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Review

Deconstructing the Neuropathic Pain Phenotype to Reveal Neural Mechanisms

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After nerve injury maladaptive changes can occur in injured sensory neurons and along the entire nociceptive pathway within the CNS, which may lead to spontaneous pain or pain hypersensitivity. The resulting neuropathic pain syndromes present as a complex combination of negative and positive symptoms, which vary enormously from individual to individual. This variation depends on a diversity of underlying pathophysiological changes resulting from the convergence of etiological, genotypic, and environmental factors. The pain phenotype can serve therefore, as a window on underlying pathophysiological neural mechanisms and as a guide for developing personalized pain medicine.

Introduction

Nociceptive pain reflects our capacity to detect the presence of potentially damaging stimuli; it is an essential early warning mechanism (Basbaum et al., 2009; Woolf and Ma, 2007). This sensation is mediated in the periphery by high threshold primary sensory neurons, the nociceptors, which transmit information via nociceptive pathways in the spinal cord to the brain (Figure 1). Following peripheral tissue injury or inflammation, reversible adaptive changes in the sensory nervous system lead to the generation of pain hypersensitivity, a protective mechanism that ensures proper healing of damaged tissue. In contrast, in neuropathic pain, the nervous system itself is injured and changes in its sensitivity can become persistent—pain can occur spontaneously, its threshold may fall dramatically such that innocuous stimuli produce pain, and the duration and amplitude of its response to noxious stimuli are amplified. Because these neural changes in susceptible individuals can be irreversible, neuropathic pain, once established, should be regarded as an autonomous disease state of the nervous system in its own right. Most patients do not develop neuropathic pain after nerve injury (Kehlet et al., 2006) and although only a handful of genetic polymorphisms have been identified that confer either an enhanced susceptibility to development of neuropathic pain, it is nevertheless clear that genotype is a substantial contributor (Binder et al., 2011; Costigan et al., 2010; Lacroix-Fralish and Mogil, 2009; Nissenbaum et al., 2010).

Neuropathic pain is common, greatly impairs quality of life, and has a high economic impact on society: the Institute of Medicine reports that at least 116 million American adults suffer from chronic pain and estimates for people suffering from neuropathic pain are as high as 17.9% (Toth et al., 2009). Comorbidities such as poor sleep, depression, and anxiety are common in neuropathic pain patients, leading to unresolved arguments about whether pain causes mood and sleep changes or whether individuals with mood and sleep disorders are at a higher risk of developing pain (Turk et al., 2010). What is clear though is that neuropathic pain is a major health problem. The first step in the clinical diagnosis of neuropathic pain is to document the disease or lesion that is presumed to have caused it, and its anatomical site. Until very recently, this was also the end of the diagnostic process, and often no attempt was made to identify the actual neural mechanisms responsible for the generation of the individual pain phenotype and how they may inform treatment decisions. A common assumption is that a single etiology causes neuropathic pain in a uniform way. However, neuropathic pain is very heterogeneous, with multiple patterns of presentation reflecting diverse combinations of etiological, genetic and environmental factors, and specifically, the neurobiological processes they engage (Figure 2). Because of their mechanistic diversity and different manifestations, these processes produce a complex profile or constellation of positive and negative sensory symptoms and signs, a ''pain fingerprint'' (Baron et al., 2009; Mahn et al., 2011; Scholz et al., 2009). It is essential to shift focus from etiology to the reaction of the nervous system to the etiological pathology—to viewing neuropathic pain as a manifestation of pathological neural plasticity. The advantage of this approach is that it will lead to an explicit dual therapeutic focus aimed both at etiological factors and the forms of maladaptive plasticity they initiate.

Sensory Nerve Damage Produces Negative Symptoms

By definition, neuropathic pain involves damage to the nervous system (Jensen et al., 2011). Often, negative symptoms are the first indication of damage to the somatosensory system and can be detected by quantitative sensory testing as well as clinical examination and to a more limited extent, history/questionnaire. The cause of negative symptoms in peripheral neuropathies is direct insult to primary sensory neurons. This may produce cell death or compromise transduction (due to terminal atrophy) or conduction (due to loss of peripheral axons) or transmission (due to loss of central terminals) of sensory information. Loss of function can manifest across the whole sensory spectrum (e.g., global numbness after a traumatic nerve injury) or it can affect specific modalities (Freeman, 2009). For example, an elevated

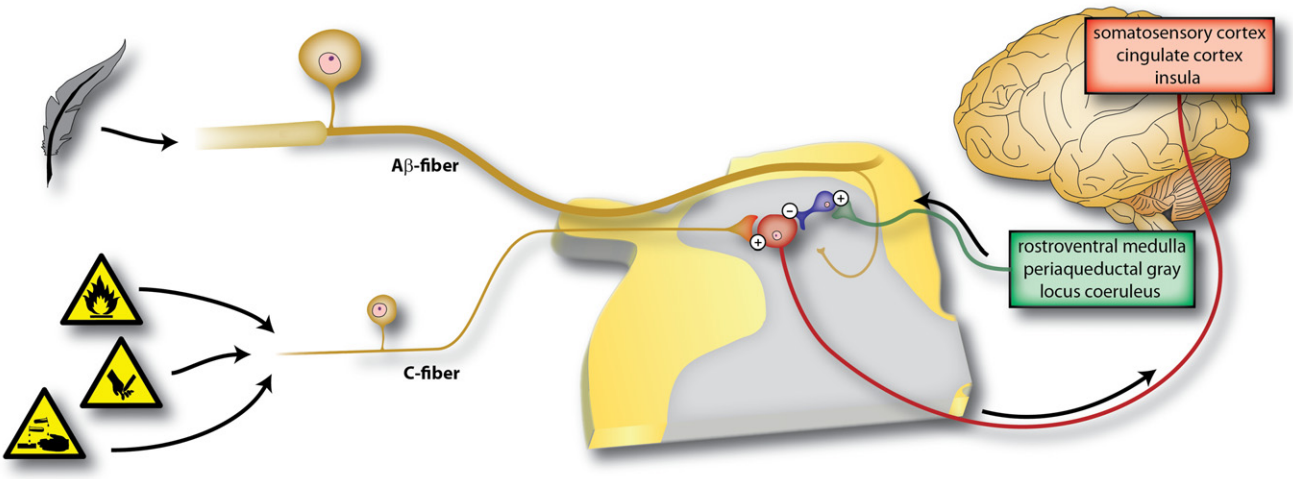

Figure 1. The Nociceptive Pain Circuit
High-threshold nociceptors are activated by intense mechanical, thermal, or chemical stimuli and feed this information to nociceptive neurons in the spinal cord, which project via the thalamus to cortical areas generating the sensory and emotional qualities of pain. These spinal cord pathways are subject to descending inhibitory and facilitatory influences from the brainstem. Normally, activity in low-threshold afferents is carried by independent peripheral and central pathways and only generates innocuous sensations.

heat threshold due to degeneration of intraepithelial C-fibers is a common early manifestation of peripheral diabetic neuropathy (Said, 2007) and in chemotherapy-induced neuropathies, where sensory but not motor axons show mitochondrial damage leading to hypoesthesia (Xiao et al., 2011). Many patients with neural damage only have negative symptoms, some though, also have positive symptoms because particular pathological processes are engaged that increase pain sensitivity or drive spontaneous activation of the nociceptive pathway.

