

Anatomy,  
Physiology, and  
Pharmacology of  
**Pain**

1.

Introduction



# Pain

- X Pain is not one way transmission of from the periphery to the brain
- X Surgery causes multiple changes to the structure and function pain pathways that magnify pain transmission
- X Many patients have pre-existing disease of their pain pathways
- X Understanding diseases of the pain pathways is crucial for treating pain

# Pain

- X Over 50% of surgical patients report poor post-operative pain control
  - Delays wound healing, prolongs hospital stays, increased complications, increased costs, increases risk of chronic post-surgical pain
- X Chronic post-surgical pain accounts for over 50% of chronic pain
  - Chronic pain is more prevalent than all forms of cancer combined
- X Long term opioid use after surgery is the most common surgical complication
  - 1:10 - 1:15



2.

Anatomy & Physiology

# Pain

- X Is an unpleasant sensory and emotional experience associated with actual or potential tissue damage.
  - Transmission
    - Peripheral nerves (1<sup>st</sup> order neurons)
    - Spine (2<sup>nd</sup> order neurons)
  - Perception
    - Brain (3<sup>rd</sup> order neurons)
      - Pain Psychology
        - Optimism vs pessimism
        - Self-efficacy vs catastrophizing
        - Happiness vs depression, anger, and fear
        - Active coping vs passive avoidance



# Peripheral Nervous System

## X A Beta

- Touch and pressure
- Interneuron

## X A Delta

- First/Fast Pain response

## X C

- Slow/long pain response
- Mechano/thermal/chemo responsive
- 15% silent respond only to inflammation

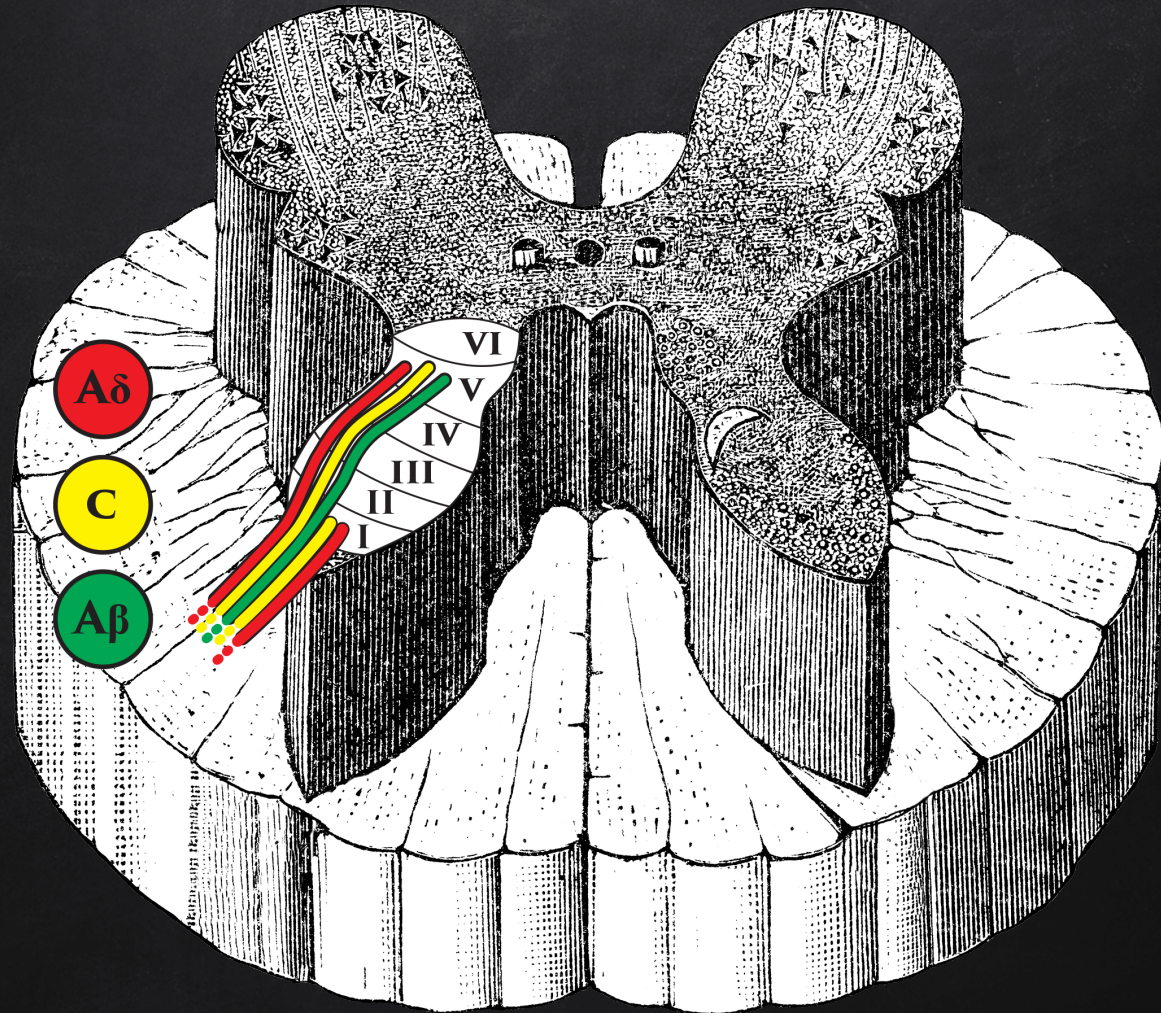
# Central Nervous System

- X Peripheral nerves synapse with the spinal nerves at the Rexed Lamina of the spinal cord
- X Each peripheral nerve ascends and descends to synapse at the Rexed Lamina of 4-5 dermatomes



