Pain and Analgesia

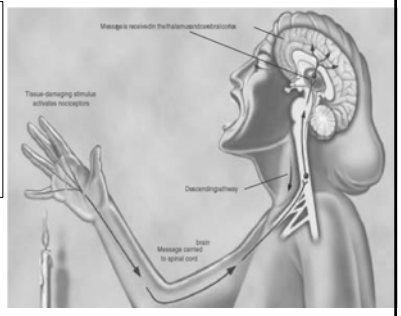
PAIN IS

-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

Amy MacDermott, PhD Department of Physiology and Cellular Biophysics and the Center for Neurobiology and Behavior.

BB 1109, 305-3889

Fig from Brain Awareness – SFN 2003

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**

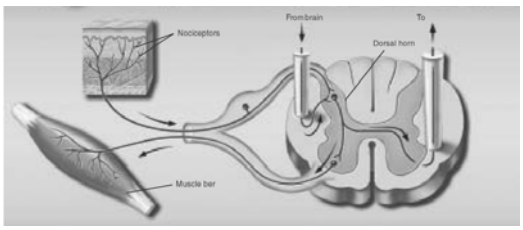
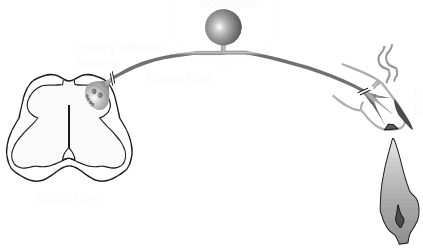


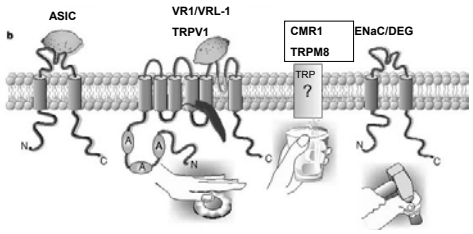
Fig from Brain Awareness – SFN 2003

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



Thermal
Mechanical
Chemical

Signal transduction in nociceptors



VR1 – vanilloid receptor 1 or TRPV1

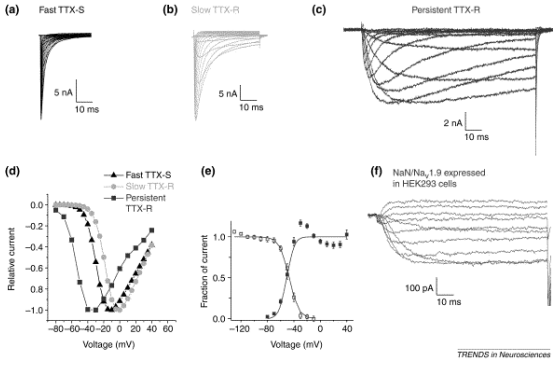
CMR1 – cold and menthol activated receptor 1 or TRPM8

ASIC – acid sensing ion channel

Degenerin family

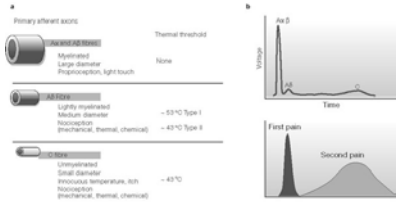
Modified from Julius and Basbaum, 2001

Nociceptor-specific Na+ channels



Dib-Hajj et al, 2002

Afferent fiber conduction and pain

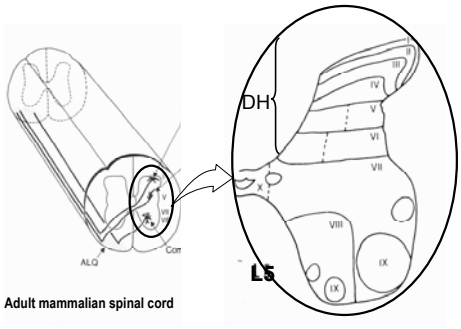


-- Nociceptors include both Aδ and C fibers

-- Most, but not all, small diameter fibers are nociceptors. Some are thermal and low threshold mechanoreceptors

Julius and Basbaum, 2001

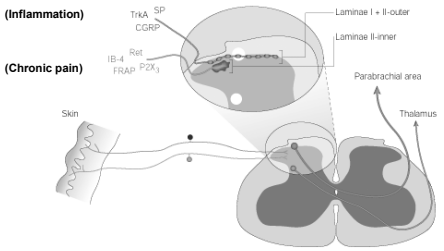
Nociceptive inputs go to lamina I, II and V in the dorsal horn