Peripheral Sensitization after Nerve Lesions Increases Pain Sensitivity

Peripheral sensitization most characteristically occurs after peripheral inflammation and comprises a reduction in threshold and an increase in the excitability of the peripheral terminals of nociceptors in response to sensitizing inflammatory mediators. This results in innocuous stimuli at the site of inflammation, such as light touch, warm or cool temperatures, being perceived as painful (allodynia), and stimuli that usually are felt as uncomfortable or slightly painful, such as a pinprick, becoming extremely painful (hyperalgesia) in the primary area of inflammation. However, peripheral sensitization can also occur after nerve lesions in the presence (peripheral neuritis) and absence of tissue inflammation, and thereby can contribute to pain hypersensitivity within the innervation zone of an affected nerve (Figure 3).

External mechanical, thermal, and chemical stimuli are converted into voltage changes in sensory neurons by ion channels that respond to specific environmental stimuli. After nerve injury, peripheral sensitization results from reduced thresholds for activation these transducer channels together with nerve injury induced changes in sodium and potassium channels. The best characterized transducer ion channel is the nonselective cation channel TRPV1, which has a well established role in peripheral inflammatory pain (Huang et al., 2006). However, after nerve damage, posttranslational changes, trafficking, and expression changes of TRPV1 also occur. After partial nerve injury, TRPV1 is upregulated in uninjured sensory fibers (Hudson et al., 2001; Kim et al., 2008), and during diabetic neuropathy changes in the expression of TRPV1 correlate with development of thermal hyper- and hypoalgesia. In addition, TRPV1 begins to be expressed in large myelinated A-fibers (Hong and Wiley, 2005; Pabbidi et al., 2008), one of several injury-induced phenotypic shifts in low-threshold sensory neurons. Inhibiting TRPV1 activity or decreasing TRPV1 levels reduces neuropathic hyperalgesia (Christoph et al., 2006; Watabiki et al., 2011), and heat hyperalgesia after peripheral neuropathy induced by chemotherapeutic agents is absent in TRPV1 knockout mice (Ta et al., 2010). Other ion channels such as TRPA1, TRPM8, or P2X3 may also be altered during nerve injury and contribute to neuropathic pain hypersensitivity, but the potential contributions of these ion channels to neuropathic pain are not well understood (Eid et al., 2008; Shinoda et al., 2007; Xu et al., 2011).

TRPV1 is also expressed in sensory nerve axons of peripheral nerves, not only at its peripheral terminal (Weller et al., 2011). Because TRPV1 activation threshold is modified by inflammatory mediators from immune cells, and injured nerves contain many macrophages and T cells (Gaudet et al., 2011), it is quite possible, therefore, that axonal TRPV1, just like peripheral terminal TRPV1, may also become sensitized. Theoretically, a reduction in TRPV1 thermal threshold to levels close to body temperature along the axon could then lead to depolarization and generation of action potentials, producing spontaneous pain (Hoffmann et al., 2008).

While TRPV1 is an attractive target for treating neuropathic pain, an unexpected obstacle for the therapeutic use of TRPV1 antagonists is the significant increase in body temperature they produce (Swanson et al., 2005), as well as the risk of damage due to loss of the warning heat pain signal. These

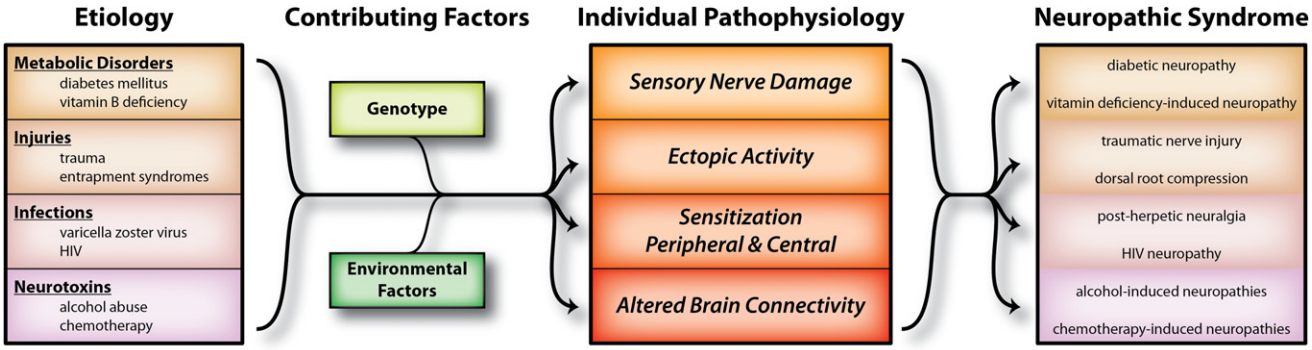

Figure 2. From Etiology to Neuropathic Pain
The neuropathic syndrome is the end result of an initiating disease combined with individual contributing factors, such as genotype and environmental factors like diet and life style, all of which lead to individual combinations of pathophysiological mechanisms, manifesting as an individual neuropathic pain phenotype.

complications may be addressed by targeting specific activation sites independent of temperature activation (Szallasi et al., 2007; Watabiki et al., 2011). A second possibility is to modulate TRPV1 activation threshold by inhibiting kinases known to target TRPV1, such as p38 and PKCε, which are under investigation in neuropathic pain clinical trials and show some efficacy (Anand et al., 2011). Also, repeated low-dose applications of the TRPV1 agonist capsaicin desensitize the channel through phosphorylation and Ca^{2+}-dependent mechanisms (Touska et al., 2011). However, a single application of extremely high concentrations leads to atrophy of peripheral terminals, most likely due to an overload of intracellular calcium and depolarization of mitochondrial membrane potential, which explains pain relief lasting up to 12 weeks after high-dose capsaicin treatments (Anand and Bley, 2011). As one would expect however, this treatment may be very painful initially. Whether such terminal atrophy, which is a feature of many forms of peripheral neuropathy, may itself lead to neuropathic pain in susceptible individuals is something to consider.

After nerve injury, increased levels of neurotrophins, particularly nerve growth factor (NGF), and cytokines are found at the site of and distal to the injury (Dogrul et al., 2011; Gaudet et al., 2011; Leung and Cahill, 2010). The neurotrophins activate kinases, which alter expression, posttranslational modification and trafficking of TRPV1 and voltage gated sodium channels (Dib-Hajj et al., 2010; Mantyh et al., 2011). Furthermore, expression of voltage-gated potassium channels is decreased by neurotrophin receptor-mediated activation of PKMζ (Zhang et al., 2012). Sequestering antibodies against NGF are effective in treating inflammatory pain (Lane et al., 2010). The preclinical picture for anti-NGF treatment for neuropathic pain, however, is mixed, and one potential concern is that while increased NGF may lead to pain by sensitizing nociceptor neurons, sequestering NGF may induce transcriptional changes and even cell death in intact neurons if an ongoing supply of target-derived NGF is required for maintenance of a specific differentiated neuronal phenotype.

