1 Anatomy and Physiology: Mechanisms of Nociceptive Transmission

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Nociception is the measurable physiological response of specialized sensory receptors (nociceptors) to overt or potential tissue damage and is perceived in the CNS—via the spinothalamic tract, the thalamus, and finally different areas in the neocortex—as pain. Initially, noxious chemical, mechanical, or thermal stimuli are detected at nerve endings of primary sensory neurons with their soma located in the dorsal root ganglion (DRG) for body sensation, and in the trigeminal ganglion (gasserian ganglion) for face sensation. Specialized receptors (**transducers**) located at the cell membrane of sensory nerve endings translate the intensity of a given stimulus into action potential frequency, which results in the emission of glutamate and peptides in the respective area in the spinal cord dorsal horn (mostly superficial laminae I and II with some projections to lamina V).

Nociceptors can be divided into different groups by means of their anatomical structure, their characteristic expression of various proteins or the distinct receptors at their terminals, as described below.

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Fibers Types of Nociceptors

Generally, A-δ and C-fibers are the major contributors to physiological nociception, with A-β fibers contributing in pathological states of central sensitization.

C-fibers are small in diameter; they are unmyelinated and conduct impulses at the slow rate of 0.5–2 m/s. C fibers have smaller receptive fields than the A-δ nociceptors and mostly terminate in lamina LII of the spinal dorsal horn. Their activation results in a more prolonged sensation of dull and burning pain. Most C-fibers are polymodal receptors and are activated by high-threshold mechanical and various chemical stimuli, as well as by heat (starting at 39–41 °C). These polymodal C-fibers are heavily influenced by both the phenomena of sensitization (enhanced response to a lasting/repetitive stimulus of same intensity) and fatigue (reduced response to a lasting/repetitive stimulus of same intensity).

A-δ fibers function as thermal and high-threshold mechanical receptors. Generally, they respond with higher discharge frequencies than C-fibers and the discriminable information supplied to the CNS is greater. Most of these fibers have polymodal properties (with high heat threshold at 40–50 °C), are thinly myelinated (conduction velocity between 5 and 35 m/s) and terminate in LI and LV of the dorsal horn. Activation of A-δ fibers generally results in a short sensation of sharp, pricking pain, in contrast to the dull sensation mediated by C-fibers.

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A-β fibers are myelinated fibers (conduction velocity 35–75 m/s) which play a major role in encoding muscle spindle information and vibration. They also conduct typically innocuous mechanical stimuli, but some also encode stimulus intensities in the noxious range and in some cases respond to noxious heating of the skin. A-β fibers are major players in mediating allodynia (a painful feeling upon gentle touch) in states of central sensitization.

Molecular Properties of Nociceptors

Under physiological conditions, nociceptors do not fire spontaneously. Their electrical action potential is triggered by transduction, which occurs when a noxious stimulus of sufficient strength depolarizes the nociceptor membrane. The specific receptive properties of nociceptors are determined by their membrane bound transducing ion-channel receptors. These ion channels are nonselective potassium or sodium channels gated by temperature, chemical stimuli, or mechanical shearing forces. Activation of these channels leads to depolarization of the membrane, which—if strong enough—results in activation of voltage-gated sodium channels, leading to further depolarization and burst of action potentials, which will finally result in glutamate release at central terminals in the spinal cord. The duration and frequency of this signal is determined by the duration and intensity of the noxious stimulus.

Heat

Several unselective cation channels have been described to transduce increased temperature into membrane depolarization. **TRPV1** is characterized by a moderate heat threshold around 43 °C and its activation by capsaicin (the pungent ingredient in chilli peppers). **TRPV2** does not respond to capsaicin and shows a high heat threshold of over 50 °C. Other TRPV channels, namely **TRPV3** and **TRPV4**, have been described with thermal activation thresholds between 31 and 39 °C and thus are probably responsible for the sensation of warmth. TRPV channels have been shown to be substantially expressed in keratocytes indicating an important role of the epidermis in heat detection. Moreover, TRPV1 plays a pivotal role in setting the heat threshold to lower levels in state of inflammation and is therefore substantially contributing to heat hyperalgesia.

