

NEUROLOGICAL REVIEW

Neuropathic Central Pain

Epidemiology, Etiology, and Treatment Options

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Background: Nociceptive pain is a major problem in clinical neurology. Peripheral nerve injury may change the physiology of the dorsal horn so that pain becomes progressively centralized.

Objective: To review mechanisms underlying the plasticity of dorsal root ganglia and dorsal horn neurons that lead to central pain from a peripheral nerve injury.

Results: Evidence is reviewed that points to molecular changes in nociceptive terminals, ectopic firing of afferent pain fibers at the level of the dorsal root ganglia, and physiologic changes of the N-methyl-D-aspartate receptor that cause chronic nociceptive pain.

Conclusions: Central sensitization is the physiologic manifestation of many severe peripherally induced pain states. It is maintained by nociceptive input and a physiologic change in the N-methyl-D-aspartate receptor. It consists of: (1) hypersensitivity at the site of injury; (2) mechanoallodynia; (3) thermal hyperalgesia; (4) hyperpathia; (5) extraterritoriality in the case of complex regional pain syndrome/reflex sympathetic dystrophy; and (6) associated neurogenic inflammation, autonomic dysregulation, and motor phenomena.

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NOCICEPTIVE central pain is an emerging concept.¹ It is well established that direct injury to the brain or spinal cord may be followed by pain but it is not generally realized that damage to peripheral nociceptive nerve endings in soft tissue, plexuses, or the nerves themselves also causes nociceptive central pain.² Inflammatory conditions such as arthritis, infection, and chemical irritation of peripheral tissues share many of the features noted following peripheral nerve damage.³ A fundamental difference between inflammatory pain with tissue hypersensitivity and neuropathic pain is that in the former the pain is relieved when inflammation has resolved and in the latter it may persist after healing of the primary event.

The epidemiology of central pain following stroke, spinal cord injury, or during the course of multiple sclerosis, brain injury, or trauma to the central nervous system, is much better understood than that following peripheral nociceptive injury.⁴ Approximately 1% to 8% of patients with stroke have central pain, whereas 10% to 30% of patients with spinal cord injury are affected during the course of their illness.⁵ There are no data

on the number of patients who have nociceptive peripheral pain from small fiber neuropathies, radiculopathy, brachial, or lumbosacral plexopathies, complex regional pain syndrome, or inflammatory peripheral conditions. However, because of the common nature of the underlying causes, there may be many patients who have this problem.

The major clinical features of nociceptive central pain are (1) hypersensitivity at the site of injury; (2) mechanoallodynia; (3) thermal hyperalgesia⁶; (4) hyperpathia⁷; (5) extraterritoriality (regional distribution of pain) in the case of complex regional pain syndrome/reflex sympathetic dystrophy⁸; and (6) associated neurogenic inflammation, autonomic dysregulation, and motor phenomena that are especially found in complex regional pain syndrome/reflex sympathetic dystrophy.⁹

Central sensitization is the pivotal physiologic phenomenon underlying the clinical symptoms of neuropathic central pain following peripheral nerve injury.¹⁰ Central sensitization is primarily induced by the firing of unmyelinated nociceptive C-fibers that project to the superficial layers of the dorsal horn (DH).¹¹ These fibers produce slow excitatory postsynaptic potentials that may last for up to

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20 seconds. Brief repetitive afferent nociceptive fiber input causes temporal summation of these slow potentials, which induces the "wind-up" phenomenon in central pain-projecting neurons (CPPNs). In this state, subsequent C-fiber input produces a progressive increase in action potential output of CPPNs. The gain of this neuronal response is controlled by an activity-dependent N-methyl-D-aspartate (NMDA) receptor.¹²

The major mechanisms that underlie nociceptive central pain are (1) autosenitization of nociceptive receptors; (2) ectopic firing of dorsal root ganglia (DRG) cells; (3) calcium-induced molecular cascades from excess nociceptor glutamate; (4) phenotypic change of afferent A β -fibers and DRG cells to the characteristics of those associated with pain; (5) changes in gene expression of sodium channels and neuropeptides both at nociceptive terminals and at the DRG; and (6) anatomic changes of the superficial layers of the DH. This is a progressive but plastic process that is clearly reversible in its early stages and requires nociceptive input for its maintenance.

