Pathophysiological Mechanisms of Neuropathic Pain

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Abstract and Introduction

Abstract

Neuropathic pain is a common problem in clinical practice and one that adversely affects patients' quality of life. Converging evidence from animal and human studies demonstrates that neuropathic pain arises from a lesion in the somatosensory system. Injured peripheral nerve fibers give rise to an intense and prolonged ectopic input to the CNS and, in some cases, also to secondary changes in dorsal horn neuronal excitability. Convincing evidence now suggests that classifying neuropathic pain according to a mechanism-based rather than an etiology-based approach might help in targeting therapy to the individual patient and would be useful in testing new drugs. This article summarizes our current understanding of the peripheral and central pathophysiological mechanisms underlying neuropathic pain and focuses on how symptoms translate into mechanisms.

Introduction

The widely accepted definition of neuropathic pain is 'pain arising as a direct consequence of a lesion or disease affecting the somatosensory system'.[1]

Neuropathic pain is a frequent problem in many peripheral and CNS diseases. The peripheral nerve diseases that most commonly cause neuropathic pain are distal symmetric peripheral neuropathies (e.g., diabetic neuropathy) and focal neuropathies related to trauma (e.g., traumatic brachial plexus injuries), as well as surgical interventions (e.g., breast surgery). Exemplary CNS diseases causing neuropathic pain include multiple sclerosis, spinal cord injury and stroke. The widely ranging etiologies suggest a high prevalence of neuropathic pain in the general population. Postal surveys designed to investigate chronic pain with neuropathic characteristics in large community samples have reported a 7–8% prevalence of neuropathic pain in the general population.[2,3]

Neuropathic pain arises through multiple and complex pathophysiological mechanisms. Convincing evidence on the relationship between the underlying pathophysiological mechanisms and neuropathic pain symptoms now suggests that classifying neuropathic pain according to a mechanism-based rather than an etiology-based approach might help in targeting therapy to the individual patient and would also be useful in testing new drugs. In this article we summarize our current understanding of the peripheral and central pathophysiological mechanisms underlying neuropathic pain and focus on how symptoms translate into mechanisms.

Mechanisms Underlying Neuropathic Pain

Animal Models

Most of our current knowledge on the complex pathophysiological processes that trigger neuropathic pain comes from animal models of peripheral nerve injuries, largely designed to mimic human diseases.[4] Although these models have the important merit of improving our knowledge on the mechanisms underlying neuropathic pain, they often poorly predict the involvement of particular targets or processes in human neuropathic pain.[4] Several studies have used total nerve transection and ligation to simulate the clinical conditions of amputation.[5] Partial nerve ligation[6] and spared nerve injury[7] have been used to simulate the clinical condition involving partial peripheral nerve injury. Spinal nerve ligation effectively simulates spinal root damage owing to a lumbar disk herniation.[8] Immune or toxin-mediated demyelination simulates demyelinating neuropathy.[9] Vincristine, paclitaxel and cisplatin have been used in animal models to mimic polyneuropathy caused by tumor chemotherapy.[10] Finally, streptozocin-induced damage to pancreatic insulin-producing cells in rats provides an experimental model of diabetic neuropathy.[11]

Peripheral Sensitization

Following nerve damage, a neuroma, consisting of regenerative nerve sprouts growing in all directions, develops at the proximal nerve stump. Electrophysiological recordings demonstrate that after nerve damage, ongoing spontaneous activity, abnormal excitability and an increased sensitivity to chemical, thermal and mechanical stimuli develop at multiple sites, including the neuroma (the site of injury with aborted axon growth), in the cell body of injured dorsal root ganglia neurons[12] and in neighboring intact afferents.[13] This 'hyperactivity' involving the nociceptive primary afferents is defined as peripheral sensitization (Figure 1).[4,14–18]
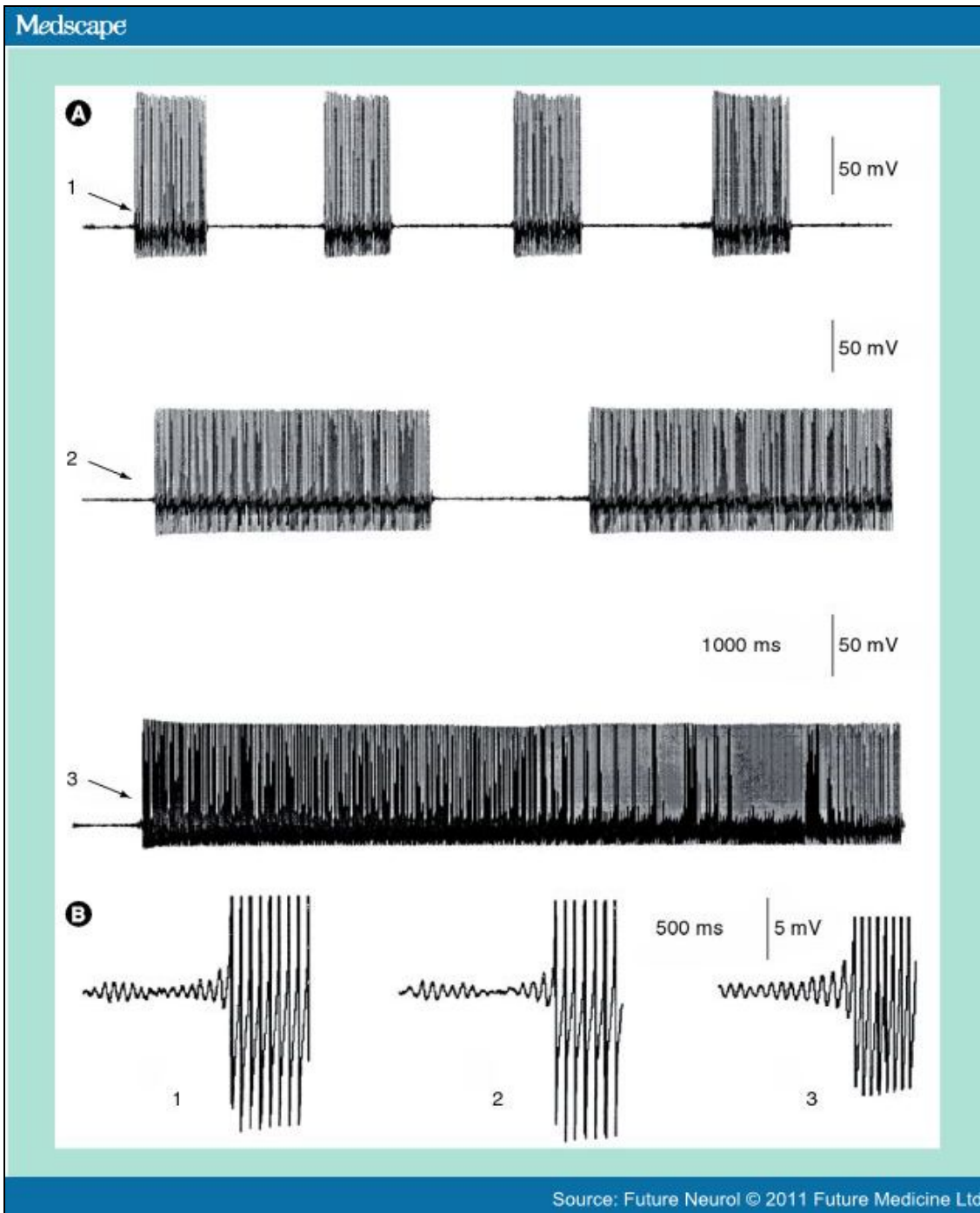
Figure 1.

