Mechanisms of pain modulation in chronic syndromes
Hayrunnisa Bolay, MD, PhD, and Michael A. Moskowitz, MD

Article abstract—Transmission of pain from the periphery to the cortex depends on integration and signal processing within the spinal cord, brainstem, and forebrain. Sensitization, a component of persistent or chronic pain, may develop either through peripheral mechanisms or as a consequence of altered physiology in the spinal cord or forebrain. Several molecular and biophysical mechanisms contribute to the phenomenon of sensitization and persistent pain, including upregulation of sensory neuron-specific sodium channels and vanilloid receptors, phenotypic switching of large myelinated axons, sprouting within the dorsal horn, and loss of inhibitory neurons due to apoptotic cell death. Recently, forebrain structures have been implicated in the pathophysiology of persistent pain. Although a number of treatment options are used, unfortunately pharmacotherapy for neuropathic pain is often ineffective. Unraveling the mysteries of chronic pain may lead to better treatment options, such as drugs that act specifically on sensory neuron-specific sodium channels or as NR2B-subunit-selective \( N \)-methyl-\( D \)-aspartate receptor antagonists.

Pain pathways. At the simplest level, the transmission of information relating to pain from the periphery to the cortex is critically dependent upon integration at three levels within the CNS: the spinal cord, brainstem, and forebrain. First-order or pseudounipolar neurons reside within the dorsal root ganglia (DRG) or trigeminal ganglia. In the dorsal horn, second-order neurons project (after crossing via the anterior commissure) and ascend in the spinothalamic tract. Third-order neurons located in the thalamus project to the primary somatosensory and cingulate cortices. The affective and motivational pathways, which are, in part, distinct from the above, involve structures such as the parabrachial nucleus, amygdala, and intralaminar nucleus of the thalamus to account for dysphoric elements of a noxious experience (figure 1).

Small myelinated \( A_\delta \)-fibers and small unmyelinated \( C \)-fibers transmit noxious stimuli from the periphery to the spinal cord and brainstem. After stimulation, high-threshold mechanoreceptors and \( A_\delta \)-fibers are recruited initially and transmit “first pain,” perceived as a well-localized, discriminative (e.g., sharp or pricking) sensation that lasts as long as the acutely painful stimulus. More intense stimuli activate polymodal nociceptors and promote a diffuse, unpleasant, and persistent burning sensation that lasts beyond the acutely painful stimulus and is slightly delayed in onset. Second pain is associated with affective–motivational aspects and may predominate during chronic pain and when pain originates from the viscera. Mechanoreceptors and polymodal nociceptors contain the neurotransmitter \( \gamma \)-glutamate, and polymodal nociceptors also contain the neuropeptides substance \( P \), calcitonin gene-related peptide (CGRP), and neurokinin \( A \). Unlike mechanoreceptors, ions, such as potassium and hydrogen, and molecules, such as prostaglandin \( E_2 \) (PGE\(_2\)), bradykinin, serotonin, and adenosine triphosphate (ATP), activate or sensitize nociceptors. Purinergic receptors (P2X3) are expressed mainly in DRG; the purinergic agonist ATP causes transient pain and activation by increasing sodium ion permeability (figure 2).

In the dorsal horn, nociception-specific neurons located in laminae I and II respond only to noxious inputs and can be sensitized by repetitive stimulation. Somatic and visceral afferents converge on these neurons, suggesting a role in pain referral. Nociception-specific neurons may be involved in the sensory–discriminative aspects of pain, whereas wide dynamic range neurons (second-order nociceptive neurons responding to both somatic and visceral stimuli) participate in the affective–motivational components of pain. Noxious stimulation can induce c-fos expression in dorsal horn neurons (chiefly in laminae I and II), which may relate to prolonged functional and adaptive responses in the spinal cord.1

Unmyelinated \( C \)-fibers (containing glutamate, substance \( P \), and CGRP) in the dorsal horn express...
receptors for cholecystokinin (CCK), opioids, and also \( \gamma \)-aminobutyric acid subtype B (GABA\(_B\)) (figure 2), which modulate transmitter release. Except for CCK, these receptors inhibit the release of transmitter from primary sensory afferent fibers. Postsynaptic neurons express \( N \)-methyl-D-aspartate (NMDA), \( \alpha \)-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and metabotropic receptors that bind glutamate, as well as a neurokinin receptor, GABA\(_A\) receptors, and voltage-gated calcium channels. GABA\(_A\) receptors are ligand-gated chloride channels that hyperpolarize dorsal horn neurons and reduce neuronal responses to peripheral activation. Glycine-binding sites reside on postsynaptic neurons in the dorsal horn to provide an inhibitory function. Modulation of nociceptive inputs in the dorsal horn contributes to the maintenance of pain, as described in more detail below.

