Neuropathic Pain: A Maladaptive Response of the Nervous System to Damage

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Abstract

Neuropathic pain is triggered by lesions to the somatosensory nervous system that alter its structure and function so that pain occurs spontaneously and responses to noxious and innocuous stimuli are pathologically amplified. The pain is an expression of maladaptive plasticity within the nociceptive system, a series of changes that constitute a neural disease state. Multiple alterations distributed widely across the nervous system contribute to complex pain phenotypes. These alterations include ectopic generation of action potentials, facilitation and disinhibition of synaptic transmission, loss of synaptic connectivity and formation of new synaptic circuits, and neuroimmune interactions. Although neural lesions are necessary, they are not sufficient to generate neuropathic pain; genetic polymorphisms, gender, and age all influence the risk of developing persistent pain. Treatment needs to move from merely suppressing symptoms to a disease-modifying strategy aimed at both preventing maladaptive plasticity and reducing intrinsic risk.

Contents

INTRODUCTION

Diseases affecting the somatosensory nervous system can provoke lasting pain in addition to sensory deficits. (See sidebar, Neuropathic Pain Symptoms.) Here we review the neurobiolog-ical mechanisms that operate at multiple sites within the nervous system to produce neuro-pathic hypersensitivity. To understand the na-ture and specific features of neuropathic pain (as defined by Treede et al. 2008, given on the next page) in Treede et al. 2008), we first compare it with the other pain syndromes: nociceptive, inflammatory, and dysfunctional pain.

NOCICEPTIVE PAIN

To guard against tissue injury, it is imperative that the body is aware of potentially damaging stimuli. This awareness is achieved by a noxious stimulus-detecting sensory system (**Figure 1**). Nociceptive pain is an alarm mediated by high-threshold unmyelinated C or thinly myelinated Aδ primary sensory neurons that feed into nociceptive pathways of the central nervous sys-tem (CNS) (Woolf & Ma 2007). These noci-ceptor neurons express specialized transducer ion channel receptors, mainly transient recep-tor potential (TRP) channels, tuned to respond to intense thermal or mechanical stimuli as well as exogenous and endogenous chemical medi-ators (Dhaka et al. 2006). For nociceptive pain to subserve its protective function, the sensa-tion must be so unpleasant that it cannot be ig-nored. Nociceptive pain occurs in response to noxious stimuli and continues only in the main-tained presence of noxious stimuli (**Figures 1** and **2**). It alerts us to external stimuli, such as pinprick or excessive heat, and internal stimuli, such as myocardial ischemia in patients with coronary artery disease. Certain diseases may generate recurrent or ongoing noxious stimuli to produce chronic nociceptive pain. One ex-ample is osteoarthritis: Normal weight bearing in the presence of mechanical deformation of the joint may produce sufficient force to acti-vate high-threshold synovial mechanoreceptors (Torres et al. 2006).

Loss of nociception, as in hereditary dis-orders associated with congenital insensitivity to pain (Cox et al. 2006, Indo 2001), leads to repeated injury and inadvertent self mutila-tion, illustrating the highly adaptive function of nociceptive pain.

INFLAMMATORY PAIN

This pain occurs in response to tissue injury and the subsequent inflammatory response. Here the imperative shifts from protecting the body against a potentially damaging noxious stimulus to addressing the consequences of damage. To aid healing and repair of the injured body part, the sensory nervous system undergoes a profound change in its responsiveness; normally innocuous stimuli now produce pain and responses to noxious stimuli are both exaggerated and prolonged (Juhl et al. 2008) (**Figure 1**). Heightened sensitivity occurs within the inflamed area and in contiguous noninflamed areas as a result of plasticity in nociceptors and central nociceptive pathways (Huang et al. 2006, Hucho & Levine 2007, Woolf & Salter 2000). Because the pain system after inflammation is sensitized, it no longer acts just as a detector for noxious stimuli but can be activated also by low-threshold innocuous inputs (**Figures 1** and **2**). Ablation of a specific set of nociceptor neurons, those expressing the tetrodotoxin-resistant sodium channel Nav1.8, eliminates inflammatory pain but leaves neuropathic pain intact, indicating a fundamental difference in the neuronal pathways responsible for these pain states (Abrahamsen et al. 2008). Typically, inflammatory pain disappears after resolution of the initial tissue injury. However, in chronic disorders such as rheumatoid arthritis the pain persists for as long as inflammation is active (Michaud et al. 2007).

DYSFUNCTIONAL PAIN

The remaining two major pain states, neuropathic pain and a group of clinical syndromes that can best be called dysfunctional pain, are maladaptive in the sense that the pain neither protects nor supports healing and repair (**Figure 1**). Instead, these pain syndromes are caused by a malfunction of the somatosensory

NEUROPATHIC PAIN SYMPTOMS

Imagine an excruciating pain every time clothes touch your skin, spontaneous burning that feels like boiling water, bursts of "pins and needles" in your feet when you walk, a continuous crushing pain after an amputation as if your phantom foot is being squeezed, a band of searing pain around your body at the level at which you have lost all sensation after a spinal cord injury. These are just some of the devastating symptoms patients with neuropathic pain may experience.

apparatus itself, and this malfunction can be considered a disease in its own right. Dysfunctional pain occurs in situations in which there is no identifiable noxious stimulus nor any detectable inflammation or damage to the nervous system. It is unclear in most cases what causes the manifestation or persistence of dysfunctional pain. In conditions such as fibromyalgia, irritable bowel syndrome, and interstitial cystitis, the pain appears to result from an autonomous amplification of nociceptive signals inside the CNS (Nielsen et al. 2008, Staud & Rodriguez 2006) with a disturbed balance of excitation and inhibition in central circuits (Julien et al. 2005) and altered sensory processing that can be detected by functional imaging (Staud et al. 2008). Dysfunctional pain syndromes share some features of neuropathic pain: temporal summation with a progressive buildup in pain in response to repeated stimuli (windup), spatial diffuseness, and reduced pain thresholds (Staud et al. 2007).

Primary erythermalgia and paroxysmal extreme pain disorder, which are caused by gain-of-function mutations in the Nav1.7 voltage-gated sodium channel (Drenth & Waxman 2007), may be considered peripherally mediated dysfunctional pain, but here the molecular causes are known. These mutations are hereditary channelopathies of the

Neuropathic pain: maladaptive plasticity caused by a lesion or disease affecting the somatosensory system alters nociceptive signal processing so that pain is felt in the absence of a stimulus, and responses to innocuous and noxious stimuli are enhanced

Nociceptive pain: physiological pain produced by noxious stimuli that activate high-threshold nociceptor neurons

Inflammatory pain: pain hypersensitivity due to peripheral tissue inflammation involving the detection of active inflammation by nociceptors and a sensitization of the nociceptive system

Dysfunctional pain: amplification of nociceptive signaling in the absence of either inflammation or neural lesions

Figure 1

Pain syndromes. A summary of key features that distinguish and characterize the four major pain syndromes; nociceptive pain (*a*), inflammatory pain (*b*), dysfunctional pain (*c*), and neuropathic pain (*d*). (Image adapted from Griffin & Woolf 2007)
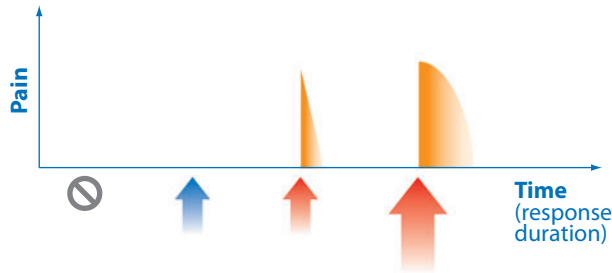
a

Nociceptive pain
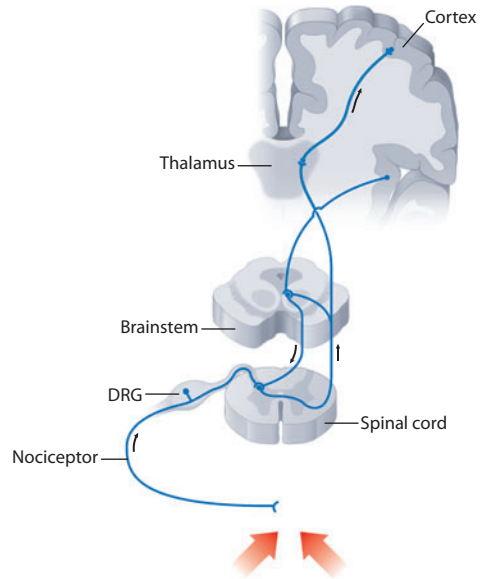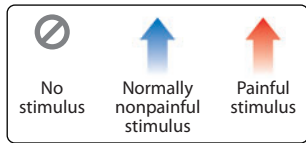
No nervous system lesion or inflammation

Stimulus-dependent pain
Evoked by high-intensity (noxious) stimuli

Pain

Time (response duration)

Adaptive

Protects by signaling potential tissue damage

No stimulus | Normally nonpainful stimulus | Painful stimulus

Cortex

Thalamus

Brainstem

DRG

Spinal cord

Nociceptor

Physiological stimuli:
mechanical (pinprick),
thermal (noxious heat or cold),
chemical injury

Clinically relevant stimuli:
abnormal mechanical
forces (osteoarthritis),
organ injury (angina,
ischemic claudication)

b

Inflammatory pain

Active inflammation

Spontaneous and stimulus-dependent pain
Sensory amplification
Evoked by low- and high-intensity stimuli

Pain

Time (response duration)
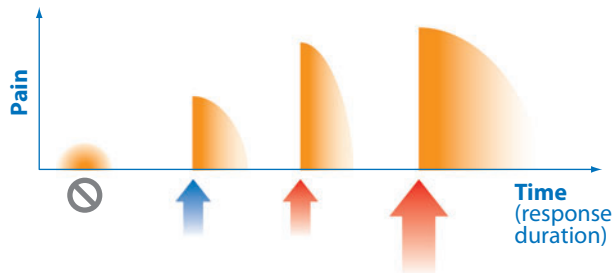
Adaptive and reversible

