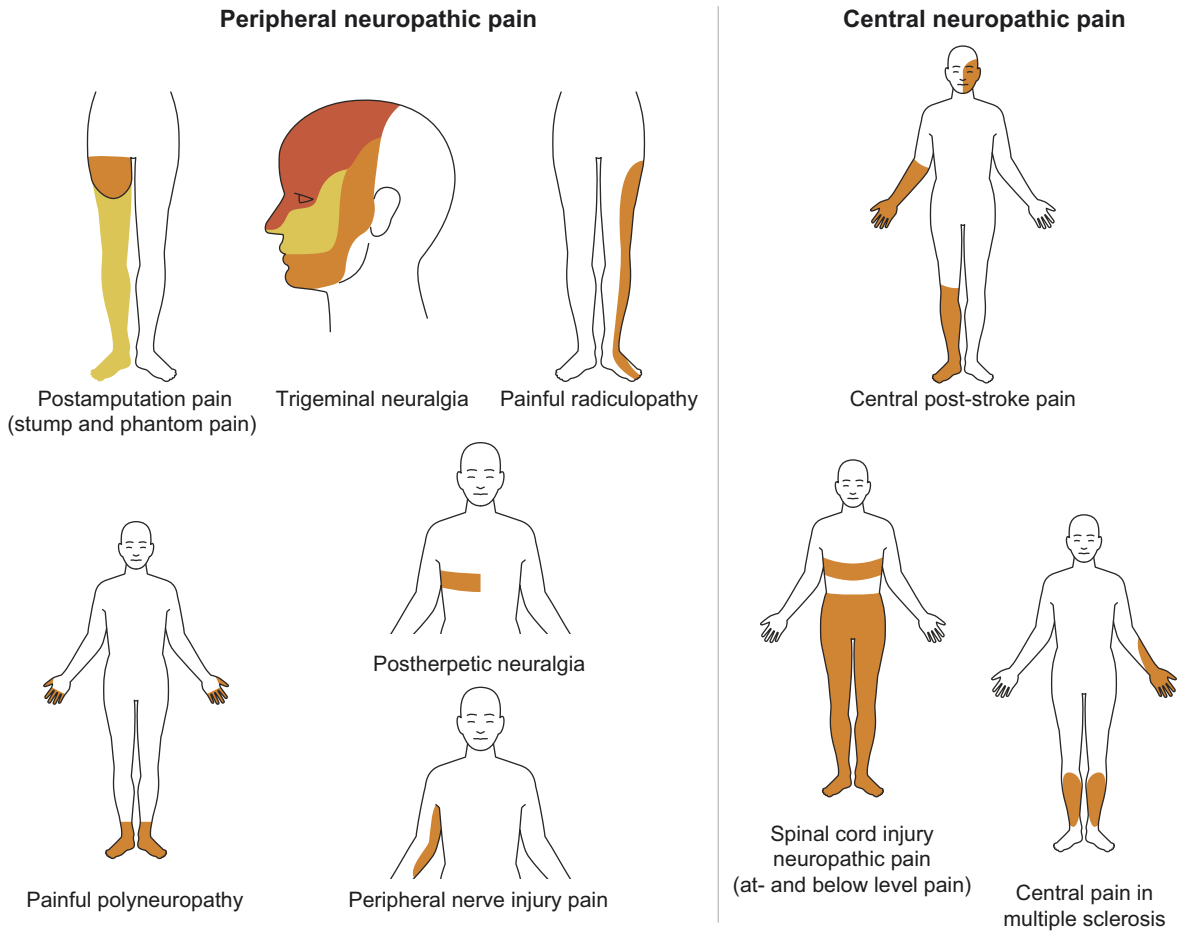

FIGURE 4. Classification of neuropathic pain and examples of the neuroanatomical distribution of pain and sensory abnormalities (139).

demyelination and myelin abnormalities as well as axonal damage, atrophy, and sprouting (101, 222, 299, 312, 404). The prevailing theory is that the spontaneous pain paroxysms are generated by spontaneous discharges in damaged neurons with lowered threshold for repetitive firing and cross-excitation to hyperexcitable neighboring neurons (5, 312, 356, 403). Since there may be an immediate relief of microvascular decompression and recovery of trigeminal nerve root conduction, it is suggested that the underlying cause can be a transient conduction nerve block (282). Functional cross-excitation between neurons may also explain pain evoked by touching trigger zones with spike activity in large myelinated A fibers activated by touch causing depolarization in neighboring C-neurons (5, 403). Progression to severe nerve root damage is likely to cause more prominent sensory loss and possible continuous pain because of continuous ectopic discharges (51, 356). Retrograde biochemical disturbances and immune reaction of the trigeminal ganglion and inflammation may also be involved (127, 312). Neuroimaging studies have also documented subtle grey and white matter loss in brain areas involved in pain perception (96–98), but it is unclear if these changes are secondary and adaptive changes to ongoing activity from focal nerve damage or if they contribute to pain (361). The unique acute response of this neuropathic pain condition to microvascular decompression, radiofrequency ablation, and other treatments targeting the nerve directly supports that the pain generator is within the damaged section of the nerve (356).

Secondary trigeminal neuralgia is caused by a neurological disease such as a tumor or multiple sclerosis (79). Multiple sclerosis is the most common cause of secondary trigeminal neuralgia, and 1–5% of patients with multiple sclerosis experience trigeminal neuralgia (79, 108, 179, 358, 496). Secondary trigeminal neuralgia in multiple sclerosis commences at earlier age and is more often bilateral and is reported to be more severe and intractable than primary trigeminal neuralgia with reduced length and duration of remissions, fewer identifiable pain triggers, and more impact on quality of life (179, 242). Secondary trigeminal neuralgia is often caused by demyelinating lesions or tumors in the cerebellopontine angle between the root entry zone and the trigeminal nuclei along the intrapontine trigeminal primary afferents (78, 108). In some cases there is a coexisting neurovascular compression (298, 496). Electron microscopy of trigeminal rhizotomy specimens has revealed demyelination, gliosis, and inflammation in the proximal part of the trigeminal nerve root, which could be a possible source of ectopic activity (281, 298).

B. Neuropathic Pain Following Peripheral Nerve Injury

This is a heterogeneous group of neuropathic pain conditions caused by a lesion of a peripheral nerve, e.g., during surgery or because of a trauma. There is a clear link between the risk of nerve damage, e.g., during surgery, and the risk of developing chronic neuropathic pain (28, 212, 225, 463), but there is no clear association between severity of injury and type (transecting, stretching, crushing) of nerve damage and the development of neuropathic pain (8, 305a). In general, it is unclear why some patients with nerve damage develop pain while others do not. Partial axonal damage including small fiber dysfunction as opposed to demyelinating damage was a risk factor in one study with iatrogenic inferior alveolar nerve injury (234a). High intraindividual concordance for neuropathic pain in patients with bilateral amputation or thoracotomy suggests that patient-related factors play a role (386, 471), and the underlying mechanisms likely involve an interplay of peripheral and central nervous system changes, and genetic and psychological factors (186, 487).

The main mechanism underlying pain in posttraumatic nerve injury, including phantom and stump pain after amputation, is likely to be ectopic impulses generated at the site of nerve injury or the DRG. This is supported by the temporary effect of surgical removals of neuromas, which are neural sprouts developing at the proximal end of a transected nerve (325, 395), and of peripheral nerve blocks (50, 61, 211, 326, 357, 509) on ongoing and evoked pain in peripheral nerve injury pain including phantom pain. In human painful neuromas, an upregulation of $Na_v1.3$, 1.7, and 1.8 as well as an upregulation of activated p38 and elongation factors associated with translation (EFT1/2) mitogen-activated protein (MAP) kinases have been found (40). These may be molecular drivers of pain, as abnormal accumulation of such sodium channels can cause hyperexcitability and ectopic impulse generation (30, 428). A low-grade inflammation and pro-inflammatory cytokines may be additional factors associated with pain after peripheral nerve injury (220, 338) as discussed further below. Central sensitization involving the spinal cord and brain stem is likely to be involved particularly in referred sensations and spread of allodynia and hyperalgesia to neighboring dermatomes (142, 205, 280). Supraspinal neuroplastic changes and cortical reorganization (148, 149) are also seen after amputation, but the association between chronic pain and reorganization after amputation is uncertain (246, 309).

C. Painful Polyneuropathy

The most common and well-described types of PPN are those due to diabetes, human immunodeficiency virus (HIV), chemotherapy, and leprosy (68, 125, 133, 466, 486). Other causes include Fabry disease (37, 332), sodium channel gene mutations (86), autoimmune diseases (86), vasculitis (71, 498, 502), chronic inflammatory demyelinating polyneuropathy (485, 502), amyloidosis (349, 391, 454), alcohol (429), nonfreezing cold injury (504), and paraneoplastic syndrome (553). Malnutrition and vitamin deficiency are other causes. PPN related to severe malnutrition was

described in detail in case reports from Far East Prisoners of War during World War II, most likely caused by deficiency of B vitamins (421), and acute or subacute forms may be seen as complications to nutrient deficiencies associated with weight loss, eating disorders, and bariatric surgery (159, 202). There may be multiple causes of PPN in the same patient (86, 184), and in many patients the etiology remains unknown (86, 185, 466, 483).

Pain may be the first symptom of a neuropathy, but often the onset is insidious starting with paresthesia and eventually dysesthesia or pain. The pain is often an ongoing squeezing, pricking, or burning pain, and evoked types of pain are less common. Dependent on the affected nerves, there may be decreased reflexes, weakness, and autonomic changes. The most common form is a symmetric length-dependent polyneuropathy with symptoms in the feet, progressing proximally affecting the lower legs and hands. A specific acute form of polyneuropathy is seen after abrupt improvement in glycemic control in patients with diabetes and poor glycemic control (172). The pain is typically a severe burning pain accompanied with hyperalgesia, allodynia, and autonomic abnormalities (172). Little is known about underlying mechanisms. Another type of acute polyneuropathy is seen after treatment with the chemotherapeutic agent oxaliplatin, which causes an acute partly reversible neuropathy in almost all patients and a chronic length-dependent sensory neuropathy in only a smaller proportion (511). The acute neuropathy develops during or within hours of receiving chemotherapy and is characterized by pricking parasthesia, cold allodynia, and muscle cramps mainly in the hands and perioral area. Nerve conduction studies are normal, indicating no axonal loss of large myelinated fibers but show neuromyotonia-like repetitive motor discharges. Nerve excitability testing shows prominent nerve excitability changes correlating to sensory symptoms and which are well modeled by a slowing of sodium channel inactivation (29, 219, 376).

The underlying pathogenesis of chronic polyneuropathy has been extensively studied and can be divided into effects on the dorsal ganglion neuron, the axon, and the myelin sheath or Schwann cells (245, 466, 505). The mechanisms are diverse and include endothelial abnormalities (35), disrupted Schwann cell function (181), capillary dysfunction (369), breakdown of the blood-nerve barrier (411), apoptosis (177), elevated oxidative stress (236), direct toxic effects (82, 245), mitochondrial DNA damage (392), loss of neurofilament polymers (445), and impaired axonal transport and microtubule function (268, 470). Less is known from clinical studies about the risk and mechanisms of pain in those with chronic polyneuropathy and why some patients remain pain free despite similar degree of polyneuropathy (68, 133, 218). Studies consistently point to increasing severity of chronic sensory neuropathy as a risk factor for pain (46, 199, 218, 316, 405, 488). It is more uncertain whether pain is related to loss of specific fiber types. Neuropathic pain is a cardinal finding in pure small-fiber neuropathies (467, 483), and sometimes pain is considered to be related to more severe small fiber loss consistent with some studies finding a relation between small fiber loss and pain (316, 394). However, patients with severe small-fiber loss may be pain free, most studies find an equally severe loss of large-fiber function in those with painful compared with nonpainful polyneuropathy, and patients with pure large-fiber loss may experience neuropathic pain (46, 116, 300, 307, 316, 388, 405, 437, 488, 497, 502). It is possible that the high frequency of pain in small fiber polyneuropathy is because pain is the symptom that leads the patient to seek medical care, and the link between pain and specific pain phenotypes and loss of specific fibers remains unclear.