A high-frequency discharge recorded in primary afferents after spinal nerve injury. In all of the trains, the spikes **(A, 1–3)** are always triggered by a subthreshold oscillation peak as seen in the expanded time and voltage scale **(B, 1–3)**.
Reproduced with permission from [123].

Peripheral sensitization arises through various pathophysiological mechanisms. Following nerve damage, voltage-gated sodium channel expression undergoes marked changes. Many studies demonstrated abnormal sodium channel Nav1.3, Nav1.7, Nav1.8 and Nav1.9 expression,[19,20] leading to primary afferent hyperexcitability (a lowered threshold and higher firing rate).[14,21,22] Clusters of sodium channels accumulate at the site of the nerve

lesion but also within the intact dorsal root ganglion. In the dorsal root ganglion there is a phasically activating, voltage-dependent sodium conductance alternating with a passive, voltage-independent potassium leak, generating characteristic membrane potential oscillations. When oscillation sinusoids reach threshold amplitude, ectopic firing ensues (Figure 2).[23,24]
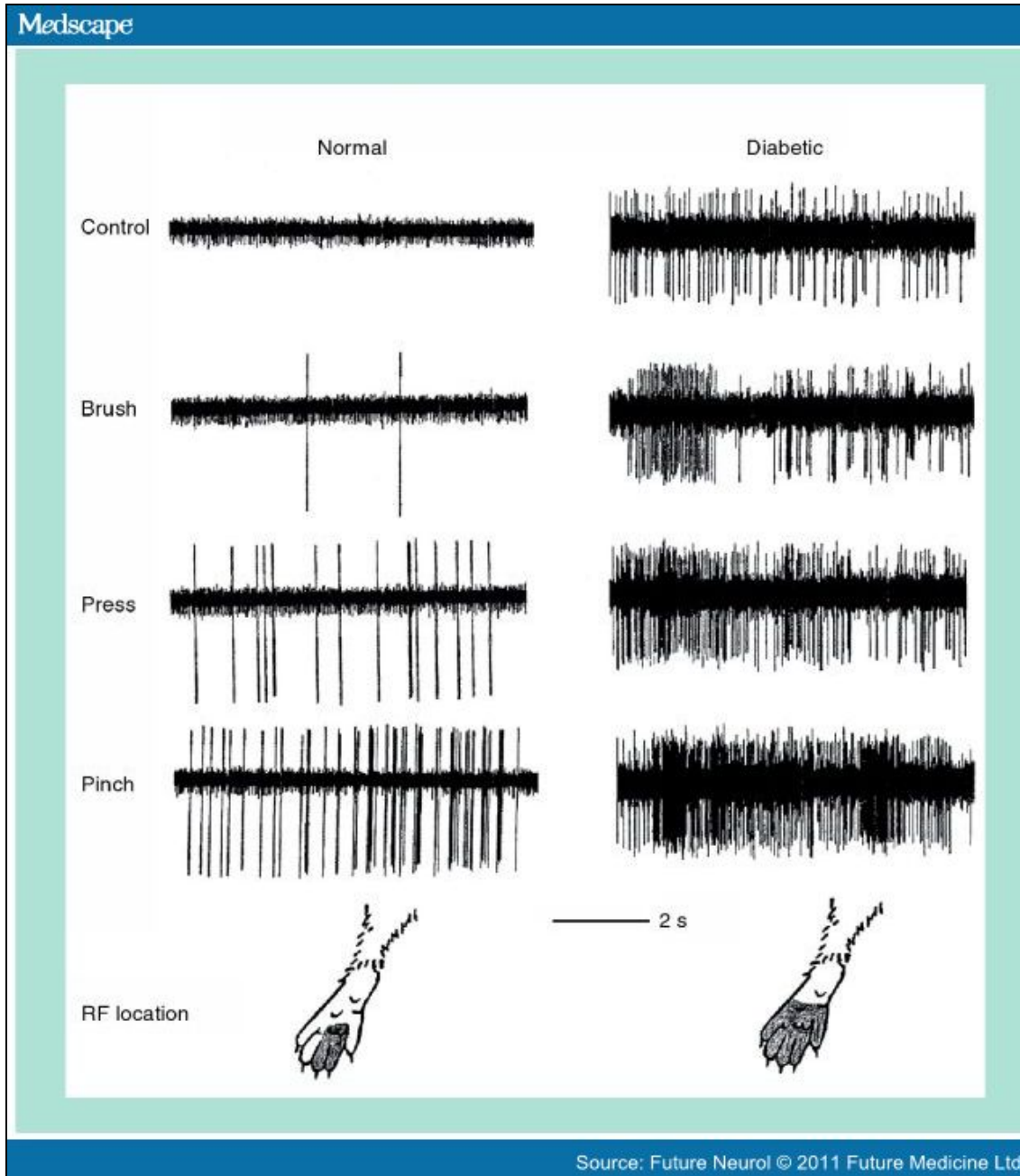