**Pathologic pain.** Pathologic pain may be the clinical manifestation of diverse disorders, such as infectious, toxic, metabolic, and hereditary diseases or trauma, but may operate through common mechanisms. Primary pain as an expression solely of pathology within the spinal cord, brainstem, thalamus, or cortex is much less common. Pathologic pain may develop in response to damage or alterations in primary afferent neurons (stimulus-dependent) or may arise spontaneously without any apparent stimulus (stimulus-independent). Hyperalgesia refers to heightened pain perception to a noxious stimulus resulting from abnormal processing of nociceptor inputs in the PNS or CNS.

Alloodynia is the sensation of pain evoked by a non-noxious stimulus. Hyperalgesia caused by inflammation usually resolves when the inflammatory process is controlled. On the other hand, chronic neuropathic pain persists long after the initiating event has healed and reflects a pathologic change within the nervous system.\(^1\)\(^2\) Both hyperalgesia and allodynia are expressions of sensitization and may reflect unusually low thresholds in primary afferents, including peripheral nociceptors, or plasticity-induced central mechanisms in the spinal cord or even the forebrain.

**Peripheral sensitization.** Sensitization can occur in nociceptor terminals via repeated stimulation, thereby reducing the amount of depolarization required to initiate a subsequent action potential (figure 3). Vanilloid receptors are important in this regard. For example, vanilloid receptors residing on small C-fibers can be sensitized on repeated heat, capsaicin, or proton exposure. Vanilloid receptors

---

**Figure 1.** Pain pathways. SS = somatosensory cortex; ACC = anterior cingulate cortex; DRG = dorsal root ganglia.

**Figure 2.** Nociceptive stimulation of the dorsal horn. CCK = cholecystokinin; SP = substance P; NMDA = \( N \)-methyl-D-aspartate; AMPA = \( \alpha \)-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; GABA = \( \gamma \)-aminobutyric acid; NE = norepinephrine; 5-HT = serotonin; EP = epinephrine; DRG = dorsal root ganglia; Glu = glutamate; Gly = glycine.
participate in the sensation of thermal and inflammatory pain and are nonselective cation channels.

Sensitization can also develop in response to molecules such as PGE$_2$, serotonin, bradykinin, epinephrine, adenosine, or nerve growth factor (NGF), acting on their respective axon receptors (figure 3). The onset is rapid, and the changes are substantial and readily reversible, representing conformational changes in receptor proteins. Sensitization is mediated through either increases in intracellular calcium levels or activation of intracellular kinases [e.g., protein kinase C (PKC) or tyrosine kinases], some of which phosphorylate sensory neuron-specific channels and VR1 receptors.\textsuperscript{2} Phosphorylation of sensory neuron-specific channels decreases the activation threshold and the rate of inactivation and increases the magnitude of the sodium current. The agonistic activity of ligands, such as the proinflammatory peptide bradykinin, is potentiated by PKC-dependent vanilloid receptor phosphorylation (figure 3). PKC activation links a range of stimuli to the activation of vanilloid receptors and sensory neuron-specific channels in the primary afferents. Its important role in pain modulation is also emphasized by PKC-knockout mice that display attenuated hyperalgesia. Finally, neurogenic inflammation (vasodilation and edema) mediated by vasoactive peptides (e.g., CGRP, substance P, neurokinin A) released from perivascular afferents may also promote sensitization and a decreased threshold for depolarization.

Recent clinical data indicate that CGRP release is increased in complex regional pain syndromes.\textsuperscript{3}

**Central sensitization.** Sensitization may also develop through central mechanisms. The phenomenon of wind-up is important and has been particularly well demonstrated in the spinal dorsal horn (figures 2 and 4). Wind-up develops when C-fibers are discharged by a sustained stimulus at a high frequency, such that the response rate of wide dynamic range neurons increases progressively after each stimulus. It is believed that wind-up can be prevented by controlling nociceptive inputs to the dorsal horn (e.g., by early and aggressive pain management).