While the classical length-dependent chronic polyneuropathy is most often characterized by sensory loss and only a few patients experience sensory gain (307, 488, 502), evoked pain to mechanical or thermal stimuli is more prevalent in painful than pain-free polyneuropathy (46, 316, 488, 502). This may suggest that neuronal hyperexcitability is involved, but our assessment of fiber structure and function is limited by our ability to mainly assess fibers that innervate the skin. Microneurography has documented hyperexcitability and spontaneous activity in C-fibers in painful polyneuropathy (363, 366, 450), and particular spontaneous activity and hyperexcitability in mechano-insensitive C-nociceptors seems to be linked to pain (259). In an open-label study, patients had complete relief of pain related to polyneuropathy after an ultrasound-guided peripheral nerve block with lidocaine supporting the notion that the pain generator is within the peripheral nerves (211). Possible molecular mechanisms that may underlie the neuronal hyperexcitability and ongoing activity within sensory neurons in chronic painful polyneuropathy, including altered expression of ion channels and receptors (47, 287, 467), increased expression of reactive metabolites such as methylglyoxal (38, 121), altered neurotransmitter release (47), and inflammatory factors (72, 125, 399, 499–501), are further described in section VI, and the possible role of genetic variants in genes encoding sodium channels (41, 133, 467) in section VII. Human studies also suggest that patients with PPN have changes in spinal (315) and ventrolateral periaqueductal grey-mediated pain modulatory systems (448), altered brain connectivity (58), and structural brain changes (449), but more studies are needed to understand the specificity of these changes to pain and a possible causal role in the pathophysiology of pain.

D. Postherpetic Neuralgia

PHN is pain that persists for more than 3 mo after herpes zoster onset (443). It occurs in 5–20% of patients with herpes zoster and more frequently in the elderly, and while it resolves over time in some patients, it may become chronic and persistent in a significant proportion (122, 152, 200,

389, 407). Both the live-attenuated and the adjuvant subunit herpes zoster vaccine reduce the risk of herpes zoster and PHN with 50–90% (49, 81, 260, 372). Patients with PHN have reduced unmyelinated and myelinated innervation on the affected side (360, 495), and a prospective study found that initial neural injury is more severe in those who develop PHN but that pain may recover despite only modest recovery of sensory function and reinnervation of the skin (384, 385, 407).

Herpes zoster is caused by reactivation of varicella zoster virus in the cranial nerve or spinal DRG, which undergoes axonal transport causing inflammation and necrosis in the ganglion, nerve, and nerve root, and thus the distribution of PHN is dermatomal (176, 216). Controversy has existed as to which ganglionic cell types harbor the latent virus, and while studies using PCR in combination with in situ hybridization suggested that latent virus resides mainly in neurons (176, 277), new models of in vitro human neuron culture systems also point to a role of satellite glial and Schwann cells (276, 547). These models are expected to give more insight into the latent state of zoster virus in the future. The mechanisms underlying PHN are similarly not well understood (170). Post mortem analysis of three early cases with severe PHN and two with no persistent pain showed loss of ganglion cells, axons and myelin and dorsal horn atrophy in patients with PHN, but the low number of subjects preclude establishing a clear link to PHN (525). A later MRI study found that high-signal intensity areas in the brain stem was found on T2-weighted MRI scans more frequently in patients with PHN at 3 mo, but none of the patients continued to experience chronic PHN (199a). A more recent post mortem analysis of a single patient with PHN for 5 wk showed inflammatory responses in the spinal cord dorsal horn with macrophage and lymphocytic infiltration and vacuolization of the dorsal horn with no signs of inflammation in the nerve roots, and the authors suggested involvement of the spinal cord in PHN (336). Varicella zoster virus DNA has been detected in blood mononuclear cells in patients with PHN, and Gilden et al. (175) suggested that PHN is a consequence of persistent chronic ganglionitis. These findings were, however, not reproduced in one study, which rather suggested that PHN is a consequence of neuronal damage accompanying replication of VZV in ganglia during zoster episodes (444). An in intro study using single cell patch clamping recordings in neuroblastoma cells infected with varicella zoster virus from patients with and without PHN found that the strains from PHN patients had altered $Na_v1.6$ and $Na_v1.7$ voltage-gated sodium channel current amplitudes, suggesting a role of sodium channels (252). Another study found increased sodium channel immunolabeling in the skin keratinocytes in a patient with PHN, and the authors speculated that this increased expression contributed to pain by activation of P2X receptors on primary afferents via epidermal adenosine triphosphate (ATP) release (549). The effect of topical lidocaine in PHN supports a role of sodium channels in the skin or nerve endings (423).

E. Painful Radiculopathy

Painful radiculopathy is caused by a lesion or disease involving the cervical, thoracic, lumbar, or sacral nerve roots (443). Herniated disks and degenerative changes of the spinal column are the most frequent causes, but it can also result from, e.g., trauma, neoplastic disease, and infections. Like other patients with neuropathic pain, the pain dimensions include burning, squeezing/pressing, pricking, paroxysmal, and evoked pain (16), and patients often present with sensory loss on quantitative sensory testing, but few patients report touch-evoked and thermal allodynia (163, 306). Despite being the most common neuropathic pain condition, we know little about underlying pain mechanisms, and no single drug treatment has yet proven to be effective (137, 313).

In a recent study, DRGs were taken from patients undergoing surgery for malignant tumors in the spine (355). Patch-clamp electrophysiological recordings and RNA-sequencing documented a link between spontaneous action potential generation and radicular neuropathic pain and nerve root compression on MRI (355). Mechanical compression of the DRG (226) and inflammation around the nerve root (9, 330, 343, 351, 379, 476) can contribute to such ectopic pulse generation. Substances and breakdown products released from nucleus pulposus in degenerating disks are thought to be involved in inducing the inflammatory response (331, 472). In addition to inflammation, acidity of the degenerating nucleus pulposus and functional expression of proton-sensing ion channels such as TRPV1 and acid-sensing ion channel (ASIC) along sensory axons may be an additional pathophysiological mechanism (110, 147, 174, 258).

F. Central Neuropathic Pain

Central neuropathic pain is pain caused by a lesion or disease of the central somatosensory nervous system (240). The most common conditions are spinal cord injury in which central pain develops in ~50% of patients (52, 140, 455), stroke in which 8–10% of patients develop chronic central pain (7, 210, 262, 359), and multiple sclerosis with a prevalence of central pain of 20% (368). The risk of developing central poststroke pain is highest in patients with lateral medullary and thalamic infarctions, in particular lesions involving the anterior pulvinar region of the thalamus, a major spinothalamic target (508). Central pain develops immediately after the insult or can have a delayed onset up to 6–12 mo but rarely longer (140, 210). It may resolve in some patients during the first year, but in others could tend

to become chronic and life-long, sometimes with severe psychosocial and functional consequences (455, 528).

Central sensitization is likely the main cause of central pain and its different characteristics, including ongoing pain, allodynia, hyperalgesia, aftersensation, and temporal summation (507). As discussed by Gary Bennett (31), spontaneous pain may not always be caused by ectopic discharges in the partially preserved or deafferented central pain pathways, but could in some patients result from decreased thresholds and temporal summation of stimulus-evoked pain occurring from stimuli from daily activities, e.g., breathing, touch from clothes, and ambient temperature. Relief of ongoing spontaneous pain by peripheral nerve block with lidocaine in an open-label study in patients with both spontaneous and evoked central poststroke pain supports this theory (213). Several studies have also found that early sensory hypersensitivity predicts the later development of central pain after spinal cord injury and stroke (144, 264, 546), further supporting a link between neuronal hyperexcitability and spontaneous pain.

As for other neuropathic pain conditions, the risk of developing central pain is related to the risk of damage to the somatosensory nervous system, but not all patients with such damage develop pain. There is a long line of research linking central pain to a lesion of the spinothalamocortical tract (for further discussion, see sect. VI*D*). Decreased sensation to pain and temperature is a hallmark of central pain (43, 255, 263), but not all patients develop central pain and a lesion is not sufficient to cause pain (169). Wasner et al. (524) examined patients with clinically complete spinal cord injury and found that 8 of 12 patients with central pain had some preserved thermal and pain sensation particularly after sensitizing the skin with capsaicin, while this was not the case in patients without pain, and they suggested that residual spinothalamic tract pathways play a role in maintaining central pain. Pain can be evoked by suprathreshold stimulation of the spinothalamic tract (397), and other studies support the hypothesis that pain is generated in the damaged spinothalamic tract following spinal cord injury (209, 527). Various disinhibition theories have been proposed but also questioned. These include imbalance between spinothalamic tract pathways and the dorsal column (36), spinoreticulothalamic pathways (373, 481), or medial pathways (76), between the medial and lateral thalamus (217), or as a loss of descending inhibitory pathways (4, 194, 237).

Central pain can also develop in patients with a complete transection of the spinal cord (322), and in these patients, the pain generator must be located at rostral deafferented sites. One possible site in both complete and incomplete spinal cord injury is the neurons in the rostral part of the spinal cord. A link between at-level sensory hypersensitivity and below-level pain (141, 145, 286), the occasional pain relief by spinal transection (117), and the effect of dorsal root entry zone lesions on pain and high-level spontaneous and evoked neuronal activity in the rostral spinal cord (117, 123, 130) support the role of this region for central pain in a subgroup of patients with spinal cord injury and central pain. Another plausible structure involved in generating pain is the thalamus. Proton magnetic resonance spectroscopy studies have documented decreased levels of *N*-acetyl possibly reflecting dysfunction of inhibitory neurons and higher levels of the glia marker *myo*-inositol in the thalamus (378, 527), and electrical stimulation in the thalamus, particularly the ventral caudal sensory nucleus of the thalamus, which receives dense STT terminations, can provoke pain to deafferented areas resembling the patient's own pain (284, 285, 482).

Central pain may also be seen in patients with brain trauma, brain tumors, and possibly Parkinson's disease (314, 365). In patients with epilepsy, a seizure can trigger the experience of pain, particularly with lesions in the operculo-insular cortex (the medial part of the parietal operculum and neighboring posterior insula), an area where electrical stimulation can also trigger pain (319). Plexus avulsion is an injury, typical after a motorcycle accident, where the nerve root is torn from its attachment at the spinal cord, and it affects both the peripheral and central nervous system in the transition zone. These patients typically complain of severe crushing pain in the deafferented hand with additional paroxysmal pain shooting down the arm (227). There is evidence suggesting that the pain originates within the spinal dorsal horn (114, 239, 370, 371), and it is the pain condition with the best success of dorsal root entry zone lesions (2, 406, 477).

VI. MECHANISTIC INSIGHTS DERIVED FROM RODENT MODELS OF NEUROPATHIC PAIN

Below, we briefly discuss major new insights gained from studies involving pharmacological, genetic, or physical manipulations at diverse somatosensory avenues in rodent models of neuropathic pain. Each of these topics is extensive and can encompass review in its own right; therefore, we will focus primarily on the newest developments and insights gained via primary studies in the last handful of years, citing reviews for older literature and specific topics that cannot be covered here in detail.

A. Rodent Models of Neuropathic Pain and Tools for Testing Mechanisms

Diverse types of neuropathies have been modeled in rodents. The most widely employed models for physical damage to peripheral nerves, including models of partial damage, such as the Spared Nerve Injury (SNI) model (89) or local inflammation-induced nerve damage, such as the Chronic Constriction Injury (CCI) model. In the SNI model, ligation

and transection of the common peroneal and tibial branches of the sciatic nerve evokes intense mechanical and cold allodynia, but not consistent heat hyperalgesia, in the cutaneous paw territory of the neighboring, undamaged sural branch of the sciatic nerve. In the CCI model, invasion of the nerve tissue following chemical pro-inflammatory substances released by the loose ligature ultimately leads to neuritis and nerve hypertrophy, resulting in mechanical and heat hypersensitivity (62). While hypersensitivity persists in the SNI model and shows a ceiling effect owing to its severity, it is more moderate in the CCI model and diminishes over the period of few weeks in parallel to the resolution of the nerve inflammation. Chemotherapy-induced neuropathic allodynia and signs of ongoing pain have also been modeled, based on the clinical finding that antineoplastic agents from the group of taxanes and platin derivatives, e.g., with models of oxaliplatin-induced nerve damage being widely used (201).

Injury to central components of the somatosensory nociceptive pathways has also been modeled. Contusion-based models of spinal cord injury (SCI) in mice and rats are frequently used to study mechanical hypersensitivity, autonomic dysfunction, and challenges to axonal regeneration. Models involving direct damage to the brain are rare. Pain can develop in response to stroke, particularly in the thalamus leading to thalamic hemorrhage, which has been recently modeled in mice (193). In contrast to the focal nature of direct injury-induced damage to the nervous system, metabolic dysfunction can damage neural pathways at peripheral and central avenues. Models for testing type 1 and type 2 diabetes are becoming increasingly studied. Type 1 diabetes is modeled by streptozotocin (STZ)-mediated toxicity to β cells in the pancreas, resulting in insulin deficiency. It is important to use a low-dose model of STZ, which leads to selective diabetes-related metabolic dysfunction and a pain phenotype several weeks after STZ treatment, as opposed to high-dose models and acute analyses which induce and reflect direct STZ-induced toxicity to nerves, respectively (158). Mice develop mechanical and heat hypersensitivity at 5–7 wk post-STZ and progressive hypoalgesia starting around 20 wk, which is accompanied by loss of epidermal nociceptor nerve endings. There are several models of metabolic syndrome, which although related to type 2 diabetes, do not entirely mimic type 2 diabetes. In studies on pain, a model of high-fat diet inducing obesity has been successfully implemented (134, 238). It should also be noted that there is increasing evidence of robust structural changes in peripheral sensory nerves in diverse models of cancer pain, suggesting that a neuropathic component is also in play. Finally, virally induced neuropathies, such as central neuropathic pain upon infection with the HIV, have been modeled via intrathecal injection of recombinant HIV glycoprotein gp120MN (178). Similarly, cutaneous herpes simplex virus type-1 (HSV-1) infection has been employed to model PHN in mice (457). In addition to hypersensitivity to heat, cold, and mechanical stimuli, studies are now increasingly incorporating nonreflexive voluntary behaviors related to well-being as well as assays for testing aversion and negative affect, such as conditional pain aversion or conditioned pain modulation (390, 479).