Figure 2.

Baseline activity and responses to brush, press and pinch in one normal and one diabetic wide dynamic range neuron. The RFs of these two spinothalamic tract neurons are indicated in the shaded area of the rat hindpaw.
RF: Receptive field.
Reproduced with permission from [124].

A useful animal model of neuropathic pain that involves dysregulated sodium channel expression in dorsal root gangli Ab-fibers (see for the glossary)

on neurons is streptozotocin-induced diabetes. In this model sodium-channels Nav1.3, Nav1.6 and Nav1.9 mRNA and protein expression is upregulated, and *Nav1.8* mRNA is downregulated.[21,25,26] Whole-cell patch-clamp recordings demonstrated an increase in the peak current density and ramp current amplitude, consistent with Nav1.3, Nav1.6 and Nav1.7 channel upregulation, which produces robust ramp currents.[27] The type III embryonic sodium channel (Nav1.3) probably plays a key role in the development of neuropathic pain. It is present at low levels in adult afferent nociceptive pathways and after an experimental nerve injury its expression markedly increases.[28–30] It rapidly recovers from inactivation and has slow closed-state inactivation kinetics, suggesting that neurons expressing Nav1.3 may exhibit changes in either reduced threshold or a relatively high firing frequency, or both.[28–30]

Box 1. Glossary.

- Aβ-fibers: large-myelinated nerve afferents or pathways that convey non-nociceptive input (e.g., tactile sensation)

- Aδ-fibers: small-myelinated nerve afferents or pathways that convey cold and nociceptive input

- Allodynia: pain sensation induced by a stimulus that normally does not provoke pain, and thus implies a change in the quality of a sensation

- Blink reflex: neurophysiological tool for assessing trigeminal large-myelinated pathway

- C-fibers: unmyelinated nerve afferents or pathways that convey thermal and nociceptive input

- Catechol- *O* -methyltransferase: enzyme that degrades catecholamines such as dopamine, epinephrine and norepinephrine

- Central sensitization: increased background activity, enlarged receptive field and increased responses to all afferent impulses of the second order nociceptive neurons

- Dysesthesias: spontaneous, nonconstant sensations that are clearly unpleasant (e.g., pins and needles)

- Hyperalgesia: increased pain response to a stimulus that normally provokes pain (e.g., the pin used in neurological examination)

- Laser-evoked potentials: scalp signals evoked by laser stimuli, which selectively assess Aδ afferent pathways

- Nerve Conduction Study: the standard electrodiagnostic tool for assessing peripheral nerve fiber function. It assesses only Aβ-fibers

- Paresthesia: spontaneous, nonconstant sensations that are not clearly unpleasant (e.g., tingling)

- Paroxysmal pain: sudden, very short-lasting pains (e.g., electric-shock-like, stabbing sensations)

- Peripheral sensitization: a reduction in threshold and an increase in responsiveness of the peripheral ends of nociceptors.

- Skin biopsy: a minimally invasive technique that assesses the density of intraepidermal fibers, which mainly consist of C-fibers

- TRPV1: the transient receptor potential cation channel, subfamily V, member 1. Also known as the capsaicin receptor, TRPV1 is a nonselective cation channel expressed predominantly in unmyelinated C-fibers

- Wide dynamic range neurons: second-order neurons located in the spinal cord dorsal horn, responsive to all sensory modalities (thermal, chemical and mechanical) and a broad range of intensity of stimulation from primary afferentsm

These data, together with experimental and clinical observations on the partial effectiveness of sodium-channel blocking agents in neuropathic pain, established a link between sodium channel activity and primary afferent hyperexcitability producing pain.[31] Recent studies have linked gain-of-function mutations in *SCN9A*, the gene that encodes Nav1.7, to two human-inherited pain syndromes, inherited erythromelalgia and paroxysmal extreme pain disorder, whereas loss-of-function mutations in *SCN9A* have been linked to complete insensitivity to pain.[32,33]