Ectopic Activity after Nerve Injury Generates Spontaneous Pain

Pain occurring in the absence of any external stimulus is a debilitating consequence of peripheral nerve injury. It can, potentially at least, originate as a result of spontaneous activity generated anywhere along the nociceptive pathway. Most frequently however, spontaneous sensations after peripheral nerve lesions appear to be generated as a result of hyperexcitability in the primary sensory neuron, leading to ectopic action potential discharge at the site of injury and resultant neuroma, but also at more proximal axonal sites, including the soma (Amir et al., 2005). Ectopic activity is a major and in perhaps most cases the exclusive driver of the spontaneous sensations that manifest after nerve injury or lesions producing paresthesia, dysthesia, and pain. The pain may be episodic or continuous, superficial, or deep, and often has shock-like bursts and a burning quality, all of which may reflect engagement of ectopic activity in different fibers with different temporal patterns of firing, as well as subsequent central changes. While many changes occur in injured neurons, uninjured fibers neighboring injured ones in partial nerve injuries can potentially also give rise to unevoked afferent input and thereby painful sensations (Wu et al., 2002); in fact, some evidence suggests that this may be a large source of neuropathic ectopic activity (Djouhri et al., 2006). Changes in the uninjured neurons may result from mediators generated by injured axons, immune cells, denervated Schwann cells and target tissue. Ectopic activity can also be generated by stimuli; for example, mechanosensitivity of neuromas is well described. Ectopic activity can also contribute to central sensitization, as discussed below.

What drives a normally quiet sensory axon, designed only to conduct action potentials, to begin to initiate action potentials? Nerve injury drastically changes the expression, distribution, and phosphorylation of many ion channels in sensory neurons leading to changes in intrinsic membrane properties and the generation of membrane potential oscillations resulting in rhythmic firing bursts in the absence of a stimulus. Which ion channels are modified as a direct or indirect consequence of a nerve injury or lesion? As for most neurons, the membrane potential in sensory neurons is largely determined by potassium channels. The two-pore domain K^+ channels TRESK ($K_{2p}18.1$) and TREK-2 ($K_{2p}10.1$) represent approximately 85% of K^+ background current in DRG neurons (Dobler et al., 2007; Kang and Kim, 2006) with TRESK being particularly highly expressed in the DRG (Allen Brain Atlas). After injury, TRESK is downregulated

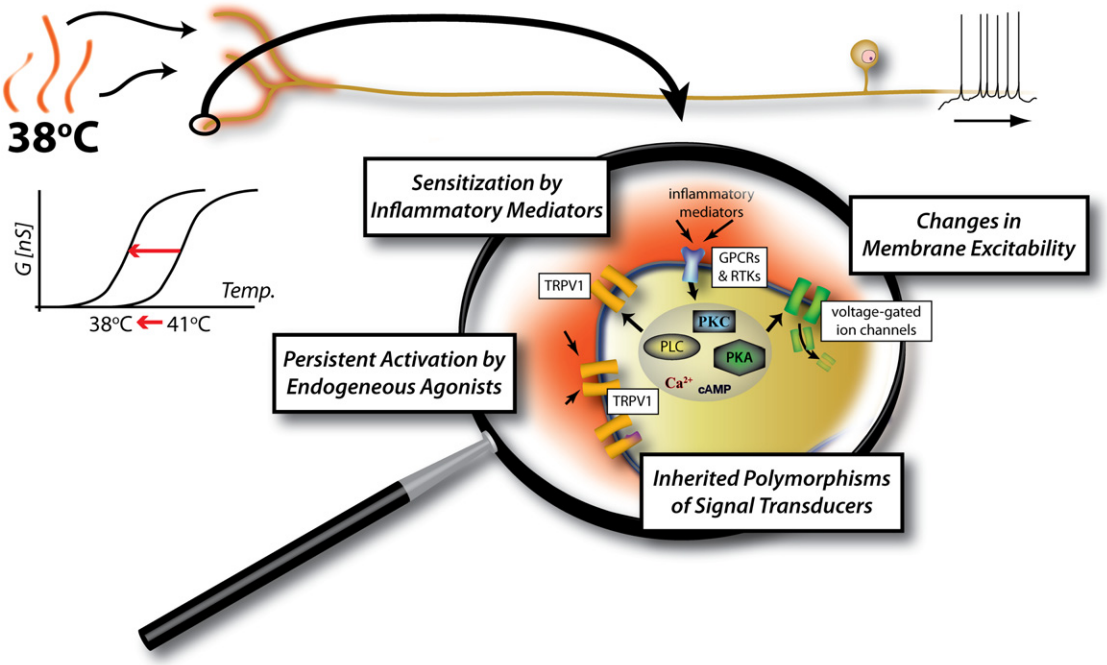

Figure 3. Peripheral Sensitization
Changes in the sensitivity of the peripheral terminals of nociceptors to stimuli can contribute to evoked pain. This can occur through inflammatory mediators sensitizing signal transducer proteins, persistent activation of transducer proteins by endogenous agonists, inherited polymorphisms of transducer proteins, or an increase in membrane excitability.

by 30%–40% leading to a steady depolarization of the sensory neuronal membrane potential (Tulleuda et al., 2011). However, reduction in potassium leak current cannot be the sole cause of ectopic activity. Subthreshold membrane potential oscillations, largely carried by the persistent component of the sodium current, I_{NaP}, are frequently seen in injured sensory neurons and may be a major contributor to ectopic spike discharge (Amir et al., 1999). Computer modeling and pharmacological inhibition support the importance of I_{NaP} for spontaneous activity in injured neurons (Kovalsky et al., 2009; Xie et al., 2011), even if the specific molecular identity of the responsible sodium channel remains uncertain. Most likely for injured sensory neurons, this current is generated by non-inactivating $Na_v1.3$- and $Na_v1.6$-mediated currents; but there is also evidence that $Na_v1.9$ is involved (Dib-Hajj et al., 2010; Enomoto et al., 2007; Herzog et al., 2001). In addition, it is possible that the persistent current is modified by changes in the expression of auxiliary sodium channel β subunits in injured and uninjured fibers, which may alter trafficking and kinetics (Pertin et al., 2005; Zhao et al., 2011).