Protects by producing pain hypersensitivity during healing

Central amplification

Peripheral amplification

Mast cell

Macrophage

Neutrophil granulocyte
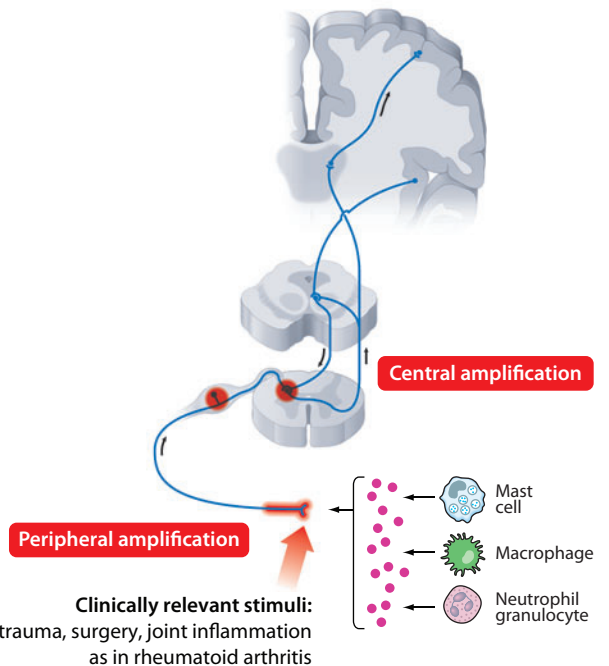
Clinically relevant stimuli:
tissue trauma, surgery, joint inflammation
as in rheumatoid arthritis

c

Dysfunctional pain

No known structural nervous system lesion or active peripheral inflammation

Spontaneous and stimulus-dependent pain
Sensory amplification
Evoked by low- and high-intensity
Present with lack of stimulus

Maladaptive and potentially persistent

Pain

Time (response duration)

Central amplification
Fibromyalgia

Peripheral amplification
Primary erythermalgia

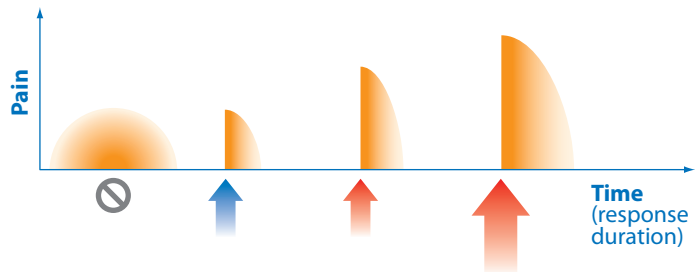|		
No stimulus	Normally nonpainful stimulus	Painful stimulus

d
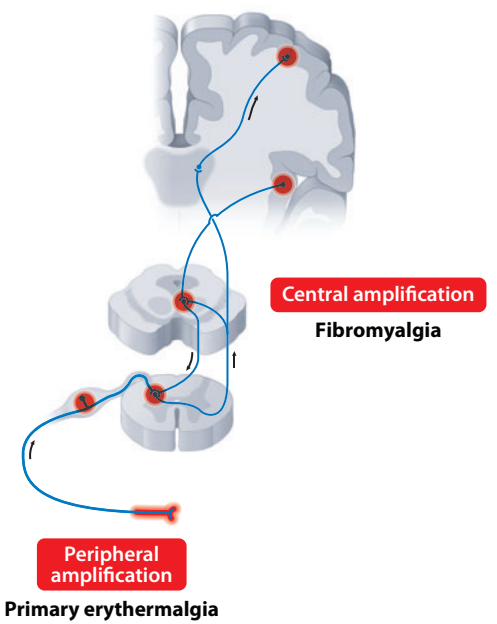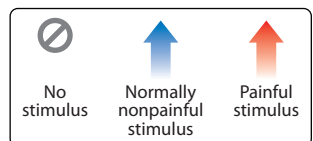
Neuropathic pain

Nervous system lesion or disease
Marked neuroimmune response

Spontaneous and stimulus-dependent pain
Sensory amplification
Evoked by low- and high-intensity stimuli

Pain

Time (response duration)
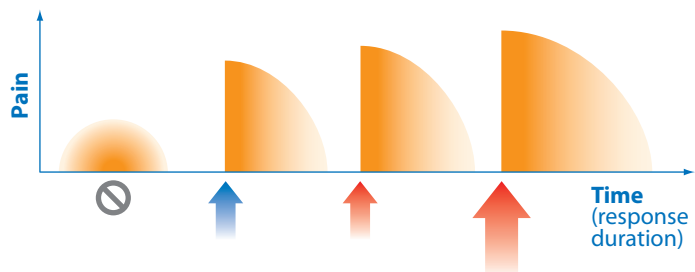
Maladaptive and commonly persistent

Abnormal amplification maintained independent of the lesion or disease

CNS lesion or disease:
Stroke, spinal cord injury, multiple sclerosis

Central amplification

Neuroimmune interactions in the periphery and the CNS

Peripheral amplification

PNS lesion or disease:
nerve trauma, toxic and metabolic neuropathies, Herpes zoster, AIDS
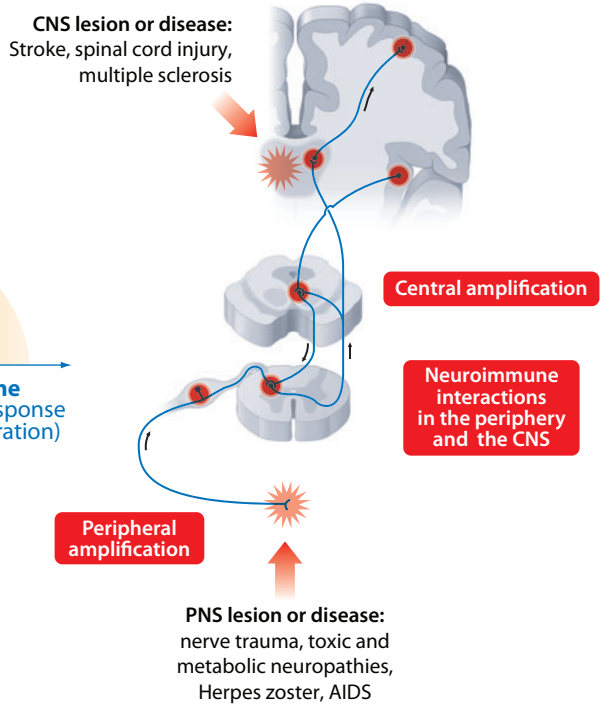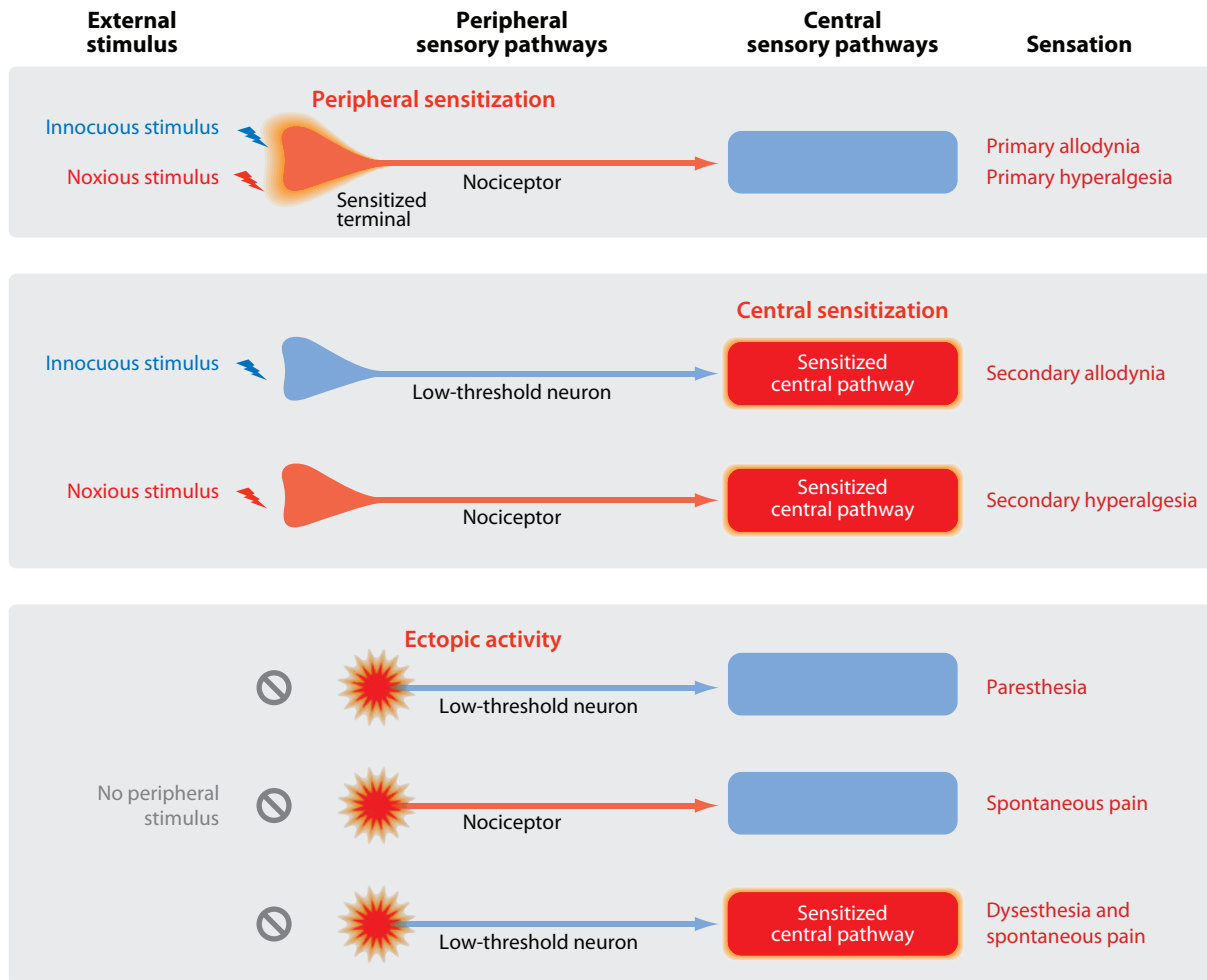
Figure 2

Stimulus-response relations and pain mechanisms. A representation of the relationship between external noxious and innocuous stimuli and the sensory responses they evoke, depending on which afferent fiber is activated (nociceptor or low-threshold neuron) and whether the sensitivity of either the peripheral nervous system (PNS) or the central nervous system (CNS) is disturbed to amplify the response to stimuli (sensitization) and generate ectopic impulses.

peripheral nervous system, which cause pain by ectopic activity of primary sensory neurons due to increased membrane excitability in the absence of axonal lesions or demyelination.