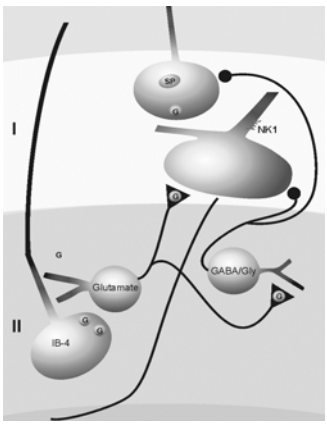
Adult mammalian spinal cord

Adapted from Fields, 1987

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



Hunt and Mantyh, 2001



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

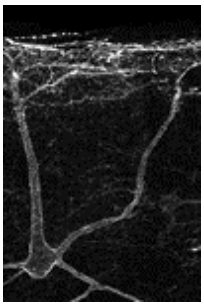
-projection neurons
-excitatory interneurons
-inhibitory interneurons

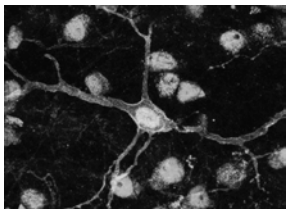
Dorsal horn neurons expressing receptor for substance P, the NK1 receptor.

Lamina I

Lamina II

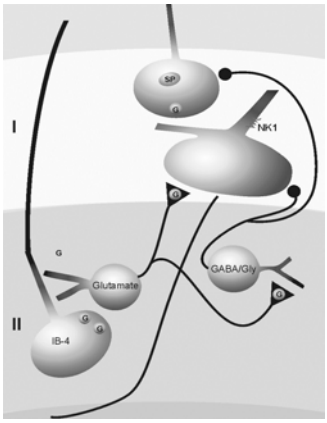
Lamina III





Lamina I projection neuron

Hunt and Mantyh, 2001



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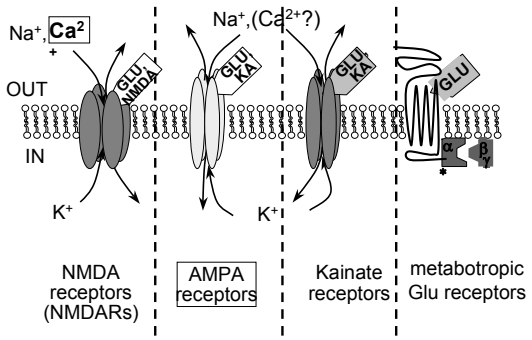
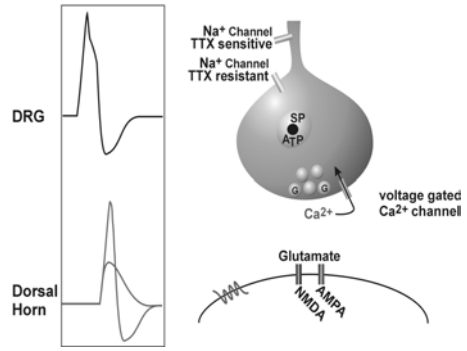
Synaptic transmission in the dorsal horn

- **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



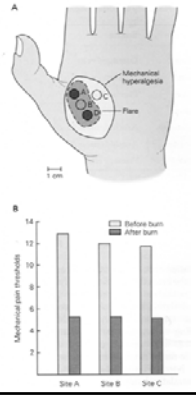
Synaptic transmission between nociceptors and dorsal horn neurons



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

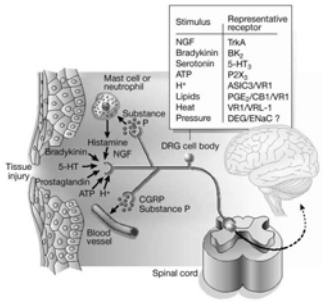


Mechanical thresholds for pain were tested at sites A,B, and C before and after burns at sites A and D.

53°C stimulus at both sites for 30 sec

Kandel, Schwartz Jessell Ch 24

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

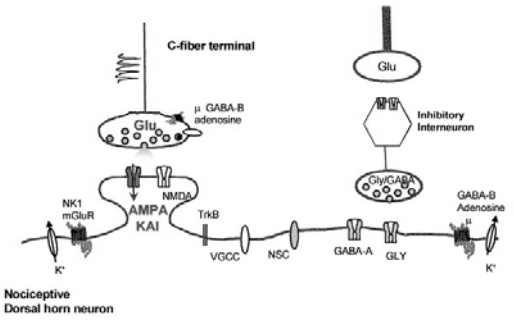
Bradykinin from plasma kininogen

Julius and Basbaum, 2001

Central sensitization is sometimes due to neural plasticity in the spinal cord dorsal horn:

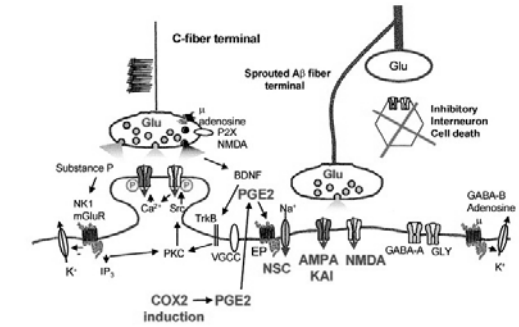
- Activation of nociceptive dorsal horn neurons
- Modulation producing long lasting central sensitization