Membrane potential oscillations, spontaneous activity, and neuropathic pain behavior have also been attributed to the mixed cation current I_h conducted by hyperpolarization-acivated cyclic nucleotide-gated (HCN) channels. Large sensory neurons mainly express HCN1, while small sensory neurons predominantly express HCN2 (Biel et al., 2009; Emery et al., 2011; Momin et al., 2008; Moosmang et al., 2001). In rodent models of neuropathic pain, low concentrations of the nonspecific HCN antagonist ZD7288 strongly reduce pain behavior and spontaneous firing in injured fibers (Chaplan et al., 2003; Lee et al., 2005). In addition, sensory neuron-specific *HCN2*$^{-/-}$ mice show hardly any signs of neuropathic pain, whereas *HCN1*$^{-/-}$ mice develop almost typical pain behavior after partial nerve ligations (Emery et al., 2011; Momin et al., 2008). The evidence for changes in HCN protein and transcript levels after nerve injury are somewhat contradictory and may be explained by somatic versus axonal compartmentalization (Chaplan et al., 2003; Jiang et al., 2008). However, even if expression changes are minimal, alterations in cAMP levels could contribute to modified I_h densities, and it is conceivable that inhibitors that block adenyl cyclase exert some of their analgesic action in neuropathic pain models in the periphery by reducing HCN channel sensitization (Wang et al., 2011). How does I_h contribute to generating ectopic discharges? Because of activation by hyperpolarizing potentials, HCN channels are also an important component for membrane potential oscillations in various neuronal networks (Biel et al., 2009). Especially in concert with low-threshold T-type calcium channels, neurons can display repetitive firing patterns, where hyperpolarization leads to activation of I_h, slowly depolarizing the membrane potential until a Ca^{2+} spike carried by T-type calcium channels is initiated, further depolarizing the potential and triggering a series of Na^{2+} spikes. The depolarization inactivates I_h until the train of action potentials is followed by a hyperpolarizing overshoot, which opens HCN channels and the cycle can repeat (Biel et al., 2009). This model also explains the observed analgesic effect of peripherally applied T-type

antagonists in neuropathic pain models (Barton et al., 2005; Dogrul et al., 2003).

Given their contribution to generator potentials in the peripheral terminal and action potentials in the axon, it is not surprising that voltage-gated sodium channels (VGSC) have been a prime target of investigation and therapeutic approaches for neuropathic pain (Devor, 2006; Dib-Hajj et al., 2010). Nav1.8 is mainly expressed by A- and C-fiber nociceptors, Nav1.9 is selective for a subset of C-fibers, whereas Nav1.1 and Nav1.6 are found mostly in nonnociceptive neurons (Fukuoka et al., 2008; Fukuoka and Noguchi, 2011). Nav1.7 seems to be expressed universally in all sensory neurons, but clearly plays an important role in nociception, as indicated by various monogenetic disorders affecting this channel, including gain of function mutations in Nav1.7 that result in ectopic firing of C-fibers in the absence of nerve injury and spontaneous pain conditions (Cox et al., 2006; Dib-Hajj et al., 2010; Faber et al., 2011). Nav1.3 is usually only expressed during development (Waxman et al., 1994); however, nerve injury drastically changes this expression profile and expression of Nav1.3 returns in adult sensory neurons (Fukuoka et al., 2008; Waxman et al., 1994). Notably, Nav1.3 has fast enough gating kinetics to contribute to depolarizing afterpotentials and with that, to membrane potential oscillations (Devor, 2006). Levels of Nav1.6, Nav1.7, Nav1.8, and Nav1.9 are decreased in the soma of injured neurons (Kim et al., 2002a). However, an increase in axonal membrane expression of Nav1.8, presumably due to trafficking and possibly axonal translation, is observed in injured sensory nerve fibers (Novakovic et al., 1998; Thakor et al., 2009). The exact mechanism of this change in sodium channel profiles is not well understood but likely involves TNFα-mediated pathways (He et al., 2010; Schäfers et al., 2003). Interestingly, changes are not limited to injured nerves, as re-expression of Nav1.3 and increased axonal levels of Nav1.8 are also seen in neighboring undamaged fibers (Gold et al., 2003; He et al., 2010) as well as in central nociceptive pathways (Hains et al., 2003, 2004, 2005). Antisense oligodeoxynucleotides against Nav1.3 and Nav1.8 significantly reduce neuropathic pain related symptoms (Hains et al., 2004; Lai et al., 2002). However, nerve injury induces typical neuropathic pain-like behavior in sensory neuron-specific conditional Nav1.3, Nav1.7, or Nav1.8, knockout mice (Nassar et al., 2005, 2006). These conflicting data may reflect developmental compensation of sodium channel expression, but this awaits a definitive answer.

In addition to expression changes, sodium channels are also targets of phosphorylation by various kinases during neuropathic pain. Mainly triggered by proinflammatory cytokines after nerve injury, mitogen-activated protein kinases (MAPK) may be the predominant ones as they are highly expressed in painful human neuromas and phosphorylate Nav1.3, Nav1.7, Nav1.8, and Nav1.9 (Binshtok et al., 2008; Black et al., 2008; Dib-Hajj et al., 2010; Hudmon et al., 2008; Stamboulian et al., 2010). One prominent effect of such phosphorylation is a relief of slow inactivation (Binshtok et al., 2008; Stamboulian et al., 2010).

Voltage-gated sodium channels are prime targets for pharmaceutical intervention, as illustrated by the multiple sodium channel blockers used to treat neuropathic pain, e.g., local anesthetics, mexilitine, and carbamazepine (Gracely et al., 1992). However, the currently available nonselective blockers come at the cost of cardiovascular and CNS side effects. Subtype-specific or state-dependent inhibition of sodium channels is a promising approach to treat the ectopic activity of neuropathic pain (Binshtok et al., 2007; Jarvis et al., 2007), as well as kinase inhibitors that prevent post-translational modifications in the channels.

Voltage-gated potassium channels are also required for action potential firing and are also involved in spontaneous trains of action potentials after nerve injury. Low voltage-activated potassium channels, which stabilize membrane potential and regulate action potential number on depolarization, are downregulated by nerve injury (Kim et al., 2002b; Rose et al., 2011). Here, particularly KCNQ (Kv7) channels came into focus because of the antinociceptive effect of the specific KCNQ opener retigabine in animal models of neuropathic pain, although it has failed in clinical trials (Blackburn-Munro and Jensen, 2003; Passmore et al., 2003). On the other hand, nerve injury has little or no effect on the expression of high voltage-activated potassium channels with fast kinetics, which determine spike duration and are required for fast firing (Kim et al., 2002b).

Ectopic activity offers several treatment opportunities. Whether a particular channel is a more prominent driver of ectopic activity in one individual versus another is not yet known; however, would have important consequences for treatment choice. Generally, treatment of spontaneous activity is likely to be an important component of neuropathic pain treatment, because it is a major contributor to spontaneous pain and to central changes in the nociceptive pathway that amplify pain, central sensitization.

Central Sensitization Amplifies Pain and Reduces Threshold

Until the early 1980s, the presence, intensity, and duration of pain, whatever its etiology, was thought to simply reflect the degree and timing of nociceptor activation. According to this view, a noxious stimulus was required to produce pain, but after tissue injury peripheral sensitization could increase the sensitivity of nociceptors in the inflamed region such that they responded to less intense innocuous stimuli, while after nerve injury ectopic activity in nociceptors could generate spontaneous pain. The discovery of central sensitization, a form of long-lasting synaptic plasticity in the dorsal horn triggered by nociceptors that facilitates nociceptive processing (Woolf, 1983), has forced a profound change in the model. It led to the realization that amplification of incoming signals within the CNS has a very substantial role in the generation of clinical pain hypersensitivity, including neuropathic pain. Indeed, central sensitization has now provided a mechanistic explanation for how low threshold A or C fibers can begin to produce pain, why there is a spread of sensitivity beyond areas of tissue injury or outside a damaged nerve territory, why repeated stimuli at a fixed intensity can lead to a progressive increase in pain, and why pain may long outlast a peripheral stimulus (Pfau et al., 2011; Seal et al., 2009; Woolf, 2011). Furthermore, we now appreciate that central sensitization in certain conditions, including after nerve injury, can become autonomous.