Although potassium channel expression has been studied less than sodium channel expression in animal models of neuropathic pain, potassium-channels probably have a key role in the development of neuropathic pain. Several studies reported a reduction in potassium channel transcript expression in the dorsal root ganglion after peripheral nerve lesions.[34–36] Furthermore, potassium channel openers act as analgesics in animal models of neuropathic pain.[37,38]

The development and maintenance of peripheral sensitization is modulated by cytokines, small proteins involved in inflammatory processes. Various animal experiments demonstrate that peripheral nerve injury increases TNF and IL-1β immunoreactivity in dorsal root ganglia of both injured and uninjured ipsilateral adjacent afferents.[39] The increased cytokine level is associated with reduced mechanical and thermal withdrawal thresholds in rats.[40–44] Epineurially-applied TNF elicited acute mechanical hyperalgesia in the awake rat[40] and antibodies neutralizing the TNF receptor injected at the site of nerve injury reduce pain behavior in mice.[41] Exogenous TNF injected into dorsal root ganglia of damaged roots is transported into the dorsal horn, precipitating allodynia in both the ligated and adjacent uninjured nerves.[42,43] Nerve biopsies of patients with painful neuropathies demonstrated higher TNF immunoreactivities in myelinating Schwann cells and serum soluble TNF receptor levels are higher in patients with centrally-mediated mechanical allodynia.[44] An endogenous IL-1β receptor antagonist, experimentally injected in mice, prevents inflammatory hyperalgesia, and antibodies neutralizing IL-1β receptors reduce pain-associated behavior in mice with experimental nerve damage.[45–47] After unilateral chronic constriction injury, IL-1β also increases in the contralateral homolog nerve.[48,49] This selective contralateral cytokine induction is probably mediated by NMDA receptors and reflects a spinal mechanism.

Peripheral sensitization also involves the upregulation of various proteins, some of them only marginally expressed under physiological conditions. Various animal studies demonstrated that peripheral nerve injury changes transient receptor potential (TRP) channel expression. TRP channels are a family of nonselective cation-permeable channels that are known to be important for sensory signaling in the peripheral nervous system. Several animal studies investigated the role of the vanilloid receptor 1 (TRPV1), a member of the TRP family, in the development of neuropathic pain.[50–53] Total or partial sciatic nerve transection, or spinal nerve ligation, reduce TRPV1 expression in the somata of all damaged dorsal root ganglia.[50–53] Following partial nerve lesion or spinal nerve ligation, TRPV1 expression is greater in the undamaged dorsal root ganglion somata than in controls. [50–53] Evidence that hyperalgesia does not develop in TRPV1-deficient mice and that TRPV1 antagonists reduce pain behavior in mice after spinal nerve ligation further supports the idea that TRPV1 plays a crucial role in the development of neuropathic pain.[50–53]

Normal nerve terminals assume signal substances that are transmitted by axonal transport to the dorsal root ganglion cell body. In the dorsal root ganglion cell body these signal substances modify gene transcription and protein synthesis.[54,55] After nerve damage, sprouts can no longer assume these molecules. Therefore, nerve damage, through complex signaling mechanisms (cAMP-dependent PKA and Ca^{2+}/phospholipid-dependent PKC) modulate gene transcription. Animal studies demonstrated that after nerve damage, there is an induction of *c-jun*, *p-38* and *ERK*.[56–60] The encoded proteins of these genes are involved in inflammatory responses, neuronal degeneration and neuronal plasticity, which maintain pain sensation. [14,56–60] Therefore, the importance of genetic factors in neuropathic pain remains an interesting question for further research, especially for their possible use as targets for new, more selective drugs.

In accordance with findings from animal studies, microelectrode recordings from transected nerves in human amputees with phantom limb pain, displayed spontaneous afferent activity (i.e., peripheral sensitization). In these patients, tapping the neuroma increases pain and afferent discharges.[61] The injection of lidocaine into the neuroma blocks nerve activity owing to the tap of the neuroma and its related pain.[16] By contrast, perineuromal injection of gallamine, a potassium channel blocker, increases pain.[62] Some investigators demonstrated an inverse relationship between ongoing pain and heat pain deficit in patients with postherpetic neuralgia.[63] In these patients, lidocaine applied to the painful skin in patients with postherpetic neuralgia produces effective pain relief.[64] Microneurographic studies demonstrated that in patients with peripheral neuropathies, pain is associated with ongoing spontaneous firing of unmyelinated C-fibers.[65–67]

Central Sensitization

Despite the increasing evidence underlying the importance of peripheral sensitization, many investigators consider central sensitization the main pathophysiological mechanism responsible for neuropathic pain.[14,68–70] The primary afferent pathways that convey human pain signals connect in the spinal cord dorsal horn with second-order nociceptive neurons. They consist of nociceptive-specific neurons and wide dynamic range neurons. [71,72] Nociceptive-specific neurons are located in the outer layers (laminae I–II) of the dorsal horn; wide dynamic range neurons lie in deeper laminae (most of lamina V neurons are wide dynamic neurons). Nociceptive-specific neurons respond selectively to noxious stimuli conveyed by Aδ- and C-fibers. Wide dynamic range neurons excited both by noxious and non-noxious stimuli, receive both large-myelinated Aβ-fibers as well as Aδ- and C-fibers. Wide dynamic range neurons can encode and project different types of sensory information, nociceptive and non-nociceptive, varying their firing rate (higher for noxious and lower for non-noxious stimuli). Nociceptive neurons have a fairly localized receptive field and probably play an important role in spatially detecting nociceptive stimuli. By contrast, since wide dynamic range neurons have a large receptive field and a stimulus-response function (the higher the stimulus intensity, the higher the firing rate of their output), their main function is to detect and discriminate the intensity of noxious stimuli.[73,74]