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



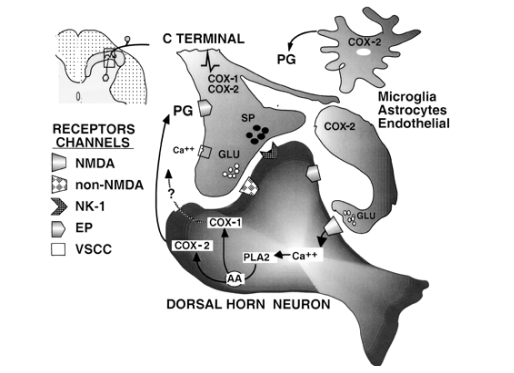
Woolf and Salter, 2000

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

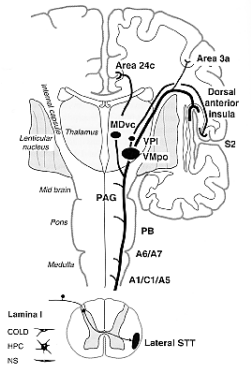


Woolf and Salter, 2000

Prostanoids and central sensitization



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 ascends to thalamus - also important in pain signaling

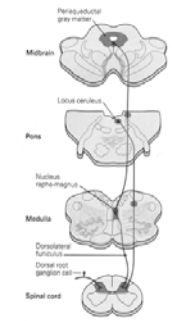
–Spinoreticular (SRT) and

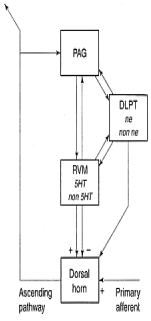
–Spinomesencephalic tract (SMT)

–Spinohypothalamic tract (SHT)

Wall and Melzack, Ch 7

Descending pathway that regulates nociceptive signaling in dorsal horn



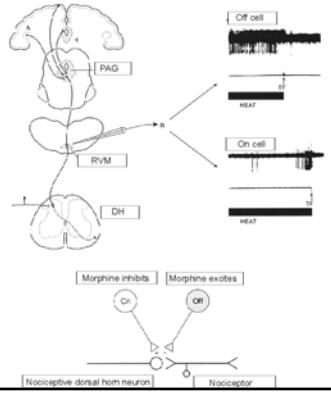


- •Descending Pathway
  - –Periaqueductal grey (PAG)
  - –Dorsolateral pontomesencephalic tegmentum (DLMT)
  - –Rostral ventromedial medulla (RVM)
    - –Nucleus raphe magnus
    - –Reticular formation
  - –Dorsal horn

Kandel, Schwartz, Jessell Ch 24

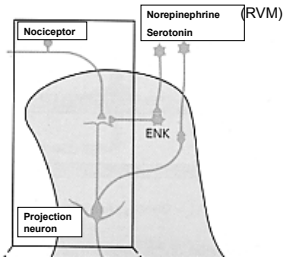
Wall and Melzack, Ch 11

Descending brainstem connections for pain modulation: on and off cells



Wall and Melzack,

Opioids are important regulators of nociceptive signaling and they act at many levels of the nervous system:
- **primary afferents**
- **dorsal horn neurons**
- **higher centers**



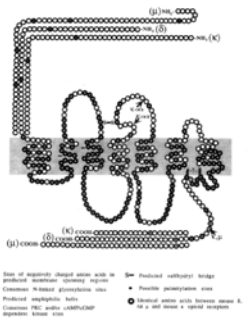
Kandel Schwartz Jessell Ch 24

Opioid receptors – 3 gene families

μ opioid receptor – activated by morphine, β endorphin and enkephalins

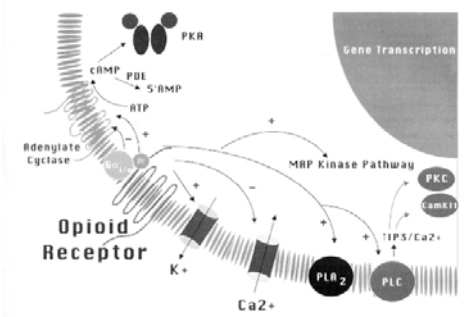
κopioid receptor activated by dynorphin

δ opioid receptors activated by enkephalins and β endorphin



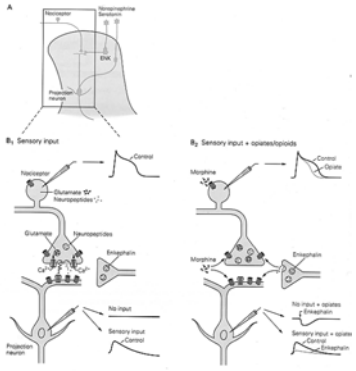
Bonica's Management of Pain Ch 4

Opioid receptor action



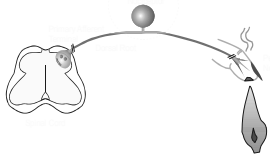
Bonica's Management of Pain Ch 4

Local circuit interneurons



Kandel, Schwartz, Jessell Ch 24

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 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