Molecular mechanisms in the dorsal horn contribute to augmented pain transmission under pathologic conditions (figure 4). Low-frequency stimulation of nociceptors by mildly noxious stimuli releases glutamate from the central terminals of primary afferent neurons terminating in laminae I, II, and V. Glutamate, acting on postsynaptic AMPA receptors, causes fast excitatory postsynaptic potentials (EPSPs) and rapid depolarization in postsynaptic cells. At rest, the NMDA receptor channel is closed due to magnesium blockade. During intense or sustained noxious stimulation (high-frequency discharge), substance P (via the NK1 receptor) and glutamate are co-released, causing sustained slow EPSPs (lasting tens of seconds), temporal summation, and removal of the magnesium blockade of the NMDA calcium channel. As a result of NMDA recep-

---

**Figure 3.** Peripheral sensitization. AP = action potential; PKC = protein kinase C; SNS = sensory neuron-specific channel; EP = epinephrine; H$^+$ = proton; PGE$_2$ = prostaglandin E$_2$; BK = bradykinin; NGF = nerve growth factor; TyrK = tyrosine kinase; TyrK$_A$ = tyrosine kinase receptor A; VR1 = vanilloid receptor 1.

**Figure 4.** Central sensitization in the dorsal horn. SP = substance P; Glu = glutamate; NMDA = N-methyl-D-aspartate; AMPA = $\alpha$-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; GABA = $\gamma$-aminobutyric acid; Gly = glycine; NK1 = neurokinin 1; NOS = nitric oxide synthase; IP$_3$ = inositol triphosphate; mGlu = metabotropic glutamate receptor.
Cell death of interneurons in dorsal horn due to excitotoxicity

Altered synaptic connections in dorsal horn (sprouting)

Chronic pain and plasticity. Chronic pain perception is associated with genotypic and phenotypic changes that are expressed at all levels (primary afferents to cortex) and alter pain modulation in favor of hyperalgesia. Several molecular and biophysical mechanisms contribute to the phenomenon of sensitization in peripheral axons and the spinal cord and are shown in the table.

<table>
<thead>
<tr>
<th>Table</th>
<th>Neuronal plasticity in pathologic pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gene expression (upregulation of sensory neuron-specific sodium channel protein and VR1)</td>
<td></td>
</tr>
<tr>
<td>Phenotype switch (SP, CGRP, and brain-derived neurotrophic factor by large myelinated A-fibers, axonal α-adrenoreceptor expression)</td>
<td></td>
</tr>
<tr>
<td>Altered synaptic connections in dorsal horn (sprouting)</td>
<td></td>
</tr>
<tr>
<td>Cell death of interneurons in dorsal horn due to excitotoxicity</td>
<td></td>
</tr>
</tbody>
</table>

Blockade of VGSCs has been partially successful as a treatment for neuropathic pain. Clinically useful agents include local anesthetics, such as lidocaine and mexiletine, and anticonvulsants, such as carbamazepine and phenytoin. Unfortunately, these agents do not distinguish among subtypes of VGSCs and can produce significant CNS and cardiovascular effects. The finding that tetrodotoxin-resistant sensory neuron-specific channels are predominantly expressed on unmyelinated, small-diameter primary afferent neurons (nociceptors) suggests that targeting these peripheral channels could provide a novel opportunity for the production of an analgesic with minimal side effects.

A-fiber phenotype switching and sympathetically maintained pain. Substance P and CGRP are normally expressed by nociceptor primary afferent C- and Aδ-fibers and are implicated in sensory transmission and central sensitization. Expression of these peptides is usually downregulated after nerve injury. However, large myelinated Aβ-fibers, normally not associated with nociception, begin to express substance P and CGRP after peripheral nerve injury. Therefore, low-threshold stimuli activating Aδ-fibers may lead to substance P release in the dorsal horn and generate hyperexcitability that is normally driven by nociceptive inputs.

Stimulus-independent pain may be sympathetically maintained. After partial nerve injury, injured and uninjured axons begin to express α-adrenoreceptors. These axons discharge in response to circulating epinephrine and norepinephrine released from the
adrenal medulla and postganglionic sympathetic terminals. Moreover, sympathetic axons projecting to the DRG sprout after nerve injury. Hence, catecholamines released locally or into the circulation can potentially stimulate primary afferents to promote sympathetically maintained pain. Specific treatment, such as sympathetic blockades, guanethidine, or α2 antagonists, may be helpful for this condition.