Activity-dependent central sensitization in normal individuals is typically induced by a burst of activity in nociceptors lasting several tens of seconds, and includes establishment both of homo- and heterosynaptic potentiation, the former sharing many features of long term potentiation (LTP) in cortical neurons (Latremoliere and Woolf, 2009; Ohnami et al., 2011; Ruscheweyh et al., 2011). Unlike classic LTP, however, heterosynaptic facilitation is particularly prominent in central sensitization and means that a nociceptor-specific conditioning input can enable subsequent long lasting facilitation of responses to inputs from low-threshold A beta- or C-fibers, and to afferent inputs from topographically quite different locations. This occurs by a spread of the change in synaptic strength from activated to neighboring non-activated synapses, as opposed to changes in LTP which are usually restricted to a single dendritic spine coactivated by two inputs. Heterosynaptic facilitation after brief nociceptor triggering input can last for hours while homosynaptic LTP may last longer. Mechanistically, central sensitization includes pre- and postsynaptic changes as well as an increase in post synaptic membrane excitability (Latremoliere and Woolf, 2009). As for LTP, alterations in postsynaptic calcium levels are a major driver in initiating change in synaptic strength: Calcium change can be caused by calcium flux through ionotropic receptors and voltage-gated calcium channels or by release from intracellular stores on activation of metabotropic receptors or receptor tyrosine kinases (Cheng et al., 2010; Ohnami et al., 2011). Cav1.2 L-type calcium channels play important roles and can undergo bidirectional regulation by miR-103 to initiate some forms of central sensitization (Favereaux et al., 2011; Fossat et al., 2010). Calcium-dependent intracellular signaling pathways produce posttranslational and transcriptional changes in many effector proteins, altering their levels, distribution, and functional activity (Asiedu et al., 2011; Katano et al., 2011; Matsumura et al., 2010; Miletic et al., 2011). The major players in the synaptic changes underlying activity-dependent central sensitization are the NMDA, AMPA, and mGluR glutamate receptors, the substance P NK1 receptor, BDNF and its TrkB receptor, ephrinB and EphBR, CaMKII, PKA, PKC, src, ERK and CREB, and Kv4.2 (D'Mello et al., 2011; Hu and Gereau, 2011; Latremoliere and Woolf, 2009; Nozaki et al., 2011).

Central sensitization in normal individuals can only be initiated by a conditioning nociceptor input, because these afferents corelease glutamate and neuropeptides, providing greater opportunity for sufficient postsynaptic calcium increase. After nerve injury, however, Aβ fibers can undergo phenotypic changes including increased expression of neuropeptides (Nitzan-Luques et al., 2011) such that they may acquire the capacity to trigger or maintain central sensitization (Figure 4). More recently, changes in dendritic spines in dorsal horn neurons mediated by the monomeric G protein Rac1 have been detected after peripheral nerve injury, indicating that spinal circuitry may physically change after nerve injury (Tan et al., 2011). In addition, it appears that some individuals have a higher susceptibility, due to genotypic differences, in producing central sensitization, and therefore have a higher risk of neuropathic pain development or persistence (Campbell et al., 2009; Tegeder et al., 2006, 2008). While synaptic plasticity contributing to central sensitization has been most extensively studied in the spinal cord, it is also found in other CNS regions, for example the anterior cingulate gyrus, prefrontal cortex, amygdala, and periaqueductal gray (Li et al., 2010; Ren et al., 2011).

Although central sensitization was originally considered to represent an increase in excitatory synaptic strength and neuronal excitability, it has become clear, particularly for neuropathic pain, that a loss of inhibition in the dorsal horn also plays an important role (Figure 5). Inhibiting GABA and glycine in the spinal cord increases A-fiber-mediated excitatory transmission in the superficial dorsal horn (Baba et al., 2003) and produces tactile allodynia (Sivilotti and Woolf, 1994). Furthermore, partial peripheral nerve injury results in a reduction of GABA-induced IPSCs in the dorsal horn (Janssen et al., 2011; Moore et al., 2002), at least a component of which appears to be due to an excitotoxic loss of GABAergic interneurons (Scholz et al., 2005). In addition, TNF-α reduces GABAergic interneuron activity via p38 (Zhang et al., 2010), and increased calcium levels in mitochondria drive reactive oxygen species production in dorsal horn neurons leading to reduced GABA release (Kim et al., 2011; Yowtak et al., 2011). The inhibitory effect of GABA is further reduced as BDNF released from microglia after nerve injury alters the anion reversal potential in some dorsal horn neurons decreasing or even phase shifting GABA's actions on these neurons (Coull et al., 2005; Prescott et al., 2006). Moreover, production of other inhibitory substances, such as adenosine, may be reduced after nerve damage (Sowa et al., 2010). Loss of local segmental inhibition in the dorsal horn will be exacerbated by loss of descending inhibitory controls from the rostroventral medulla (De Felice et al., 2011). A loss of neurons in this brainstem region after nerve injury indicates that injury-induced apoptosis occurs at multiple neuraxial levels (Leong et al., 2011).

Central sensitization provides, then, a mechanism whereby normally subthreshold synaptic input is recruited into driving a novel output from nociceptive neurons, reducing their threshold, increasing receptive field size, and altering firing temporal dynamics. All these changes contribute to the generation of dynamic mechanical allodynia in response to low threshold mechanoreceptor activation, pin prick or mechanical hyperalgesia and temporal summation. There is substantial opportunity for therapeutic intervention in patients with manifestations of the presence of central sensitization: a major driver of central sensitization is ectopic activity originating from a damaged nerve. Injection of a regional anesthetic to the injured nerve can lead to a temporary reduction in allodynia and secondary hyperalgesia (Gracely et al., 1992). Similarly, a reduction in transmitter release by blocking N-type calcium channels (Brittain et al., 2011) or by interfering with calcium channel trafficking (Bauer et al., 2009; Tran-Van-Minh and Dolphin, 2010), both reduce central sensitization and are effective in the treatment of neuropathic pain. Another widely used approach for treating neuropathic pain are dual amine uptake inhibitors, such as duloxetine and nortriptyline, which likely affect the noradrenergic descending inhibitory pathway (De Felice et al., 2011). Targeting specific $GABA_A$ α-subunits to directly increase inhibitory input in the spinal cord may also provide a novel treatment avenue (Knabl et al., 2008). The NMDA receptor is also an attractive target for reducing central sensitization (Woolf and Thompson, 1991),