# Central Nervous System

- X Rexed Lamina I
  - A Delta and C fibers
  - Nociceptive specific cells
- X Rexed Lamina V
  - A Beta, A Delta, and C fibers
  - Wide Dynamic Range neurons
- X Others
  - II, III, IV, VI





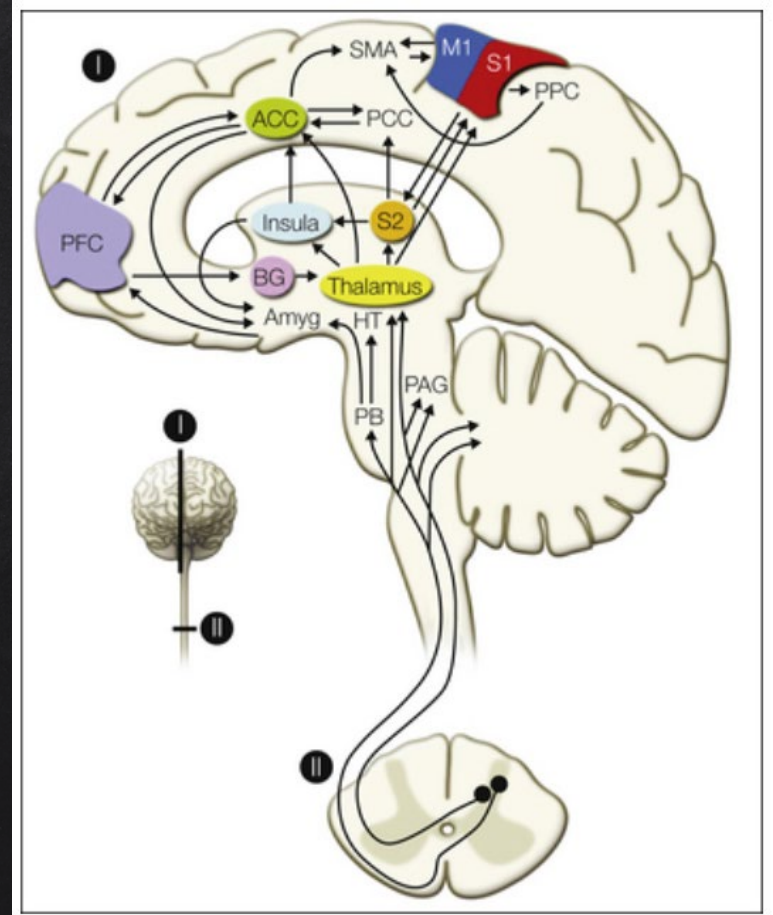
# CNS Ascending Tracts

## X Spino-Thalamic Tract

- Primary Ascending Tract
  - Spino-reticular, spino-mesencephalic, spino-parabrachial

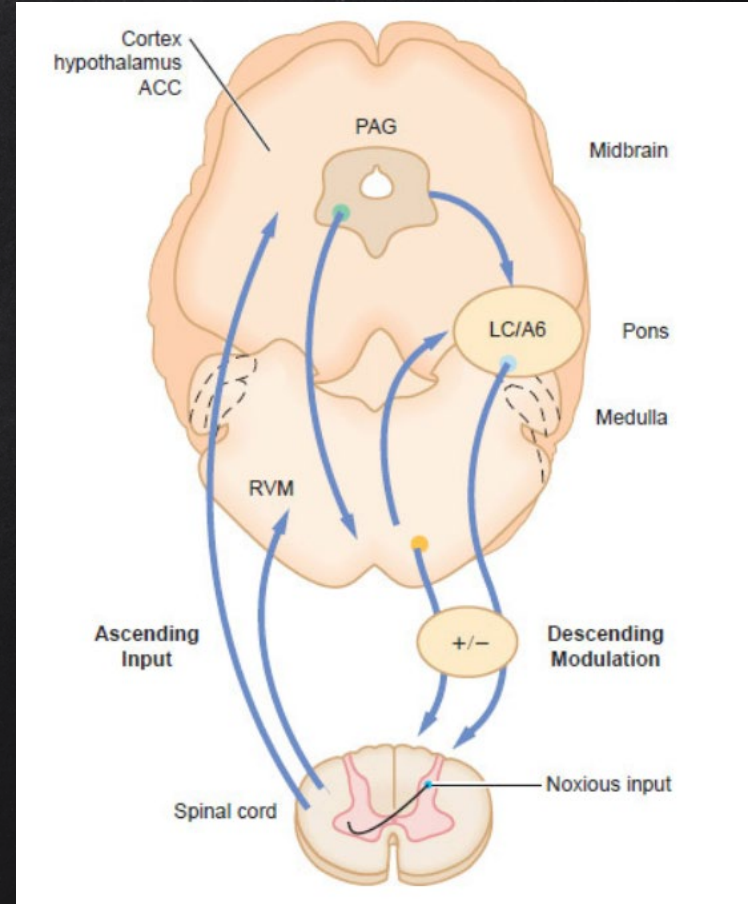
## X Thalamus

- Somatosensory Cortex
- Limbic System
- Prefrontal Cortex



# CNS Descending Tracts (DNIC)

- X Diffuse Noxious Inhibitory Control
- X Periaqueductal Gray
  - Endorphins, dynorphins, enkephalins
- X Rostral Ventral Medial Medulla, Locus Cereulus
  - Norepinephrine, Serotonin, Descending pain pathways