A-fiber sprouting. A-fiber sprouting in the spinal cord is one of the central mechanisms that may also account for the development of allodynia. Peripheral nerve injury (more specifically, injury to peripheral axons of C-fibers) induces sprouting of Aβ-fiber (myelinated, low-threshold) terminals from deeper laminae (III and IV) to lamina II.9 This rewiring may lead to the misperception of non-noxious as noxious inputs. Hence, low-threshold stimuli activating Aβ-fibers may now cause central hyperexcitability. As a possible correlate, innocuous brushing of the skin (which does not activate C-fibers or induce early-immmediate response genes) causes c-fos expression within laminae I and II in the alldylic state.10 The latter findings indicate that neurons in laminae I and II (and possibly lamina V) may mediate the allodynia of chronic neuropathic pain. Plasticity within the spinal cord may also explain why tactile allodynia develops in patients with postherpetic neuralgia after loss of nociceptor cutaneous innervation.

Cortical NMDA receptors and persistent pain. In addition to peripheral and segmental changes, recent data implicate forebrain structures in the pathophysiologic responses to painful conditions. NMDA receptors in the anterior cingulate cortex (ACC) and insular cortex enhance persistent chronic behavioral responses to tissue injury and inflammation, apparently without affecting acute nociception in the spinal cord. Transgenic mice that overexpress NR2B (a protein subunit of the NMDA receptor) selectively in the forebrain (but not the spinal cord) showed delayed behavioral responses and greater mechanical allodynia after peripheral injection of formalin or CFA. Their responses to acute pain were indistinguishable from those of wild-type mice.11 In parallel with these behavioral studies, increased c-fos expression was detected in the ACC, insular cortex, and other brain areas, but not in the brainstem or spinal cord of transgenic mice. This study implicates forebrain NMDA receptors in the susceptibility to persistent pain and suggests that NR2B-selective NMDA receptor antagonists may be useful as therapeutic targets in the treatment of persistent pain.

Inflammatory molecules affect peripheral and central pain processing. Pain during inflammation is caused by both central sensitization and an increase in noxious inputs peripherally. In addition to triggering sensitization of primary afferents, inflammatory cells at the site of injury or infection may also produce a chemical signal that enters the blood and penetrates the CNS to generate interleukin-1β (IL-1β) and cyclo-oxygenase (COX) expression in the CNS.12 One candidate, PGE2, generated in part by COX activity, is released not only at the site of injury but also after induction, throughout the CNS. Furthermore, the synthesis of PGE2 by COX-2 may contribute to the development of inflammatory pain and to more generalized pain-associated symptoms, such as anorexia and depression.

The trigeminovascular system, migraine, and allodynia. In headache models, sensitization occurs in meningeal nociceptors and central trigeminal neurons.13,14 After chemical irritation or electrical stimulation of the dura mater, trigeminal neurons respond to “subthreshold” stimulation of either the dura or periorbital skin. A similar phenomenon (i.e., reduced threshold of skin and cutaneous allodynia) has also been described in patients during migraine headache and presumably reflects heightened responses of central trigeminal neurons to convergent inputs from cutaneous and meningeal afferents. During migraine attacks, 79% of patients exhibited cutaneous allodynia in the ipsilateral head or extending beyond the referred pain area.14 Allodynia may be limited to the pain area in the ipsilateral head, reflecting an increase in the sensitivity of central (second-order) trigeminal neurons that receive convergent inputs. More widespread allodynia could be explained by a temporary increase in the sensitivity of at least third-order neurons that receive convergent inputs from the skin at different body sites, as well as from the dura and periorbital skin.

Therapeutic targets. Carbamazepine, phenytoin, and lidocaine and its oral analogue (mexiletine) block sodium channels unspecifically and reduce neuronal excitability in sensitized C-nociceptors. Lamotrigine stabilizes a subtype of sodium channel, thereby suppressing neuronal release of glutamate. Development of drugs that act specifically on sensory neuron-specific sodium channels will provide more effective treatment for chronic pain. Desensitization of vanilloid receptors or NGF receptors may also be useful for pain management. Capsaicin acutely and chronically depletes the neurotransmitter substance P from sensory nerves and has achieved some success topically. Serotonin agonists, opioids, baclofen (a GABA receptors agonist), and clonidine inhibit antidromic release of substance P by acting presynaptically. Sympathetically maintained pain may benefit from use of specific α-adrenergic receptor antagonists, guanethidine, phentolamine, or from sympathetic blockade. NMDA receptors play a significant role in the wind-up phenomenon and central sensitization. Blocking NMDA receptors abolishes hypersensitivity in patients with neuropathic pain. Systemic ketamine reduces allodynia and hyperalgesia.

