Basic Anatomy and Physiology of Pain Pathways

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KEYWORDS

• Hyperalgesia • Allodynia • Peripheral sensitization • Spino-thalamic tract • Gait control theory • Descending systems

KEY POINTS

- Pain signals are transmitted along Aδ and C nociceptive nerve fibers to the central nervous system.
- Most peripheral nerve fibers will synapse in the Rexed lamina and then ascend in the contralateral spinothalamic tract before terminating in the ventral posterior nuclei and central nuclei of the thalamus.
- The receptive fields of the thalamus may reorganize following injury.
- The primary and secondary somatosensory cortex receive the bulk of direct projections from the thalamus; the insula, orbitofrontal cortex, dorsolateral prefrontal cortex, amygdala and cingulate are additional early relay sites important in pain processing.
- The rostral ventromedial medulla, the dorsolateral pontomesencephalic tegmentum, and the peri-aquaductal gray region are important structures in the descending regulation of noxious stimuli at the dorsal horn.
- The neuromatrix theory of pain incorporates the gate control theory of pain that focused on pain regulation at the spinal cord with more recent evidence that expands the role of the cortex.

INTRODUCTION

The pain pathways form a complex, dynamic, sensory, cognitive, and behavioral system that evolved to detect, integrate, and coordinate a protective response to incoming noxious stimuli that threatens tissue injury or organism survival.[1] This defense system includes both the primitive spinal reflexes that are the only protection for simple organisms all the way up to the complex emotional responses humans consciously and subconsciously experience as pain. The mental representation of pain is stored as both short-term and long-term memory and serves as an early warning avoidance system for future threats.[1] When severe, mental anguish may be projected with a physical complaint or symptom. Although many of the basic structures of the pain pathways have been defined, a more complete understanding of the interactions that would enable the development of targeted therapies remains elusive.

PERIPHERAL SENSORY SYSTEM AND MECHANISMS OF SENSITIZATION

The location, intensity, and temporal pattern of noxious stimuli are transduced into a recognizable signal through unmyelinated nociceptors at the

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terminal end of sensory neurons. Through physical deformation or molecular binding, membrane permeability and, consequently, the membrane potential fluctuate.[2] If depolarization reaches a critical threshold, an action potential is propagated along the length of a sensory nerve toward the spinal cord.

Most sensory receptors respond to a single stimulus modality. Nociceptors, designed to detect tissue injury, are excited by three noxious stimuli: mechanical, thermal, and chemical. Mechanical stimuli deform the receptor to augment receptor ion permeability,[3] whereas chemicals such as bradykinin, serotonin, histamine, potassium ions, acids, acetylcholine, and proteolytic enzymes[2] bind directly to receptors to influence membrane permeability. Prostaglandins and substance P (SP) do not directly activate pain receptors but indirectly influence membrane permeability.

Nociceptive receptors sit at the ends of pseudounipolar sensory neurons with cell bodies in the dorsal root, trigeminal, or nodose ganglia (**Fig. 1**).[4] Pain receptors are unencapsulated free nerve endings. Sensory nerve fibers range from 0.5 to 20 μm in diameter and can conduct impulses at speeds ranging from 0.5 to 120 m/sec. Larger diameter neurons conduct information at a faster speed.[2] Nerve fibers are divided up into two main categories: type A, which are medium to large diameter myelinated neurons, and type C, small diameter unmyelinated neurons.[2] Pain transmission is divided into two categories, fast and slow. A-delta fibers detect and transmit pain quickly. These fibers are relatively small (1–6 m), thinly myelinated neurons that can conduct at speeds of 6 to 30 m/sec.[3] C fibers are small (<1.5 m) and unmyelinated, conducting pain at 0.5 to 2 m/sec.[2] A-beta are large (6–12 m) myelinated fibers that are high speed (30–70 m/sec).[2] They have encapsulated receptors and transmit information about touch, pressure, and vibration.[3] Most A-delta fibers are associated with thermo or mechanoreceptors. C fibers can be associated with polymodal receptors, suggesting a role in monitoring the overall tissue condition.[3]

Innocuous stimuli may elicit excitation of neurons in the peripheral nociceptive system following repeated injury or inflammation. These pathologic changes contribute to phenomena such as sensitization, allodynia, or hyperalgesia. In peripheral sensitization, neurons fire at a lower threshold and have greater response magnitude to a given stimuli,[5] may fire spontaneously, or may even have altered receptive field areas.[6,7] This occurs via inflammatory mediators, including bradykinin, prostaglandins, serotonin, tumor necrosis factor alpha, and histamine.[8] After integration in the brainstem, descending pronociceptive and antinociceptive pathways contribute to peripheral sensitization. When the function of these pathways becomes abnormal, chronic pain may occur.

The expression of molecules, including GABA, histamine, serotonin, and opiate receptors in nociceptive neurons, may be modulated by inflammation or injury.[8] Near the receptor there is a high concentration of sodium channels. Increased channel expression can alter sensitivity of nerve endings to noxious stimuli by modulating integration of stimuli and threshold potential for action potential generation.[3] Increased sodium channel expression has been reported after nerve injury and may contribute to hyperexcitability and associated abnormal sensation.[9] C fibers have long response times and are slow to adapt. Because of this, they show summation of response to noxious stimuli in the presence of tissue injury,[10] perhaps contributing to sensitization and hyperalgesia.

Inflammation results in an upregulation of SP, including in A-beta fibers.[11] In this setting, A fibers may play a role in central sensitivity, perhaps contributing to hypersensitivity.[11,12] A-beta fibers terminate in lamina III of the spinal cord where SP receptors are present. They may contribute to ongoing activation of SP expressing nociceptive neurons in chronic pain states.[12]

DORSAL ROOT GANGLIA

Sensory neuron cell bodies are located in the dorsal root ganglia (DRG). DRG neurons are classically pseudounipolar; one process extends into the peripheral nerve and the other process extends centrally, transmitting information through the dorsal root into the spinal cord. Each DRG contains thousands of unique sensory neuron cell bodies that are capable of encoding and then transmitting specific information gathered from external stimuli.[13] Cells in the DRG are subclassified into peptidergic neurons and nonpeptidergic neurons. Peptidergic neurons contain peptides such as SP, calcitonin gene–related peptide (CGRP), and somatostatin.[14] Each DRG neuron is surrounded by glial cell cytoplasm. The surface of the DRG neuron cell bodies are covered with perikaryal projections that are invested in the surrounding glial cytoplasm, increasing the surface area.[15]

The soma of DRG neurons synthesizes and transports the substances needed for neuron functioning to the far reaches of the axon terminals, including receptors, ion channels, as well as