# DNIC

## X A Beta

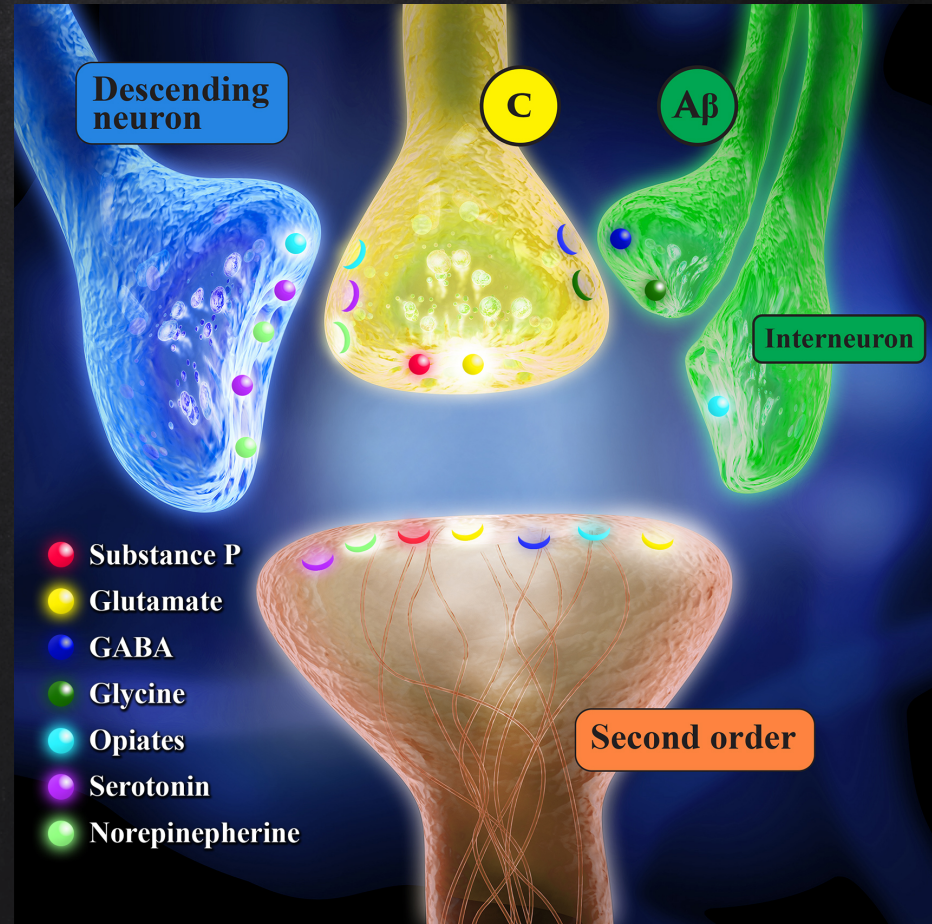
- Interneuron release GABA, Glycine
- Inhibits peripheral and spinal neurons

## X Periaqueductal Gray

- Releases endorphins, dynorphins, enkephalins
- Activates rostral ventral medial medulla, locus coeruleus
  - Serotonin, norepinephrine
  - Descending pain pathways

# Excitatory Neurotransmitters

- X Glutamate
  - Primary neurotransmitter
  - AMPA/Na, NMDA/Ca, Kainate/Na & Ca, 8 mGluR
- X Substance P
  - NK1
- X Microglial Cells
  - Peripheral nerve injury causes release inflammatory mediators