B. Tools for Delineating Functional Contributions and Studying Plastic Changes

The study of neuropathic pain mechanisms has been galvanized by recent advances in the ability to specifically alter activity of specific cells or pathways using light stimuli in combination with genetically encoded expression of light-activated channels, enabling reversible and temporally precise activation or silencing of neuronal activity (optogenetics) (254). Similarly, chemogenetics involves genetic expression of designer receptors activated by designer drugs (DREADDs), which are G protein-coupled receptors that can be specifically activated by an exogenous chemical stimulus noninvasively to activate or inhibit neuronal activity (422). Both types of manipulations can be coupled with region- or cell type-specific promoters, thereby permitting enabling highly specific manipulations in pathways, which are reversible. Cell ablation methods, employing toxins such as diphtheria toxin, have also advanced our understanding of pain mechanisms, although they suffer from the caveat of being irreversible and eliciting major damage and glial and inflammatory responses. These methods now replace older techniques for silencing cells (using glutamate receptor antagonists or GABA agonists) or ablation (using excitotoxins), which largely lacked cellular specificity, although some examples of cell-specific toxins exist, e.g., substance P-conjugated saporins that destroy cells expressing neurokinin 1 (NK1) receptors (310).

These advances come on top of advances in genetic tools enabling deletion of specific genes in specific cells (conditional knockout mice using Cre-loxP technology) or their overexpression (transgenic mice). Moreover, there have been rapid advances in viral-mediated gene delivery, again achieving cell type specificity with the aid of gene promoters, which can also be employed to knock-down genes using RNA interference. Viral tools are now also available for anterograde and retrograde tracing of axonal projections in an unbiased or cell-restricted manner. These developments have been matched by advances in noninvasive or minimally invasive imaging of neuronal circuits at the level of networks (small animal functional MRI) or at cellular resolution via calcium imaging using multiphoton microscopy (408).

With the advent of these tools, a major quest in recent research has been on the functional dissection of which cells, pathways, circuits, and networks contribute to neuropathic pain. The backdrop for the quest of functionally active cells and circuits is given by the large amount of seeming

redundancy in somatosensory pathways of pain. Below we discuss functional contributions of peripheral afferents and spinal circuits.

C. Contributions of Primary Sensory Populations in Neuropathic Pain

Spontaneous pain is difficult to study in rodents, and thus a major thrust has been placed in understanding the cellular basis of how signs of allodynia come about, whereby normally innocuous intensities of mechanical and thermal stimulation evoke nociceptive responses. Along these lines, it is critical to understand the individual contributions of specific types of primary afferent neurons.

A study by Abrahamsen et al. (1) reported that diphtheria toxin-induced ablation of $Na_v1.8$-expressing nociceptive neurons in mice resulted in loss of acute mechanical and cold nociception and inflammatory hypersensitivity, but not mechanical or heat allodynia after nerve injury. These data matched the classical view that C-fibers do not change their activation threshold in neuropathic pain. A recent study reported that ablation of TRPV1-lineage nociceptors, which covers a large proportion of C- and Aδ fibers, resulted in loss of neuropathic cold allodynia, but not neuropathic tactile hypersensitivity (70). These reports thus implicate myelinated low-threshold fibers (LTMRs) in neuropathic mechanical allodynia.

This view was supported in part by a recent study employing cutting-edge optogenetic and photo-ablative approaches to manipulate a population of peripheral sensory neurons expressing Trk-B, which span Aβ fiber neurons and D-hair subpopulation of Aδ fiber neurons. Ablating Trk-B-expressing sensory neurons abrogated responsivity to light touch under physiological conditions and mechanical allodynia in mice in the SNI model of neuropathic pain (107). Conversely, in two independent studies (107, 480), optogenetic activation of low-threshold mechanoceptor neurons evoked phenotypic responses representative of allodynia, thereby making a strong case that Aβ fibers are both necessary and sufficient to produce injury-evoked mechanical allodynia. Importantly, the peripheral involvement of Aβ fibers in neuropathic mechanical allodynia would indicate that central mechanisms, not peripheral contributions, account for the aberrant switch whereby Aβ-mediated tactile inputs are perceived to be unpleasant (discussed in the section below).

In contrast to studies suggesting an exclusive role for Aβ fibers for mechanical allodynia, human electrophysiology data point to changes that are more aligned to an involvement of C-nociceptors in chronic pain. This has triggered a long-standing debate as to whether nociceptors or non-nociceptive low-threshold afferents mediate mechanical hypersensitivity. Several recent studies on mouse models support a role for C-fibers. In direct contrast to the results of Abrahamsen et al. (1), Séguéla and colleagues (83) report that reversible optogenetic silencing of $Na_v1.8$ (nociceptive) fibers significantly reduces thermal and mechanical hypersensitivity in a model of neuropathic pain. This was supported by findings from Eisenach and colleagues (42), who directly measured mechanical thresholds of activation of sensory afferents following nerve injury. They observed a reduction in C-fiber thresholds, while large-diameter myelinated low-threshold fibers actually demonstrated a desensitization and loss of receptive field area, supporting a model with reduced activation of tactile low-threshold afferents and increased responses of nociceptive afferents. Moreover, Stucky and colleagues (75) directly tested the contributions of the peptidergic class of nociceptors, expressing calcitonin gene-related peptide (CGRP), using Arch-mediated optogenetic silencing. In mice with nerve injury, they found that suppression of activity of peptidergic nociceptors inhibited mechanical and thermal hypersensitivity and behavioral correlates of spontaneous pain. By performing comparative analyses in a model of postoperative (largely inflammatory) pain, they suggest that CGRP-expressing nociceptive afferents contribute pivotally to nerve injury-induced hypersensitivity, while CGRP signaling per se is more important in postoperative pain (75). Peripheral effects of CGRP in rodents may be strain-dependent. Recent evidence suggests that CGRP released at the central terminals of nociceptors facilitates central sensitization (234).

This is also largely consistent with insights emerging in other animal models of other types of neuropathic pain. Most studies have addressed circuit contributions in neuropathic pain induced by peripheral nerve trauma, while functional studies on other clinical states of neuropathic pain are just emerging. In models of spinal cord injury-induced neuropathic pain, heat hypoalgesia, mechanical allodynia, and spontaneous pain were accompanied by a marked sprouting of C-nociceptors in spinal sensory-motor circuits in injured mice (347). Both, pain sensitivity and C-fiber sprouting were reversed by physical training. Moreover, in a model of type 2 diabetes, a study by Menichella and colleagues (238) reported that chemogenetic silencing of nociceptive afferents selectively depressed mechanical and thermal hypersensitivity. In a model of type 1 diabetes, Dhandapani et al. (107) observed a blockade of mechanical hypersensitivity by optogenetic inhibition of low-threshold mechanoceptors (i.e., Aβ fibers), suggesting a role also of these fibers. Taken together, this suggests that the precise contributions of different types of afferent fibers are state- and context-dependent and vary between disorders. Viewing the current literature, we do however, note that the old notion of lack of involvement of nociceptors in neuropathic mechanical allodynia is increasingly being questioned, and evidence to the contrary is mounting.

There are additional subtypes of primary afferents that still require clarification in terms of contributions to neuropathic pain. For example, a clinically-relevant subtype of nociceptors, termed "silent nociceptors," comprises mechano-insensitive neurons that gain mechanosensitivity in an inflammatory milieu. It should be noted, however, that a majority of these "mechano-insensitive" C-nociceptors respond to heat and show distinct membrane attributes, as seen by their pronounced activity-dependent slowing properties (526). Their chemical identity, however, was long unknown. A recent study described the nicotinic acetylcholine receptor subunit α-3 (CHRNA3) to be a molecular marker for silent nociceptors. Using mouse genetics and electrophysiology, Prato and co-workers (435) demonstrated their switch from mechanically insensitive in physiological conditions to sensitized and mechanically responsive under inflammatory conditions. It remains to be determined whether this class of afferents contributes to neuropathic pain. Similarly, the molecular identity of thinly-myelinated Aδ fibers was recently decoded by a study, which found that NPY2R-expressing sensory neurons represent this subpopulation of nociceptors that functionally mediates acute pinprick pain (11). Complementary to the analysis of the peptidergic subclass of nociceptive primary neurons [see above, Cowie et al. (75)], it will be interesting to test the contribution of the NPY2R population to neuropathic pain.

A small subpopulation of C-fibers is comprised of low-threshold mechanoceptors (C-LTMRs). However, their role remains ambiguous (167). Based on the observation that C-LTMRs express the glutamate transporter VGLUT3 and that mice constitutively lacking VGLUT3 are markedly impaired in their ability to develop mechanical allodynia after nerve injury, C-LTMRs were suggested to play a role in mechanical hypersensitivity (446). However, a subsequent study using cell-type-specific mouse genetics demonstrated that the loss of VGLUT3 expression in a specific population of interneurons in the spinal cord, but not in any population of peripheral sensory neurons (including C-LTMRs), Merkel cells, or the brain, determines the loss of mechanical allodynia (167, 381). Taf4, a protein derived from C-LTMRs, has been reported to be required for mechanical allodynia (91), which acts by modulating GABAergic transmission and microglial activation in the spinal cord (249). While this implicates C-LTMRs in mechanical hypersensitivity, studies on silencing or ablation of C-LTMRs which establish that their activation is essential for injury-induced mechanical allodynia are still lacking.

Dissecting the precise contributions of individual types of afferents and sensory neurons to various neuropathic pain symptoms and signs is important not only from the standpoint of academic interest in mechanisms, but also from the point of view of developing and improving therapeutic strategies (410). Analysis of specific mediators of sensitization of these neuronal types can lead to illuminating knowledge on druggable targets; the recent surge of efforts towards single cell profiling on sensory neuron types is testimony to this concept (503). Moreover, knowledge on significance of different classes of sensory afferents can help improve efficacy of pain therapies involving electrical modulation of peripheral nerve activity, such as transcutaneous nerve stimulation.

D. Contributions of Spinal Cord Circuits to Neuropathic Pain

Our current knowledge on spinal circuitry and mechanisms stems to a large extent from rodent experiments. Therefore, species differences and divergence from human circuitry cannot be excluded.

The laminar organization of the spinal cord based on patterns and groups of cell bodies, first defined by Rexed, also entails specific afferent connectivity. Thus inputs from nociceptive and thermoreceptive afferents are predominantly seen in the superficial dorsal horn laminae (I and II), while inputs from mechanoreceptive and proprioceptive fibers mostly synapse in deeper dorsal horn laminae (III-V). A number of ascending tracts carry information processed in the spinal dorsal horn to distinct brain structures, including predominantly the spinothalamic tract conveying nociceptive and non-nociceptive information to diverse cortices over the thalamic relay and the spino-parabrachial and spino-periaqueductal grey projections originating in lamina 1, which is believed to be pain-specific. This intricate complexity of the spinal dorsal horn, with its diverse populations of projection neurons and interneurons, subserving both excitatory and inhibitory functions, enables both a delineation of nociceptive and non-nociceptive percepts under physiological conditions as well as aberrations thereof in pathological states.

Indeed, a major drive in the field of pain research has been recently directed towards uncovering the cellular and molecular identity of the elusive spinal circuits mediating allodynia. Both structural and functional changes have been discussed (167). A popular notion, which originates back to the Gate Control theory by Melzack and Wall (323), postulates that non-nociceptive afferents can suppress the spinal flow of noxious information to the brain by virtue of activating spinal inhibitory neurons, and that a loss of balance between excitatory and inhibitory neurotransmission in the spinal cord underlies allodynia. While there have been a number of studies supporting this hypothesis over decades, the precise identity of the underlying circuits was not decoded. Recent breakthroughs in genetics, viral tracing, and opto/chemogenetics are now helping to close this critical gap. Although a coherent picture is beginning to emerge, there are still several inconsistencies across studies, and open questions prevail (329, 380), including relevance to the human context.