A sharp distinction between an inflammatory and a primarily neuropathic process at the site of injury cannot be made. Specifically, inflammatory lesions may injure polymodal C-fiber nociceptors, while soft tissue injuries release algescic molecules and induce cytokines that may damage these same nociceptors. Either form of tissue injury increases the local production and retrograde transport of nerve growth factors and other small molecules that may affect the DRG and the DH.¹³ Transducer proteins and the ion channels of nociceptor receptors generate depolarizing currents to specific external stimuli at the site of injury. Irritant chemicals and a low pH stimulate vanilloid, acid-sensing ionic channels, and purine transducer proteins. Noxious heat stimulates vanilloid and vanilloid-like 1 receptors.¹⁴

Sensitization of nociceptive terminals occurs from repeated stimulation, which causes a decreased threshold of activation, an increased response to a given stimulus, and spontaneous depolarization. These changes are rapid following injury and are secondary to conformational changes of the transducer proteins or increased influx of calcium into the nociceptive terminals that activate secondary messenger systems. This sensitization is induced by neurotrophic factors, algescic molecules, leukotrienes, and cytokines released at the site of injury.¹⁵ Sensitization of nociceptive terminals is responsible for a component of primary hyperalgesia of injured tissue, while the remainder is due to the hyperexcitability of CCPNs of the DH.¹⁶

The molecular mechanisms that underlie this sensitization of terminal nociceptors are activation of intracellular kinase membrane-bound receptors¹⁷ and phosphorylation of tetrodotoxin-resistant sensory neuron-specific sodium ion channels.¹⁸ Functional changes also occur in the peptide profile of primary afferent nociceptive fibers following injury, which are important in this process.¹⁹

Present evidence supports the central importance of the NMDA receptor of the DH in the induction and maintenance of central sensitization observed in many chronic pain states.²⁰ In the setting of a maintained C-fiber nociceptive input, the magnesium blockade of the

NMDA receptor on CPPNs is lifted because of cumulative depolarization by summated nociceptor-evoked slow synaptic potentials. Increased intracellular calcium influx by enhanced NMDA gating is effected by several signaling cascades that include (1) G protein-coupled neurokinin receptors and receptor tyrosine kinases; (2) phosphokinases²¹; and (3) presynaptic NMDA receptors.²² Important calcium-dependent second messenger cascades initiated from persistent injury generate nociceptive input that sustains CPPN plasticity. The maintenance of this plasticity is further enhanced by activation of A δ primary afferent fibers that synapse on inhibitory γ -aminobutyric acid (GABA)/glycinergic interneurons of DH lamina II and initiate long-term depression of inhibitory DH circuitry.²³

Structural changes in pain systems occur after nociceptive terminal tissue injury. These are effected by local increased production of growth factors from fibroblasts, macrophages, and lymphocytes, which are retrogradely transported back to the DRG and substantia gelatinosa. Their effects are reflected by alterations of growth associated with structural proteins, G protein-coupled receptors, transmitters, and synaptic modulators.¹ It has also recently been demonstrated that electrical potentials alone of a damaged nerve after a prolonged injury can alter transcription in sensory neurons that changes their neurophysiologic characteristics.²⁴

Injury to peripheral nerves or their terminal twigs in soft tissue is frequently associated with sympathetically maintained pain.²⁵ Following experimental peripheral nerve injury, there is a proliferation of DRG satellite cells and a change in their gene expression that is manifested by upregulation of the p75 receptor and neurotrophins. The neuroactive cytokine, leukemia inhibitory factor, which is induced at the site of injury and retrogradely transported to the DRG, may initiate sympathetic nerve sprouting.²⁶ This sprouting occurs around large-diameter touch neurons and may be associated with mechanoallodynia.²⁷ Nerve injury and inflammatory conditions also upregulate constitutively expressed genes and induce novel genes.²⁸ Sustained nociceptive input induces transcriptional changes in CPPNs that are partly mediated by induction of the mitogen-associated protein kinase/cyclic adenosine monophosphate-dependent protein binding cascade. This cascade causes changes in DH receptors, neuropeptides, and transmitters, further altering the neurophysiology of the DH.²⁹