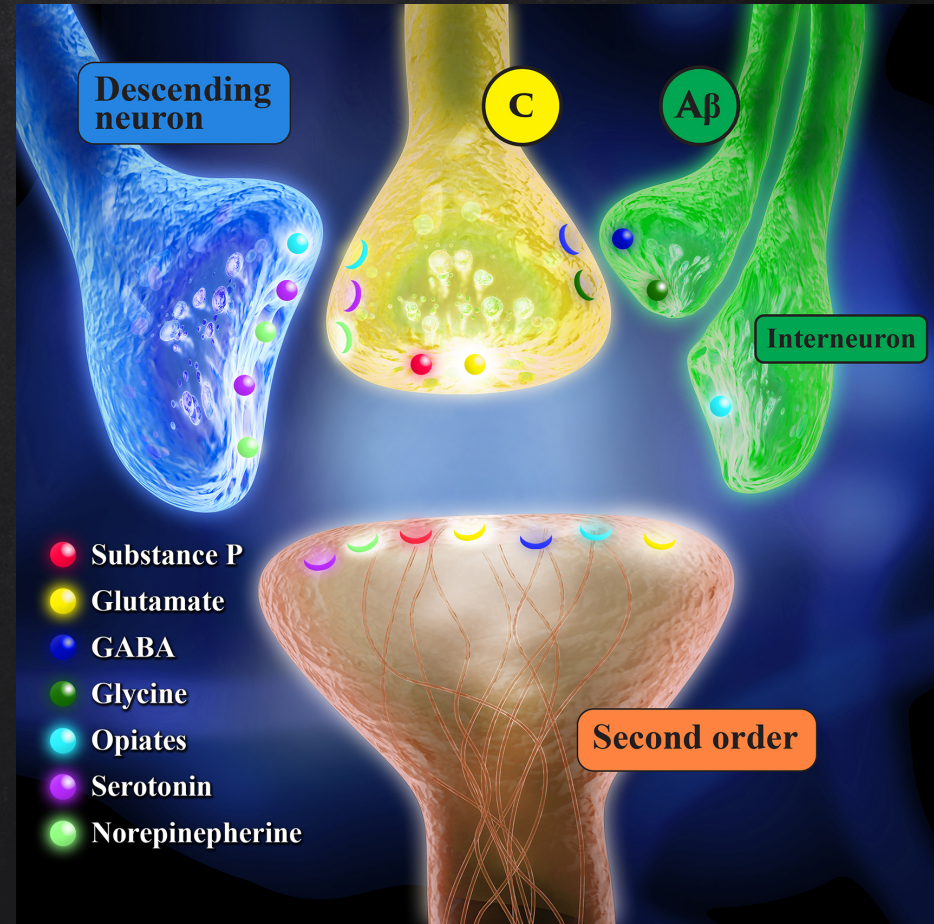
# Inhibitory Neurotransmitters

## X GABA

- GABA A & B receptor
- Pre & Post synaptic

## X Glycine

- Strychnine receptors
- Pre & Post Synaptic





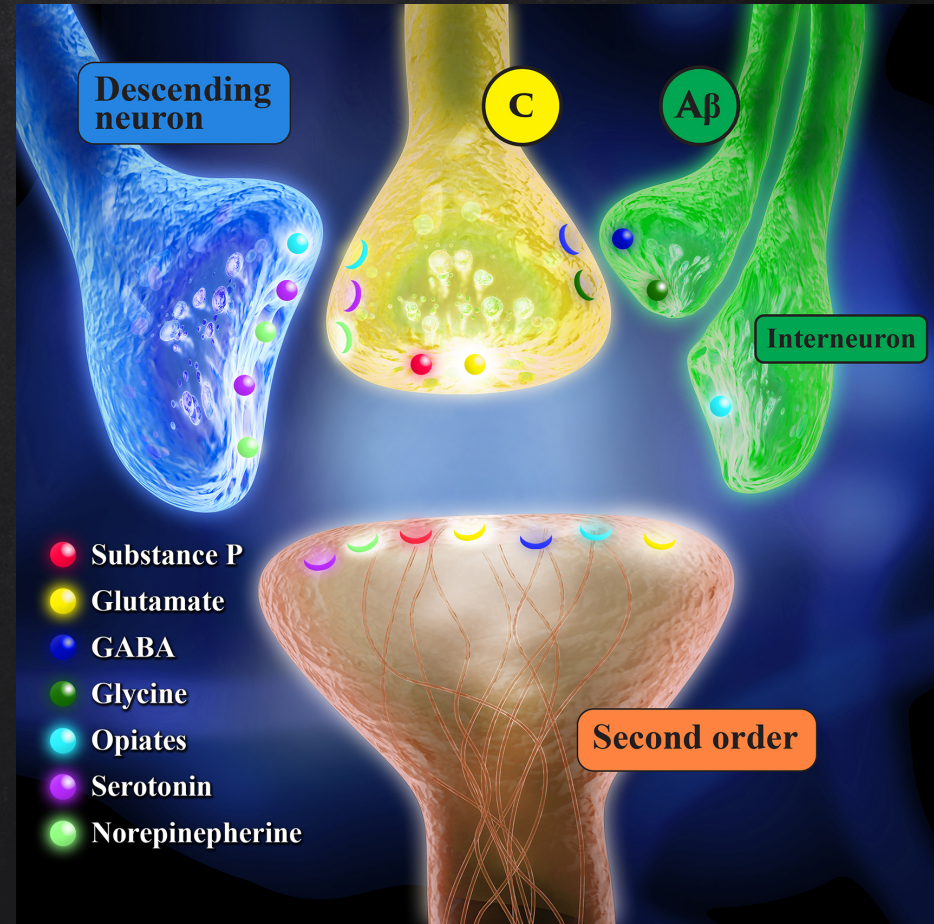
# Inhibitory Neurotransmitters

## X Norepinephrine

- Alpha 2 receptor
- Pre & Post Synaptic

## X Serotonin

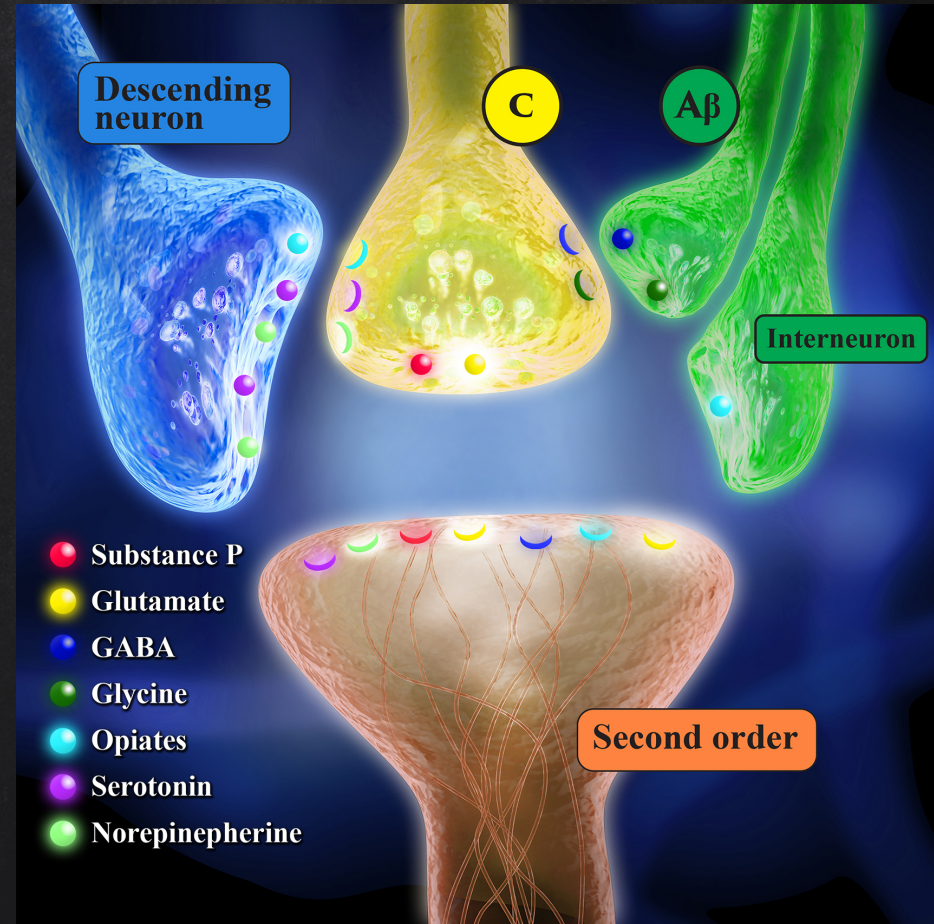
- 5HT2 receptor
- Post-synaptic





# Inhibitory Neurotransmitters

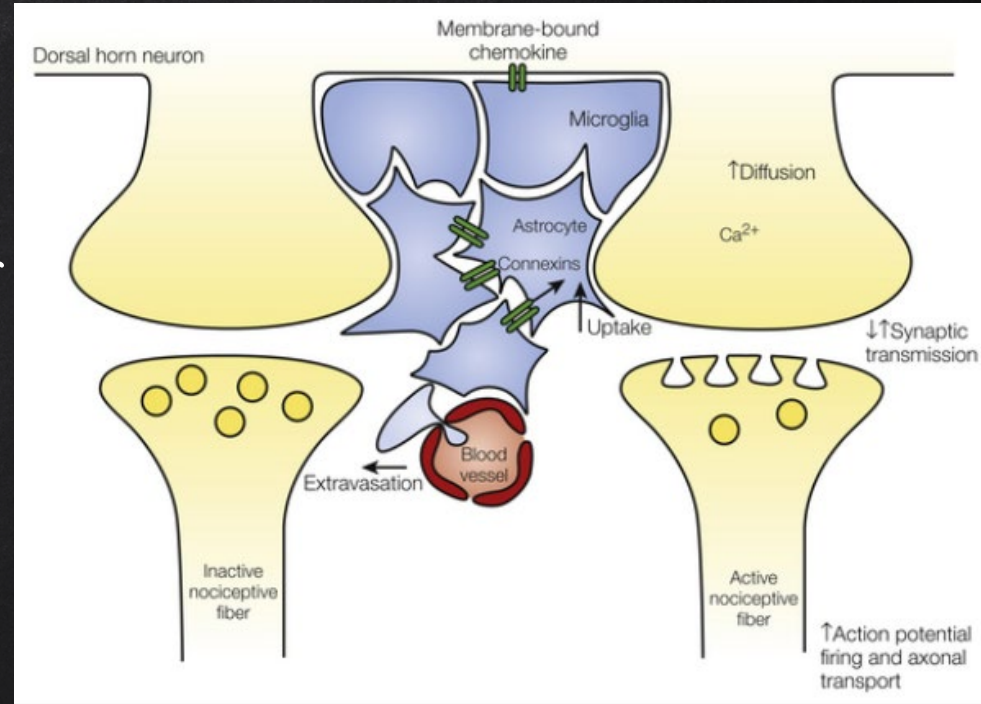
- X Endorphin, dynorphin, enkephalin
  - Mu, Kappa, Delta
  - Pre & Post Synaptic
  - Inhibit Ca & Kion channels



# Inhibitory Neurotransmitters

## X Endocannabinoids

- Anandamide & 2AG
- CB1 & CB2 receptors
- Inhibit microglia release of inflammatory mediators







3.

Pathophysiology

# Acute Surgical Pain

- X** Pathophysiologic process
  - Pain without stimulation
  - Hyperalgesia
- X** Changes to function and structure of the nerves
  - Peripheral sensitization
  - Central sensitization
  - Inflammation induced central sensitization
  - Allodynia



# Peripheral Sensitization

(primary Hyperalgesia)

- X Tissue damage causes release of inflammatory and immune mediators
- X Sensitizing soup
  - Bradykinin, Substance P, Histamine, Leukotrienes, Interleukins, etc