Animal studies demonstrated that after nerve damage, owing to the ongoing spontaneous activity arising from primary nociceptors (peripheral sensitization), background activity in second-order nociceptive neurons increases, receptive fields enlarge and responses to afferent impulses, including innocuous tactile stimuli, increase (Figure 2). In this pathological condition, Aβ low-threshold mechanoreceptors can activate second-order nociceptive neurons, thus gaining access to the pain-signaling pathway. This phenomenon is termed central sensitization.[4,16,68,75] Central sensitization has been documented in animals and may explain persistent neuropathic pain in patients.[14,69,70]

Peripheral nociceptor hyperactivity causes major secondary changes in the spinal cord dorsal horn. In response to pain stimuli, the central terminals of primary nociceptive afferents in the dorsal horn of the spinal cord release the neurotransmitters glutamate and substance P, as well as brain-derived neurotrophic factor. The amino acid glutamate, the major excitatory neurotransmitter found throughout the whole nervous system, is essential for pain signaling at every anatomical level. Primary nociceptive afferents release glutamate in response to acute and persistent noxious stimuli, and through AMP acid (AMPA) receptor activation, set the initial baseline response of spinal dorsal horn neurons. Delivering repetitive and high-frequency stimulation to primary nociceptive afferents amplifies and prolongs the responses of spinal dorsal horn neurons. This enhanced activity results from NMDA-receptor activation. Acute or low-frequency stimuli delivered to second-order neurons cannot activate the NMDA receptor because in normal physiological conditions the magnesium ion (Mg^{2+}) levels found in nervous tissues block the receptor's ion channel. A sustained membrane depolarization is required to activate and open the NMDA receptor-channel.[72] The contact between neurotransmitters and receptors produce an increase of intracellular Ca^{2+} and cAMP concentrations, which activates protein kinases. Protein kinases consist of the signaling cascade that modulates gene transcription (i.e., *c-fos*, *c-jun*).[69,76]

Like peripheral sensitization in neuropathic pain, recent studies demonstrate that central sensitization arises also through changes in ion channels. Peripheral nerve injury leads to changes in sodium-channel expression within nociceptive dorsal horn neurons, strongly suggesting that sodium channel changes in the dorsal horn contribute to neuropathic pain. For example, experimental spinal cord injury upregulates Nav1.3 in dorsal horn neurons. This upregulation is associated with hyperexcitability in second-order nociceptive neurons and pain. Antisense knockdown of Nav1.3 reduces second-order nociceptive neuronal hyperexcitability and pain behavior in spinal cord-injured rats.[77,78] Several lines of evidence suggest that the mechanisms underlying central sensitization at the dorsal horn level also involve molecular mechanisms other than sodium channels, for example, prostaglandins and cytokines, the proinflammatory substances that facilitate pain transmission.[14,22,79]

Although most investigators consider central and peripheral sensitization as the main mechanisms underlying neuropathic pain, peripheral nerve damage also leads to other central changes.[79] For example, mild afferent signal loss might induce major changes in dorsal horn neuron excitability. When large Aβ-fiber input decreases, the interneurons that inhibit nociceptive neurons become hypoactive (loss of afferent inhibition).[80] Earlier research suggested changes in the descending modulatory systems[81] subsequently confirmed by the efficacy of serotonin and noradrenalin reuptake-blocking antidepressants in neuropathic pain.[14] During massive deafferentation, after presynaptic terminal buttons are lost, the postsynaptic receptors on spinothalamic tract (STT) neurons become exposed to neurotransmitters, and STT neurons begin to fire spontaneously (deafferentation supersensitivity).[14]

This article again underlines the role of glial cells in neuropathic pain. Glial cells, including microglia and astrocytes, are non-neuronal cells that have various functions in the spinal cord. Glial cells act as physical support, release mediators that modulate neuronal activity and alter axonal and dendritic growth. Under normal conditions they account for 70% of CNS cells.[82] Several lines of evidence indicate that spinal cord microglia and astrocytes are implicated in creating exaggerated pain states.[83–87] Glial cells play a crucial role in maintaining neuronal homeostasis in the CNS and immune factors produced by microglia are believed to play an important role in nociceptive transmission. Increasing evidence demonstrates that uncontrolled glial cell activation under neuropathic pain conditions induces the release of proinflammatory cytokines and other substances that facilitate pain transmission.[83–87] Glial cells also enhance the release of substance P and excitatory amino acids from nerve terminals, including primary afferents in the spinal cord.[83,84] Glial cell activation can also lead to altered opioid system activity.[85–87] During strong neuronal excitation, such as that induced by neuropathic pain, fractalkine, a protein expressed by neurons, breaks free.[88] The soluble portion of fractalkine diffuses away and binds to and activates glial cells.[89] Intrathecal fractalkine creates both thermal hyperalgesia and mechanical allodynia, and fractalkine receptor blockade blocks inflammatory neuropathy-induced pain.[90]

Mechanism-based Symptoms

At the bedside examination, neuropathic pain can been distinguished from spontaneous pain, (i.e., stimulus independent) and provoked pain.[70] Spontaneous pain can have several different qualities. The most typical spontaneous pains are ongoing pain (usually superficial burning or deep pressing pain, or both), and paroxysmal pain (electrical shock-like, stabbing pain).[79,91] Provoked pain includes allodynia, pain in response to a normally nonpainful stimulus, and hyperalgesia, an increased response to a normally painful stimulus. Unfortunately, unlike animal studies, neuropathic pain mechanisms in humans remain largely unclear; current clinical and neurophysiological research has proposed various mechanisms for each type of pain.

