Peripheral and Central Sensitization

4

Daniel Vardeh and Julian F. Naranjo

Neuronal excitation in nociception is not a static process of the kind "same stimulus–same response," but rather underlies dynamic plasticity to adapt to different situations. **Allodynia** (pain due to a stimulus that does not usually provoke pain) and **hyperalgesia** (increased pain from a stimulus that usually provokes pain) both exemplify these dynamic changes, and are the result of a leftward shift of the stimulus–response curve to a specific (e.g., a mechanical or temperature) stimulus. Hyperalgesia/allodynia is typically divided into two types. While hyperalgesia occurring at the site of injury is termed primary hyperalgesia, enhanced pain sensitivity in the sourrounding uninjured area is termed secondary hyperalgesia**. Primary hyperalgesia** is contributed to by sensitization of peripheral nerve endings (**peripheral sensitization**), whereas **secondary hyperalgesia** is due to changes in the spinal cord and higher brain areas (**central sensitization**). Depending on the provoking stimulus, hyperalgesia can be divided into **heat hyperalgesia** and **mechanical hyperalgesia**.

D. Vardeh, MD (✉)
Interventional Headache and Neck Pain Management, Department of Neurology and Anesthesia, Lahey Hospital & Medical Center, 41 Mall Road, Burlington, MA 01805, USA
e-mail: dvardeh@partnes.org

J.F. Naranjo, MD
Comprehensive Interventional Pain Medicine, 7000 SW 62 Street Suite 535, Miami, FL 33143, USA

Functional Changes

Altered sensitivity in response to mechanical or heat stimuli can be attributed to **different mechanisms**:

- Mechanically insensitive afferent A-δ and C-fibers show **lowered thresholds** after injury or inflammation and are therefore recruited to fire in response to nonhazardous stimuli;
- Other A-δ and C-fibers exhibit **enhanced responses** to suprathreshold mechanical stimuli;
- adjacent naïve receptive fields of A-δ and C-fibers start expanding into the injured area therefore **increasing innervation** and thus sensibility of the injured site;
- **recruitment of myelinated low-threshold A-β fibers**, usually mediating light touch, can under pathological circumstances convey painful stimuli (e.g., mechanical allodynia) due to changes in their central projection neurons in the spinal cord;
- Changes in the spinal cord mediated by altered neuronal gene expression, immune cell activation and modulation of descending inhibitory pathways results in **disinhibition** of pain pathways and secondary hyperalgesia

R.J. Yong et al. (eds.), *Pain Medicine*, DOI 10.1007/978-3-319-43133-8_4

Molecular Mechanisms of Sensitization

Peripheral Sensitization

Peripheral sensitization is a decrease in threshold, an increase in responsiveness and sometimes a spontaneous activity of peripheral ends of nociceptors. It occurs after **tissue damage and inflammation** and arises due to the action of inflammatory chemicals released at the affected site by both sensory nerve fibers and inflammatory cells. Some of these compounds can **directly activate peripheral nociceptors** (such as protons, ATP, serotonin) while others have a more **modulating role** leading to enhanced responsiveness of nerve endings. Two processes have been implicated in this increased sensitivity: (1) Early posttranslational changes in the peripheral terminals of nociceptors, e.g., phosphorylation of ion channels, and (2) altered gene expression.

Posttranslational Changes

Some inflammatory markers (e.g., bradykinin, histamine, prostaglandins, nerve growth factor) mediate their effects by activating **G-protein-coupled receptors** or receptor **tyrosine kinases** that initiate second-messenger pathways resulting in activation of **Protein kinases A and C**. Both protein kinases modulate activity of the sensory neuron-specific channels like $\mathbf{Na_{v1.8}}$ and $\mathbf{Na_{v1.9}}$ as well as transducer molecules like **TRPV1** by **phosphorylation**. This increases the excitability of nociceptors by lowering the threshold at which ion channels open and/or result in longer opening times, eventually resulting in prolonged depolarization and enhanced response.

Altered Gene Expression

In contrast to altered activity of ion channels, some responses to inflammatory stimuli travel back to the DRG cell body and **change transcription or translation** of certain proteins. Whereas local changes in terminal nerve fibers take minutes, transcriptional changes can take up to a day. A good example is upregulation of the TRPV1 channel by the release of nerve growth factor (NGF) triggered by local inflammation NGF.