Cold

Similar to the TRPV family, a closely related **TRPM8** receptor has been described, with a thermal activation threshold of 26 °C and chemical activation by Menthol. While TRPM8 with its moderate cold threshold is responsible for the perception of gentle cooling, the **TRPA1** receptor might be a sensor of "noxious cold" since it responds to temperatures below 17 °C. Other contributing and rather modulating mechanisms have been suggested, such as the inhibition of ubiquitously expressed K-channels by cool stimuli.

Mechanosensation

Evidence for mechanical transducer channels has been elusive and various theories exist to explain this mechanism. Whereas low pressure touch and muscle tension are generally detected by A-β and A-α fibers, high threshold mechanosensation is conducted by A-δ and C-fibers. Some studies suggest osmosensitive ion channels, which are directly gated by membrane stretch and distortion. Another hypothesis favors the model of ion channels being tethered to cytoskeletal or extracellular matrix molecules so that displacement relative to the cell surface can be detected.

Voltage-Gated Channels

Once transducing ion channels are activated by adequate stimuli, voltage-gated sodium channels are responsible for the rising phase of the action potential. They play a key role in determining

the excitability of the sensory neurons and in conduction currents from the periphery to the CNS. DRG neurons express several distinct types of sodium channels, including the **$Na_{v1.7}$, $Na_{v1.8}$, and $Na_{v1.9}$ channel**. The importance of these sodium channels in transmitting nociceptive stimuli is exemplified by the rare but dramatic human mutation of $Na_{v1.7}$, which results in loss of function and complete inability to sense pain. In contrast, autosomal dominant mutations leading to excessive channel activity of $Na_{v1.7}$ cause erythromelalgia, a condition characterized by episodes of burning pain in feet and hands, erythema and increased skin temperature in affected areas.

Central Projections

Once a stimulus has reached sufficient intensity and duration, transducers and subsequently voltage gated ion channels will produce robust action potentials which will travel from the nerve endings via the DRG into the **specific lamina of the dorsal horn** (LI, II, and V).

To transmit these incoming signals upon the central projection neuron, every central nociceptive terminal holds multiple neurotransmitters, usually an excitatory amino acid such as glutamate or aspartate, and modulating peptides such as substance P (SP), vasoactive intestinal peptide (VIP), somatostatin, and calcitonin gene-related peptide (CGRP). Incoming signals can be dampened or completely calmed by descending pathways originating in brain stem centers like the **periaqueductal grey (PEG)**, the serotoninergic **nucleus raphe,** and the norepinephrinergic **locus coeruleus**, which project mainly to superficial spinal laminae (LI and LII) and lead—via g-aminobutyric acid (GABA) and glycine—to inhibitory postsynaptic potentials (IPSPs) on central projection neurons. Further modulation of incoming signals is mediated by a complex network of inhibitory and excitatory **spinal interneurons**.

Projection neurons in the dorsal horn propagate the summation of this information via the **anterior and lateral spinothalamic tracts (STT)** to the thalamus. These tracts decussate within a few segments of the level of entry and terminate directly on central neurons of the **ventral posterior lateral (VPL) subnucleus** of the thalamus, conveying sensations of pain, temperature, and itch from the contralateral side of the body. **Trigeminothalamic axons** join the STT after decussating at the level of the medulla to convey equivalent sensation from the contralateral face. Other collaterals synapse on the **posterior Ventral Medial Nucleus (VMpo)**, which further projects to the posterior insula, where information is integrated with visceral afferent activity (e.g., vagal and gustatory afferents) to influence autonomic responses. Other projections run to the **medial dorsal nucleus (MDvc)**, which relies information to the anterior cingulate cortex and is important for the affective/motivational aspect of pain . Yet other projections reach **intralaminar thalamic nuclei** and have widespread cortical projections contributing to arousal and attention.

Suggested Reading

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