Pain is a complex biopsychosocial process, often involving the peripheral nervous system (PNS) and always involving the central nervous system (CNS). For example, tissue injury may activate the PNS, which may transmit nociceptive signals through the spinal cord to the brain, where pain perception occurs. In other instances, such as in central post-stroke pain, the role of the PNS is minimized. This monograph focuses on an important mechanism of pain processing within the CNS—central sensitization.

Pain Classification

Pain is often categorized based upon its duration (acute vs chronic) as well as its underlying pathophysiology (nociceptive, inflammatory, neuropathic). Nociceptive and inflammatory pain conditions are frequently self-limiting and often involve identifiable painful stimuli. Neuropathic pain may be caused by a lesion or dysfunction in the peripheral and/or central nervous system. Typically persistent and frequently perceived as spontaneous pain in the absence of an identifiable stimulus, as well as exaggerated responses to painful stimuli (hyperalgesia) or normally nonpainful stimuli (allodynia). Clinical examples of neuropathic pain conditions include diabetic peripheral neuropathy, postherpetic neuralgia, and central neuropathic pain associated with multiple sclerosis. Not all pain syndromes are easily categorized, however, because certain conditions are neither clearly nociceptive, inflammatory, nor neuropathic. Some have hypothesized that these types of conditions are the result of abnormal central processing. A possible clinical example of this type of pain is the pain associated with fibromyalgia. Clinicians must keep in mind that two or more types of pain may co-exist in the same patient, and therefore they must evaluate and treat the patient accordingly.

Central Sensitization

An Overview

The key component involved in triggering nociceptive and inflammatory pain signals—activation of high-threshold nociceptors—originates in the PNS. Inflammation also induces nociceptor excitability and hypersensitivity, known as peripheral sensitization. In inflammatory pain, neuropathic pain, and pain caused by abnormal central processing, amplification of excitability of neurons within the CNS may also occur. This process and the state of excitability itself are often referred to as central sensitization. Central sensitization appears to play a key role in some chronic pain disorders, especially neuropathic pain. It also may be an important pathophysiological mechanism of pain caused by abnormal central processing (eg, fibromyalgia).

Central sensitization has two phases: the first is an immediate and acute phase, and the second is of slower onset but longer duration (Figure 1). Of significant interest is the evidence regarding the proposed mechanisms of central sensitization that suggest that the first phase depends on changes to existing proteins, whereas the second phase relies on new gene expression.

The acute phase of central sensitization reflects changes in synaptic connections within the spinal cord, after a nociceptive signal has been received from peripheral nociceptors. The central terminals of these nociceptors release a host of signal molecules, including the amino acid glutamate, an excitatory synaptic transmitter; neuropeptides such as substance P and calcitonin gene–related peptide (CGRP); and synaptic modulators such as brain-derived neurotrophic factor. Acting on specific receptors of the spinal cord neurons, these neurotransmitters and neuromodulating agents activate intracellular signaling pathways that lead to the phosphorylation of various membrane receptors and ion channels. These include especially the N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors, both of which are involved in glutamate transmission.

These post-translational changes lower the activation threshold and the opening characteristics of these ion channels, increasing the excitability of the neurons. The net effect of these changes is that normally minimal inputs begin to activate the neurons, and normal pain sensitivity is drastically altered. There might be heightened pain sensitivity to normally nonpainful levels of sensory input, which manifests clinically as allodynia. Allodynia is a common symptom in patients with various chronic pain syndromes in which stimuli that ordinarily do not produce pain (eg, touch, light pressure, clothing, a hairbrush) are perceived as if they are painful. Heightened sensitivity to painful stimuli (hyperalgesia) and spread of sensitivity to noninjured areas (secondary hyperalgesia) may also manifest.

