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Nociceptive Nerve Fibers

Pain is transmitted to the central nervous system via thinly myelinated A δ and unmyelinated C-fibers. The former convey the sensation of sharp, lancinating “first” pain, whereas the latter conduct the dull, longer-lasting “second” pain. A δ -fibers predominantly respond to mechanical stimuli (Type I or “high-threshold mechanoreceptor”) or to noxious heat (Type II). Conversely, the C-fibers are polymodal, the same fiber responding to mechanical, thermal and chemical stimuli. Both A δ - and C-fibers terminate in the superficial dorsal horn, mainly in Rexed Laminae I and II, although some A δ -fibers also terminate in the deeper lamina V. In the periphery, the distal endings terminate freely in the tissues. These free nerve endings express a variety of signal transducing molecules, one of the most extensively investigated being the transient receptor potential ion channel TRPV1, also known as the capsaicin receptor [1].

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From Pain Transduction ...

Apart from thermal or mechanical stimuli, several endogenous or exogenous compounds can activate the nociceptors. Examples for exogenous compounds include capsaicin or menthol, provoking heat and cold sensations via the TRPV1 and TRPM8 channel, respectively. Endogenous activators comprise histamine, serotonin, prostaglandins, bradykinin, substance P as well as H⁺- and K⁺-ions. They either directly activate the nociceptor or modulate its activation threshold—a process called peripheral sensitization. Neurogenic inflammation serves as an example for peripheral sensitization of nociceptors: noxious stimulation of a free nerve ending causes release of substance P and calcitonin-gene related peptide (CGRP) from adjacent nerve endings via axon reflex. These mediators in turn attract leukocytes that release cytokines and mast cells that release histamine. The cytokines (IL-1 and TNF- α) and histamine stimulate and sensitize the nociceptors, thus causing ongoing pain and hyperalgesia.

... to Pain Transmission

Upon activation by a noxious stimulus, the primary afferent neurons release excitatory neurotransmitters in the dorsal horn. A δ -fibers mainly release glutamate while the so-called

“peptidergic” C-fibers release neuropeptides, in particular substance P. Glutamate excites the second-order neuron in the dorsal horn primarily via the ionotropic AMPA-receptor, resulting in immediate propagation of a sharp, localized pain signal. Substance P, on the other hand, binds to the neurokinin-1 receptor, a member of the G-protein coupled receptor family. The ensuing intracellular signaling cascade is complex and involves activation of arachidonic acid pathways, nitric oxide synthesis and NMDA-Receptors (see below). Changes in gene expression, receptor upregulation or downregulation and dendritic spine formation may occur, ultimately leading to a state of sustained hyperexcitability. This so-called central sensitization is characterized by enhanced response to noxious stimuli, enlargement of receptive fields and painful response to usually non-noxious stimuli [2].

Selected Key Players in Pain Processing

- **NMDA-Receptors** are ion channels that are blocked by a Mg^{2+} -ion in the resting state. Binding of glutamate to the receptor does not cause activation unless the Mg^{2+} -ion has been removed by prior depolarization of the cell membrane. This may occur after sustained excitation of the cell, e.g., by AMPA-receptors or substance P. NMDA-receptors are therefore said to be both ligand- and voltage gated ion channels. Following opening of the channel, Ca^{2+} -ions enter the cell and initiate a signaling cascade that is thought to be responsible for long-term potentiation and wind-up. Ketamine, methadone, and dextromethorphan are examples of substances acting as (partial) antagonists at the NMDA-receptor.
- **Voltage-gated calcium channels (VGCC):** Several classes of VGCC exist throughout the body, of which the N-type and the T-type channel play a role in nociception. The N-type channels are found presynaptically and are involved in transmitter release (glutamate and substance P) upon arrival of an action potential. They can pharmacologically be inhibited by several medications (Gabapentin, Lamotrigine, Ziconotide), thereby reducing excitation of the postsynaptic neuron. The T-type channels are present on both first- and second-order neurons and have more a complex function. They take part in sensitization of neurons by co-activating NMDA-receptors or decreasing the threshold for action potential generation. No T-type-selective drugs are available to date, but anticonvulsants such as Pregabalin or Gabapentin may exert some of their effect by blocking a subunit of these channels.
- **Opioid receptors** belong to the family of G-protein coupled receptors. They are abundantly present all along the neuraxis and mediate both spinal and supraspinal analgesia. They are even expressed at peripheral nociceptive nerve endings in states of tissue injury and inflammation. According to their respective endogenous ligand, they are classified as μ -, δ -, and κ -opioid receptors which differ in terms of localization and function. However, effects common to most subtypes are inhibition of VGCC (thereby reducing release of excitatory neurotransmitter) and opening of potassium channels leading to hyperpolarization (rendering neurons less sensitive to excitatory transmitters). Endogenous opioids (endorphins, enkephalins, dynorphin) are found in the CNS and in the periphery. In the CNS they are released by spinal interneurons or brainstem projection neurons, in the periphery they stem from opioid-secreting leukocytes. Morphine and its semi-synthetic analogues are among the most potent analgesics that are currently available.
- **Gamma-aminobutyric acid (GABA)** is the most abundant inhibitory neurotransmitter in the CNS. There are two types of GABA-receptors: the $GABA_A$ -Receptor is a ligand-gated chloride channel causing hyperpolarization of the cell membrane when activated. The $GABA_B$ -Receptor is a G-protein coupled receptor which stabilizes the membrane potential via opening of K^+ -channels. GABAergic interneurons in the dorsal horn form axo-axonal synapses with first-order

nociceptive neurons, thereby causing presynaptic inhibition of excitatory neurotransmitter release. GABA_A-agonists have been shown to exert anti-hyperalgesic effects in animal and human experimental pain models. Benzodiazepines are allosteric modulators of the GABA_A-receptor, increasing its affinity for GABA. Baclofen is a GABA_B-agonist used to treat spasticity.

Descending Pain Modulation

Spinal processing of nociceptive signals is modulated by projection neurons descending from the brainstem to the dorsal horn. The most important brainstem sites include the periaqueductal gray (PAG) and the rostral ventral medulla (RVM) for serotonergic cells as well as the locus coeruleus for norepinephrinergic cells.

Serotonin is released in the spinal cord after stimulation of the RVM and the PAG. However, its role in pain processing is less clear as it produces both pro- and anti-nociceptive effects, depending on the type of receptor activated. Currently, there is no pharmacologic means that specifically targets the serotonergic system. Although both tricyclic antidepressants and the newer serotonin-norepinephrine reuptake inhibitors (SNRI, e.g. duloxetine) act on the serotoner-

gic system, norepinephrinergic mechanisms are more likely to explain their analgesic properties.

Norepinephrine binds to presynaptic α_2 -adrenoceptors located on the primary afferent neuron, thus reducing the amount of glutamate and substance P released. The result is a strong antinociceptive effect at the level of the dorsal horn. This mechanism possibly explains the analgesic effect of the commercially available α_2 -adrenergic agonists clonidine and dexmedetomidine.

Dysfunction or loss of descending pain modulation has been implicated in many chronic pain disorders. But despite considerable efforts, these endogenous modulatory systems are far from completely understood. Other inhibitory pathways are currently being investigated, including the neurotransmitters glycine and oxytocin. New receptors and transmitters continue to be discovered and pharmacologic modulation of inhibitory pathways might be a promising therapeutic target in the future.

References

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