MECHANISMS COMMON TO DIFFERENT CHRONIC PAIN STATES

Although inflammatory, dysfunctional, and neuropathic pain are distinct in terms of their etiology and clinical features (**Figure 1**), they have some mechanisms in common.

Immune Mediator Detection

Nociceptors respond directly to cytokines, chemokines, and other inflammatory mediators produced in inflamed tissues (Binshtok et al. 2008). Interleukin-1β (IL1β), tumor necrosis factor (TNF), bradykinin, and nerve growth factor elicit action potential discharge by

increasing sodium and calcium currents at the nociceptor peripheral terminal. After neural damage, these same inflammatory mediators are produced by peripheral immune cells and microglia in the spinal cord and contribute to neuropathic pain by activating nociceptive neurons.

Peripheral Sensitization

Inflammatory mediators activate intracellular signal transduction pathways in the nociceptor terminal, prompting an increase in the production, transport, and membrane insertion of transducer channels and voltage-gated ion channels. The threshold for activation is reduced and membrane excitability increases (**Figure 2**). A reduction in thermal and mechanical pain thresholds also occurs in some patients with peripheral nerve lesions, which might reflect nociceptor sensitization owing to increased membrane excitability without inflammation (irritable nociceptors) (Fields et al. 1998).

Central Sensitization

Central sensitization, a form of use-dependent synaptic plasticity, is a major pathophysiological mechanism common to inflammatory, neuropathic, and dysfunctional pain (**Figure 2**). Activity generated by nociceptors during inflammation produces rapid-onset homo- and heterosynaptic facilitation in the dorsal horn of the spinal cord. In neuropathic pain, ongoing activity originating in injured nerves is the trigger for central sensitization. In dysfunctional pain, the trigger is unclear. Central sensitization resembles activity-dependent synaptic plasticity in the cortex with involvement of various synaptic modulators and excitatory amino acids, alterations in ion channel kinetics and properties, increased density of ionotropic receptors, and activation of kinases pre- and postsynaptically. The increase in synaptic strength enables previously subthreshold inputs to activate nociceptive neurons, reducing their threshold, enhancing their responsiveness, and expanding their receptive fields. Homosynaptic

facilitation of nociceptor inputs in the spinal cord is a form of long-term potentiation (LTP). For heterosynaptic facilitation, the initial input that triggers nociceptor activation is different from the facilitated input. Low-threshold afferents convert to pain drivers, and input outside the injury site is recruited.

NEUROPATHIC PAIN

Pain and loss of function are intimately associated with the reaction of the nervous system to neural damage, and both provide important diagnostic clues that such damage has occurred. Peripheral neuropathic pain results from lesions to the peripheral nervous system (PNS) caused by mechanical trauma, metabolic disease, neurotoxic chemicals, infection, or tumor invasion and involves multiple pathophysiological changes both within the PNS and in the CNS (Dworkin et al. 2003, Woolf & Mannion 1999). Central neuropathic pain most commonly results from spinal cord injury, stroke, or multiple sclerosis (Ducreux et al. 2006). The conventional approach to neuropathic pain has been to classify and treat it on the basis of the underlying disease (Dworkin et al. 2007). However, such an etiological approach does not capture the essential feature of neuropathic pain, which is the manifestation of maladaptive plasticity in the nervous system. The primary disease and the neural damage it causes are only the initiators of a cascade of changes that lead to and sustain neuropathic pain. Although treatment targeted at the primary pathology is obviously essential, understanding the mechanisms responsible for the maladaptive plasticity offers specific therapeutic opportunities to prevent the development of neuropathic hypersensitivity and normalize function in established neuropathic pain.

Transformation of Acute Neural Injury to Neuropathic Pain

Once neuropathic pain is generated, the sensory hypersensitivity typically persists for prolonged periods, even though the original

PNS: peripheral nervous system

CNS: central nervous system

cause may have long since disappeared, as after nerve trauma. The syndrome can nevertheless progress if the primary disease, such as diabetes mellitus or nerve compression, continues to damage the nervous system. Neuropathic pain is not an inevitable consequence of neural lesions, though. On the contrary, the pain associated with acute neural damage usually transitions to chronic neuropathic pain in a minority of patients. This transition to chronicity is most obvious after surgical nerve lesions where the extent and timing of the lesion are defined (Kehlet et al. 2006).

For damage of a relatively small nerve, such as the ilioinguinal nerve during hernia repair, the risk of persistent (more than two years) pain is on the order of ~5% (Kalliomaki et al. 2008), whereas sectioning a large nerve, such as the sciatic nerve or multiple intercostal nerves during thoracotomy, produces sustained neuropathic pain in 30%–60% of patients (Ketz 2008, Maguire et al. 2006). Understanding why one individual develops chronic pain and another with an effectively identical lesion is spared is obviously crucial to developing strategies to abort such transitions. Injury such as brachial plexus avulsion during birth does not produce pain in neonates (Anand & Birch 2002), whereas ~40% of adults develop severe chronic pain when subjected to the same injury (Htut et al. 2006), indicating that neuropathic pain depends in some way on the maturity of the nervous system (Moss et al. 2007).

Epidemiological studies on the prevalence of neuropathic pain indicate a high incidence (~5%) (Bouhassira et al. 2008, Dieleman et al. 2008, Torrance et al. 2006). Associated risk factors include gender, age, and anatomical site of the injury. Smaller studies on persistent neuropathic pain after surgery indicate that pain at the time of surgery and the severity of acute postoperative pain increase the incidence of chronic pain (Poleshuck et al. 2006), although it is unclear whether the risk increases because acute

postoperative pain was inadequately managed or individuals who have a higher inherent susceptibility to developing persistent pain also suffer more intense acute pain. Emotional and cognitive factors influence how patients react to chronic pain (Haythornthwaite et al. 2003), but it is much less certain if these factors contribute to the risk of developing pain.

Two interdependent processes appear to be major general contributors to developing neuropathic pain: the balance between compensatory and decompensatory reactions of the nervous system to neural damage, and a genetic background that either enhances or protects an individual from the establishment of neuropathic pain. Many of the changes that occur in response to neural injury are potentially adaptive: removal of cell and myelin debris, changes in receptors that counterbalance the loss of input, other alterations that dampen ion fluxes and metabolic stress after the acute injury, recruitment of antiapoptotic survival strategies to prevent neuronal cell death, induction of axonal growth and sprouting, synaptic remodeling, and remyelination (Benn & Woolf 2004, Cafferty et al. 2008). However, many are clearly maladaptive: abnormal stimulus thresholds and sensitivity, ectopic impulse generation, conduction slowing or block, reduced inhibition, inappropriate connectivity, abortive growth, neuronal loss, and glial scarring. Some of these changes occur early after the initial damage and participate in the induction phase of neuropathic pain, others develop later and help maintain the pain, and in some individuals, there may occasionally be a slow resolution.

MECHANISMS OF NEUROPATHIC PAIN
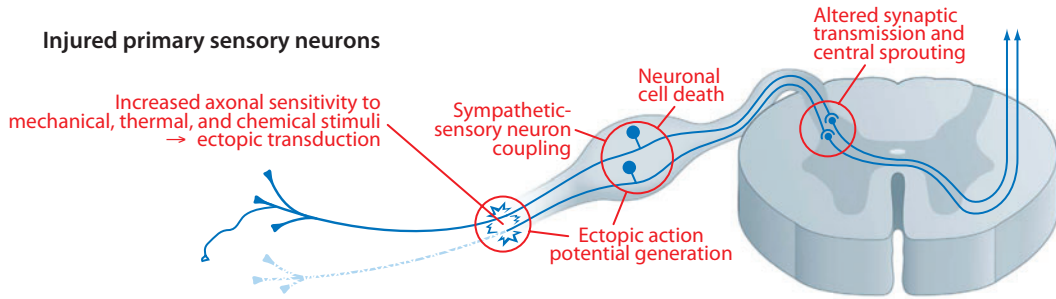
Major known mechanisms responsible for peripheral neuropathic pain are represented in **Figure 3** (Campbell & Meyer 2006, Finnerup et al. 2007a). Much less is understood about

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Figure 3

A summary of the major mechanisms underlying peripheral neuropathic pain, their location, and the triggers responsible for their activation. (Image adapted from Griffin & Woolf 2007)

a   **Injured primary sensory neurons**

Altered synaptic transmission and central sprouting

Neuronal cell death

Increased axonal sensitivity to mechanical, thermal, and chemical stimuli → ectopic transduction

Sympathetic-sensory neuron coupling

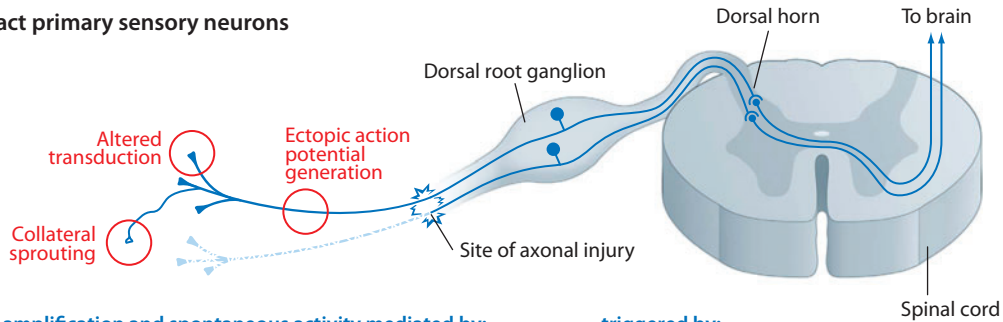Ectopic action potential generation

Peripheral and central amplification mediated by:

Changes in transmitter synthesis and signaling
Increased membrane excitability
Peripheral and central axon growth

... triggered by:

Loss of peripheral neurotrophic factors
Spontaneous and receptor-mediated activity
Retrograde signaling
Signals from immune cells and denervated Schwann cells

b   **Intact primary sensory neurons**

Dorsal horn

To brain

Dorsal root ganglion

Altered transduction

Ectopic action potential generation

Collateral sprouting

Site of axonal injury

Spinal cord

Peripheral amplification and spontaneous activity mediated by:

Altered expression and trafficking of receptors and ion channels
Change in ion channel threshold and kinetics
Collateral axon growth

... triggered by:

Neurotrophic factors
Signals from immune cells and denervated Schwann cells

c   **Second order sensory neurons**
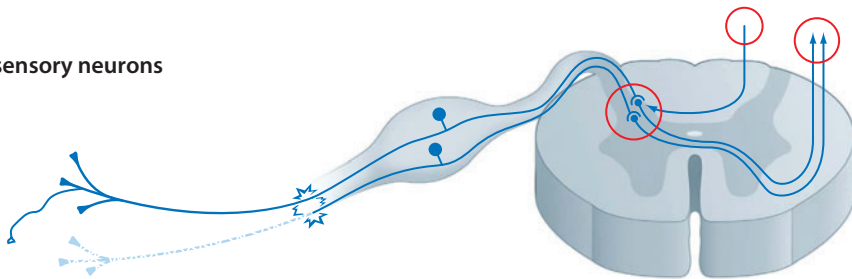
Central amplification mediated by:

Homo- and heterosynaptic facilitation
Disinhibition
Altered synaptic connectivity
Changes in central nociceptive circuits

... triggered by signals from:

Injured and uninjured primary afferents
Descending pathways from brainstem nuclei
Invading immune cells, microglia, and astrocytes

the mechanisms underlying central neuropathic pain (Crown et al. 2008, Detloff et al. 2008, Finnerup et al. 2007b).

Ectopic Impulse Generation

An important feature of neuropathic pain is pain in the absence of an identifiable stimulus. Spontaneous pain arises as a result of ectopic action potential generation within the nociceptive pathways and does not originate in peripheral terminals in response to a stimulus (**Figures 2** and **3**). Theoretically, ectopic activity could be generated at any anatomical level proximal to those brain regions that mediate the sensory experience. Compelling evidence for peripheral neuropathic pain, however, points to substantial ectopic activity arising in primary sensory neurons. After peripheral nerve damage, spontaneous activity is generated at multiple sites, including in the neuroma (the site of injury with aborted axon growth), in the cell body of injured dorsal root ganglia (DRG) neurons (Amir et al. 2005), and in neighboring intact afferents (Wu et al. 2002). Spontaneous pain may arise both from ectopic activity in nociceptors (Bostock et al. 2005) and from low-threshold large myelinated afferents (Campbell et al. 1988) due to central sensitization and altered connectivity in the spinal cord (Woolf et al. 1992) (**Figure 2**). After spinal cord injury, spontaneous pain may result from increases in the intrinsic excitability of second-order neurons (Balasubramanyan et al. 2006, Hains & Waxman 2007).

Voltage-gated sodium channels contribute largely to the generation of ectopic activity as indicated by the robust inhibitory effects of local anesthetics, which are nonselective sodium channel blockers (Sheets et al. 2008). DRG neurons express several sodium channels that are either sensitive or resistant to tetrodotoxin (TTX) (Fukuoka et al. 2008). However, which of these channels is responsible for the abnormal generation of action potentials is not entirely clear. Studies using gene knockdown with antisense oligonucleotides support a specific role for the Nav1.3 channel, which is up-regulated in DRG neurons after nerve injury

(Hains et al. 2003), but knockout of the channel fails to alter neuropathic pain–like behavior or ectopic activity (Nassar et al. 2006). On the other hand, preclinical models cannot directly measure spontaneous pain, a major failing that limits their utility as models of pain in patients. The TTX-resistant channel Nav1.8, which is predominantly expressed by nociceptors, does not support propagation of full-amplitude action potentials (Pinto et al. 2008) and instead modulates membrane excitability, particularly when phosphorylated (Hudmon et al. 2008). Experiments using Nav1.8 antisense and shRNA knockdown as well as pharmacological blockade with conotoxin and small-drug antagonists indicate a major role for this channel in generating neuropathic pain (Dong et al. 2007, Ekberg et al. 2006, Gold et al. 2003, Jarvis et al. 2007, Joshi et al. 2006, Roza et al. 2003). However, Nav1.8 knockout does not reduce the neuropathic pain phenotype (Nassar et al. 2005), low-dose TTX blocks the expression and development of neuropathic pain (Nieto et al. 2008), and Nav1.8 is markedly downregulated after axonal injury, producing a substantial reduction in TTX-R current densities (Berta et al. 2008). Although conditional deletion of Nav1.7 in nociceptors does not reduce neuropathic pain (Nassar et al. 2005), selective blockers for the channel display efficacy as antineuropathic agents (Hoyt et al. 2007, Schmalhofer et al. 2008). Global or conditional knockout of single ion channels does not appear to be a useful way to tease out their value as targets for analgesics because of compensation and redundancy.

The hyperpolarization-activated cyclic nucleotide-modulated channel (HCN), which contributes to the pacemaker current I(h), also generates ectopic activity in DRG neurons after nerve injury (Luo et al. 2007). Opening the neuronal voltage-gated potassium channel subfamily Q (KCNQ), which is a mediator of the M current, selectively reduces activity in axotomized but not uninjured axons (Roza & Lopez-Garcia 2008) and in human C-fiber axons (Lang et al. 2008), suggesting that this channel may be involved in regulating ectopic

activity. Similarly, axotomy reduces calcium-activated potassium currents in DRG neurons, which will also result in increased membrane excitability (Sarantopoulos et al. 2007). There are likely several ectopic ion channel drivers that raise membrane excitability in different ways and in different neurons.

What triggers the changes in sensory neuron ion channel expression? An importin-dependent retrograde signal that involves RasGTPase (Yudin et al. 2008) activates massive transcriptional changes (∼2000 transcripts) in the soma of injured neurons, including altered regulation of ion channels (Costigan et al. 2002) and their accessory subunits (Pertin et al. 2005). It is likely that master switches such as the transcription factors Sox11, c-Jun, and ATF3 orchestrate these changes (Seijffers et al. 2007). Gene translation in axons appears to be important, both to signal the injury (Yudin et al. 2008) and to synthesize local effectors (Jimenez-Diaz et al. 2008). Neighboring uninjured neurons show fewer phenotypic changes than do injured ones (Decosterd et al. 2002), and these may be generated by signals from denervated Schwann cells (Wu et al. 2002). Some of these signals, including cytokines and growth factors, may increase sodium and TRP channel currents in the axon and cell soma of neurons by posttranslational changes (Jin & Gereau 2006, Zhu & Oxford 2007).

Mice with a deletion of Cav2.2 (the N-type calcium channel) show reduced neuropathic pain-like behavior (Saegusa et al. 2001). Intrathecal delivery of ω-conopeptide MVIIA, which blocks Cav2.2 in a non-use-dependent fashion, decreases neuropathic pain in preclinical models and patients, presumably by reducing transmitter release from nociceptors (McGivern 2006). The calcium channel auxiliary α2δ1 subunit helps stabilize the pore-forming α subunit of these channels in the membrane. Gabapentin and pregabalin, among the first-line treatments for neuropathic pain (Dworkin et al. 2007), bind to the α2δ1 protein, interfere with the interaction between the auxiliary subunit and the α subunit, and impair membrane insertion of the channel (Hendrich

et al. 2008). Both Cav2.2 and α2δ1 subunits are upregulated in DRG neurons following nerve injury (McGivern 2006), which suggests that an N-type calcium channel complex may play a dominant role in pathological nociceptive signal transmission from the periphery. Different Cav2.2 splice forms, including one that is highly enriched in nociceptor neurons, constitute molecular switches for different nociceptor functions during neuropathic pain (Altier et al. 2007).

Ectopic Transduction

Enhanced sensitivity of injured sensory neurons to endogenous thermal and chemical stimuli may initiate spontaneous pain, whereas enhanced mechanical sensitivity can elicit dysesthesia or pain in response to tapping an injured nerve (Tinel's sign). Peripheral nerve axons exhibit sensory transduction capacities to noxious heat identical to their peripheral terminals in the skin, with the threshold characteristic of the noxious heat-sensitive TRPV1 channel (41°C) (Hoffmann et al. 2008). Isolated peripheral nerves can also be sensitized to heat by intracellular signal transduction pathways (Fischer & Reeh 2007). Therefore, normal body temperature may elicit spontaneous activity after nerve injury if the threshold of TRPV1 in axons were reduced to 38°C (Biggs et al. 2008). Knockdown of the channel with shRNA reduces neuropathic pain–like behavior (Christoph et al. 2008).