Central Sensitization

Central sensitization differs fundamentally from peripheral sensitization. Peripheral sensitization is due to posttranslational and transcription changes in the terminal ends of high-threshold nociceptors resulting in primary hyperalgesia. Central sensitization in contrast typically manifests in **tactile allodynia** and **secondary hyperalgesia** (in tissue not affected by any harmful condition). Pain is generated as a consequence of changes within the CNS that lead to alterations of how to interpret sensory inputs, rather than reflecting the presence of peripheral noxious stimuli. The newly proposed **definition by the IASP** describes "central sensitization" as the "increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input."

This sensitization in the CNS, which ultimately results in enhanced synaptic transfer, is characterized by a number of distinct mechanisms:

Shorter lasting, activity triggered mechanisms include wind-up and heterosynaptic potentiation, whereas **long lasting effects** are due to alterations in microglia, astrocytes, gap junctions, membrane excitability, and gene transcription, all of which can contribute to the maintenance of central sensitization.

Wind-Up (Homosynaptic Potentiation)

Wind-up describes a phenomenon of increasing action potential output from dorsal horn neurons during a train of low frequency firing of C-fibers. By this repetitive C-fiber stimulus, higher calcium levels are achieved in the C-fiber central presynaptic terminal, which leads to release of increasing glutamate and peptides (like SP and CGRP), resulting in increasing postsynaptic depolarization. **This process results in progressively increasing output of the dorsal horn neuron during a train of identical incoming C-fiber stimuli**. The temporary plasticity created by wind-up is dependent on constant incoming activity and thus **does not outlast the stimulus**.

Heterosynaptic Potentiation

Heterosynaptic sensitization in the spinal cord differs in two ways from the wind-up phenome-

non: the increased responsiveness of the dorsal horn neuron outlasts the primary stimulus by hours; these changes affect not only the response triggered by the primary stimulus, but also the response to stimuli from other afferents converging on the same dorsal horn neuron. Ultimately, **subthreshold incoming stimuli from converging nociceptors as well as high threshold Aβ fibers are converted to suprathreshold action potentials due to the changes at the dorsal horn neuron**. This manifests clinically as hyperalgesia (stimuli originating from C and Aδ nociceptors), allodynia (stimuli originating from Aβ fibers) as well as secondary hyperalgesia due to recruitment of fibers supplying sensation to areas outside the primarily injured area.

Other Mechanisms

While the above changes can outlast the stimulus for hours, **longer lasting changes** in the CNS contribute to the maintenance of hyperalgesia, allodynia and secondary hyperalgesia for a much longer time. These changes are due to alterations in posttranslational processing (e.g., phosphorylation of ion channels) and gene transcription, immune cell/glial activation, and disinhibition at a spinal and supraspinal level.

Excitation of central synapses will eventually lead to activation of nuclear proteins like cyclic AMP response element-binding protein (CREB), resulting in **neuronal transcription** of early response genes like c-FOS and COX-2 and late response genes like NK1 and TrkB.

Neuron-immune cell interactions are increasingly recognized as playing a pivotal role in hyperalgesia elicited in states of inflammatory and neuropathic pain. Microglia at the affected level in the spinal dorsal horn respond to injury to peripheral nerves with a stereotypic response, including upregulation of the purinergic receptor $P2X_4$. In addition, there is evidence for T-lymphocyte recruitment into the spinal cord in experimental models for neuropathic pain. In this activated state, immune cells release cytokines which sensitize nociceptive signaling and disinhibit neurons in the spinal nociceptive network. Recent research has suggested that microglia activation might be closely linked to opioid induced hyperalgesia.

Inhibitory dorsal horn interneurons synapse with the central terminals of primary sensory neurons as well as postsynaptic projection neurons and thus are able to modulate nociceptive transmission (via release of GABA and glycine). On a higher level, **descending inhibitory pathways** originating in the anterior cingulate cortex (ACC), amygdala and hypothalamus reach the spinal cord via brain stem nuclei in the periaqueductal gray (PEG) and rostroventral medulla and exhibit a tonic inhibition of central projection neurons through release of norepinephrine, serotonin, and endogenous opioids. Impaired inhibition as a result of peripheral inflammation or spinal cord injury may unblock these pathways and lead to inappropriate spread of incoming afferents across modalities and somatotopic borders.

Suggested Reading

Costigan M, et al. Neuropathic pain: a maladaptive response of the nervous system to damage. Annu Rev Neurosci. 2009;32:1–32.

Vardeh D et al. Pain management in clinical practice: towards a mechanism-based approach to a pain diagnostic ladder. J Pain 2016 (in press)

Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. Pain. 2011;152(3 Suppl):S2–15.