PAIN IS
- a submodality of somatic sensations like touch
- an unpleasant sensory and emotional experience associated with actual or potential tissue damage
- 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

There are multiple types of nociceptors: they can be classified by sensory modality, conduction velocity, sensitivity to growth factors, peptide expression, site of termination in the dorsal horn
Signal transduction in nociceptors

- VR1 – vanilloid receptor 1 or TRPV1
- CMR1 – cold and menthol activated receptor 1 or TRPM8
- ASIC – acid sensing ion channel

Modified from Julius and Basbaum, 2001

Nociceptor-specific Na+ channels

Afferent fiber conduction and pain

- Nociceptors include both Aβ and C fibers
- Most, but not all, small diameter fibers are nociceptors. Some are thermal and low threshold mechanoreceptors

Julius and Basbaum, 2001
Nociceptive inputs go to lamina I, II and V in the dorsal horn

Adult mammalian spinal cord

Adapted from Fields, 1987

Two populations of nociceptors project to different sub-regions of the superficial dorsal horn

Inflammation
Chronic pain

Hunt and Mantyh, 2001

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 projection neuron

Lamina I
Lamina II
Lamina III

Hunt and Mantyh, 2001

The spinal cord dorsal horn has a heterogeneous cell population including:
- projection neurons
- excitatory interneurons
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Synaptic transmission in the dorsal horn

- Nociceptors synapse with dorsal horn neurons in lamina I, II, and V
- Nociceptors and local excitatory interneurons release glutamate as the fast transmitter, some also release co-transmitters such as peptides with slower excitatory action
- Local inhibitory interneurons release GABA and glycine as fast transmitters, some also release co-transmitters.
- Descending inputs synapse with projection neurons, interneurons, and terminals of the nociceptors
Glutamate receptor families

NMDA receptors (NMDARs)
AMPA receptors
Kainate receptors
metabotropic Glu receptors

Synaptic transmission between nociceptors and dorsal horn neurons

Sensitization in the pain pathway may result in hyperalgesia (hypersensitivity to a noxious stimulus) and allodynia (pain that results from a non-noxious stimulus).

- Peripheral sensitization
  skin and viscera
- Central sensitization
  dorsal horn
  higher centers
Thermal injury can cause hyperalgesia

Mechanical thresholds for pain were tested at sites A, B, and C before and after burns at sites A and D.

53°C stimulus at both sites for 30 sec

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

Central sensitization is sometimes due to neural plasticity in the spinal cord dorsal horn:
- Activation of nociceptive dorsal horn neurons
- Modulation producing long lasting central sensitization
Activation of neural plasticity in the spinal cord dorsal horn: fast EPSPs

Modulation of neural plasticity in the spinal cord dorsal horn: altered connectivity and cell death

Prostanoids and central sensitization

[Diagrams and text fragments not legible due to image quality]
Ascending nociceptive pathway

- Spinothalamic tract (STT)
  - Lamina I - mostly high threshold input, fibers cross to lateral funiculus - many projections ascend to the thalamus - carry pain and temperature info
  - Lamina V - some low and high threshold input, fibers cross to anterior STT - many projections as ascend to thalamus - also important in pain signaling

- Spinoreticular (SRT)
- Spinomesencephalic tract (SMT)
- Spinohypothalamic tract (SHT)

Descending pathway that regulates nociceptive signaling in dorsal horn

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

Descending brainstem connections for pain modulation: on and off reflexes
Opioids are important regulators of nociceptive signaling and they act at many levels of the nervous system:
- primary afferents
- dorsal horn neurons
- higher centers

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
- 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 and receive descending regulatory input from 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