Central Sensitization

Stimulus-evoked neuropathic pain could arise either as a result of peripheral sensitization of intact afferents (Fields et al. 1998) or from amplification within the CNS due to central sensitization (Woolf & Salter 2000). Synaptic facilitation seems to predominate in most patients with peripheral neuropathic pain and in all patients with central neuropathic pain. It contributes to dynamic tactile allodynia as well as secondary hypersensitivity (**Figure 2**) (Campbell & Meyer 2006). Presynaptic functional changes after peripheral nerve

Peripheral sensitization: an increase in the sensitivity of the peripheral terminals of nociceptors due to a decrease in transduction threshold and an increase in membrane excitability

Allodynia: a painful response to a usually innocuous stimulus

Secondary hypersensitivity: pain from normal peripheral sensory inputs outside inflamed tissue due to plasticity (sensitization) within the CNS

TRP: transient receptor potential

injury that increase synaptic strength include alterations in the synthesis of transmitters and neuromodulators (Obata et al. 2003) and in calcium channel density (Hendrich et al. 2008, Li et al. 2004). Postsynaptic changes involve phosphorylation of N-methyl-D-aspartate (NMDA) subunits (Ultenius et al. 2006) and increased receptor density due to trafficking and enhanced synthesis of ion channels and scaffold proteins (Cheng et al. 2008, Iwata et al. 2007, Miyabe et al. 2006, Takasusuki et al. 2007, Tao et al. 2003). Drugs that attenuate central sensitization by acting on calcium channel subunits to decrease transmitter release and on NMDA channels to reduce transmitter action (Chizh et al. 2007; Jorum et al. 2003) are effective treatment options in neuropathic pain (Dworkin et al. 2007). Although central sensitization was first described in the dorsal horn, similar synaptic changes occur in structures involved in the emotional aspects of pain such as the amygdala, anterior cingulate gyrus, and prefrontal cortex (Fu et al. 2008, Pedersen et al. 2007), and these may represent a substrate for long-term cognitive and mood changes that are learned and retained, for example, conditioned fear and addictive behavior.

Central sensitization is different from centralization, which hypothesizes that, after peripheral nerve injury, changes intrinsic to the CNS develop and maintain pain independent of any ongoing peripheral input (Devor 2006). These changes potentially include increased excitability (Balasubramanyan et al. 2006), structural alterations in synaptic circuitry (Woolf et al. 1992), degeneration of inhibitory interneurons (Scholz et al. 2005), and alterations in the brain stem regulation of nociceptive transmission (Vera-Portocarrero et al. 2006).

Low-Threshold Aβ Fiber-Mediated Pain

Neuropathic pain involves a profound switch in sensitivity such that low-intensity input can generate pain, a disruption of the normal pattern of pain specificity (Perl 2007). The hypersensitivity occurs largely in the absence of peripheral sensitization; includes areas outside of injured nerve territories; is typically associated with a loss of C-fiber peripheral terminals, and sensitivity (Devigili et al. 2008); and disappears when conduction in large myelinated fibers is blocked (Campbell et al. 1988). Furthermore, ablation of the vast majority of nociceptor neurons does not alter the development and manifestation of neuropathic pain (Abrahamsen et al. 2008), whereas selective pharmacological blockade of large neurofilament-200-positive Aβ fibers abolishes dynamic tactile allodynia in nerve injury models (Yamamoto et al. 2008). The obvious conclusion from these data is that low-threshold Aβ fibers, which normally signal innocuous sensations, begin after neural lesions to produce pain (Khan et al. 2002; Witting et al. 2006). In keeping with this finding, loss of the PKCγ interneurons in the ventral part of the superficial dorsal horn (lamina IIi) that are driven only by Aβ fiber innocuous input (Neumann et al. 2008) leads to reduced neuropathic but preserved nociceptive pain (Malmberg et al. 1997). Furthermore, after nerve injury polysynaptic and monosynaptic Aβ fiber input to neurons increases in the most superficial laminae of the dorsal horn (Okamoto et al. 2001), an area that normally only receives input from Aδ and C fibers (Lu & Perl 2005). Although noxious stimuli activate ERK MAP kinase in superficial dorsal horn neurons in noninjured animals (Ji et al. 1999), after peripheral nerve injury Aβ fiber stimulation acquires this capacity (Matsumoto et al. 2008). Tactile stimulation also begins to induce c-Fos in these nociceptive neurons (Bester et al. 2000). Somehow, as a consequence of peripheral nerve injury, low-threshold input from large myelinated fibers is transferred from nonnociceptive to nociceptive circuits in the spinal cord. How does this plasticity occur?

Disinhibition

A number of changes either independently or together can promote Aβ fiber–mediated pain:

central sensitization, disinhibition, and central afferent terminal sprouting. Inhibitory dorsal horn interneurons synapse with the central terminals of primary sensory neurons and presynaptically modulate afferent input. Spinal interneurons also regulate activity in postsynaptic transmission neurons through GABAergic and glycinergic inhibition. Pharmacological removal of GABAergic or glycinergic control provokes tactile allodynia (Thompson et al. 1993) and increases synaptic currents from Aβ fibers to nociceptive lamina I neurons (Baba et al. 2003, Miraucourt et al. 2007, Torsney & MacDermott 2006).

Descending pathways that modulate the spinal transmission of nociceptive input originate in the anterior cingulate gyrus, amygdala, and hypothalamus and are relayed to the spinal cord through brain stem nuclei in the periaqueductal gray and rostroventral medulla. The inhibitory transmitters in these pathways include norepinephrine, 5-hydroxytryptamine, and endogenous opioids. After nerve injury, this intricate system of inhibitory control shifts. Tonic noradrenergic inhibition that acts on α2-adrenoceptors appears to be suspended (Rahman et al. 2008), and the net effect of descending serotoninergic input changes from inhibition to facilitation (Bee & Dickenson 2008, Vera-Portocarrero et al. 2006). Amine uptake inhibitors like tricylic antidepressants or serotonin norepinephrine reuptake inhibitors (SNRIs) boost endogenous inhibition by increasing the levels of norepinephrine (Matsuzawa-Yanagida et al. 2008).

Following nerve injury, primary afferents reduce their expression of μ opioid receptors, and dorsal horn neurons are less sensitive to inhibition by μ opioid agonists (Kohno et al. 2005). Furthermore, several different mechanisms contribute to a loss of pre- and postsynaptic GABAergic inhibition in the spinal cord. In nociceptive lamina I neurons, the transmembrane gradient for chloride ions changes after nerve injury so that activation of GABA$_A$ receptors no longer leads to hyperpolarization. Instead, it may induce depolarization,

provoking paradoxical excitation and spontaneous activity (Keller et al. 2007). BDNF released from active microglia causes this disturbance by inducing a downregulation of the potassium chloride cotransporter isoform 2 (Coull et al. 2005). Independently, inhibition in the superficial dorsal horn of the spinal cord is compromised by a loss of GABAergic interneurons (Scholz et al. 2005), reducing afferent stimulation-evoked GABAergic inhibitory postsynaptic currents (IPSCs) (Moore et al. 2002). Preventing apoptotic cell death fully restores GABAergic IPSCs and attenuates mechanical allodynia, hyperalgesia, and cold allodynia after nerve injury (Scholz et al. 2005). Loss of spinal inhibitory interneurons may contribute to the persistence of neuropathic pain, although pain-like behavior after sciatic nerve injury in the absence of neuronal cell death has been reported (Polgar et al. 2005). Despite the apparent role of GABAergic disinhibition in neuropathic pain, GABA$_A$ receptor modulators such as benzodiazepines or GABA$_B$ receptor agonists are rarely used to treat neuropathic pain because they have a narrow therapeutic window. Specific GABA agonists that bind to the α$_2$ or α$_3$ but not α$_1$ subunits of spinal GABA$_A$ receptors may allow analgesia without sedation or motor impairment (Knabl et al. 2008).

Structural Changes

Peripheral axonal injury prompts sensory neurons into an actively growing state by increasing the expression of regeneration-associated genes (Costigan et al. 2002). This peripheral sprouting aids the reconnection of damaged peripheral axons with their targets. However, increasing the intrinsic capacity to grow can also lead to a sprouting of the central axon terminals of injured neurons in the spinal cord (Woolf et al. 1992). Large myelinated Aβ fibers normally terminate in the ventral laminae of the dorsal horn (lamine III-V), whereas thinly myelinated Aδ fibers and unmyelinated C-fiber nociceptors terminate in the superficial laminae (I and II). Following peripheral nerve

GABA: gamma amino butyric acid

Hyperalgesia: a heightened response to a noxious stimulus

injury, bulk-labeling, single afferent filling, and Aβ fiber marker experiments all suggest that Aβ fibers sprout into lamina II (Kohama et al. 2000; Soares et al. 2002, 2007; Watanabe et al. 2007 ; Woolf et al. 1992). However, these findings remain controversial because some of the labeling techniques lack specificity, and uninjured A-fibers are present in lamina II in some species (Bao et al. 2002, Woodbury et al. 2008). Nevertheless, these structural changes, if they do occur, may be an anatomical substrate for the entry of low-threshold Aβ fiber input into nociceptive pathways after nerve injury.

Neurodegeneration and Chronic Pain

Both primary sensory and dorsal horn neurons die after peripheral nerve injury. Primary afferents degenerate after transection of their peripheral axons, with a much greater loss of small-diameter neurons, including nociceptors, than large myelinated neurons (Okamoto et al. 2001, Tandrup et al. 2000). A loss of ~20% of superficial dorsal horn neurons occurs after partial peripheral nerve injury. The degeneration of spinal neurons occurs protracted over several weeks and is most likely a consequence of sustained ectopic activity of primary sensory afferents and glutamate-mediated excitotoxicity (Scholz et al. 2005). Magnetic resonance imaging (MRI) investigations in patients with chronic neuropathic pain hint that neurodegeneration may also occur in the brain. Voxel-based morphometry shows decreases in gray matter volume and density in MRIs of the brain of patients with chronic back pain, phantom pain, migraine, tension-type headache, and fibromyalgia, although with varying degree and regional distribution (May 2008). The nature of these structural changes remains to be determined, as well as whether neurodegeneration is a cause and if analgesic treatment can prevent the changes. These findings raise the possibility that neuropathic pain may have elements that resemble neurodegenerative diseases and requires neuroprotective treatment strategies.