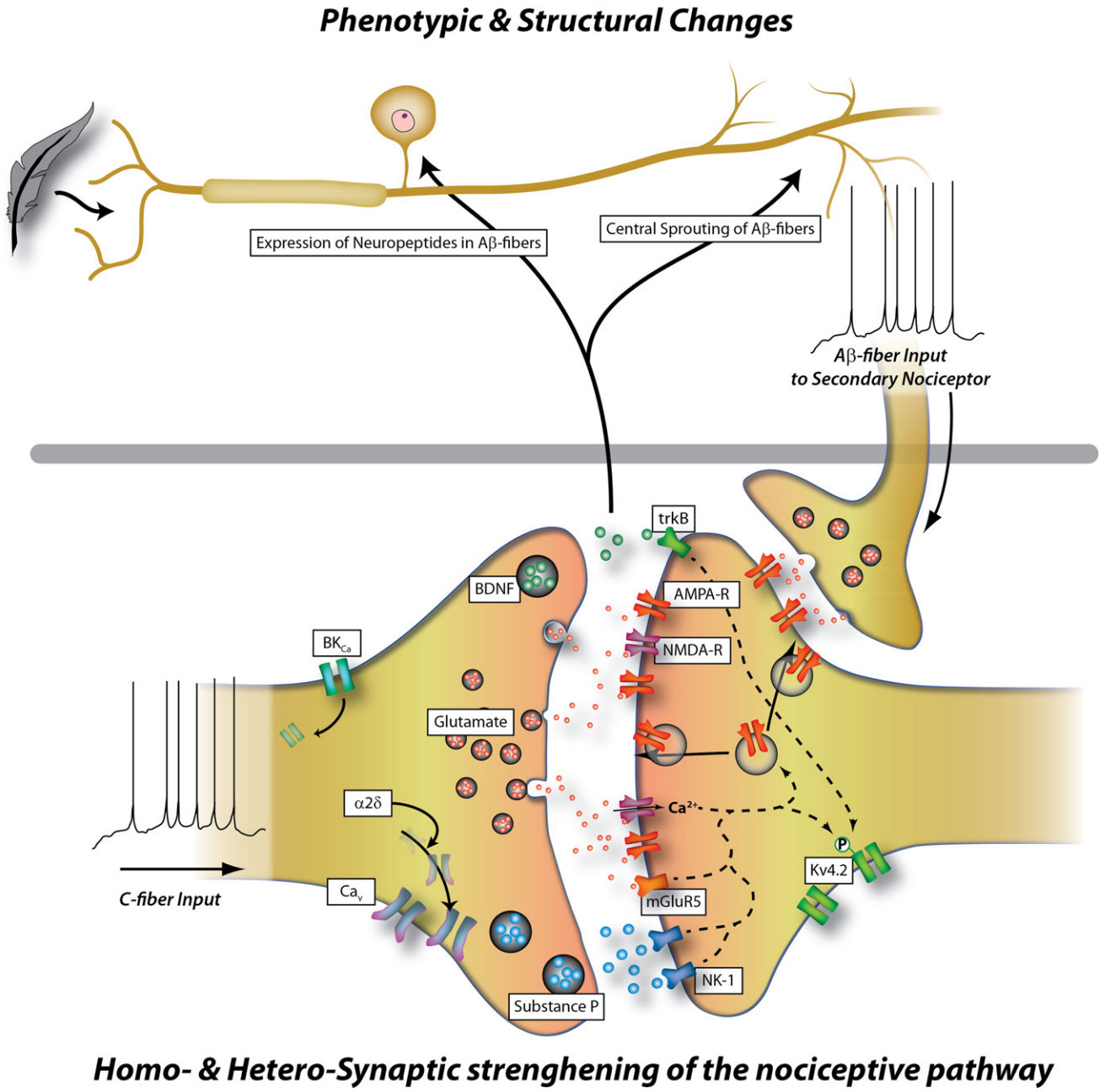

Figure 4. Central Sensitization

Changes in the spinal cord that lead to the strengthening of synaptic input from both nociceptor and low-threshold mechanoreceptors onto nociceptive neurons contribute to an amplification of pain, with a reduction in its threshold, an expansion in its spatial extent, and a change in its temporal characteristics. The recruitment of normally innocuous afferent inputs to the nociceptive pathway is an important aspect of central sensitization.

however psychotomimetic effects limit the clinical utility of NMDA receptor antagonists.

Activation of Immune Cells during Neuropathic Pain

Peripheral axonal injury results in a massive macrophage infiltration at the site of and distal to injury, as well as into the neuroma and dorsal root ganglion, where they provide a rich source of immune mediators that can act on sensory neurons (Figure 6). In addition, substantial microglial activation is generated in the dorsal horn of the spinal cord in close vicinity of the central terminals of injured primary sensory neurons (Beggs and Salter, 2010; Tsuda et al., 2003). The development of spinal microgliosis requires both axonal injury and nociceptive afferent input (Hathway et al., 2009; Suter et al., 2009). Following nerve injury, signaling molecules released from primary afferents drive microglial chemotaxis, proliferation and activation (Calvo et al., 2011; Calvo et al., 2010;

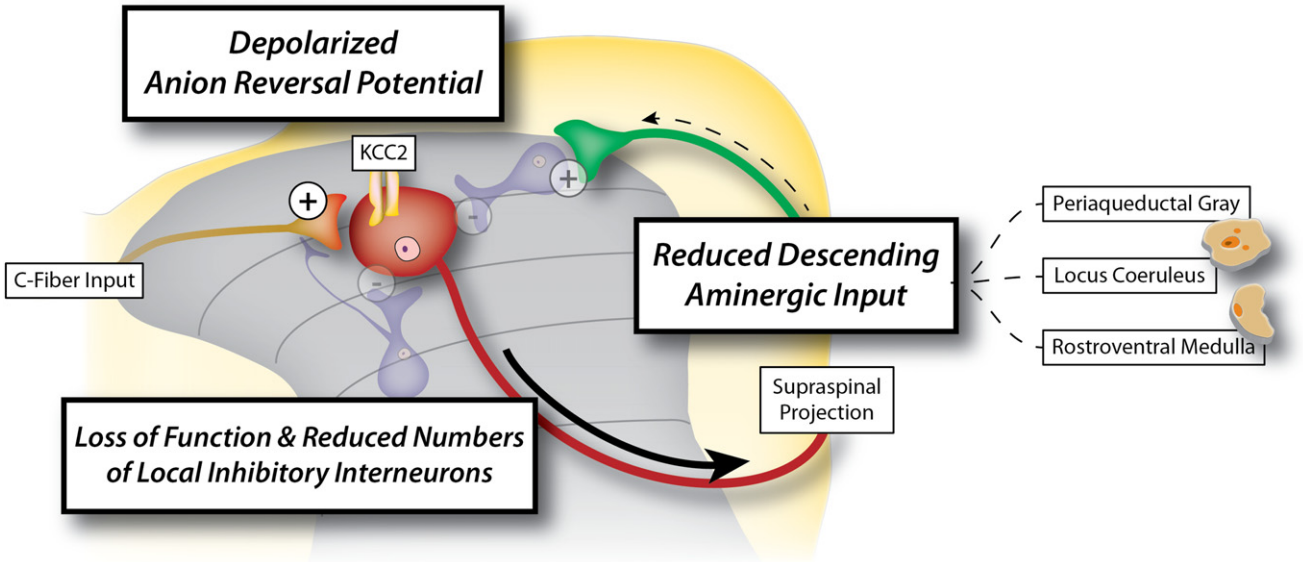

Figure 5. Spinal Disinhibition
Excitatory nociceptive signals are enhanced after nerve injury by a reduction in normal inhibitory regulation through a loss of local inhibitory interneurons, a depolarized anion reversal potential and reduced descending inhibition.