1. Excitatory neuron populations

Using intersectional genetic approaches to ablate specific populations of excitatory and inhibitory neurons in mice, Ma and colleagues (119) identified a population of excitatory neurons expressing the marker peptide somatostatin (SOM+) to be important for propagating information regarding mechanical pain. They subsequently reported that SOM+ neurons are largely sufficient and necessary to mediate mechanical hypersensitivity in neuropathic pain (119). Peirs et al. (381) implicated a distinct population of spinal excitatory neurons in the deeper laminae of the dorsal horn, which is marked by transient expression of VGLUT3, in mechanical pain and mechanical allodynia. This population receives Aβ fiber input and further transmits it to lamina I neurons as well as calretinin-expressing excitatory neurons in lamina II (381). Recently, Petitjean et al. (387) advanced this knowledge by showing that the calretinin population of neurons feeds into the spino-parabrachial pathway. There is also previous evidence for the involvement of protein kinase C (PKC)-γ-expressing spinal excitatory neurons in inner lamina II in pathological pain. Interestingly, Piers et al. (381) suggested a divergence between circuits mediating mechanical allodynia in inflammatory versus neuropathic conditions, suggesting that the calretinin population and the PKC-γ population selectively contribute to mechanical hypersensitivity in inflammatory and neuropathic conditions, respectively. However, other recent studies have linked the PKC-γ population of neurons to inflammatory pain (3). Another recent study has addressed the role of spinal neurons expressing a receptor for neuropeptide Y (NPY-Y1R) using a chemical ablation method, and reported that their loss selectively attenuated neuropathic mechanical and cold allodynia without affecting basal mechanical or thermal processing (348). Thus current evidence points to involvement of at least five distinct populations of excitatory neurons in neuropathic pain; however, it remains to be determined how these come together to orchestrate the flow of nociceptive information in the spinal cord-brain axis.

2. Inhibitory neuron populations

Similar efforts have been recently devoted to decoding the identity of spinal inhibitory interneurons in "gating" of nociceptive processing by Aβ inputs. The spinal dorsal horn harbors a rich diversity of inhibitory neurons, with GABAergic interneurons being more prevalent in the deeper dorsal horn laminae, while glycinergic neurons are more abundant in the more superficial laminae. Both GABAergic and glycinergic neurons are reported to directly receive inputs from peripheral low-threshold Aβ mechanoceptors (119, 155). Along these lines, Duan et al. (119) reported that SOM+ spinal excitatory neurons are gated by a subpopulation of GABAergic inhibitory interneurons expressing the marker peptide dynorphin; these cells, in turn, receive input from Aβ fibers and mediate suppression of mechanical pain. Similarly, Petitjean et al. (387) reported that activating GABAergic fast-spiking interneurons expressing parvalbumin (PV neurons) selectively rescued mechanical allodynia without altering thermal sensitivity and their inhibition in naive mice induced mechanical allodynia, suggesting the existence of modality-specific spinal circuits. Moreover, ablation of glycinergic inhibitory neurons using genetic models has been reported to broadly induce mechanical, heat, and cold hypersensitivity as well as spontaneous pain-related behavior in naive mice, and their chemogenetic activation alleviated neuropathic allodynia (155).

3. Excitation-inhibition balance

Over several decades, converging lines of evidence have established that the balance between excitation and inhibition in spinal circuits is disrupted in neuropathic pain (278). This was further corroborated by experiments showing that transplantation of GABAergic precursor cells to the spinal dorsal horn alleviates neuropathic mechanical allodynia (48). At least two mechanisms have been proposed to account for reduction in spinal inhibition in neuropathic pain. One entails the hypothesis that spinal GABAergic neurons undergo cell death upon nerve injury. Although these findings have been contested and discussed critically, a recent study has reported involvement of *N*-methyl-D-aspartate (NMDA) receptors in glutamate-induced neurodegeneration using diverse anatomical and functional assays (233). The second mechanism involves a shift in anionic conductance in spinal lamina I neurons resulting from reduced expression of the potassium-chloride exporter KCC2, resulting thereby in reduced inhibition (74). In support, recent evidence shows that restoring this impaired chloride homeostasis pharmacologically by enhancing KCC2 function alleviates neuropathic allodynia (165).

It also deserves to be noted that spinal inhibitory interneurons not only modulate the activity of their target cells postsynaptically, but also have the ability to regulate spinal circuits presynaptically on afferent terminal fibers. Although spinal presynaptic inhibition has been studied to a much lesser extent than postsynaptic mechanisms, there is already evidence to suggest that it may play a key role in neuropathic pain. One study has reported that in neuropathic mice, presynaptic GABA conductance on primary afferent terminals is reduced, accompanied by a brain-derived neurotrophic factor (BDNF)-dependent shift in the reverse potential of GABA, suggesting that presynaptic inhibition caused by the depolarizing effects of GABA is attenuated after nerve injury (63). The study went on to demonstrate that selectively disrupting presynaptic GABAergic inhibition led to allodynia in naive mice, showing that GABAergic inhibition of presynaptic excitability, presumably neuro-

transmitter release, represents an important defense mechanism against neuropathic allodynia (63).

4. Impact of descending pathways

It has been long appreciated that pathways descending from the midbrain and brain stem nuclei profoundly modulate the processing of nociceptive information in the spinal cord. The emerging view is that while descending noradrenergic and serotonergic inhibition dominates over descending serotonergic facilitatory pathways under physiological conditions, this balance can switch during pain chronicity. It is believed that spinal 5-HT_{2A} receptors mediate facilitatory actions of descending serotonergic axons via several mechanisms, including unsilencing of silent synapses in the spinal dorsal horn. Recent evidence indicates that spinal 5-HT_{2A} receptor activation leads to morphological plasticity of PKC-γ interneurons and reproduce their role in mechanical allodynia following inflammation (3). Sensitization of TRPV1 expressed presynaptically on central terminals of primary afferents by descending serotonergic axons via 5-HT_{3A} receptor channels has also been reported (256).

Moreover, three new descending pathways have been described which directly impact upon excitatory and inhibitory cell populations in the spinal cord. First, a direct cortico-spinal pathway originating in the anterior cingulate cortex (ACC) was described to facilitate spinal excitatory synaptic transmission and lead to nociceptive hypersensitivity. Optogenetically inhibiting this pathway exerted antinociceptive effects and also reduced nerve injury-induced spinal synaptic potentiation (65). Descending corticospinal tract fibers originating in the somatosensory cortex project not only to the spinal ventral horn but synapse also in the spinal dorsal horn and gate tactile sensitivity (292). Importantly, activation of this pathway was implicated in mechanical allodynia in neuropathic mice (292). Finally, GABAergic projections from the brain stem to a subset of spinal GABAergic/enkephalinergic interneurons were recently described to enhance spinal nociceptive transmission via disinhibition (156). It remains to be determined whether their potential dysfunction in neuropathic pain states contributes to hypersensitivity.

Taken together, these recent developments make it clear that there is a large degree of dynamism in research on neural circuitry of neuropathic pain, and that recent findings have rapidly advanced our understanding of specific circuits mediating allodynia. Another dimension, which is being fervently pursued in ongoing work, is to link this functional specificity to the transcriptional repertoire of the cells involved in single cell RNA sequencing. Finally, it must be stressed that the field has moved away the neurocentric view on circuits and has expanded it to study involvement of glia, both in the peripheral and central arms of the pain pathway; their contributions are discussed in section VI*E*.

E. Molecular Mediators and Plasticity

A governing principle in the nervous system is given by its plasticity, which is physiologically required in terms of learning and adaptation to changed circumstances; however, maladaptive plasticity can result in pathologies, with chronic pain disorders constituting prominent examples. A number of cell-cell interactions and molecular signaling come into play in orchestrating sensitization of nociceptive pathways.

Maladaptive changes can also come about at the structural level. Indeed, diverse types of structural remodeling processes have been described. We refer readers to recent reviews that have extensively discussed this topic (274, 275). A frustrating caveat of a majority of studies describing structural changes in chronic pain is that they do not reveal whether these changes constitute the cause or a consequence of neuropathic pain. Therefore, more studies employing noninvasive longitudinal analyses of structure in conjunction with functional and behavioral experiments in mouse models over the time course of pain chronicity are warranted.

Major advances have been made in uncovering molecular players of sensitization, both in the peripheral and spinal avenues, while little is known about plasticity mechanisms in the brain. Below, we will review the contributions of distinct cell groups and mediator classes in sensory-spinal circuits.

1. Alterations in ion channels

The peripheral nociceptive endings are the first point of contact between noxious stimuli and activation of the pain pathways. For this interaction to occur, physical, chemical, and mechanical stimuli need to be transduced to membrane potential differences in axons and thereby to trigger action potentials if a certain threshold is reached. Diverse ion channels of the TRP family as well as others, such as ASIC channels or ATP-gated purinergic channels (P2X), are involved in transducing different types of noxious stimuli with a high degree of specificity. At this point, diverse types of voltage-gated sodium channels come into play to amplify transient receptor potentials and thus reach depolarization levels sufficient to trigger action potentials. Conversely, transient potentials can be blocked by hyperpolarization induced by diverse types of potassium channels. Voltage-gated calcium channels at nerve endings govern neurotransmitter release by virtue of facilitating SNARE (soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor) complex-mediated vesicle fusion, a process which is particularly important at the central terminals of primary afferents synapsing in the spinal cord. Not surprisingly, all of these types of ion channels are under strong regulatory control via posttranslational modifications and at the transcriptional level, which can be deregulated upon nerve injury **(FIGURE 5)**.

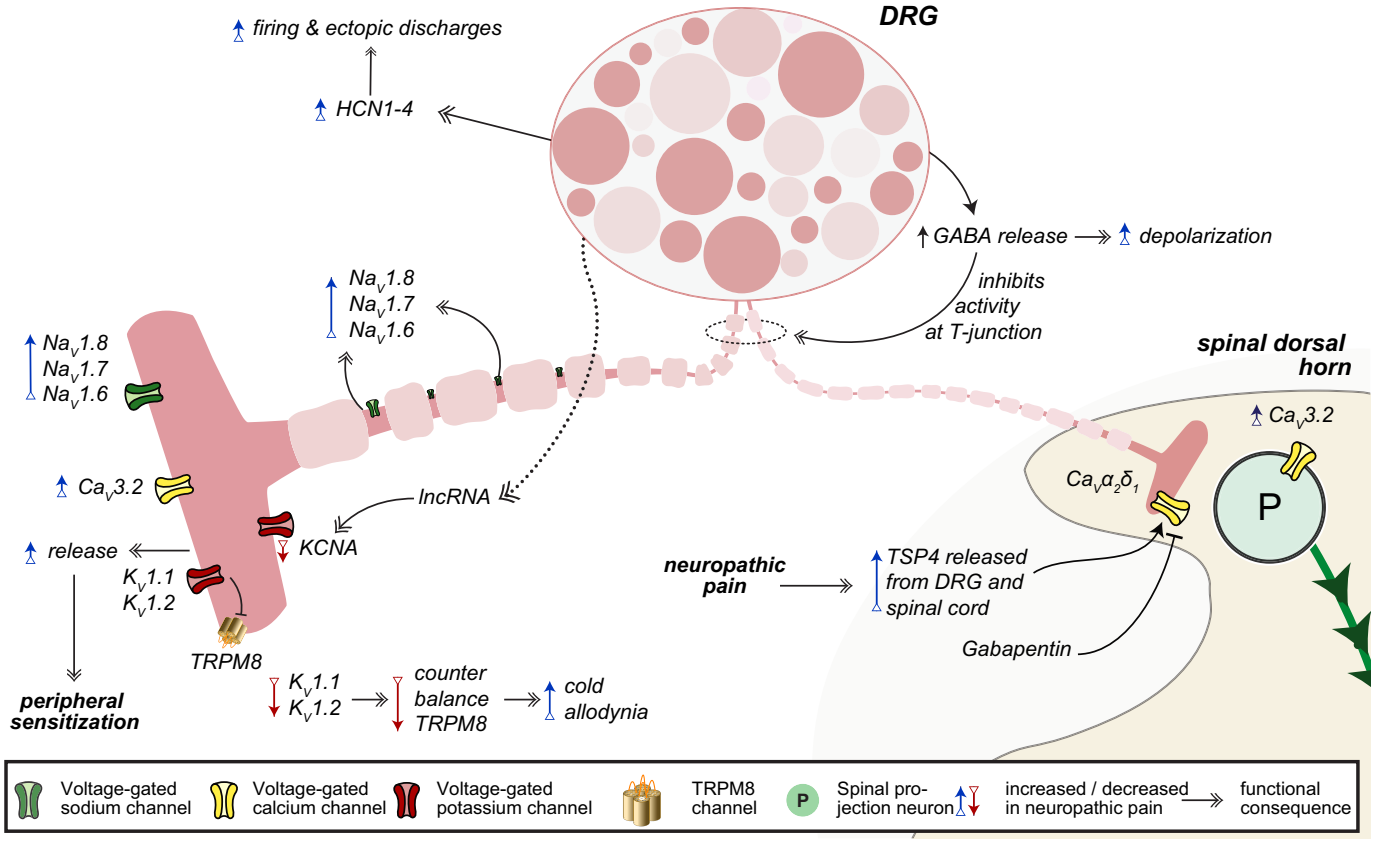

FIGURE 5. Ion-channel dysregulation in sensory-spinal circuits in neuropathic pain. Upregulation, increased density and function of pro-excitatory ion channels, including voltage-gated sodium channels (Na_vs), voltage-gated calcium channels (Ca_vs), and hyperpolarization-activated cyclic nucleotide-gated channels (HCNs) enhances neurotransmitter release, excitability, and ectopic firing of peripheral sensory neurons. This is further augmented by downregulation of potassium channels, e.g., repression of KCNA by long non-coding RNA (lncRNA) and reduced repression of the cold transducer transient receptor potential melastatin 8 (TRPM8) by voltage-gated potassium channels (K_vs). Thrombospondins (Tsp1–4) acting via $\alpha_2\delta_1$ subunits of Ca_v mediate enhanced synaptogenesis in response to activity. DRG, dorsal root ganglion.