# Peripheral Sensitization

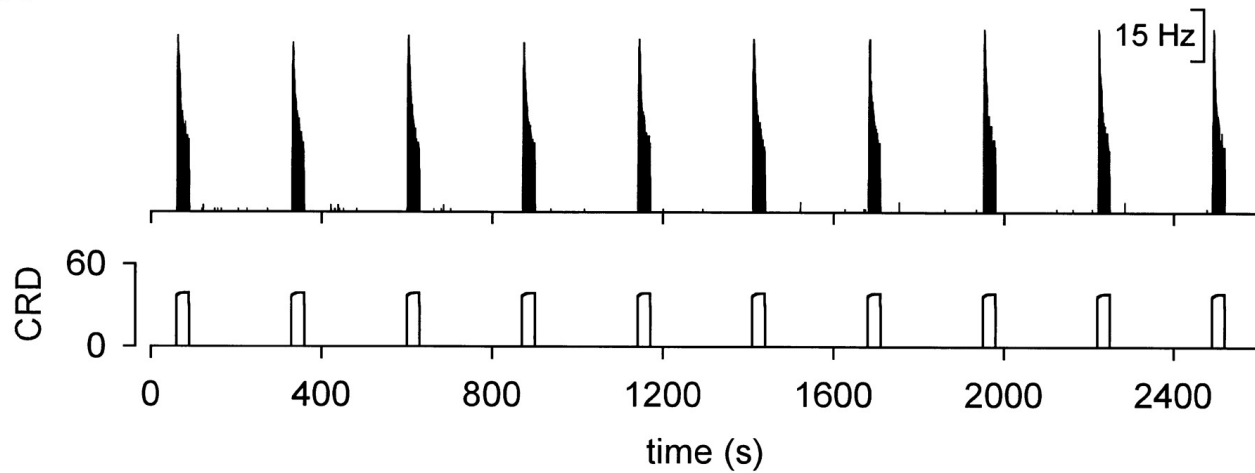
(primary Hyperalgesia)

## X C Fibers

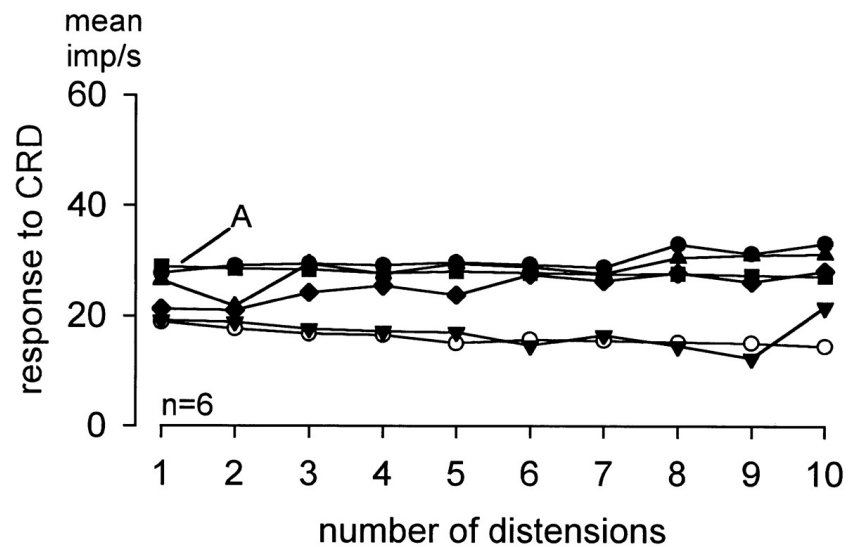
- Activation of silent fibers
- High threshold become low threshold
- Produce stronger stimulus with same stimulation
- Continue firing after stimulation has stopped
- Lose mechano/thermo/chemo specificity
- Nerve memory
  - Repeat exposure within 21 days leads to more severe changes
  - Can lead to permanent changes in nerve function

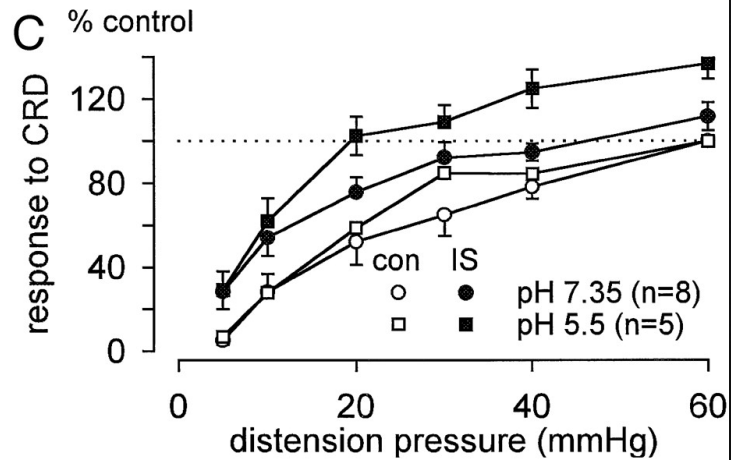
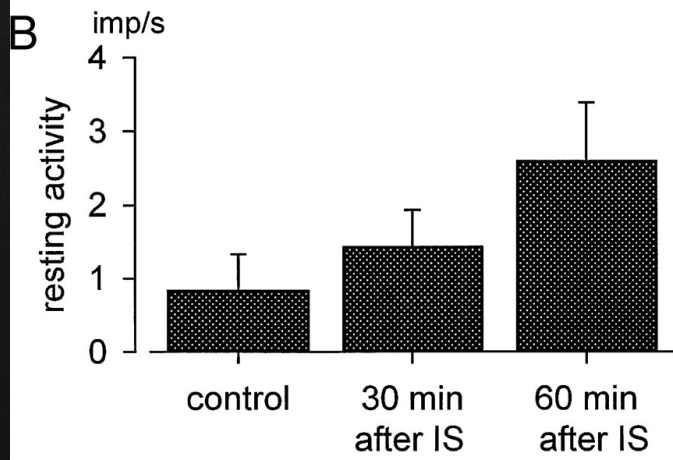
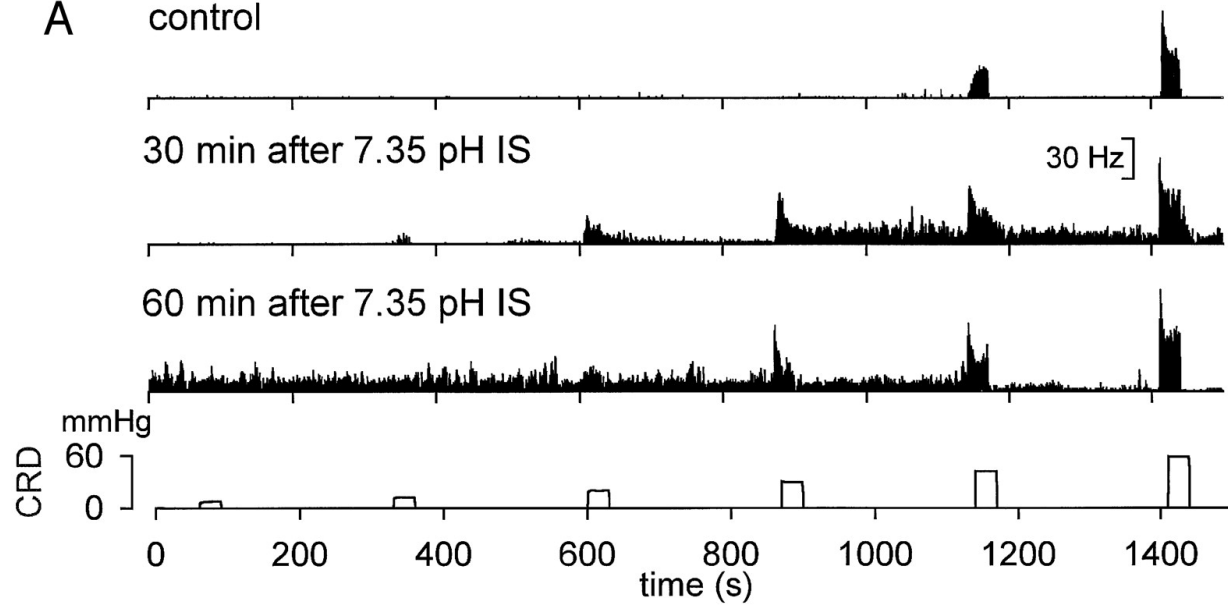