Kawasaki et al., 2008). Inhibiting microglial activation after injury reduces allodynia and hyperalgesia after nerve injury (Beggs and Salter, 2010; Calvo and Bennett, 2011) but it is not clear how these microglial changes alter nociceptive transmission.

Adaptive immune cells are also found in the spinal cord after peripheral nerve injury. After recruitment into the dorsal horn from the circulating system, $CD4^+$ T cells release cytokines, such as interferon γ, to activate microglia. Both, T cell-deficient mice and interferon γ knockout mice, show diminished mechanical allodynia following acute nerve injury (Costigan et al., 2009; Tsuda et al., 2009). It remains to be established what effect preventing T cell recruitment into the CNS may have on neuropathic pain. Nevertheless, the contribution of peripheral immune cells and microglia to the development of neuropathic pain offers a novel potential treatment strategy, as immunosuppressive drugs show some efficacy in animal models of nerve injury even though they have no intrinsic analgesic activity (Orhan et al., 2010; Scholz et al., 2008). However, it remains uncertain if similar immune activation occurs in humans, and if so in what conditions and to what extent. Certainly the effects of most treatments targeted at microglia in preclinical studies appear to work best soon after nerve injury, implying that microglia are somehow involved in establishing neuropathic pain, but perhaps not in its maintenance.

CNS Plasticity after Nerve Injury

Neuronal plasticity during neuropathic pain is not limited to the spinal cord and multiple changes are observed in response to acute and chronic pain stimuli (Apkarian et al., 2011; Tracey, 2011). Functional neuroimaging has identified a network of brain regions activated by experimental noxious stimuli (the so-called "pain matrix") that includes medial prefrontal cortex, nucleus accumbens, anterior cingulate cortex, insula, amygdala, periaqueductal gray, locus coerulus, and rostrovental medulla. More recent work is revealing changes in the resting state of the brain in patients with spontaneous pain (Apkarian et al., 2011; Tracey, 2011). In addition to "traditional" CNS areas involved in pain processing, the cerebellum may also be part of pain and general aversive processing (Moulton et al., 2011). Brain regions activated during acute nociceptive pain differ from those activated during chronic pain (Schweinhardt et al., 2006), and the same pain areas are activated differently by an identical noxious stimulus administered to healthy subjects compared to subjects with chronic pain (Baliki et al., 2011). There are also documented differences in the processing of spontaneous and evoked pain (Friebel et al., 2011; Parks et al., 2011). The finding that functional connectivity patterns during painful experiences are flexible and context dependent (Ploner et al., 2011), underscores the dynamic nature of the pain network.

Regional decreases in gray matter volume as detected by magnetic resonance imaging-based volumetry have been reported in several chronic pain cohorts (Apkarian et al., 2011). However, these volume changes do not indicate neuronal degeneration since they are reversible after successful pain treatment (Gwilym et al., 2010), and their nature and significance remain uncertain, although they may be a useful biomarker. Interestingly, no significant regional gray matter volume change was detected, in chronic non neuropathic facial pain, whereas in patients with trigeminal neuralgia, the gray matter was reduced in the primary somatosensory cortex, anterior insula, putamen, nucleus accumbens, and the thalamus and increased in the posterior insula (Gustin et al., 2011). This suggests that the pathogenesis of neuropathic and nonneuropathic pain conditions maybe fundamentally different. Furthermore, when comparing different neuropathic disorders, different gray matter density changes were observed (Baliki et al., 2011), which may indicate

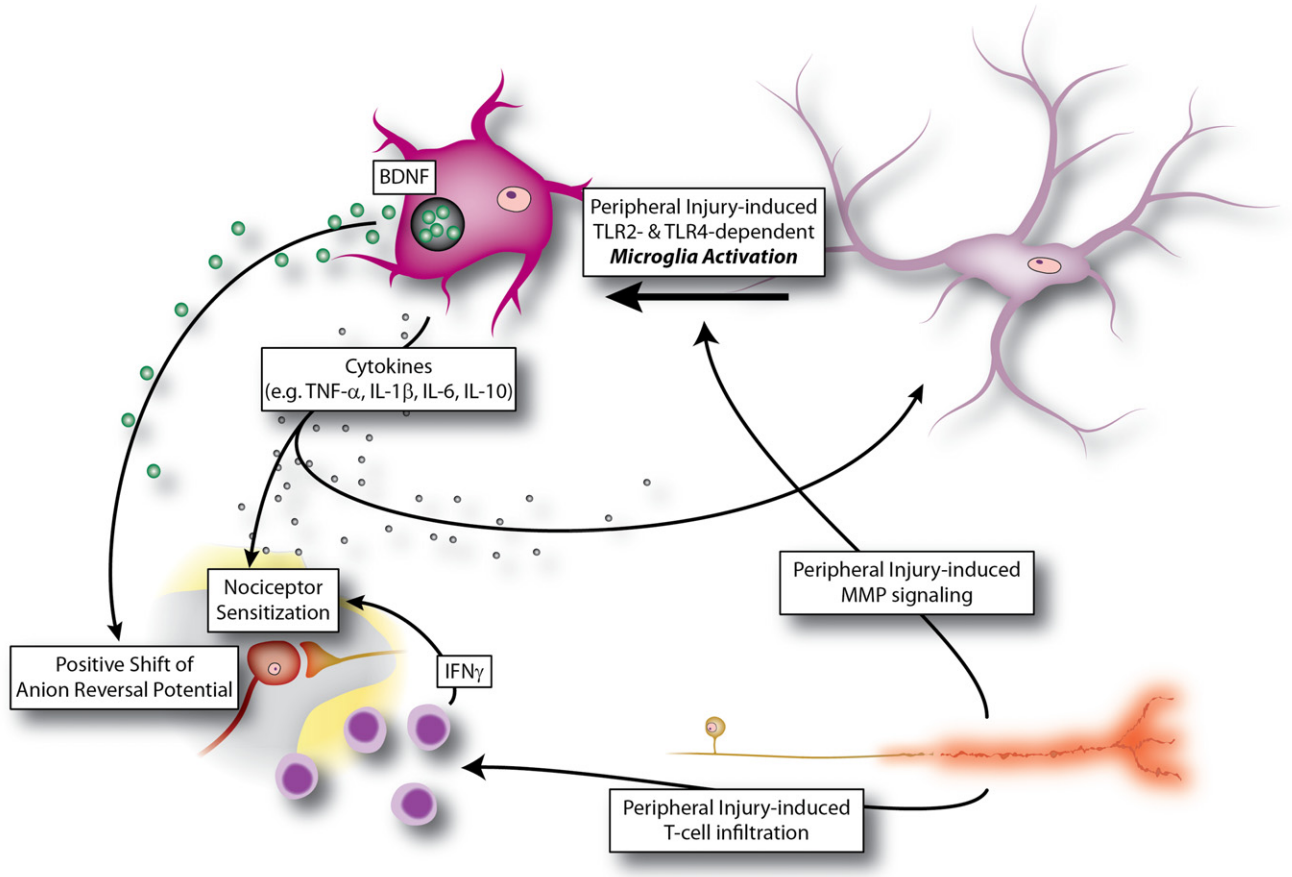

Figure 6. Immune Contribution to Neuropathic Pain
Innate and adaptive immune cells in the periphery and spinal cord can sensitize primary nociceptors and secondary nociceptive neurons respectively to produce pain hypersensitivity.