At least eight different members of the TRP channel family [TRPV1, TRPV2, TRPV3, TRPV4, TRPM2, TRPM3, TRPM8, and TRP ankyrin 1 (TRPA1)] are expressed in peripheral sensory neurons and implicated in diverse aspects of nociceptive transduction and thermal encoding. Human genetic studies have not revealed major links from neuropathic pain syndromes to mutations in TRP channels, and knockout mice did not show major deficits in neuropathic pain. However, there is pharmacological evidence that blockade of some TRP channels, particularly TRPV1 and TRPA1, alleviates neuropathic hypersensitivity in rodent models (26). It is likely that this arises from a central locus of action, particularly on spinal terminals of nociceptors (see above).

The voltage-gated sodium channels $Na_v1.1$, $Na_v1.6$, $Na_v1.7$, $Na_v1.8$, and $Na_v1.9$ are expressed in varying patterns in peripheral sensory neurons and function as critical regulators of excitability of sensory nerves. There has been rapid progress in linking mutations in voltage-gated sodium channels to multiple pain disorders, ranging from congenital insensitivity to pain to paroxysmal pain disorders (30, 112). As discussed in the clinical sections of this review, recent studies also implicate them in human neuropathic pain disorders. Thus genetic variations in $Na_v1.7$ have been linked recently to enhanced pain in painful diabetic neuropathies (41). Similarly, mutations in $Na_v1.8$, a tetrodotoxin (TTX)-resistant channel which is expressed predominantly in peripheral nociceptive neurons, have been linked to painful small fiber neuropathy, and a recent study analyzing the mutant channels biophysically reported increased resurgent sodium currents as the mechanism underlying hypersensitivity (538). A role for sodium channels in neuropathic pain is supported by phenotypic analyses in studies on mouse mutants, particularly $Na_v1.7$, $Na_v1.8$, and $Na_v1.9$ as well as by the fact that drugs used in some neuropathic disorders, such as carbamazepine and lamotrigine, are sodium channel blockers (30, 112). Importantly, a recent study reported that genetic deletion of $Na_v1.6$, a TTX-sensitive channel, in a random population of (mostly large-diameter) sensory

neurons in mice attenuated neuropathic mechanical allodynia partly, while their deletion in the $Na_v1.8$ population of nociceptive neurons was without any effect (64). There is also evidence that diverse sodium channels, particularly $Na_v1.8$, accumulate at nodes of Ranvier and are overexpressed at neuromas, which are highly sensitive bulb-like structures at the end of severed nerve fibers, in neuropathic conditions. This observation was also recently extended to $Na_v1.6$ in the SNI model of neuropathic pain (64). This overexpression of sodium channels has been associated with a lowering of activation thresholds of nociceptors as well as ectopic activity, thereby offering tremendous scope for therapeutic interventions with new sodium channel blockers that target specific sodium channels or even specific channel activation states.

Hyperpolarization-activated and cyclic nucleotide-gated (HCN) channels constitute another family of excitatory channels that has been closely linked to neuropathic pain. All four known HCN channels are expressed in peripheral sensory neurons, and HCN1 and HCN2 are known to be particularly important in generating a hyperpolarization-activated inwardly-rectifying current (I_h) in sensory neurons. The expression of HCN1 and HCN2 as well as I_h rise significantly in sensory neurons, spinal cord, and some brain regions in rodent neuropathic models (126); conversely, their blockade by drugs such as ivabradine attenuates neuropathic hypersensitivity in rodent models (540) and inhibited spontaneous activity of C-nociceptors, but not Aβ fibers, in neuropathic rats (113). Specific deletion in HCN2 in $Na_v1.8$-expressing nociceptors completely abrogated neuropathic mechanical and thermal allodynia in mice (126), while Djouhri et al. (113) reported a selective effect of HCN antagonists on cold, but not mechanical, allodynia. It should be also noted that the therapeutic potential of HCN channels is not limited to their roles in peripheral neurons. There are also exciting new insights emerging on the role of HCN channels and I_h in brain circuits of pain. In mice with neuropathic pain, HCN channel dysfunction was reported in dendrites of neurons in the anterior cingulate cortex, resulting in increased excitation (432).

Voltage-gated calcium channels profoundly shape cellular excitability and neurotransmission at diverse avenues in the somatosensory nociceptive pathways. Their biophysical characteristics enable determining neuronal activation as well as rhythmicity, which is why they have constituted highly "druggable" targets in a variety of neural disorders, including chronic pain. Gapapentin, ethosuximide, and ziconotide are currently used in pain management, and several additional drugs, including state-dependent calcium channel blockers, are being investigated. Neurological and cardiovascular side effects with these drugs remain highly problematic, thereby rationalizing the need to understand precise signaling mechanisms and develop more specific, subtype-specific blockers.

Along these lines, there has been much excitement about the calcium channel subtype $Ca_v3.2$ in recent years, which is expressed in neurons of the DRG as well as the spinal cord. $Ca_v3.2$ expression is increased in models of traumatic nerve injury, such as SNI as well as chemotherapy-induced neuropathy, accompanied by increases in T-type calcium channel current amplitude and density. Recently, paclitaxel-induced neuropathic allodynia as well as spontaneous activity in sensory neurons was reported to be prevented, but not reversed, by a $Ca_v3.2$ inhibitor, suggesting effects early during the establishment of neuropathic pain (288). In the same study, $Ca_v3.2$ interactions with Toll-like receptor 4 signaling were suggested, which has been also implicated in nociceptive sensitization. Similarly, attenuation of SNI-induced mechanical allodynia upon peripheral blockade of $Ca_v3.2$ by the cardiovascular drug mibefradil was also demonstrated (66). In the DRG, there are some discrepancies between reports on expression and functions of $Ca_v3.2$ across different fiber types. For example, using highly-specific genetic tools with reporter mice, François et al. (157) reported that the expression is specific to low-threshold mechanoceptors (Aδ-LTMRs and C-LTMRs), indicating selective actions against tactile hypersensitivity involving these afferents. In contrast, some other studies, e.g., Chen et al. (66), reported not only broader expression, but also a functional increase in response thresholds with channel blockers in high-threshold C- and Aδ nociceptors as well as in Aβ LTMRs. This is supported by studies showing that blockade of T-type calcium channels in nociceptors reduces stimulated CGRP release (468). These differences could also arise from less specific actions of the drug rather than in $Ca_v3.2$ expression. Interestingly, $Ca_v3.2$ expression was also recently reported in lamina 1 as well as lamina 2 of the spinal dorsal horn, with knockout mice showing modified intrinsic properties and reduced excitability (57). Therefore, there is much anticipation about development of novel classes of T-type calcium channel blockers (465).

$Ca_v\ \alpha_2\ \delta_1$, a target of the analgesic drug gabapentin that is frequently employed in neuropathic pain patients, albeit with low estimated efficacy, continues to stay in research focus. Fresh perspectives for mechanisms were opened when it was found that $Ca_v\ \alpha_2\ \delta_1$ participates in synaptogenesis upon interactions with thrombospondins, which are blocked by gabapentin, in the context of epilepsy. Recent studies show that this mechanism also holds true for the analgesic effects of gabapentin in the sensory-spinal system (375). Both $Ca_v\ \alpha_2\ \delta_1$ and thrombospondin-4 are upregulated in sensory neurons and the spinal dorsal horn in neuropathic mice. Thrombospondin-4 was reported to elicit development of new synapses in the spinal dorsal horn via presynaptic interactions with $Ca_v\ \alpha_2\ \delta_1$, which is blocked by gabapentin administrated at early stages, but not at chronic stages, of neuropathic pain (542). This offers exciting new avenues for development of more specific blockers of synaptogenesis in preventing the establishment of chronic pain.

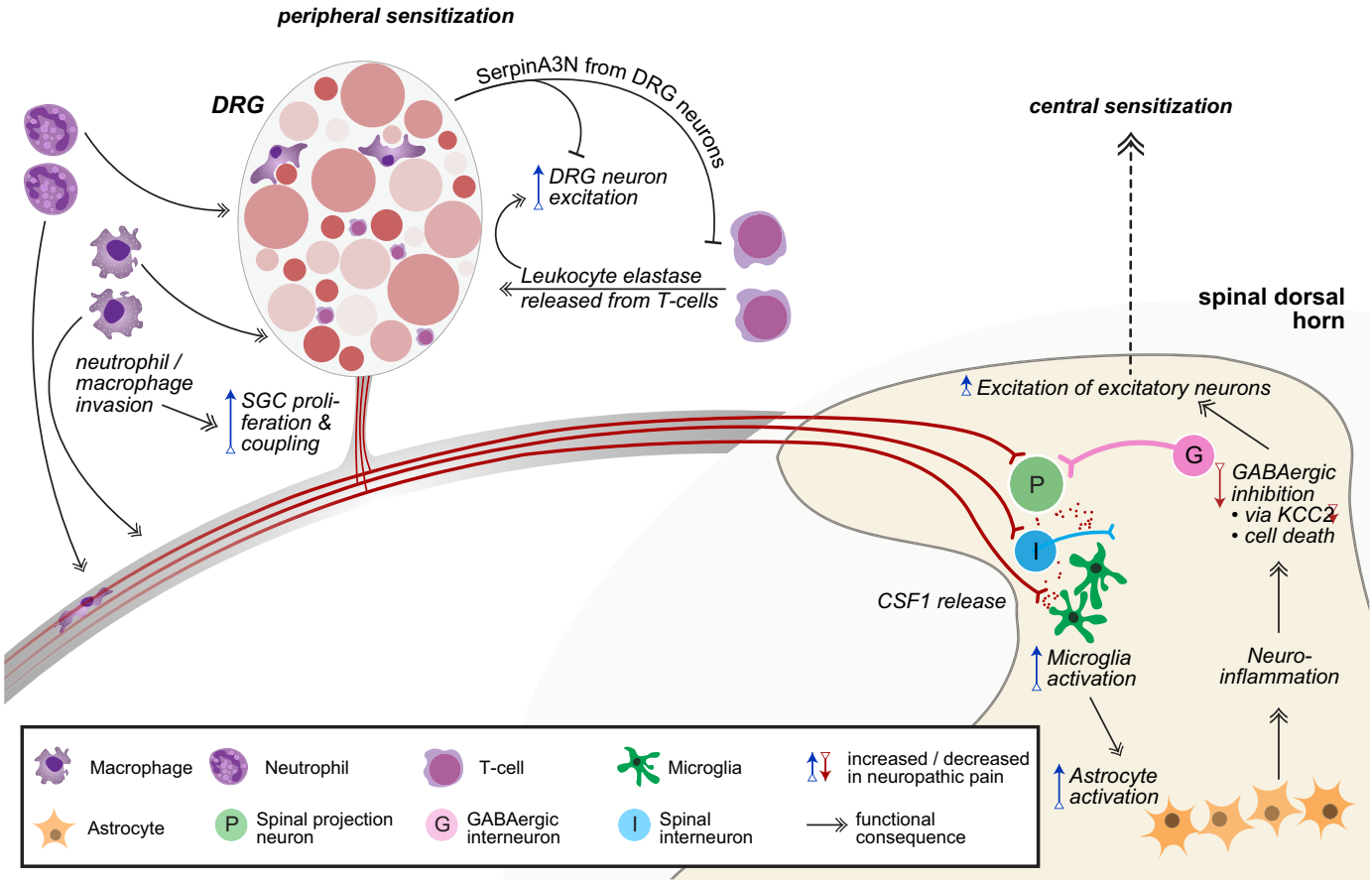

FIGURE 6. Temporal sequelae and role of peripheral and central neuroinflammatory processes in neuropathic pain. Invading neutrophils and macrophages sensitize sensory neurons of the dorsal root ganglion (DRG) via mediators such as interleukins and tumor necrosis factor-α, while invading T cells release leukocyte elastase, which is counteracted by SerpinA3N upregulation in sensory neurons over early stages of neuropathic pain. Sensitized afferents release colony stimulating factor 1 (CSF1) spinally to activate microglia, which in turn elicit astrocyte activation and proliferation. The resulting release of neuroinflammatory mediators elicits cell death of GABAergic neurons and shift in the chloride conductance of target neurons in lamina I, resulting in reduced inhibition and sensitization of spinal neurons processing nociceptive and non-nociceptive information. SGC, satellite ganglion cell.