A useful way to draw parallels between symptom and mechanism is to combine patients' sensory profiles, obtained by specific questionnaires such as the Neuropathic Pain Symptom Inventory (NPSI), using data obtained with neurophysiological tools (blink reflex, nerve conduction studies and laser-evoked potentials).

Patients with neuropathic pain syndromes typically describe their pain as constant and burning. In a group of 150 patients with various types of polyneuropathy (68 with neuropathic pain) approximately 90% complained of burning pain.[92] Previous neurophysiological studies demonstrated that in patients with various neuropathic pain conditions (postherpetic neuralgia, carpal tunnel syndrome and polyneuropathy) burning pain is associated

with nociceptive pathway damage as assessed by laser-evoked potential recordings (Figure 3).[92–94] Microneurographic studies demonstrated that in patients with peripheral neuropathies the spontaneous burning pain was associated with the ongoing spontaneous firing of C fibers.[65–67] Skin biopsy studies described reduced intraepidermal nociceptive terminals in patients with ongoing pain related to peripheral neuropathy.[95,96] These data suggest that ongoing burning pain is probably due to the abnormal spontaneous activity originating in damaged nociceptive fiber axons that have lost their intraepidermal endings. Although the spontaneous activity causing burning pain presumably originates from axonal sprouts, a concurrent mechanism might include long-term CNS changes provoked by nociceptive pathway damage, such as hyperactivity in the second-order neurons (central sensitization).[22,97] A recent microneurographic study provided new evidence of a specific C-fiber set that have a bimodal thermoreceptive properties and are activated by cooling, heating and menthol.[98] Activity of this specific set of C-fibers could be responsible for the stinging, hot and burning sensations evoked by innocuous cold stimuli.[99] Ongoing burning pain might also be related to the central hyperactivity resulting from deafferentation. In patients with postherpetic neuralgia, the ongoing burning pain is associated with a severe heat pain deficit, thus suggesting a severe C-afferent-fiber loss. A previous study used the C-fiber-mediated histamine axon reflex in patients with postherpetic neuralgia to determine C-fiber activity, demonstrating an abolished response in the area of maximum pain.[16] Ongoing burning pain frequently manifest as sequelae related to deafferentation, produced by a brachial plexus avulsion. Direct recordings of spinal neuron activity in a patient with injury to the dorsal roots of the cauda equina disclosed high-frequency, regular and paroxysmal bursting discharges.[16] The patient suffered from spontaneous burning pain in a region where the lesion had caused anesthesia (anaesthesia dolorosa).
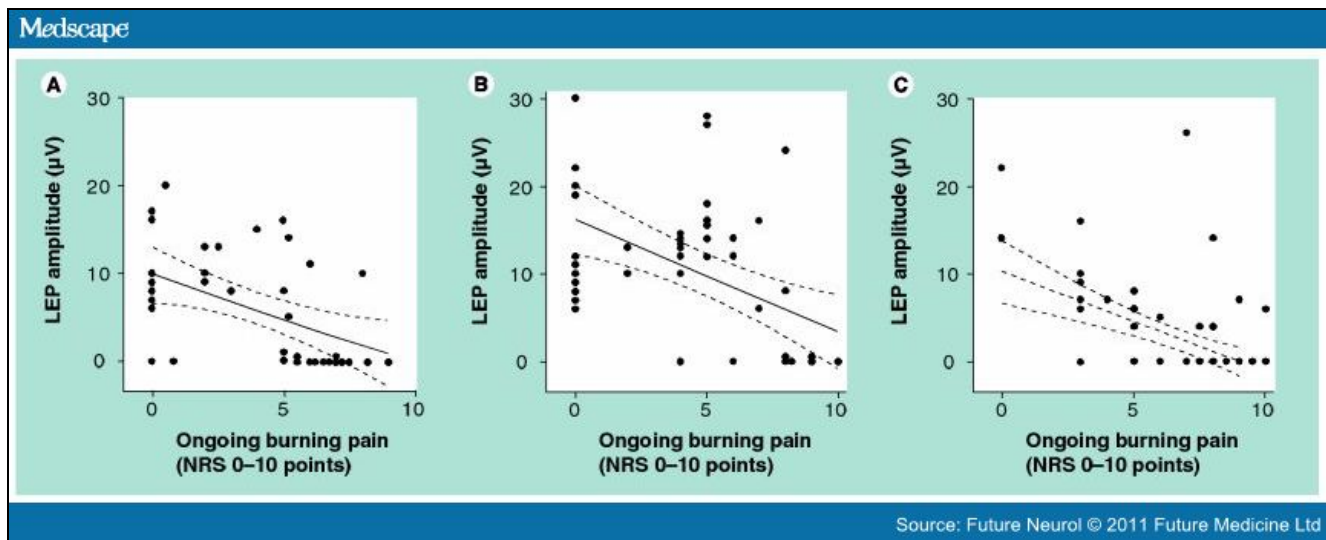

Figure 3.