Neuro-Immune Interactions

In the PNS, immune surveillance is performed by macrophages, which identify and clear cellular debris and present surface antigens to activate T-lymphoctyes. Both macrophages and T-lymphocytes communicate via cytokines and chemokines with neurons, Schwann cells, and DRG satellite cells. Macrophage activation is a central component of the Wallerian degeneration distal to axonal injury, and immune activation in the injured nerve and DRG appears to contribute to pain hypersensitivity (Scholz & Woolf 2007). Microglia, the macrophages of the CNS, are massively activated in the dorsal horn soon after peripheral nerve injury. Microglial activation occurs in a topographically organized fashion close to the central terminals of injured afferents (Beggs & Salter 2007, Scholz et al. 2008), and microglial cells release many immune modulators that contribute to the induction and maintenance of neuropathic pain by altering neuronal function (Saab et al. 2008, Suter et al. 2007) (**Table 1**). Fractalkine (CX3CL1), for example, is expressed by neurons and astrocytes, whereas its receptor CX3CR3 is expressed on microglia, suggesting a signaling role by the chemokine between these cells (Milligan et al. 2008). CCL2 (MCP-1) and its receptor CCR2 are both upregulated in the DRG and distributed to the spinal cord after nerve injury (White et al. 2007). Intrathecal administration of CX3CL1 or CCL2 produces pain in naïve animals, while their neutralization prevents neuropathic pain hypersensitivity (Abbadie 2005, Watkins et al. 2007).

Signaling molecules that act on microglia in the spinal cord after nerve injury include ATP which through activation of P2X4 and P2X7 receptors (Inoue 2006, Inoue et al. 2007, Trang et al. 2006) leads to BDNF release and IL1β synthesis, respectively. Microglia both produce and are a target of the C5a anaphylatoxin peptide, a member of the complement system (Griffin et al. 2007, Mika 2008). The Toll-like receptors TLR-2, TLR-3 and TLR-4 are also critically involved in immune-mediated pain

Table 1   Immune modulators of neuropathic pain

Drug	Mechanism of action	Effect in preclinical neuropathic models	Review/reference
Minocycline	Tetracycline antibiotic. Immunosuppression in part mediated through p38 MAP kinase inhibition.	Inhibits microglial activation. Reduces tactile allodynia most effectively when treatment begins prior to nerve injury	Mika 2008, Scholz & Woolf 2007
Propentofylline, AV-411, Pentoxifylline	Nonselective phosphodiesterase inhibitors	Reduce mechanical allodynia by suppressing microglial and astrocyte activity. Often associated with a decrease in proinflammatory cytokines	Mika 2008, Scholz & Woolf 2007
Methotrexate	Reduces folate, blocks de novo purine and thymidylate synthesis	Inhibits microglial activation and proliferation. Most effective when given early after nerve injury	Scholz et al. 2008
Nucleotide receptor antagonists	Activation of P_2X and P_2Y receptors modulates the activity of peripheral immune cells and microglia	Block the activation of peripheral macrophages and spinal microglia	Inoue et al. 2007
p38 MAP kinase inhibitors	Inhibit important signaling pathways in microglial cells	Reduce tactile allodynia. Most effective when treatment begins prior to nerve injury	Ji & Suter 2007
Neutralizing antibodies and receptor-trapping strategies	Modulators of cytokine synthesis and activity directed against IL1, IL6, IL10, TNF, and others	Reduce the biological effects of proinflammatory cytokines. IL10 has antiinflammatory activity	Mika 2008, Watkins et al. 2007
Complement inhibitors	Block activation of complement factors expressed by microglia	Inhibition of complement pathways including the activation of C5, which acts as an immune cell chemoattractant in the spinal cord dorsal horn	Mika 2008, Griffin et al. 2007
Cannabinoids	Activate the CB_2 receptor, which is expressed predominantly on microglia	CB_2 regulates immune cell proliferation and migration. CB_2 agonists reduce mechanical allodynia	Romero-Sandoval et al. 2008

signaling in the dorsal horn (DeLeo et al. 2004, Guo & Schluesener 2007, Obata et al. 2008). Microglial responses to nerve injury are characterized by activating p38-MAP kinase, extracellular signal–related kinase (ERK), and Src-family kinases (Ji & Suter 2007). Another example for neuron-glia interactions contributing to neuropathic pain are the matrix metalloproteinases MMP2 and MMP9. They are produced by both neurons and glia and mediate pain hypersensitivity by initiating IL1β cleavage and microglial and astrocytic activation (Kawasaki et al. 2008). Inhibition of immune function represents a major avenue for therapeutic intervention for neuropathic pain (**Table 1**).

Seeing Pain in Patients

Preclinical research focuses largely on single molecules, changes in particular neurons or defined circuits, and how they contribute to behavioral alterations that are considered surrogates of neuropathic pain. Functional magnetic resonance imaging (fMRI) uses blood oxygen level dependent (BOLD) signals to detect changes in cerebral activity in patients with neuropathic pain, and this technique allows the

study of discriminative sensory, emotional, motivational, and modulatory responses in particular regions of the brain and brain stem (May 2007, Tracey 2008, Tracey & Mantyh 2007). The reorganization of the somatosensory cortex after peripheral nerve lesions reveals the plasticity of the brain (Flor 2003). Patients with chronic pain show strong activation of the prefrontal cortex, the same area that shows reduction in gray matter density (Baliki et al. 2008), as well as disruption in resting functional connectivity of widespread cortical areas (Baliki et al. 2008). Imaging studies provide an opportunity to obtain objective measures of subjective sensations to identify which areas of the brain are likely involved in the processing of neuropathic pain and to evaluate the location and mechanisms of treatment effects (Becerra et al. 2006).

THE NEUROPATHIC PAIN PHENOTYPE

Animal Surrogate Models

Many rodent models of neuropathic pain have been developed (**Table 2**). Some have been designed to mimic human diseases, others to explore pathophysiological mechanisms in the nervous system, and some as a convenient means to screen for putative analgesics. Although these models collectively have great utility in exploring the maladaptive plasticity induced by neural damage, they are generally less useful as direct surrogates of pain phenotypes in patients and, by themselves, not always good predictors of the involvement of particular targets or processes in human neuropathic pain. How distinct forms of neural damage activate different sets of changes in the nociceptive system, particularly over a time course that is relevant to the transition from acute to chronic pain, and how these changes engage different outcome measures need to be carefully explored. Reflexive changes in the thresholds to defined stimuli, complex behaviors that capture sensory and mood disturbances, and alterations in operant behavior or choice paradigms that may reflect spontaneous pain also need to

be investigated further. We still do not have enough insight into which specifically pain-related mechanisms in the nervous system are responsible for behavioral outcome measures in animals. Because subjective symptoms cannot be evaluated, the representation of neuropathic pain in animal models is necessarily incomplete and the human experience of pain too complex to be fully reproduced.

Outcome measures in rodent models rely on motor activity, such as withdrawal or reduced weight bearing, and therefore locomotor as well as sensory function are assayed (Vierck et al. 2008). Nevertheless, tactile allodynia in rodent models appears to correspond with neuropathic mechanical hypersensitivity in patients (Koltzenburg et al. 1994, Rowbotham & Fields 1996). Pharmacological studies show that effective analgesic drugs for human neuropathic pain (gabapentin, morphine, fluoxetine) but not ineffective ones (indomethacin) also reduce rodent tactile allodynia (LaBuda & Little 2005). Furthermore, heat hyperalgesia and tactile sensitivity do not correlate in mice (Mogil et al. 1999b) or in humans (Koltzenburg et al. 1994, Rowbotham & Fields 1996).

Lost in Translation

Treating neuropathic pain in patients remains a major challenge because relief is only partial in most patients, and responders to treatment cannot be identified. One reason for the lack of clinical improvement is the inability to determine active pain mechanisms in patients. Quantitative sensory testing and electrophysiological investigations such as nerve conduction studies or evoked potentials, though they reveal information on the function of different types of sensory nerve fibers, do not provide insight into the cellular and molecular processes responsible for the pain (Hansson et al. 2007). Functional imaging reveals abnormal processing of sensory input in patients but is limited to research studies (Tracey & Mantyh 2007). Skin biopsies document sensory fiber loss as an indicator of deafferentation; however, they are invasive and not suitable for routine clinical practice. These

Table 2   Animal models of neuropathic pain[a]

Model	Nature of injury	Extent of neural damage and lesion site	Behavioral phenotype	Clinical correlate
Sciatic nerve transection (Wall et al. 1979)	Transection and ligation of sciatic nerve	~60% of DRG cells; mid nerve.	A	Nerve trauma, iatrogenic nerve injury
Partial sciatic nerve ligation (Seltzer et al. 1990)	Partial ligation of sciatic nerve	~30% of DRG cells; mid nerve; intact axons interacting with Schwann cells	MA, MH, TH, CA	Partial peripheral nerve injury
Spinal nerve ligation (Kim & Chung 1992)	Ligation of the L5 and L6 spinal nerves	~100% DRG cells; proximal nerve; intact axons interacting with Schwann cells	MA, MH, TH, CA	Proximal peripheral nerve damage, e.g., after disc prolapse
Spared nerve injury (Decosterd & Woolf 2000)	Ligation and transection of two of three distal sciatic nerve branches	~40% of DRG cells; distal nerve.	MA, MH, CA	Partial peripheral nerve damage
Chronic constriction injury (Bennett & Xie 1988)	Loose ligature of the sciatic nerve with chronic gut suture	Mainly myelinated axons, <30% of DRG cells; mid nerve; intact axons interacting with Schwann cells	MA, MH, TH, CA	Nerve entrapment, e.g., carpal tunnel syndrome
Sciatic inflammatory neuropathy (Chacur et al. 2001)	Perineural injection of immune activator (zymosan or CFA)	No axonal loss; secondary DRG cell damage; mid nerve	MA	Peripheral neuritis
Peripheral nerve demyelination (Wallace et al. 2003)	Immune- or toxin-mediated demyelination	Minimal axon loss; secondary DRG cell damage; mid nerve	MA, TH	Demyelination, e.g., diabetic neuropathy
Diabetic neuropathy (Sullivan et al. 2008)	Streptozotocin, diet, genetic models	Primarily distal axon loss; systemic injury of the PNS; intact axons interacting with Schwann cells	MA, THypo	Diabetic neuropathy
Viral neuropathy (Wallace et al. 2007)	Herpes simplex virus, varizella zoster virus, HIV (gp120)	Distal axon damage; DRG cell damage; distal nerve; intact axons interacting with Schwann cells	MA	Zoster-associated pain, postherpetic neuralgia HIV-associated neuropathy
Drug-induced neuropathy (Peltier & Russell 2002)	Vincristine, paclitaxel, cisplatin	Distal axon loss; DRG cell damage; systemic injury of the PNS; intact axons interacting with Schwann cells	MA	Polyneuropathy caused by tumor chemotherapy

