Basic mechanisms of pain

PAIN
- an unpleasant sensory and emotional experience associated with actual or potential tissue damage.
- has a dedicated neural pathway
- individual and subjective
- more than a symptom

DIFFERENT KINDS OF PAIN:
- Acute
- Inflammatory
- Neuropathic

To understand the pharmacology of pain, you must know the anatomy and physiology of the system.
1. Peripheral nociceptors
2. Dorsal horn – major center for integration of afferent and efferent signaling
3. Ascending pathway
4. Descending pathway

Different levels of pain processing and different sites for sensitization.

How are peripheral temperature and pain signals detected?
Signal transduction in nociceptors

ASIC – acid sensing ion channel
VR1 – vanilloid receptor 1
CMR1 – cold and menthol activated receptor 1
Degenerin family

Modified from Julius and Basbaum, 2001

Nociceptor-specific Na+ channels
Nav 1.8 and 1.9 are expressed exclusively in small diameter peripheral sensory neurons. Channel expression changes induced by nerve injury contribute to neuropathic pain.

Nav 1.8
Nav 1.9

Julius and Basbaum, 2001

Afferent fiber conduction and pain

Thermal nociceptors, A\(\delta\), C fibers, extreme heat and cold
Mechanical nociceptors A\(\delta\) and C
Polymodal nociceptors C

Julius and Basbaum, 2001

Two populations of C and A\(\delta\) fibers projecting to the superficial dorsal horn

There are multiple types of nociceptors: they can differ by sensitivity to growth factors, peptide expression, conduction velocity, sensory modality

Hunt and Mantyh, 2001

Different levels of pain processing and different sites for sensitization.

Julius and Basbaum, 2001

Molecular mechanisms associated with peripheral sensitization

Julius and Basbaum, 2001
Peripheral terminals of primary afferent nociceptors respond to inflammatory mediators

- ATP, Ach and serotonin released from damaged endothelial cells and platelets
- Histamine from mast cells
- Bradykinin from plasma kininogen

The peripheral signal is carried to the spinal cord

Nociceptive inputs go to lamina I, II and V in the dorsal horn

Nociceptors terminating in the superficial dorsal horn release glutamate and peptides to excite dorsal horn neurons.

Synapses between primary afferent C fibers and dorsal horn

Classes of neurotransmitter receptors

Out

IONOTROPIC

G Protein coupled receptor

IN

OUT
Glutamate receptor families

- NMDA receptors (NMDARs)
- AMPA receptors
- Kainate receptors
- Metabotropic Glu receptors

Current-voltage relationship for synaptic currents mediated by AMPA and NMDA receptors

Kandel, Schwartz and Jessell, 2000

The spinal cord dorsal horn has a heterogeneous cell population including:

- Projection neurons
- Excitatory interneurons
- Inhibitory interneurons

Dorsal horn neurons expressing receptor for substance P, the NK1 receptor.

Lamina I
Lamina II
Lamina III

Hunt and Mantyh, 2001

Different levels of pain processing and different sites for sensitization.
Thermal injury can sensitize nociceptors

Activation of neural plasticity in the spinal cord dorsal horn: fast EPSPs

Central sensitization

Increased number of astrocytes in spinal cord in model of bone cancer

Increase in number of microglia following peripheral nerve injury accompanies tactile allodynia

Ascending nociceptive pathway—anterolateral white matter to the thalamus
Ascending Pain pathways:
- traditional
- lamina I

The thermal-grill illusion of pain
-burning pain with innocuous warm (40°) and cool (20°) bars.

Demonstrates central inhibition of a polymodal C nociceptive sensory channel by innocuous thermosensory activity.

Activation of the interoceptive or homeostatic cortex (the dorsal posterior insular cortex) by various modalities

Descending pathway that regulates nociceptive signaling in dorsal horn

- Periaqueductal grey (PAG)
- Dorsolateral pontomesencephalic tegmentum (DLMT)
- Rostral ventromedial medulla (RVM)
- Nucleus raphe magnus
- Reticular formation
- Dorsal horn

Opioid receptors – 3 gene families

µ opioid receptor – activated by morphine, β endorphin and enkephalins
κ opioid receptor activated by dynorphin
δ opioid receptors activated by enkephalins and β endorphin

Opioid receptor action
Opioids are important regulators of nociceptive signaling

Summary:
- There are multiple types of nociceptors: they can differ by sensitivity to growth factors, peptide expression, conduction velocity, sensory modality.
- All nociceptors release glutamate thus glutamate receptors are potential targets for pain management.
- Sensitization occurs peripherally and centrally.
- Dorsal horn neurons project to multiple higher levels in the brain, notably the parabrachial nucleus, the thalamus and the insular cortex and receive descending input, directly or indirectly, from all of those same areas.
- There are good targets for pain management on peripheral and central terminals of nociceptors as well as through regulation of inhibition in the dorsal horn.