Correlations between the severity of ongoing burning pain and laser-evoked potential abnormalities in various neuropathic pain conditions. **(A)** 41 patients with ophthalmic postherpetic neuralgia. LEPs elicited from supraorbital stimulation. **(B)** 40 patients (75 hands) with carpal tunnel syndrome. LEPs elicited from the hand (median nerve territory). **(C)** 150 patients with polyneuropathy. LEPs elicited from the foot. The more severe the burning pain, the more abnormal the LEPs, changes that reflect nociceptive pathway damage.
LEP: Laser-evoked potential.

Previous neurophysiological studies in patients with postherpetic neuralgia and carpal tunnel syndrome demonstrated that paroxysmal pain is associated with abnormalities involving non-nociceptive Aβ-fibers.[93,94] More specifically, in patients with postherpetic neuralgia and carpal tunnel syndrome, the correlation between the blink reflex delay and median-nerve sensory conduction velocity slowing, suggests that this type of pain is related to focal Aβ-fiber demyelination. In accordance with previous studies in animals describing spontaneous ectopic discharges recorded in large myelinated Aβ-fiber axons after nerve injuries,[9,100,101] paroxysmal pain may be related to high-frequency bursts generated in demyelinated Aβ-fibers. It is still unclear whether these high-frequency bursts in demyelinated Aβ-fibers are sufficient to provoke pain *per se* or do so only after ephaptic transmission to the neighbouring unmyelinated C-fibers, or by involving wide dynamic range neurons.[94] Although most investigators consider paroxysms as peripheral phenomena related to spontaneous firing, a clinical study provided evidence that paroxysmal pain is associated with decreased small-fiber function, thus raising the possibility that paroxysms originate centrally in the second-order neurons.[102]

No general agreement exists regarding the pathophysiological mechanism underlying allodynia.[18] Two opposing views currently exist, one peripheral[67,103] and the other central.[104] According to some investigators, allodynia reflects peripheral sensitization.[105] Over the past decades, a

possible role for hyperexcitable peripheral nociceptors as primary determinants of pain in humans has received ample support. Microneurographic recordings in patients with painful neuropathy demonstrated that allodynia was related to C nociceptor firing.[67] A recent study in patients with polyneuropathy found that allodynia was associated with a relative sparing of nociceptive fibers, as assessed with laser-evoked potentials.[92] These findings suggest that allodynia reflects an abnormal reduction in the mechanical threshold in sensitized peripheral nociceptors.[79,92,106]

According to many investigators, allodynia is generated at a central level.[16,18] The spontaneous firing in damaged nociceptive afferents may evoke ongoing pain and, as a secondary effect, sensitize central nociceptive neurons.[68,107–109] As a result, a large skin area surrounding the initial lesion site may become hypersensitive to light touch (i.e., allodynia). Microneurographic studies demonstrated that allodynia is mediated by large myelinated Aβ-fiber low-threshold mechanoreceptors.[110] In chronic neuropathic pain, differential nerve blocks demonstrate that allodynia is abolished concomitantly with loss of innocuous tactile sensation at a time when Aδ- and C-fiber mediated modalities are unaffected.[107,111] In patients with neuropathic pain, a selective Aβ-fiber block eliminates allodynia[107,112] but ongoing burning pain persists, indicating that it is mediated by C-nociceptors.[16] Central sensitization as the main mechanism underlying allodynia also receives support from the link between this pain symptom and abnormal pain summation on repetitive mechanical stimulation, a sign of central sensitization.[16] Future research efforts, designed to translate mechanisms into symptoms, should therefore seek more information to clarify the peripheral mechanisms underlying neuropathic pain.

Sensory Profiles

Patients experiencing neuropathic pain suffer from sensory deficits, as well as various types and different combinations of pain. Neuropathic pain may be ongoing (e.g., burning and pressing), paroxysmal pain (e.g., stabbing and electric shock-like sensations) or pain provoked by various stimuli (e.g., gentle brushing [allodynia] or cold water [cold allodynia]). Specific types of pain may predominate in some neuropathic pain conditions but none of them are etiologic specific.[113,114] Thus, patients suffering from the same disease may present with a heterogeneous profile of symptoms and sensory signs. Therefore, the aim of diagnostic workup should be to define specific sensory profiles through clinical examination, questionnaires dedicated to neuropathic pain and laboratory tools.

Current research findings strongly indicate that the different profile of sensory signs and symptoms, (including provoked pain and spontaneous pain) arise through different pathophysiological mechanisms. Clinical, neurophysiological and neuropathological investigations show that in patients with peripheral neuropathy of various etiologies, spontaneous burning pain is invariably related to the nociceptive pathway damage.[92–95] By contrast, recent neurophysiological studies suggest that spontaneous paroxysmal pain reflects demyelination of non-nociceptive, large-myelinated fibers (as described previously).[93,94] Overall, these findings suggest that neuropathic pain can be classified by sensory profiles (quality of pain) rather than etiology, as the recent European guidelines recommend.[115] Classifying neuropathic pain according to a mechanism-based rather than an etiology-based approach might minimize pathophysiological heterogeneity within the groups under study and thus help in targeting therapy to the individual patient.