Neuropathic pain-related alterations in ion channels are not restricted to pronociceptive ion channels, but also extend to several ion channels that diminish neuronal excitability. Along these lines, there have been considerable new developments in our understanding of regulation of potassium channel function in sensory-spinal circuits in neuropathic pain. A large part of this regulation is related to epigenetic mechanisms and is therefore discussed in the eponymous section below. New insights have also emerged on the involvement of shaker-like potassium channels, $K_v1.1$ and $K_v1.2$, and their selective modulation of cold allodynia in neuropathic models. It has been postulated that by virtue of generating the excitability brake current I_{KD}, Shaker-like $K_v1.1$–1.2 channels counterbalance activity of TRPM8, a cold sensor, in determining cold sensitivity. A recent study has reported an increase in the proportion of cold-sensitive neurons (CSNs) in DRGs contributing to the sciatic nerve, and a decrease in their cold temperature threshold in the context of nerve-injury evoked cold allodynia; this was found to be associated with a decrease in I_{KD} density rather than an increase in TRPM8 currents (182).

GABA channels not only shape pre- and postsynaptic inhibition in central circuits as discussed in the section on spinal circuits above, but have also been recently found to be regulators of excitability of DRG somata. GABA receptor channels are surprisingly expressed in populations of DRG neurons (118, 204), which are more classically associated with glutamatergic transmission. A recent study demonstrated that GABA infusion in the DRG repressed excitability of sensory neuron somata and attenuated neuropathic hypersensitivity, while application of antagonists exacerbated nociception-induced excitation (118). Intriguingly, owing to the high chloride concentration in DRG neurons, GABA-induced effects were actually depolarizing at the level of individual somata, but the overall effect was

inhibitory owing to a suppression of incoming nociceptive activity at T-junctions, likely representing a depolarization block (118). These results suggest that GABAergic channels and certain classes of potassium channels offer hope for peripherally directed novel analgesics.

2. Role of immune cells in neuropathic pain

There is a large body of previous literature on the seminal contributions of diverse types of immune cells, including mast cells, neutrophils, macrophages, and T lymphocytes, in peripheral as well as central sensitization **(FIGURE 6)**. A number of immune cell-derived factors have been described and functionally validated, including prominently tumor necrosis factor (TNF)-α, diverse interleukins, such as interleukin (IL)-10, IL-1β, IL-4, and IL-17, and interferon-γ, for which we refer readers to previously published comprehensive reviews (243, 329, 484, 490). Here, we will focus on covering some of the newest findings that are highly relevant to neuropathic pain. Initially thought to be mostly relevant to inflammatory pain disorders, it is now clear that neuropathic pain states are also associated with considerable infiltration of diverse types of immune cells in the vicinity of or within peripheral nerves. A very important class in this regard is given by T cells, which profoundly shape the development of neuropathic pain. Mice lacking T cells entirely lack the ability to develop neuropathic mechanical allodynia after nerve injury (515). A genomic screen recently identified Serpina3n to be a pivotal molecule determining resilience against neuropathic pain in rats and mice and reported that Serpina3n acts by blocking the pro-nociceptive effects of T cell-derived leukocyte elastase in peripheral sensory neurons (515). Genetic loss of leukocyte elastase as well as pharmacological inhibition were found to dampen allodynia and spontaneous pain in diverse forms of neuropathic pain, including nerve injury (21, 515), diabetic neuropathy (21), cancer pain involving nerve remodeling (21), as well as osteoarthritic pain (337).

Novel insights have also emerged on the involvement of natural killer cells in the development of painful neuropathy. Following peripheral nerve injury, a ligand activating the natural killer cell receptor is upregulated in DRG neurons and mediates degeneration of injured neurons by invading natural killer cells (84).

Among macrophages, it is now being increasingly appreciated that different classes come into play in promoting sensitization (classically, M1 type) and inhibiting sensitization and promoting healing (M2 type). There is mounting evidence for a role for macrophages in the pathophysiology of neuropathic pain (88, 492, 541). Recently, macrophage activation has been closely linked to clinical observations of peripheral analgesic effects attributed to angiotensin receptor 2 antagonists, which were surprising given the lack of expression of the receptor in sensory neurons. It is now known that expression of angiotensin receptor 2 on invading macrophages at the site of nerve injury mediates attenuation of neuropathic allodynia (453). Taken together, there is enormous therapeutic potential in targeting immune cells and their mediators in neuropathic pain, at least for its peripherally driven components.

3. Metabolites, hypoxia, and mitochondrial factors

A common element shared by human conditions and animal models of diverse types of neuropathic pain is given by pronounced mitochondrial dysfunction in peripheral sensory neurons, induced by direct nerve injury or mitochondrial toxicity induced by chemotherapeutics, anti-HIV treatment, and high glucose and its metabolites in diabetic neuropathy (32, 493). Mitochondrial dysfunction and generation of reactive oxygen species (ROS) are tightly interlinked and lead to energy deficits and degeneration. Peripheral sensory neurons with their long axons and high energy demands are particularly vulnerable to bioenergetic crises induced by injury. Mechanisms underlying mitochondrial toxicity and regulation of ROS generation are now only beginning to be analyzed in neuropathic pain and open an exciting chapter with new insights. Mitochondrial toxicity induced by cancer chemotherapeutics was shown to be associated with high levels of peroxynitrite, which has the ability to sensitize nerves (235). Agents, which lead to peroxynitrite decomposition, were shown to alleviate neuropathic allodynia in chemotherapy-induced neuropathy (235). Willemen et al. (530) reported the expression of FAM173B, a novel enzyme with mitochondrial lysine methyltransferase activity in sensory neurons, and demonstrated that the enzyme hyperpolarized mitochondria and led to ROS production, thereby facilitating the activation of macrophages in peripheral nerves in models of neuropathic pain. Taken together, these data suggest the clinical benefits for lowering or preventing ROS production in neuropathic conditions. This can be achieved by stabilizing the hypoxia-inducible factor 1 (HIF1α), which is a key transcription factor activated by hypoxia, hyperglycemia, nitric oxide, as well as ROS. Rojas et al. (418) demonstrated that HIF1α is as an upstream suppressor of ROS production in peripheral sensory neurons and thereby limits nerve damage and promotes nerve integrity in a model of type 1 diabetic neuropathy.

Recent studies also suggest that the harmful effects of mitochondrial toxicity and ROS are not restricted to peripheral nerves in neuropathic pain. Upon peripheral nerve injury, mitochondrial superoxide levels increase in the spinal dorsal horn in a superoxide dismutase-2-dependent manner and lead to an increase in the frequency of miniature excitatory postsynaptic currents in excitatory neurons of the spinal cord (19). Thus overexpressing the superoxide dismutase-2 enzyme led to protection against neuropathic allodynia induced by nerve injury. Another mechanistic link comprises the role of ryanodine

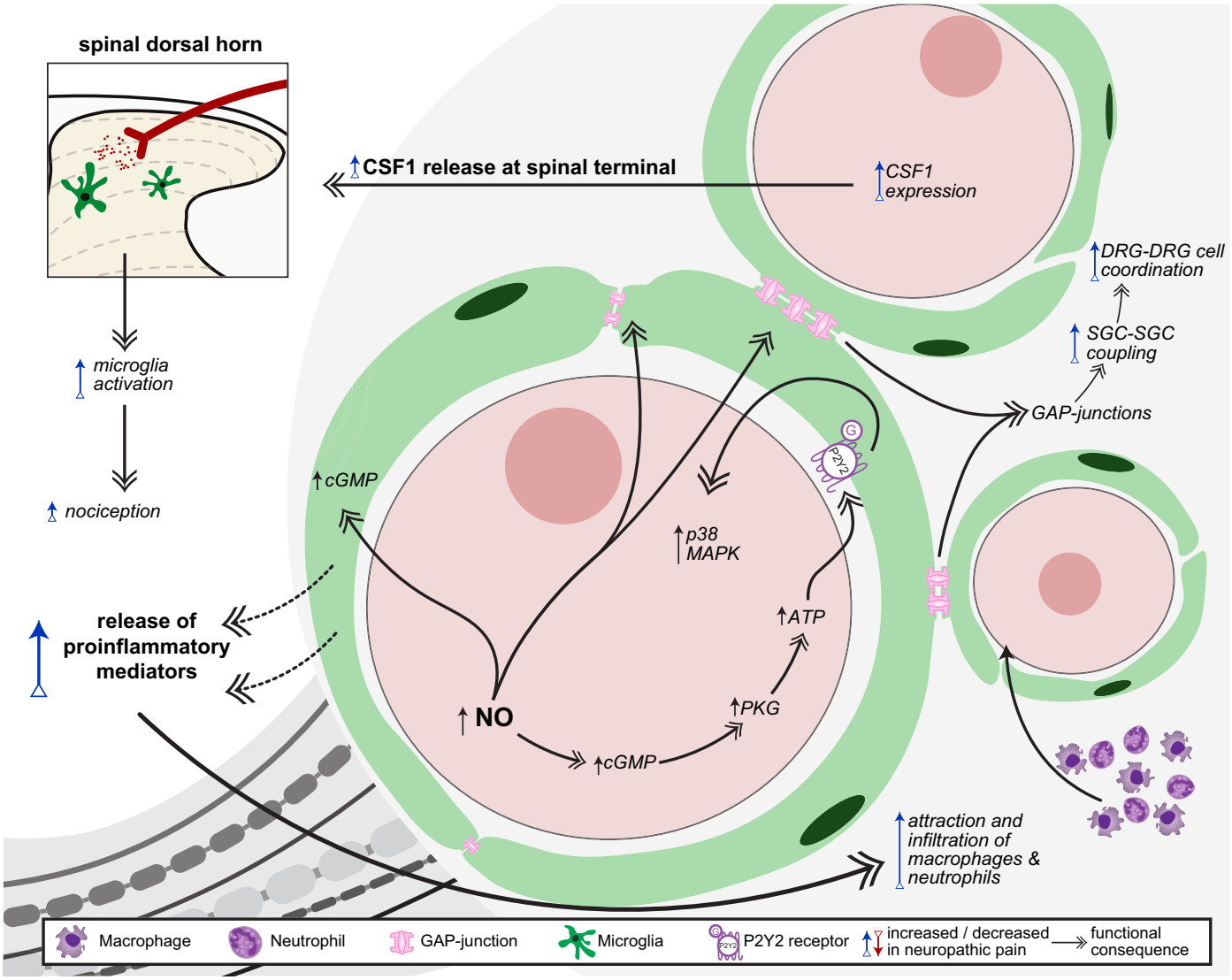

FIGURE 7. Interplay between satellite ganglion cells (SGCs), dorsal root ganglion (DRG) neurons, and immune cells in neuropathic pain. Nitric oxide (NO) signaling in sensory neurons of the DRG enhances cGMP and activates purinergic signaling in SGCs, leading to increased gap junction coupling between SGCs. This, in turns, enhances firing of DRG neurons, leads to release of mediators attracting immune cells, and, importantly, triggers release of colony stimulating factor 1 (CSF1) from central terminals of sensory neurons, thereby eliciting microglia activation. MAPK, mitogen-activated protein kinase; PKG, protein kinase G.

receptors (RyR), which were shown to mediate increased mitochondrial superoxide expression in spinal cord neurons, but not glia, in mice with HIV neuropathy (178). Accordingly, inhibition of RyR was reported to lower neuropathic allodynia.

4. Glial-derived mediators in peripheral nerves and spinal cord in neuropathic pain

Over the past decade, both peripheral and central glia have taken center stage in research on neuropathic pain. Glial contributions to neuropathic pain have been the topic of a series of excellent reviews (e.g., Refs. 243, 430). We will therefore restrict the following discussion to the most recent work on microglia, astrocytes, and peripheral glial cells.