Opioid receptors are present on the terminals of primary afferent nociceptive fibers that enter the spinal cord. Opioids block the potassium-evoked release of substance P and also act postsynaptically in...
the dorsal horn. Excitatory inputs from primary af-
ferents in the dorsal horn are modulated by segment-
al and descending activation of inhibitory neurons
(co-release of glycine and GABA). Therefore, GABA-
mediated inhibition reduces the activity in dorsal
horn neurons, which is the basis of GABAergic drugs
and transcutaneous electrical nerve stimulation, ac-
tivating the segmental inhibitory pathways or brain
stimulators that activate the descending inhibitory
pathways.

Valproic acid increases the efficacy of GABA by
inhibiting its catabolism. Valproate is now being
used for migraine prophylaxis and neuropathic pain
in the United States. Butalbital (a barbiturate that
acts through the potentiation of $\mathrm{GABA}_A$ receptors) is
also used for migraine treatment in the United
States. The benzodiazepine midazolam has been
shown to be effective in experimental neuropathic
pain.\textsuperscript{15} Gabapentin is a structural analogue of GABA
but its receptor and biochemical function remain un-
known, although there is some suggestion that gaba-
pentin may affect GABA release or synthesis.
Gabapentin has been shown to be effective in post-
herptic neuralgia and has received increased atten-
tion as a useful treatment for other neuropathic pain
syndromes.\textsuperscript{16}

The use of norepinephrine and serotonin reuptake
inhibitors [e.g., tricyclic antidepressants or selective
serotonin reuptake inhibitors (SSRIs)] also aims to
increase inhibition in the dorsal horn. In addition,
selective COX-2 inhibitors with the ability to pene-
trate the brain also represent potential therapeutic
options.

Unfortunately, pharmacotherapy for neuropathic
pain is unsatisfactory. Resistance to opiates is com-
mon; nonsteroidal anti-inflammatory drugs (NSAIDs)
are disappointing; and tricyclic antidepressants, SSRIs,
and anticonvulsants (e.g., unspecific sodium channel
blockers) have significant side effects. The efficacy
of these agents is controversial (except that of carbam-
azepine for trigeminal neuralgia). Understanding
the mechanisms of chronic pain may lead to more
specific and effective treatment strategies for chronic
pain, such as sensory neuron-specific sodium chan-
nel blockers or NR2B NMDA receptor antagonists.

References

1615.
2. Woolf CJ, Salter MW. Neuronal plasticity: increasing the gain
of neuropeptides in complex regional pain syndromes. Neuro-
ology 2001;57:2179–2184.
4. Rabben T, Skjelbred P, Oye J. Prolonged analgesic effect of
ketamine, an N-methyl-D-aspartate receptor, in patients with
5. Akopian AN, Sivilotti L, Wood JN. A tetrodotoxin-resistant
voltage-gated sodium channel expressed by sensory neurons.
channels and pain. Proc Natl Acad Sci USA 1999;96:7635–
7639.
channel augmentation in response to inflammation induced by
agents increase a tetrodotoxin-resistant Na$^+$ current in noci-
triggers central sprouting of myelinated afferents. Nature
10. Bester H, Beggs S, Woolf CJ. Changes in tactile stimuli-
induced behavior and c-Fos expression in the superficial dor-
sal horn and in parabrachial nuclei after sciatic nerve crush.
inflammatory pain by forebrain NR2B overexpression. Nat
12. Samad TA, Moore K, Saperstein A, et al. Interleukin 1beta-
mediated induction of COX-2 in the CNS contributes to inflam-
13. Moskowitz MA, Waebel C. Migraine enters the molecular era.
An association between migraine and cutaneous allodynia.
15. Kontinen VK, Dickenson AH. Effects of midazolam in the
spinal nerve ligation model of neuropathic pain in rats. Pain
16. Rowbotham M, Harden N, Stacey B, Bernstein P, Magnus-
Miller L. Gabapentin for the treatment of postherpetic neural-
gia: a randomized controlled trial. JAMA 1998;280:1837–
1842.