Genetic Inheritance of Neuropathic Pain

Because not all patients with nerve injury experience neuropathic pain, the heritable predisposition for neuropathic pain probably varies between subjects. Animal studies indicate that neuropathic pain sensitivity encompasses a large heritable component,[116] hence genetic risk factors are probably important in the various clinical neuropathic pain conditions.[117]

Some genetic diseases are associated with an increased risk for the development of neuropathic pain. For example, Fabry disease is a rare X-linked recessive (inherited) lysosomal storage disease that causes painful neuropathy.[118] Gain-of-function mutations in *SCN9A*, the gene that encodes Nav1.7, cause two extremely rare inherited neuropathic pain conditions, erythromelalgia and paroxysmal extreme pain disorder.[32] In these rare conditions traditional genetic techniques can be applied for studying genetic susceptibility. Yet, because the nervous system diseases that most commonly cause neuropathic pain are sporadic, neither family history nor classic genetic techniques can be relied upon to evaluate the heritable susceptibility to this condition. Reasonably, the genetic risk of developing neuropathic pain after nervous system damage results from multiple risk-conferring genes. In an attempt to highlight the role of genetic susceptibility in neuropathic pain, Costigan and colleagues (2010) investigated a single nucleotide polymorphism association of the potassium channel α subunit, KCNS1, in humans with neuropathic pain.[117] They found that a common amino acid changing-allele, the 'valine risk allele', was significantly associated with higher pain scores. Other studies investigated catechol-O-methyltransferase polymorphisms that modulate nociceptive and dysfunctional temporomandibular joint disorder pain.[119,120] A recent study demonstrated that a single nucleotide polymorphism in *SCN9A* increased firing frequency of DRG neurons; this single nucleotide polymorphism was subsequently shown to be associated with chronic pain.[121,122] Therefore, in defining sensory profiles we need to take into account the increasing evidence that each patient has a unique genomic fingerprint. A new future approach to neuropathic pain should therefore include genetic analysis among the more conventional diagnostic tools.

Conclusion

Neuropathic pain arises directly from a lesion or disease affecting the somatosensory system. Our current knowledge on the mechanisms of neuropathic pain comes largely from animal models of peripheral nerve injury. Animal models demonstrate that after a peripheral nerve injury, spontaneous activity develops in damaged axons, excitability becomes abnormal and sensitivity to chemical, thermal and mechanical stimuli increases, resulting in the development of peripheral sensitization. Owing to the ongoing activity arising from primary afferents, background activity in second-order nociceptive neurons increases, receptive fields enlarge and responses to all afferent impulses increase, resulting in the development of central sensitization.

Although animal models help to understand the mechanisms responsible for neuropathic pain, they poorly reflect clinical conditions. Therefore, data from animals cannot invariably be applied in humans. In humans, different pathophysiological mechanisms are responsible for the development of neuropathic pain that manifests with heterogeneous sensory disturbances. Although specific types of pain may predominate in some etiological categories of neuropathic pain, none of them are etiology-specific. Thus, regardless of the disease, patients suffering may present with heterogeneous sensory signs and symptoms, even with the same disease. Our findings in this article show that we now have the information needed for classifying neuropathic pain according to a mechanism-based, rather than an etiology-based, approach and targeting therapy to the individual patient.

Future Perspective

Neuropathic pain owing to lesions or disease of the nervous system remains a major neurological challenge. We now have to change the way we classify, diagnose and treat neuropathic pain from an etiology-based to a mechanism-based approach. In clinical practice, the diagnostic work-up should aim at defining specific sensory profiles, thus targeting therapy to the individual patient and improving drug testing. Although a possible future direction for managing neuropathic pain might be mechanism-based therapy, clinical experimental studies indicate that a specific symptom might be generated by several entirely different underlying pathophysiological mechanisms, suggesting a wider phenotypical approach to the patient with neuropathic pain. Future studies should also clarify how genetic factors contribute to the risk of neuropathic pain. Improved knowledge of the genes involved in neuropathic pain conditions might help us in targeting novel analgesics and biomarkers of neuropathic pain.

Sidebar

Executive Summary

Mechanisms Underlying Neuropathic Pain

- Electrophysiological recordings demonstrate that the regenerating C-fibers of damaged axons develop ongoing spontaneous activity, abnormal excitability and an increased sensitivity to chemical, thermal and mechanical stimuli. This phenomenon is termed peripheral sensitization.

- Following nerve damage, as a consequence of the peripheral sensitization, second order nociceptive neurons develop an increased background activity, enlarged receptive field and increased responses to all afferent impulses. This phenomenon is termed central sensitization.

Mechanism-based Symptoms

- Neuropathic pain may be ongoing (e.g., burning pain), paroxysmal (e.g., electrical shock-like sensations) or provoked by various stimuli. The different types of neuropathic pain probably arise through variations in the underlying mechanisms.

- Burning pain probably reflects the abnormal, spontaneous activity originating in damaged nociceptive fiber axons.

- Paroxysmal pain may be related to high-frequency bursts generated in demyelinated Aβ-fibers.

- Allodynia may be due to a peripheral mechanism, reflecting an abnormal reduction of the mechanical threshold in sensitised nociceptors, or to a central mechanism, reflecting the sensitization of central nociceptive neurons to mechanically evoked input.

- Successful neuropathic pain management requires the definition of precise sensory profiles. The diagnostic process should aim at finding specific sensory profiles through clinical examination, questionnaires dedicated to neuropathic pain and laboratory tools.

- A classification per sensory profile rather than etiology might minimize pathophysiological heterogeneity and increase the power to detect a positive treatment result.

Genetic Inheritance of Neuropathic Pain

- Reasonably, the genetic risk of developing neuropathic pain after nervous system damage results from multiple risk-conferring genes.

Future Perspective

- An increased knowledge of the mechanisms underlying pain and their translation into signs and symptoms in patients might lead to an optimal therapeutic approach, with drugs that address the specific combination of mechanisms occurring in each patient.

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Papers of special note have been highlighted as:
• of interest
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