Recent studies have helped resolve orchestration between different types of glia in neuropathic pain. Pathological activity in peripheral afferents following injury was recently reported to lead to release of colony stimulating factor 1 (CSF1) from central terminals of injured afferents, triggering microglial activation via activation of CSF1 on their surface (196). Previously, ATP has also been implicated in this process. Proliferation, shape change, and activation of microglial populations in the spinal dorsal horn have been reported in several models of neuropathic pain, and microglial activity has been postulated to underlie sex differences in mechanisms of neuropathic mechanical allodynia (243).

Diverse ensuing changes in the transcriptional and secretory profile of microglia have been linked to neuropathic pain, including release of TNF, diverse interleukins, fractalkine, ATP, chemokines, among others. It is thought that this neuroinflammatory cascade is further propagated by recruitment of other microglia and eventually neighboring astrocytes, which also release pro-inflammatory agents. Moreover, astrocyte activation further promotes neuronal activity, e.g., via enhanced secretion of D-serine, which potentiates NMDA receptor function on spinal neurons, thereby promoting central sensitization (243, 329). Importantly, astroglial activation can also impact on the bioenergetic state of neurons in the spinal dorsal horn, triggering further dissemination of aberrant activity along spinal circuits. Owing to lack of their specificity, it has not been possible to derive strong inferences from microglial and astrocytic inhibitors in alleviating neuropathic pain. Thereby, translation of the vast literature from rodent studies on to human disorders has been conspicuously lacking.

Secretion of BDNF by activated microglia has also been linked to alterations in KCC2-mediated chloride gradients in spinal neurons in several studies (430), which is discussed as a mechanism of spinal disinhibition in neuropathic pain (see sect. VI*D*). Because BDNF is not found in the transcriptome of microglia (94), either in resting or activated state, the source of BDNF requires further verification. BDNF is known to be secreted from central terminals of primary afferents, and recent studies with conditional knockout mice suggest a pivotal role for BDNF derived from sensory neurons (107, 456).

Microglia are also important mediators of activity-dependent synaptic pruning during development and disease (430). It remains to be determined whether glia-mediated pruning contributes to neuropathic pain. Interestingly, in chronic inflammatory pain, the downregulation of C1q-dependent complement signaling in spinal neurons, not glia, leads to increase in synaptic density; however, this mechanism was found to not be operational in neuropathic pain (459).

Peripheral glia have been studied to a lesser extent than spinal glia and could contribute to delayed and prolonged structural and functional changes following nerve injury. The recent years have brought a number of new insights into the functions of satellite glia, which form ringlike envelopes around DRG neuronal somata. Indeed, communication between satellite glia and sensory neurons has been an area of emerging importance in pain research **(FIGURE 7)**. Like astrocytes in the central nervous system, satellite glia form gap junctions and show dye coupling, which is strikingly increased upon application of a peripheral noxious stimulus. Gap junction coupling is mediated by electrical synapses comprising connexin family proteins, which are expressed in satellite glia cells, but not in sensory neurons. A recent study performed dual patch-clamp recordings on DRGs and observed coupling between satellite glia with themselves and with neurons as well as between sensory neurons (469), suggesting that satellite glia form an essential bridge synchronizing the activity of sensory neurons. Recent studies also suggest a role of damage to Schwann cells for neuropathy and neuropathic pain (87, 88, 181). Schwannopathy has been coupled to myelin disruption, changes in axonal conduction, impaired regeneration, and neuroinflammation (87, 88, 181).

This leads to the question of what brings about satellite glia activation. Recent studies suggest that the signals may originate from sensory neurons themselves. It is well-known that the nitric oxide (NO)-cGMP-protein kinase G1 pathway in primary sensory neurons plays a key role in both peripheral sensitization and spinal long-term potentiation (301). Recently, NO generated in sensory neurons was proposed to activate cGMP signaling in satellite glia, thereby augmenting gap junction coupling (27) **(FIGURE 7)**. Conversely, activation of ATP-mediated purinergic signaling via P2Y12 receptors in satellite glia was recently implicated in neuronal sensitization in a model of HIV neuropathy (539).

Downregulation of potassium channel Kir4.1 in satellite glial cells has been recently reported in post-herpetic neuralgia-induced mechanical allodynia and is thought to be triggered by TNF-α released by invading neutrophils and macrophages (457). This suggests that satellite glia form an accessory unit or even an intermediate to neuroimmune interactions in neuropathic pain. This concept was also supported by a recent study showing that knocking down the IKK/NF-κB-dependent proinflammatory pathway selectively in satellite glia cells in mice led to a reduction in infiltration of macrophages, suggesting that satellite glia act both downstream and upstream of macrophages (291). Importantly, this change also impeded CSF1 production in sensory neurons and the ensuing microglia activation in the spinal cord (291). Thus satellite glial activation is linked to microglial activation via sensory neuron stimulation.

Taken together, these results suggest diverse reciprocal interactions between sensory neurons and satellite glial cells, which form a unit connecting peripheral immune cell activation to central immune cell activation and spinal sensitization in neuropathic pain.

5. Epigenetic regulation in neuropathic pain models

Epigenetic regulation is the cornerstone of mechanisms underlying gene-environment interactions and has been proposed to largely account for selective susceptibilities versus resilience towards developing chronic pain (94, 95). Chromatin remodeling and ensuing alterations in gene expression are regulated via enzymes mediating methylation of DNA (Dnmts) or deacetylation of histones (HDACs). Recently, several studies have described deregulation of diverse Dnmts and HDACs along the somatosensory nociceptive pathway as well as their functional actions in

neuropathic pain models (95). For example, both Dnmt1 and Dnmt3 were found to regulate expression of the potassium channel Kcna2 in peripheral neurons following nerve injury, thereby contributing to hyperexcitability (473). However, additional studies are needed to establish specificity before these enzymes can be therapeutically targeted given their broad expression and functions across the body.

Another form of epigenetic regulation is given by noncoding RNAs (ncRNAs). These exert tremendous posttranscriptional and translation control in physiology and disease states (20). They have the ability to modulate neuronal excitability at diverse avenues in the somatosensory nociceptive pathway and neuroimmune interactions (272). After nerve injury, hundreds of miRNAs can be up- or downregulated in sensory neurons. Using a model of neuropathic rats with differential susceptibility to developing neuropathic pain-like behavior, Bali et al. (20) found differential regulation of only three miRNAs, namely, miR-30d-5p, miR-125b-5p, and miR-379-5p, which are known to regulate expression of key mediators in neuropathic pain, such as TNF-α, the transcription factor Stat-3, and BDNF. Simeoli et al. (458) studied the role of miRNA21-5p, which was known to be upregulated upon nerve injury, and observed that it is released from DRG neurons upon nociceptive activation and acts to recruit macrophages. In keeping with the important role allocated to immune cells in neuropathic allodynia, suppressing miRNA21 expression alleviated hypersensitivity in mice with nerve injury (458). Although most of the initial analyses were focused on microRNA species (miRNAs), including the let-7 family of miRNAs, recent studies on other forms of ncRNAs, such as long noncoding RNAs (lncRNAs) are now emerging (20). An important recent development in this direction was the discovery of a lncRNA targeting the potassium channel Kcna2 in sensory neurons (550). Upregulation of this lncRNA following nerve injury was shown to repress Kcna2 expression and thereby contribute to neuropathic hypersensitivity (550). Baskozos et al. (25) comprehensively tested expression of lncRNAs in sensory neurons from murine DRGs and human induced pluripotent stem cell (iPSC)-derived cultures and observed strain- and gender-dependent alterations in their expression induced by nerve injury.

VII. GENETICS OF NEUROPATHIC PAIN

As discussed above, rare monogenic pain disorders caused by mutations in the sodium voltage-gated channel alpha subunit 9 (SCN9A) causing gain-of-function mutations in $Na_v1.7$ include inherited erythromelalgia and paroxysmal extreme pain disorder (30, 111, 112). Also, gain-of-function mutations in $Na_v1.9$ and other sodium channels have been linked to pain disorders (30, 112). Mutations in sodium channels have also been associated with common neuropathic pain conditions. De novo gain-of-function missense variants in $Na_v1.7$ were found in 30% and in $Na_v1.8$ in 9% of patients with idiopathic painful small-fiber neuropathy (128, 129), and mutations in $Na_v1.7$ and 1.8 have also been found in up to 10% of patients with painful diabetic polyneuropathy (41, 203). The role of Nav1.8 in neuropathic pain is supported by rodent studies showing that the channel is essential for the expression of spontaneous activity in damaged sensory axons (427). In a recent study of 1,139 patients with small fiber neuropathy, 12% had 73 different potentially pathogenic variants in voltage-gated sodium channels, of which 50 were found in more than 1 patient. This study found that erythromelalgia-like symptoms and warmth-induced pain were more common in patients with these variants (124). In a study in patients with idiopathic or diabetic peripheral neuropathy, missense variants were common in SCN9A, SCN10A, and SCN11A but not more common in painful than pain-free neuropathy, and the authors suggested that other factors than the presence of these variants are important for the development of neuropathic pain (520). Gain-of-function mutations in TRPA1 are another example of a monogenic pain disorder as it is shown to cause familial episodic pain syndrome (271). Rare genetic variants in the genes coding for TRPA1 and TRPV1 have also been found in patients with erythromelalgia (548).

Genetic epidemiology genome-wide association studies in neuropathic pain have included relatively few patients (53, 350, 510). A recent systematic review of 29 studies identified variants in 28 genes involved in neurotransmission, receptor signaling and binding, immune response, iron metabolism and binding, and drug metabolism that showed study-wide association with neuropathic pain (510). Genetic variants in catechol-O-methyltransferase (COMT), major histocompatibility complex genes, opioid receptor mu 1 (OPRM1), GCH1, IL-6, and TNF-α were identified to have an association with neuropathic pain in more than one study. In general, more and larger studies are needed to replicate these findings. The heterogeneity of underlying causes and profiles of neuropathic pain may preclude finding polymorphisms related to a specific cause or profile in large population-based studies. A few studies have also examined the relation between genetic variants and specific somatosensory profiles. In one study, single nucleotide polymorphisms in TRPA1, TRPM8, and TRPV1 did not differ between 371 patients with neuropathic pain and 253 healthy controls, suggesting that these variants are unlikely to play a role as susceptibility factors of chronic neuropathic pain (39). However, subgroup analyses suggested that specific single nucleotide polymorphism were associated with specific sensory profiles supporting a role of TRP channel polymorphisms in the somatosensory function in patients with neuropathic pain.

VIII. PHARMACOLOGY OF NEUROPATHIC PAIN

Based on a systematic review and meta-analysis of published and unpublished randomized controlled double-blind trials,

the Neuropathic Pain Special Interest group (NeuPSIG) of the International Association for the Study of Pain (IASP) has published recommendations for the pharmacological treatment of neuropathic pain (137). Drugs with a moderate-to-high quality of evidence and strong recommendation were tricyclic antidepressants (TCA), gabapentin, pregabalin, and serotonin noradrenaline reuptake inhibitors (SNRI: duloxetine and venlafaxine), and these are recommended as first-line drugs. Drugs with a weak recommendation included capsaicin 8% patches, lidocaine patches, and subcutaneous injections of botulinum toxin type A for peripheral neuropathic pain only (137). There is also some evidence for the effect of tramadol and opioids, but these drugs are generally not recommended for chronic non-cancer pain (12, 136). There were inconclusive evidence for sodium channel blockers like carbamazepine, lacosamide, and lamotrigine, but these drugs are suggested to be effective in subgroups of patients with neuropathic pain (85, 93), and carbamazepine and oxcarbazepine are recommended first-line treatments for trigeminal neuralgia (80, 544). Despite the evidence for efficacy of drugs with different mechanisms, the effect sizes are small and treatments are often associated with side effects, and many patients will not obtain sufficient pain relief in tolerated doses (137). When treatment with one drug is partially but not sufficiently effective, combination therapy is often used. In refractory cases, spinal drug administration or neuromodulation may be considered, although there is little evidence from randomized controlled trials (77, 136).

TCAs and SNRIs inhibit the presynaptic reuptake of serotonin and noradrenaline, and their analgesic activities are thought to be through activation of descending aminergic pathways at spinal or supraspinal sites, although peripheral mechanisms are also suggested to be involved (270, 462). The Ca_v α_2 δ antagonists gabapentin and pregabalin were designed as GABA analogs but do not have clinically relevant agonist-like effects (377). The analgesic actions are thought to involve inhibition of voltage-gated calcium channels and reduced activity-dependent calcium signaling and thereby inhibition of excitatory transmitter release and reduced neuronal hyperexcitability (377). Other actions such as an effect on glia cells and expression of proinflammatory cytokines may also be involved (270). The drugs may act at peripheral, spinal, and supraspinal levels (214, 270, 335). Lidocaine-medicated patches are used for PHN and peripheral neuropathic pain. Lidocaine acts by a use-dependent blockade of voltage-gated sodium channels and thereby a stabilization of nerve membranes and inhibition of ectopic discharges (106). Capsaicin, the active pungent ingredient in chili peppers, binds to TRPV1. Repeated application or a single application of a high concentration causes a reversible in intraepidermal nerve fiber density and desensitization of nociceptors (6, 393). Capsaicin 8% patches are applied for 30–60 min, and the treatment is repeated every 3 mo. Botulinum toxin type A can be given subcutaneously or intradermally in the area of peripheral neuropathic pain every 3 mo. The exact analgesic mechanisms are not known but suggested to involve reduced inflammation, inhibition of neuropeptide and neurotransmitter release from primary afferents, reduced sodium and TRPV1 channel activity, or central effects via retrograde axonal transport (328).