The later protein transcription–dependent phase of central sensitization is associated with increased levels of protein production, which help sustain neuronal excitability and pain sensitivity. Neuroplasticity is defined as “the capacity of neurons to change their structure, function, or chemical profile.” Activation, modulation, and modification are all forms of plasticity that may contribute to pain hypersensitivity. Neuropathy is not unique to sensory phenomena and may be seen as a consequence of motor function as well. Neuropathy, as it pertains to pain, may occur in multiple regions of the body during pain processing and contribute to the pain hypersensitivity observed in neuropathic pain. The mechanisms of both peripheral and central sensitization are part of this process; thus, pain hypersensitivity and allodynia are symptoms of neuropathic pain.

There are several types of neurons that synapse on dorsal horn neurons of the spinal cord; they include nociceptors, descending afferents from the brain, γ-amino butyric acid (GABA)-ergic interneurons, and inhibitory interneurons.

### Figures

**Figure 1.** Contributions of spinal cord dorsal neurons to pain.

**A. Central Sensitization—Acute Phase**

Nociceptor Central Terminal → Spinal Cord Transmission Neuron → Brain

**B. Central Sensitization—Late Phase**

Pain Sensitivity → Inhibitory Interneuron → Diffuse Pain Sensitivity Syndrome

interneurons, and glial cells. The combined activity of these neurons may affect the output of the dorsal horn neurons. Among nociceptors, there are thermal nociceptors that detect extreme temperatures, mechanical nociceptors that detect intense pressure, and polymodal nociceptors that are activated by high-intensity mechanical, chemical, and thermal stimuli. All are made up of sensory nerve fibers; pain processing specifically involves Aδ and C fibers. Thermal and mechanical nociceptors are made up of Aδ fibers, which are thinly myelinated and conduct signals at a velocity of 5 to 30 m/s. C fibers are unmyelinated neurons that have a slower conduction velocity of approximately 1 m/s or less, and they are the primary neuronal type of polymodal nociceptors.

Both Aδ and C fibers are capable of releasing the excitatory neurotransmitters glutamate and substance P. Glutamate is believed to have localized actions on postsynaptic neurons within the dorsal horn, because glutamate reuptake transporters are found on both glial cells and neurons. Specifically, AMPA receptors have been localized on dorsal horn neurons. Substance P is thought to enhance the output of the dorsal horn neurons. Specifically, AMPA receptors are found on both glial cells and neurons. Substance P is thought to enhance the output of the dorsal horn neurons. Specifically, AMPA receptors are found on both glial cells and neurons.

By itself, substance P likely activates inhibitory interneurons in laminae II and III. Conversely, nociceptive neurons (C, Aδ) have been shown to do the opposite. These actions form the basis of the gate-control theory, which proposes that non-nociceptive neurons "close" a gate to the central transmission of painful stimuli, whereas nociceptive neurons "open" it. Thus, a balance between inhibition and disinhibition by non-nociceptive and non-nociceptive fibers can centrally modulate pain.

Recent evidence suggests that spinal microglial cells actively participate in the pain response, especially in neuropathic pain. The traditional view of glial cells involved in neuropathic pain sensitization is that non-nociceptive neurons "close" a gate to the central transmission of painful stimuli, whereas nociceptive neurons "open" it. Thus, a balance between inhibition and disinhibition by non-nociceptive and non-nociceptive fibers can centrally modulate pain. The term central sensitization refers to hyperexcitability of neurons within the spinal dorsal horn. Central sensitization plays a key role in the pathophysiology of peripheral diabetic neuropathic pain, and pain caused by abnormal central processing. Clinically, it reveals itself as exaggerated responsiveness to painful stimuli, painful responses to non-nociceptive stimuli, and spread of pain to noninjured areas.

This review has described pain signaling pathways at the spinal level of the neuraxis. The central mechanisms of pain are clearly complex and involve various neuromodulating agents and receptor systems. The numerous mediators at play represent potential therapeutic targets. As we continue to understand and identify the pathophysiologic modulators of pain, we move closer to an improved, mechanism-based approach to therapy.

References

Figure 2. Neuroplasticity in pain processing.1,2