Ectopic firing of DRG nociceptive neurons induced by experimental nerve injury is an important mechanism behind the constant nociceptive afferent barrage critical to maintaining central sensitization. Induction and coexpression of abnormal combinations of several types of sodium channels in DRG nociceptive cell membranes following nerve injury may allow subthreshold membrane potential oscillations to initiate ectopic firing.³⁰ Nerve blocks may fail in chronic pain states since the nociceptive barrage is generated far from the affected site. Pain is primarily limited in extent and severity by segmental and descending activation of GABA and glycinergic inhibitory interneurons.³¹ A major pathway of central pain modulation originates in the periaqueductal gray (PAG) of the midbrain, which contains a high

concentration of opioid receptors and peptides. Animal studies have shown that electrical stimulation or local application of neuroactive substances into the PAG produces analgesia.³² Much of the output from the PAG projects to the rostral ventromedial medulla, which in turn projects largely to the DH of the spinal cord. Activation of the rostral ventromedial medulla electrically or chemically produces effects similar to PAG activation. The resulting inhibition of nociceptive afferent spinothalamic tract neurons is believed to involve descending cholinergic and monoaminergic systems as well as activation of intrinsic glycinergic and GABAergic DH inhibitory circuitry.³³

The PAG is a major nociception integration site that receives afferent fibers from the prefrontal and insular cortex, hypothalamus, amygdala, nucleus cuneiformis, reticular formation, and the locus ceruleus. The rostral ventromedial medulla is a major relay between the PAG and the spinal cord and has 2 types of neurons: on-cells and off-cells, which modulate nociceptive input from the spinal cord. Both types project to lamina I, II, and V of the DH and are activated by stimulation of the PAG. Off-cells are activated and on-cells are inhibited by morphine.³³ Off-cells are part of the descending inhibitory system mediated from the rostral ventromedial medulla through the dorsolateral funiculi, while on-cells constitute a descending nociceptive facilitation pathway traveling through the ventrolateral funiculi to the DH. Descending facilitation may function to counterbalance descending inhibition to maintain some degree of pain responsiveness.

Anatomic changes occur in the periphery, dorsal root ganglia, and DH of the spinal cord during prolonged pain states.¹ Peripheral nerve injury seems to preferentially affect C-fiber nociceptive neurons to a greater degree than A-fiber neurons. In experimental pain models, C-fiber-denervated territory in lamina II of the DH was shown to be invaded by touch afferent fibers from lamina III and IV.³⁴ As noted earlier, products of Wallerian degeneration—cytokines and neurotrophic factors—were found to induce sympathetic nerve sprouting in the DRG with consequent basket formation around large-diameter touch neurons. These touch neurons may have undergone a phenotypic switch to pain neurons so that a sympathetic discharge evoked pain. Most importantly, severe chronic pain in the experimental pain model leads to the death of inhibitory interneurons (small dark neurons) in lamina II of the DH, which may further facilitate pain projections.³⁵

Treatment of nociceptive central pain is difficult and frequently unrewarding. The basic principles are (1) the identification and elimination of the underlying pathologic mechanism that maintains central sensitization. These mechanisms vary widely and include poorly healed fractures, neuromas, brachial plexus traction injuries, unsuspected neuropathies, and radiculopathies; (2) the use of nonsteroidal antiinflammatory drugs to reduce peripheral sensitization and modulate the activity of nociceptors; (3) the use of tricyclic antidepressants to induce sleep and decrease lancinating and burning neuropathic pain; (4) a trial of Gabapentin, lamotrigine, and topamax; (5) intravenous lidocaine for treatment of

widespread hyperalgesia, allodynia, and hyperpathia; (6) sympathetic blockade for complex regional pain syndrome/reflex sympathetic dystrophy while patients are still sympathetically maintained; (7) dorsal column stimulation for areas that can be completely covered by induced paraesthesia; and (8) intrathecal therapies including morphine, clonidine, and GABA(b) agonists when other less invasive therapies have failed.³⁶

A recent report demonstrates that glial cell line-derived neurotrophic factor prevented and reversed sensory abnormalities in the rat partial sciatic nerve ligation pain model without affecting pain-related behavior in normal animals. It is postulated that glial cell line-derived neurotrophic factor reverses injury-induced plasticity of several sodium channel subunits. The most exciting aspect of this report is the demonstration that glial cell line-derived neurotrophic factor may reverse some aspects of central sensitization.³⁷ Another drug under clinical investigation is ziconotide, a selective neuronal N-type calcium channel blocker. Intrathecal ziconotide has been shown to be more potent, longer lasting, and more antinociceptive than morphine. It may also block aspects of central sensitization.³⁸ These new developments offer hope to a large number of patients.

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