that CNS changes detected by imaging reflect the individual pain phenotype. Certainly relating individual pain response to individual imaging signals may help link pain phenotype to pain genotype (Tracey, 2011). In a clinical research setting at least, brain imaging should become a very useful component of phenotyping pain patients, thereby helping assess the mechanisms present in individual patients and how they manifest.

From Pain Phenotype to Individualized Analgesic Treatment

Clinicians encounter neuropathic pain patients with diverse genetic and environmental backgrounds and various degrees of nerve damage, all of which contribute to a complex combination of neural pathophysiological mechanisms, which in turn manifest as the individual pain phenotype. As typically only 30% of patients respond to even the gold standard FDA approved treatments (Finnerup et al., 2010), identification of the pattern of mechanisms present in an individual should be a useful approach for identifying patients more likely to respond to a particular treatment and establishing individualized pain treatment. The pattern of expression of pain-related sensory abnormalities, the individual sensory phenotype, should reveal clues of the underlying pathophysiological dysfunction.

Since one specific symptom (e.g., burning pain) may be generated by several different underlying pathophysiological mechanisms (e.g., peripheral sensitization, gain of function mutations in Nav1.7, or ectopic activity due to alteration in HCN2), it is more likely that a specific constellation of many sensory symptoms and signs might better predict underlying mechanisms. Patient reported outcomes, as well as quantitative sensory testing, or a combination of both, are beginning to be used to analyze sensory profiles in neuropathic pain patients and distinct subgroups of patients can be detected who are characterized by different specific sensory profiles (Baron et al., 2009; Bouhassira et al., 2005; Scholz et al., 2009).

In a large group of patients with diabetic peripheral neuropathy and postherpetic neuralgia, a sensory profiling approach revealed five subgroups of patients with distinct pain-related sensory phenotypes (Baron et al., 2009). For example, patients who suffer from considerable burning pain and paresthesias but minimal mechanical allodynia and thermal hyperalgesia and who additionally show numbness as a prominent finding probably have sensory terminal deafferentation in the skin with

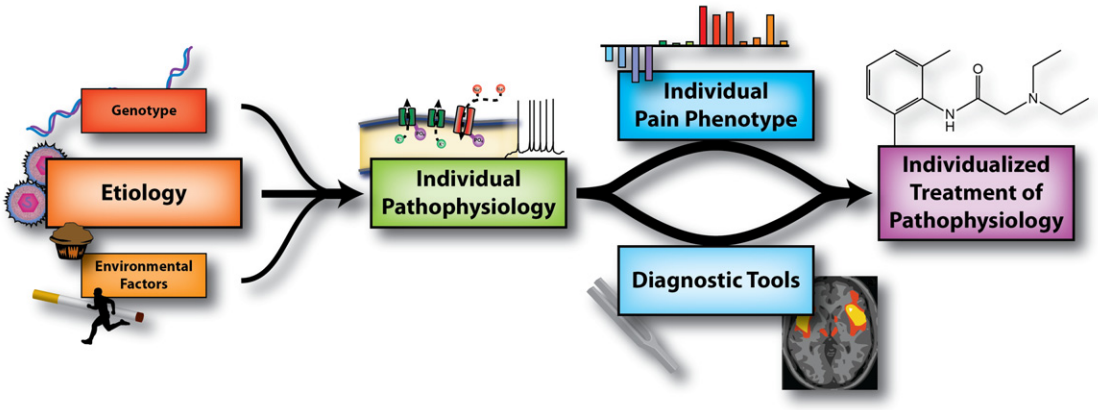

Figure 7. Individual Pathophysiology Requires Personalized Treatment
Etiology, genotype, and environmental factors lead to individual pathophysiological changes and individual neuropathic pain profiles. Precise clinical examination and diagnostic tools are a prerequisite to define the pain phenotype and then to use this to identify personalized treatment options.

little or no central sensitization. A length-dependent dying-back or atrophy of sensory terminals innervating the extremities together with ectopic activity in heat nociceptors, best explains these findings. Patients with spontaneous burning pain in combination with dynamic mechanical allodynia and minimal negative symptoms (no reduced thermal threshold), reflects the presence of relatively preserved and sensitized nociceptors in the skin together with central sensitization (Baron et al., 2009). A major goal is to identify the most relevant and discriminatory aspects of the pain phenotype that most robustly reflect different mechanisms or combinations of mechanisms.

Given that it is possible then to identify subgroups of neuropathic pain patients with distinct sensory phenotypes, does a particular treatment perform better in one sensory profile subgroup of patients than another, and is this because of the different neural mechanisms engaged in the subgroup? Several encouraging trials indicate that this is likely. Following intracutaneous botulinum toxin, for example, better pain reduction correlates with the relative preservation of cutaneous innervation, as documented by normal thermal thresholds (Ranoux et al., 2008). On the contrary, the response to systemic opioids correlates with a loss of peripheral terminals and a higher heat pain threshold (Edwards et al., 2006). Furthermore, lidocaine produces better results in patients with mechanical allodynia at baseline, than in those who did not have this symptom (Attal et al., 2004; Finnerup et al., 2002). An exploratory post-hoc analysis within a negative pregabalin trial for painful HIV-neuropathy has revealed that only a subgroup of patients with pinprick hyperalgesia, presumably indicative of central sensitization, showed a significant response to pregabalin (Simpson et al., 2010). If pregabalin works by reducing transmitter release and thereby central sensitization, identifying patients in whom central sensitization plays a role in pain generation can identify patients who respond better to the drug.

Personalized pain treatment is in its infancy, but the advances both in the understanding of pathophysiological mechanisms in the somatosensory system that can occur after neural damage, and in defining the individual pain phenotype, promise to transform diagnosis, from disease to mechanism, and treatment, from empirical to evidence-based (Figure 7). Whether an etiological factor, such as nerve injury, or a disease like diabetes, results in pain will depend on its interaction with genotypic polymorphisms and environmental factors. These interactions will produce particular maladaptive changes in the nervous system that manifest as spontaneous pain or pain hypersensitivity. The ability to infer presence of specific pathophysiological mechanisms from the pain phenotype will vastly improve treatment choice.

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