Mechanisms of Chronic Pain

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Key Concepts

- Sensitization is a process in which repeated stimulus of a receptor results in the progressive amplification of a response.
- The key excitatory neuromodulators are glutamate, aspartate, and substance P.
- The main inhibitory neuromodulators are GABA, glycine, enkephalins, and somatostatin.
- Mechanisms of persistent pain include the following: peripheral sensitization, central sensitization, ectopic excitability of sensory neurons, physical rearrangement of neurons' circuitry, and disinhibition.
- Research into the mechanisms that generate and maintain chronic pain are necessary to develop new interventions and improved treatment outcomes.

Introduction

After inflammation or tissue injury, pain sensation may continue long after the withdrawal of the noxious stimuli. This transition from acute to chronic pain has been a long-standing medical enigma. Recent advances in the study of pain transmission and processing have begun to unravel the cellular mechanisms that underlie the maintenance of chronic pain. The term sensitization refers to the process in which a repeated stimulus results in the progressive amplification of a response. Sensitization is a key factor in the genesis of chronic pain and a demonstration of plasticity within the nervous system. As an example, repeated stimulation of nociceptive C fibers entering the dorsal root can elicit a progressive increase in the number of action potentials generated. The dorsal root ganglia may become hyperexcitable and display continuous spontaneous electrical activity. This activity results from the expression of many cell-specific molecules in modified cells, which alter the complex neuronal circuits of our nervous system. These neuronal changes are the mainstay of sensitization. Chronic pain sensation can result from such injury. Understanding the changes that follow in neural structures at a molecular level may help lead to new therapeutic interventions.

There are various primary excitatory and inhibitory neurotransmitters implicated in the propagation of chronic pain. The amino acids glutamate and aspartate are the key excitatory neurotransmitters in the somatosensory system. The four types of excitatory amino acid receptors are the N-methyl-D-aspartate (NMDA), alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), kainite, and metabotropic receptors. Gamma-aminobutyric acid (GABA) and glycine are the key inhibitory neurotransmitters. Substance P is the key excitatory neuropeptide. The enkephalins and somatostatin are the key inhibitory neuropeptides.

Peripheral Sensitization

Nociceptive stimulation of tissue in a neuron's receptive field causes release of inflammatory mediators (prostaglandins, bradykinin, histamine, cytokines, growth factors) that may reduce the threshold for excitation of peripheral receptors. When changes occur in the response characteristics of the primary afferent fibers which transmit pain, the A-delta and C fibers, the peripheral nervous system is said to be sensitized. Peripheral sensitization causes the nerve to be responsive to benign, normally nonpainful stimuli, and this is termed allodynia. This may also provoke an exaggerated response to painful stimuli, known as hyperalgesia. Changes

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in cellular transduction such as increases in the cAMP-PKA mechanism may be involved in further sensitization. Inflammation leads to upregulation of nitric oxide synthase that can cause neuropeptides to be released from nociceptive nerve terminals, and these neuropeptides therein produce inflammatory hyperalgesia. The recruitment of previously silent nerve fibers which become sensitive to stimuli after exposure to inflammatory mediators is another mechanism of peripheral sensitization. The final common pathway for peripheral sensitization appears to involve an increase in intracellular calcium and protein kinase levels.

Central Sensitization

Central sensitization amplifies the synaptic transfer from the nociceptor terminal to the dorsal horn neurons. Initial sensitization is an activity, which is dependent on stimulated nociceptors, but subsequent transcriptional changes at the molecular level sustain the sensitization. Previously subthreshold synaptic input to nociceptive neurons will now generate an augmented action potential output. The NMDA receptor plays an important role as its responsiveness to glutamate is increased, leading to increased excitability of the dorsal horn cell. Inflammation may contribute to both peripheral and central sensitization. Neuroimmune interaction produced by peripheral inflammation causes changes in brain-derived neurotrophic factor, substance P, neurokinin, dynorphin, and cyclooxygenase 2 which may lead to transcription-dependent central sensitization. Also, neuroglial interactions contribute to sensitization by releasing cytokines and chemokines after nerve injury, altering gene transcription. The main causes of central sensitization-maintained pain include neuronal sensitization, reduction in inhibitory interneuron activity, and modulation of descending pathway activity.

Neuronal sensitization is triggered by intense electrical or noxious stimulation of C fibers which promote wide-dynamic-range (WDR) neuron hyperexcitability in the dorsal horn. Repetitive electrical stimulation provokes increased excitability leading to action potential "windup." Windup refers to slow, prolonged depolarization and ultimate burst of action potentials with stimulation. WDR neuron sensitization is associated with excitatory amino acids, tachykinins, and calcitonin gene-related peptide. These neuromodulators affect the dorsal horn neuron by increasing cation fluxes, impinging on intracellular transduction mechanisms, and modulating receptor and transmitter gene transcription. Synaptic transmission augmentation at NMDA receptors is the final common pathway. Adequate depolarization causes an increase in intracellular calcium level leading to protein kinase phosphorylation that antagonizes the magnesium blockade at the NMDA receptor.

Interneurons, as well as descending signals arising from the brain, may be excitatory or inhibitory. Stimulation of some cortical and subcortical areas may cause analgesia. Reduction in inhibitory interneuron activity results in increased WDR neuron excitability consistent with clinical hyperalgesia and allodynia. The loss of GABA and glycerine activity in the dorsal horn produces a state of neuronal hyperexcitability.

Modulation by supraspinal descending pathways is likely due to increases or decreases in several neurotransmitters causing descending facilitation or inhibition. The endogenous opioid, noradrenergic, and serotonergic systems are involved in descending control of nociceptive pain perception. There is evidence that serotonin receptors provoke the release of substance P from the spinal cord. This release of substance P correlates with the receptors' ability to increase nociception at the level of the neurons. Increases in noradrenaline in the dorsal horn may potentiate descending noradrenergic inhibitory circuits, thereby reducing nociceptor stimulation. Diminished cerebral GABA can lead to disinhibition of descending facilitation.

It has been demonstrated that the injured neurons within the DRG are markedly more sensitive to activation, creating the potential for a therapeutic window for treatment of chronic pain with electrical stimulation.

Conclusion

The major causes of hypersensitivity to pain after injury are peripheral and central sensitization. Substances released after tissue injury can be nociceptor sensitizers. NMDA receptor changes can increase dorsal horn excitability. Activated glial cells may produce cytokines that alter gene transcription and contribute to further sensitization. Other mechanisms for persistent pain include but are not limited to the following: ectopic excitability of sensory neurons due to upregulation of voltage-gated sodium channels or downregulation of potassium channels, physical rearrangement of neurons' circuitry in the dorsal horn, and disinhibition due to loss of GABA and glycine-mediated inhibition.

Suggested Reading

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