Merck's manual from 1901 provided detailed treatment recommendations for neuralgia based on underlying cause, e.g., anemic, sciatic, malarial, or from cold. Combination treatment was recommended including three or four oral and topical agents for each treatment. These included mercury ointment and arsenous acid, treatments later abandoned because of serious long-term side effects, but also treatments with are used today and have a proven effect on neuropathic pain such as morphine and tincture of capsicum, and treatments that are used despite no proven effect from randomized controlled trials such as menthol, nutmeg, and extract of *Cannabis indica*. Interestingly, antifebrin, which is an aniline derivative like paracetamol and with medicinal qualities similar to those of antipyrine, and oil Wintergreen, which contains methyl salicylate, the primary metabolite in salicylic acid, were also recommended drugs, but today we have no randomized controlled trials that have estimated the efficacy of paracetamol and nonsteroidal anti-inflammatory drugs for neuropathic pain (137, 334, 516, 529). Surprisingly few new treatments have been introduced and proven effective and safe for neuropathic pain over the past 120 yr, and they have not been developed through bottom-up translational approaches but rather through empirical clinical observations (12, 136). Furthermore, they probably act by a general pain modulating and neuronal depressant activity rather than targeting specific underlying mechanisms (206). The few drugs acting on new targets that have be developed though bottom-up translational approaches, such as neuronal nicotinic receptor agonists (424), angiotensin type II receptor antagonists (409), the substance P receptor NK1 antagonists (180), and chemokine receptor 2 antagonists (248) have either failed in clinical trials or been abandoned because of intolerability. Mutations in *SCN9A* causing loss-of-function in $Na_v1.7$ cause congenital insensitivity to pain, and recently there has been an interest in developing $Na_v1.7$ blockers as analgesics (321). Results of randomized controlled trials have been disappointing, with no effect on the primary outcomes (398, 545), but a recent study using human iPSC-derived nociceptors has shown that some $Na_v1.7$ blockers lack specificity (321).

The unmet need for effective treatments and the limited success from the classic translational approach have led to attempts to refine older drugs and an inverse translational approach where results from clinical experience are translated to animal models to investigate mechanisms (12). One is tincture of aconite, another recommended treatment from Merck's manual, which is used today in traditional medicine

to treat pain and numbness. Promising results from open label studies of goshajinkigan, which has a main ingredient of aconite (269, 478), are being back translated into preclinical studies aimed at identifying active ingredients of processed aconite root (474, 478).

IX. MECHANISM-BASED CLASSIFICATION

Neuropathic pain is generally classified according to underlying etiology **(FIGURE 4)**, but it is recognized that mechanisms and pain phenotypes differ within each diagnosis and at the same time may be shared across diagnoses. Dr. Mitchell Max noted in a commentary in *Pain* in 1990 that "Despite the diversity of the pathology, physiology, and symptoms of neuropathic pain syndromes, there is virtually no information guiding the clinician in matching a particular treatment to a particular patient" (318). As he also noted, development of an individualized treatment algorithm requires the development of drugs that correct particular pathophysiological mechanisms, identification of a classification based on underlying physiology, and stratified clinical trials. Despite an increasing focus on mechanism-based classification and individualized treatments for neuropathic pain over the past two decades (16, 487, 519, 532), these three requirements are still challenging. A predictive biomarker assesses baseline characteristics that categorize patients by their likelihood of response to a particular treatment (464). Unlike the oncology field, where molecular profiling and precision medicine are advanced (273), we do not have good biological knowledge of the mode-of-action of the drugs currently used for neuropathic pain or of the mechanisms underlying a specific pain phenotype. It is therefore recommended that precision medicine in the pain field involves a two-step approach (464). The first exploratory step involves assessment of biomarkers at baseline in clinical trials and performing secondary analyses of treatment effects to identify likely responders. This is challenging because studies are often underpowered for such secondary analyses, and up to now, there has been reporting bias with positive predictors more likely to be mentioned in the publications. With the requirement for study registration and open access to predefined primary and secondary outcomes from most journals, reporting bias should become a decreasing concern. The next confirmatory step involves clinical trials, where patients are prospectively enrolled on the basis of biomarkers. This step is also challenging as it requires large sample sizes and the interpretation is often complicated because of a complex interaction of treatment and placebo responses and difficulty in separating predictive from prognostic biomarkers (171, 447).

In a classic paper from 1998, patients with PHN were classified into three groups based on clusters of symptoms and signs (135). One group, termed irritable nociceptor, had preserved cutaneous innervation and marked dynamic mechanical allodynia (425, 426), one group had thermal sensory deficits with mechanical allodynia and hyperalgesia, and the last group was characterized with deafferentation and general sensory loss. The authors speculated that these phenotypes represent different underlying pain mechanisms that may be weighted differently in the groups. A later large multinational study in 902 patients with different neuropathic pain conditions using the German Research Network on Neuropathic Pain (DFNS) protocol for standardized detailed quantitative sensory testing of 13 different parameters of thermal and mechanical sensory loss or gain (419) found three groups with similar distinct sensory profiles in a hypothesis-free cluster analysis (23). One cluster was characterized by sensory loss of small and larger fiber functions and the presence of paradoxical heat sensation, which is the sensation of warm with decreasing temperatures to cold and is a marker of cold and warm sensory loss (436, 513). A second cluster termed thermal hyperalgesia was characterized by relatively preserved large and small fiber sensory functions in combination with heat and cold allodynia and only low-intensity dynamic mechanical allodynia, and the third cluster termed mechanical hyperalgesia had predominantly loss of thermal sensation in combination with blunt pressure allodynia, pinprick hyperalgesia, and marked and more frequent dynamic mechanical allodynia (23). These sensory phenotypes were compared with human pain models in healthy subjects in another study (518). The sensory profile after nerve block with either compression or topical lidocaine resembled the sensory loss phenotype, the profile in the primary area after sensitizing the skin with UVB or topical capsaicin resembled the thermal hyperalgesia phenotype, and finally the profile in the secondary hyperalgesia area after intradermal capsaicin and electrical high-frequency stimulation resembled the mechanical hyperalgesia phenotype (518). The authors speculated that the clusters represent different underlying mechanisms with deafferentation hypersensitivity underlying pain in the sensory loss phenotype, irritable nociceptors and peripheral sensitization underlying pain in the thermal hyperalgesia phenotype, and reorganization and central sensitization underlying the mechanical hyperalgesia phenotype. Similar sensory profiles are, however, found in patients without pain, and it has also been suggested that they are correlates of neuropathy rather than reflecting neuropathic pain mechanisms (220, 438). In line with this thinking, the sensory phenotypes seen in patients with neuropathic pain may rather reflect the loss or preservation of primary afferents and their central projection pathways with the absence of, e.g., dynamic mechanical allodynia being a natural consequence of loss of Aβ fibers.

Patient-reported outcomes with the assessment of symptoms is another approach to identify clusters of patients with potential different mechanisms (16, 24, 161). Different questionnaires have been developed to characterize pain characteristics, such as the Neuropathic Pain Symptom Inventory (45) and the painDETECT (162), and different subgroups have been identified in patients with neuropathic pain (16, 24, 161). Other biomarkers possibly predictive of

a specific mechanism or treatment response include psychological assessment, molecular profiling, assessment of conditioned pain modulation as an indirect possible measure of the function of pain modulating pathways, and electrophysiology or functional imaging (464, 487).

There is some evidence from clinical trials that patient profiling might be informative for deciding on certain treatments. The effect of subcutaneous injections of botulinum toxin type A have in two studies been shown to be associated with preserved thermal sensation based on quantitative sensory testing and intra-epidermal nerve fiber density and more allodynia assessed both with sensory testing and using questionnaires suggesting that preservation of small-fiber innervation and evoked pain are predictors of response (15, 402). Studies on predictors for other topical agents are, however, conflicting, with small studies suggesting both a better effect of topical lidocaine in patients with degenerated nociceptors (523) and preserved nociceptors (92) and uncontrolled studies showing mixed results for topical capsaicin (198, 308). Different studies have in post hoc analyses found evoked pain to be a predictor for the response to intravenous lidocaine (18) and lamotrigine (146), both of which are sodium channel blockers, but other studies have failed to reproduce these findings (17, 138, 183, 187). In one of the few studies performed with the "a priori" aim to test the use of stratification for predicting treatment response, the sodium channel blocker oxcarbazepine was more effective in peripheral neuropathic pain in patients with the irritable nociceptor phenotype compared with those without this phenotype (93). Irritable nociceptor phenotype was defined using the DFNS quantitative sensory testing protocol and required normal cold and warm detection thresholds and evoked pain with either dynamic mechanical allodynia, reduced cold, heat, pressure, or mechanical pain threshold or increased mechanical pain sensitivity (93) **(FIGURE 8)**.

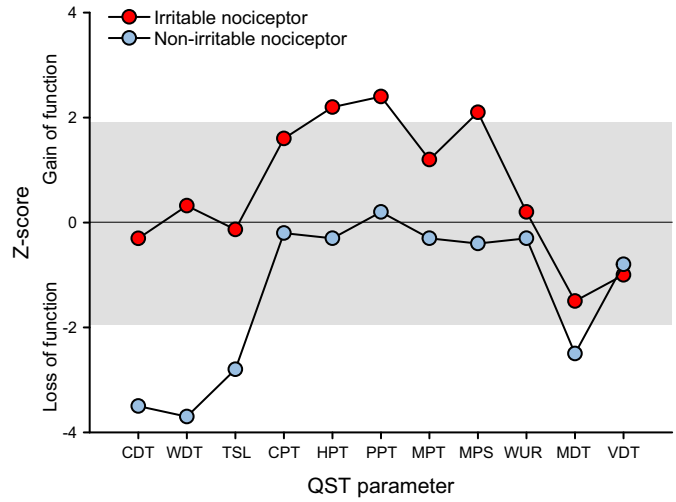

FIGURE 8. Sensory profiles of two patients with the irritable and the non-irritable nociceptor phenotypes based on quantitative sensory testing. The requirement for the irritable nociceptor phenotype is normal thermal cold and warm detection thresholds and sensory gain with reduced pain threshold to cold, warm, pressure, or pinprick stimuli of dynamic mechanical allodynia (not shown). If one of these two requirements is not fulfilled, the phenotype is classified as the non-irritable nociceptor phenotype. QST, quantitative sensory testing; CDT, cold detection threshold; WDT, warm detection threshold; TSL, thermal sensory limen; CPT, cold pain threshold; HPT, heat pain threshold; PPT, pain pressure threshold; MPT, mechanical pain threshold; MPS, mechanical pain sensitivity; WUR, wind-up ratio; MDT, mechanical detection threshold; VDT, vibration detection threshold.

X. CONCLUSIONS

Neuropathic pain is a complex condition caused by a nervous system lesion or disease. It remains difficult to treat and represents a huge unmet medical need. Neuropathic pain has different manifestations, such as ongoing burning or pricking pain, paroxysmal pain, or cold or touch-evoked allodynia. The pathophysiology similarly varies and involves ectopic activity in damaged or adjacent nerves, DRG or central pathways, and peripheral and central sensitization and a range of molecular mechanisms. Underlying circuits are just beginning to be unraveled and yield critical new knowledge which can be harnessed for new pharmacological and neurostimulation-based therapeutic strategies.

Our understanding of the underlying pathophysiology has increased considerably in the last decades, although not to the extent that treatment has improved considerably. Considering the substantial morbidity of chronic neuropathic pain, it is imperative that we understand the obstacles for successful development of targeted therapies, and the challenges in the translation between animal and human studies need further attention. Improved patient stratification and clinical trial design, advanced genetic sequencing technology, whole-genome association studies, use of human tissue and iPSCs-derived cultures, validation of ethologically relevant behavioral assessments of pain in animals, further use of new molecular techniques, such as single cell sequencing, as well as circuit dissection tools, will hopefully pave the way for better understanding of pathophysiology and eventually prevention and treatment.

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Correspondence: N. B. Finnerup (e-mail: finnerup@clin.au.dk).

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