[a]Abbreviations: A, autotomy; CA, cold allodynia; MA, mechanical allodynia; MH, mechanical hyperalgesia; TH, thermal (heat) hyperalgesia; THypo, thermal hypoalgesia
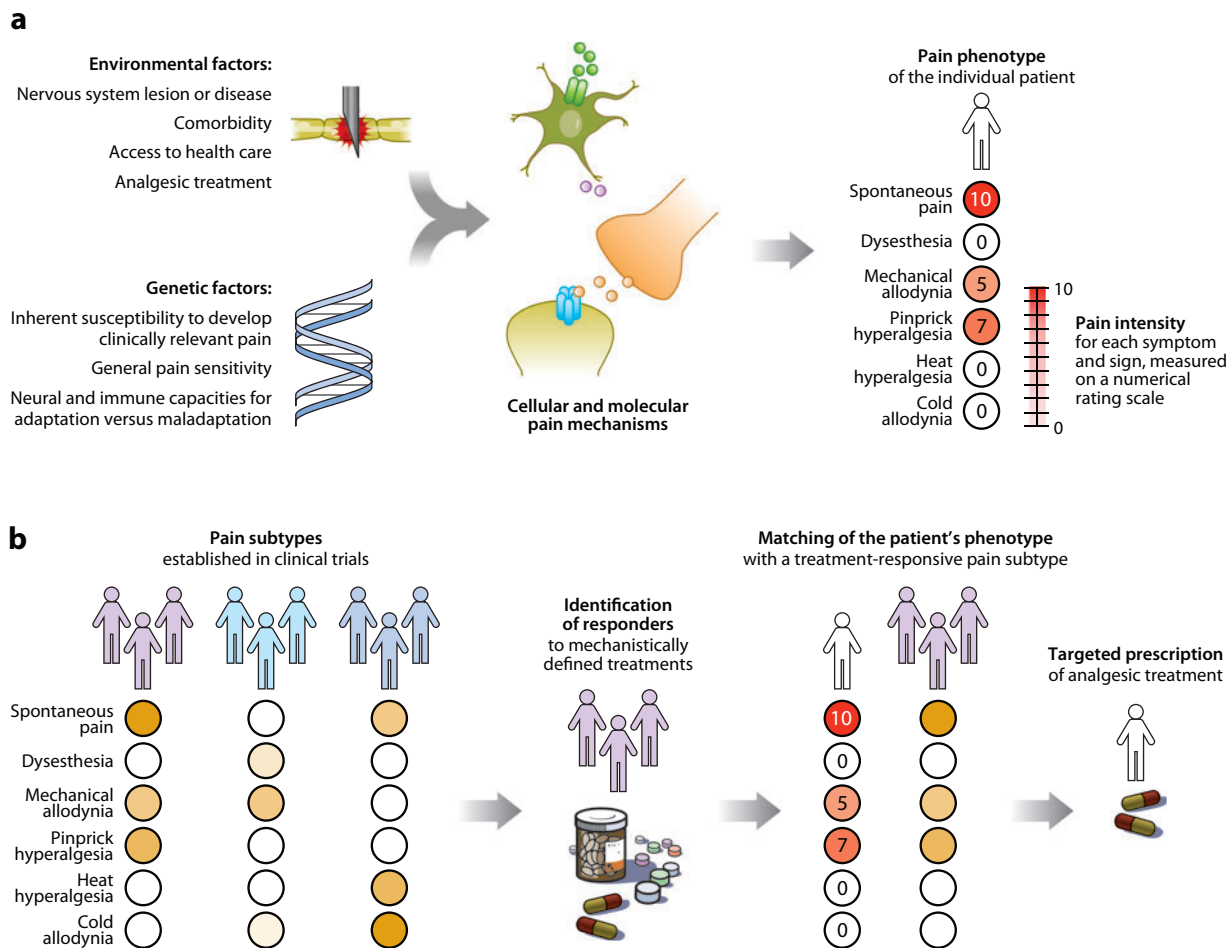
Figure 4

Phenotypic classification of pain. (*a*) Environmental and genetic factors determine the recruitment of adaptive and maladaptive neurobiological mechanisms. Patients will, depending on the mechanisms active, exhibit distinct constellations of symptoms and signs that constitute their pain phenotype. (*b*) When symptoms and signs are evaluated with standardized assessment tools, the phenotype of an individual patient can be compared with pain subtypes established in clinical trials. Correlation of treatment response with a matching pain subtype will then allow targeted analgesic therapy.

difficulties have prevented the establishment of mechanism-based classifications of neuropathic pain and the development of treatment strategies targeted at particular mechanisms (**Figure 4**).

Subtypes of Clinical Neuropathic Pain

Diagnostic labels for neuropathic pain conditions are usually based on anatomy, as for

example in small fiber neuropathy or radicular low back pain, or etiology, as in postherpetic neuralgia or diabetic polyneuropathy. They designate the underlying lesion or disease of the nervous system without revealing features of the pain that may reflect the mechanisms responsible. Conditions associated with neuropathic pain produce a variety of symptoms and signs, some of which correlate closely with a particular disease, such as tic douloureux

in trigeminal neuralgia. More often, however, symptoms and signs overlap across diagnostic entities, indicating both that some mechanisms responsible for the manifestation of pain-related symptoms and signs may be common among different conditions and that different mechanisms may produce a similar outcome.

To develop a successful targeted approach to pain management, it will be important to determine, for example, if a patient is suffering from spontaneous or evoked pain, which mechanisms are causing the pain, and how these mechanisms respond to drugs with different mechanisms of actions. Instead, crude rating scales of global pain intensity are usually employed in clinical practice and research trials to measure pain and the efficacy of analgesic drugs. Pain assessment often constitutes an evaluation of sensory pain qualities, the affective response to pain, and physical and psychosocial functioning, but none of these parameters reveals neurobiological features of pain that can be targeted by treatment interventions.

Treatment recommendations for neuropathic pain are issued for particular conditions defined by disease etiology (Finnerup et al. 2005), despite the fact that the etiology of neural damage is not equivalent to the neurobiological mechanisms responsible for persisting pain. Assuming that all forms of neuropathic pain are similar, evidence of analgesic efficacy in one disease is often applied to neuropathic pain in general (Finnerup et al. 2005). As a consequence, algorithms designed to determine the best analgesic treatment for an individual patient focus on comorbidities and associated risks of adverse effects and not on the nature or phenotype of pain (Dworkin et al. 2007). Given the inability to identify pain mechanisms in patients, a standardized and comprehensive classification of pain phenotypes may provide the next best approach to capture relevant information that may indirectly reflect pain mechanisms. To define such subtypes of pain, it would be necessary to comprehensively examine constellations of pain-related symptoms and signs and reveal distinct and reliable patterns

of association. Single symptoms or signs are not suitable because they may be caused by different mechanisms; for example, mechanical allodynia is observed in models of peripheral or central sensitization, reduced inhibitory control in the spinal cord, or after microglial activation in the dorsal horn. A standardized assessment of symptoms and signs would allow investigators to test the effects of analgesic drugs on unique features of particular pain subtypes and thus improve the translation of preclinical findings (Joshi et al. 2006). This information might help predict treatment response in individual patients by matching their pain profiles with established pain subtypes that are known to respond to certain treatments (**Figure 4**).

GENETIC DETERMINANTS OF NEUROPATHIC PAIN

Genetic variants that alter the risk of developing neuropathic pain and the degree of its severity offer an opportunity for investigators to define molecular mechanisms; they may also provide diagnostic tools and targets for treatment. Two general strategies are possible for human genetic studies: identifying rare mutations with large effects that produce distinct genetic diseases, or studying common genetic variants with smaller effects in large patient cohorts. Inbred mouse strains can be used to establish the extent to which neuropathic pain–like behavior is heritable, whereas expression profiling and mutation studies can identify those genes that affect the pain phenotype, and by which mechanism. Analysis of analgesic targets can also identify genetic modulators of neuropathic pain (**Table 3**).

Pain Heritability

Because many causes of neural damage associated with neuropathic pain are sporadic, it is rarely possible to rely on family history and classic genetic techniques to evaluate the degree to which a heritable susceptibility for

Table 3   Pharmacological evidence for genes involved in neuropathic pain

Gene product (drug target)	Site of action	Drug	Molecular mechanism of action	Clinical utility in neuropathic pain
Opioid receptor (μ, OPRM1)	CNS	Morphine, oxycodone, fentanyl	OPRM1 agonists inhibit synaptic transmission, activate central inhibitory circuits	Mixed results; some utility in PHN and DPN. Multiple routes of administration available
Voltage-gated sodium channels	PNS	Lidocaine, bupivacaine	Nonselective sodium channel blocker	Topical application in peripheral NP, e.g., in PHN
	CNS/PNS	Carbamazepine, lamotrigine, mexiletine, amitryptiline	Nonselective sodium channel blockers stabilize an inactive channel state	Trigeminal neuralgia, phantom limb pain
Calcium channel (N-type, Cav2.2)	CNS	ω-conotoxin	N-type calcium channel blocker reduces neurotransmitter release	Intrathecal delivery for severe chronic pain
Calcium channel auxiliary subunits (α2δ1 or CACNA2D1)	PNS/CNS	Gabapentin, pregabalin	Bind to the α2δ1-subunit of voltage-gated calcium channels, reduce trafficking of the channels, decrease transmitter release from primary afferents	Effective in peripheral NP
NMDA receptor	CNS	Ketamine, memantine, dextromethorphan	NMDA receptor antagonists reduce central sensitization	Limited by adverse effects
Monoamine transporters (NAT and SERT)	CNS	Tricyclic antidepressants, selective noradrenaline (SNRIs) or serotonin (SSRIs) reuptake inhibitors	Block monoamine reuptake, reinforce brain stem inhibitory pathways	Effective in NP, especially PHN and painful diabetic neuropathy
Cannabiniod receptors (CNR1 and CNR2)	PNS/CNS	δ-9-tetrahydrocannabinol, cannabidiol, synthetic cannabinoids	CNR1 agonists reduce nociceptor activation and transmitter release. CNR2 suppress immune reactions	Effective in central pain (multiple sclerosis)
TRPV1	PNS	Capsaicin, resiniferatoxin	TRPV1 agonists desensitize C-fiber nociceptors and provoke their degeneration	Topical application in peripheral NP

Abbreviations: DPH, diabetic peripheral neuropathy; NP, neuropathic pain; PHN, post-herpetic neuralgia.

developing the pain is involved. However, two recent twin studies using experimental (nociceptive) pain models in healthy volunteers have estimated the impact of inherited heritability of pain sensitivity with a broad range 20%–60% (Nielsen et al. 2008, Norbury et al. 2007), the significance of which is difficult to interpret. A study using 11 inbred mice strains tested with 12 different pain measures revealed heritability between 30% and 76% (Mogil et al. 1999a).

With respect to pain-like behavior following nerve injury, three measures were recorded: the paw withdrawal threshold for mechanical stimuli, the thermal pain threshold (latency of response), and autotomy (scratching and biting of the denervated hindpaw). These behaviors gave heritability estimates of 45%, 45%, and 63%, respectively, and suggest that the neuropathic pain phenotype varies widely in outbred rodent strains, as it does in patients.

Genetic Risk of Developing Neuropathic Pain

In humans, the genetic risk of developing neuropathic pain after neural injury, its extent, presentation, and duration are very likely to result from multiple risk-conferring genes. Case-control studies using whole-genome analysis or candidate gene association studies can be conducted to identify these genes. Association studies compare allele frequencies between unrelated subjects with and without a particular trait to identify DNA regions correlated with the trait. Alleles are DNA codes at a given position on the genome that constitute markers of coinherited regions of DNA known as haplotype blocks. A haplotype block significantly coinherited with a trait is a strong indication that the DNA contains a version of a gene that in some way modifies the carriers' phenotype to create the trait.

Candidate gene association studies have preliminarily identified polymorphisms in catechol-O-methyltransferase (COMT) that modulate nociceptive and dysfunctional (temporomandibular joint disorder) pain (Diatchenko et al. 2005, Nackley et al. 2006). COMT is an enzyme in the metabolism cascade for dopamine, norepinephrine, and epinephrine. Higher COMT activity leads to lower transmitter and pain levels (Diatchenko et al. 2007). Other such association studies have linked polymorphisms in the μ-opioid receptor 1 (OPRM1) to morphine sensitivity (Lotsch & Geisslinger 2007) and in the melanocortin-1 receptor (MCR1) to κ-opioid-induced analgesia in females (Mogil et al. 2003).

No whole-genome association study has been conducted yet for neuropathic pain. The problems are formidable: how to phenotype patients in a standardized way to eliminate spurious associations, which controls to use, and how large the cohorts need to be to retain sensitivity but eliminate false positive results that may arise from multiple testing. An estimated 2000–5000 patients and controls would be required for studies assaying 1 million SNPs at a significance level of $<10^{-7}$ (Wellcome-Consortium 2007). Potential whole-genome association studies include comparisons of patients who do and do not develop neuropathic pain after iatrogenic nerve injury and diabetic patients with peripheral neuropathy with and without pain. Another approach is to use alternative experimental methods to identify potential gene targets that can then be tested in smaller cohorts for association. This approach has led to the identification of a haplotype in the enzyme GTP cyclohydrolase 1 (GCH1) that reduces the risk of persistent radicular back pain after discectomy (Tegeder et al. 2006). This GCH1 haplotype has a population frequency of 15.4% ($\sim$2%–3% of individuals have two copies and 20% have one copy), and homozygous carriers display lower experimental pain thresholds than do individuals with no copy (Tegeder et al. 2006, 2008). White blood cells from individuals with the haplotype have normal basal BH4 levels, but GCH1 activity fails to increase in response to a stress challenge (Tegeder et al. 2006).

GCH1 was identified in a study using expression profiles to identify genes regulated in the DRG of rats after peripheral nerve injury (Tegeder et al. 2006). Analysis of three distinct nerve injury models consistently indicated *de novo* expression of enzymes involved in the synthesis and recycling of tetrahydrobiopterin (BH4). BH4 is an essential cofactor for aromatic amine hydroxylases that synthesize serotonin and catecholamines and for all nitric oxide synthases (Tegeder et al. 2006) (**Figure 5**). Increased BH4 synthesis in the injured DRG contributes to increase nitric oxide release and produces a large calcium flux in DRG neurons. GCH1 is the rate-limiting enzyme for the synthesis of BH4, and inhibition of GCH1 produces analgesia in rodent models of neuropathic pain. These findings demonstrate the validity of translational pain research and the power of studying neuropathic pain in parallel in preclinical and clinical models.
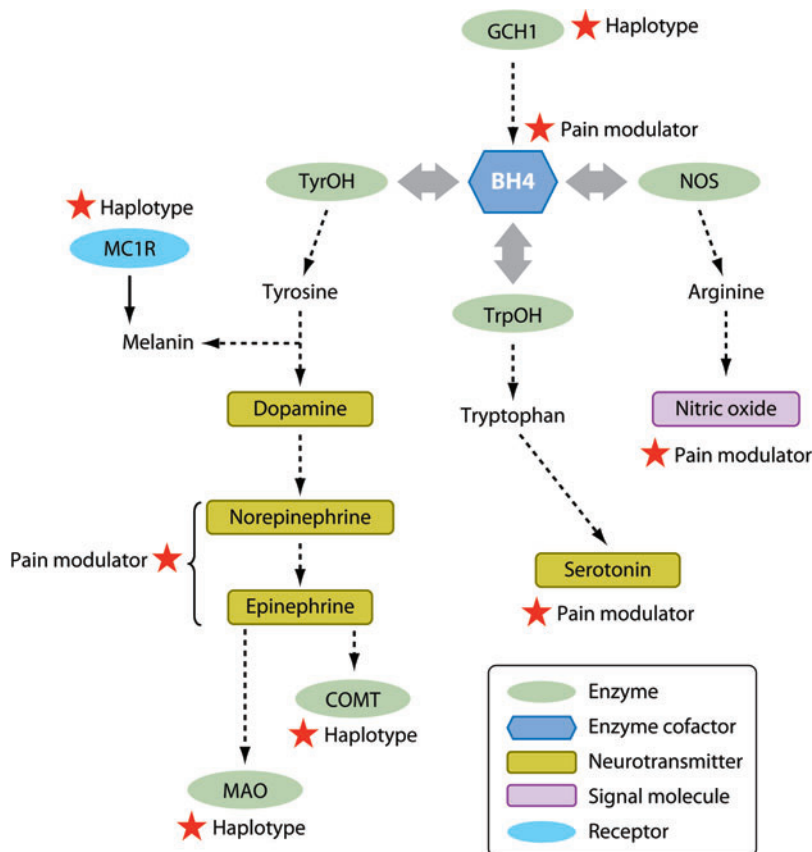
Figure 5

A summary of the major mechanisms connecting tetrahydrobiopterin (BH4) functions as a cofactor and its role in chronic pain.

SUMMARY POINTS

1. Neural damage to either the PNS or CNS provokes maladaptive responses in nociceptive pathways that drive spontaneous pain and sensory amplification. This maladaptive plasticity leads to persistent changes and, therefore, needs to be considered a disease state of the nervous system in its own right, independent of the etiological factor that triggered it.

2. Multiple mechanisms are responsible for neuropathic pain. In the PNS, they include altered gene expression and changes in ion channels that lead to ectopic activity. In the CNS, the regulation of many genes also changes. In addition, synaptic facilitation and loss of inhibition at multiple levels of the neuraxis produce central amplification. Neuronal cell death and aberrant synaptic connectivity provide the structural basis for persistently altered processing of both nociceptive and innocuous afferent input.

3. Neural damage provokes vigorous and highly organized neuroimmune interactions that play a key role in initiating many cellular mechanisms that underlie persistent neuropathic pain.

4. Genetically determined susceptibility is likely to combine with the environment to determine the risk of developing neuropathic pain.

5. Given the complexity of numerous intertwined genetic, cellular, and molecular components that cause neuropathic pain, clinical classifications need to incorporate multiple aspects of the pain phenotype to guide the identification of underlying mechanisms and help assess the likelihood of response to treatment.

FUTURE ISSUES

1. Will selective sensory neuron–specific sodium channel blockers have utility in peripherally derived neuropathic pain?

2. The utility of preclinical models of neuropathic pain, for candidate gene identification and validation, pain mechanisms definition, and the investigation of treatment interventions need to be critically evaluated.

3. Will it be possible to reveal mechanisms of neuropathic pain in humans?

4. Will a mechanism-based clinical approach lead to improvements in diagnosis and treatment?

5. Will disease-modifying therapy prevent the development of neuropathic pain?

6. Once established, can neuropathic pain ever be reversed?

7. Will genes identified by expression profiling and SNP association studies provide targets for novel analgesics and biomarkers of neuropathic pain?

8. Whole genome association studies in carefully phenotyped cohorts are needed to identify genetic contributions to the risk of developing neuropathic pain.

DISCLOSURE STATEMENTS

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