A



B







# Inflammation Induced Central Sensitization

- X Peripheral Nerve Injury activates microglial cells
- X Microglia release inflammatory mediators that bind to receptors on spinal nerve fibers causing sensitization
- X Can be blocked through CB receptors on microglia and COX 2 inhibitors that prevent inflammatory mediators from binding to receptors on spinal nerve fibers

# Central Sensitization

## (Secondary Hyperalgesia)

### X Wind Up

- Peripherally sensitized C fibers release excess glutamate into synaptic cleft
- Mg plug blocking Ca channel is lost
- Body creates more AMPA receptors
- Starts in minutes



Descending neuron

C

Aβ

Interneuron

Glutamate

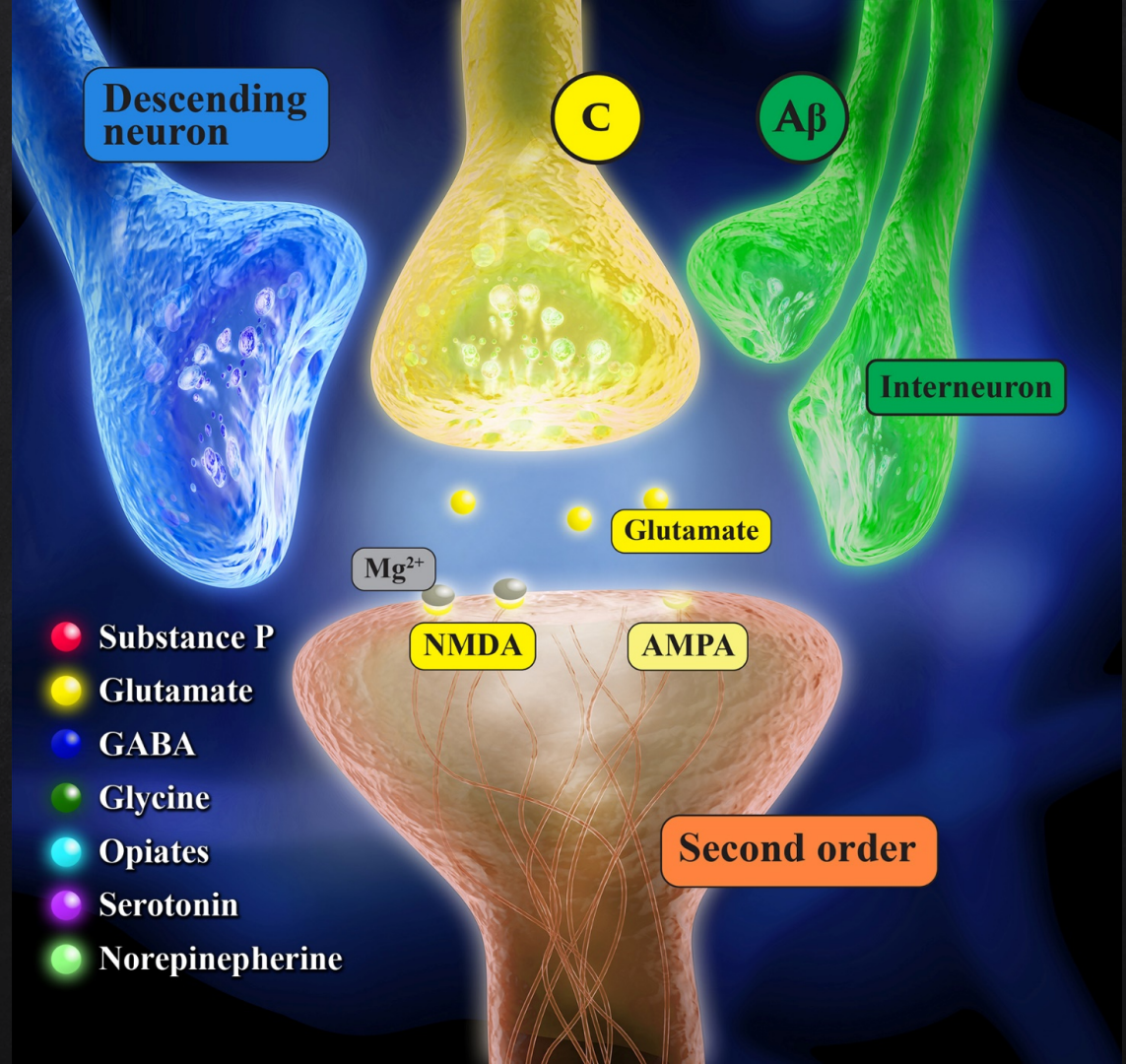
Mg<sup>2+</sup>

NMDA

AMPA

Second order

- Substance P
- Glutamate
- GABA
- Glycine
- Opiates
- Serotonin
- Norepinephrine



Descending neuron

C

A $\beta$

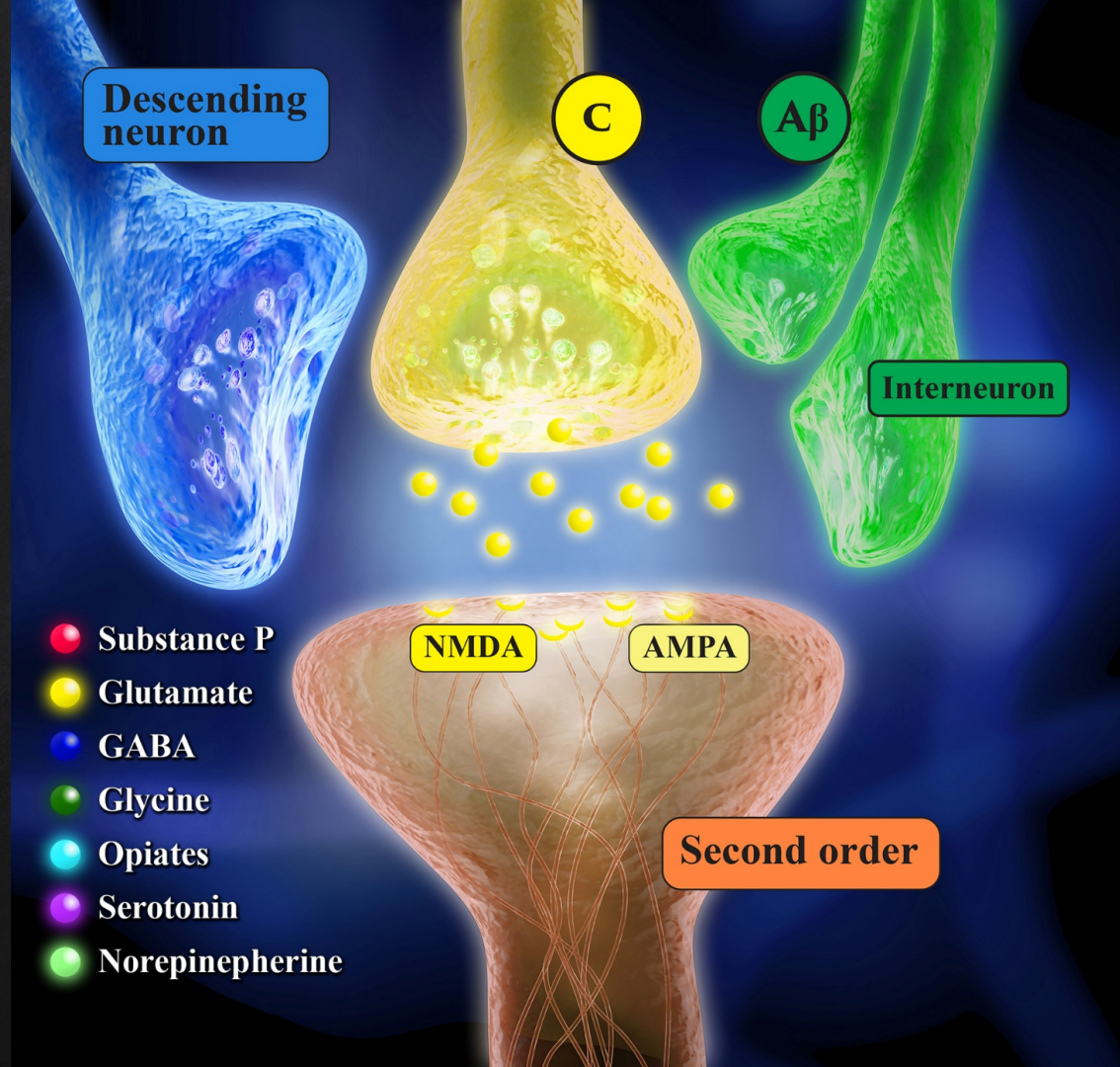
Interneuron

- Substance P
- Glutamate
- GABA
- Glycine
- Opiates
- Serotonin
- Norepinephrine

NMDA

AMPA

Second order





# Allodynia

- X Inactivation of the interneuron
- X A Beta fibers lose inhibitory effect
- X Touch and pressure becomes painful

Descending neuron

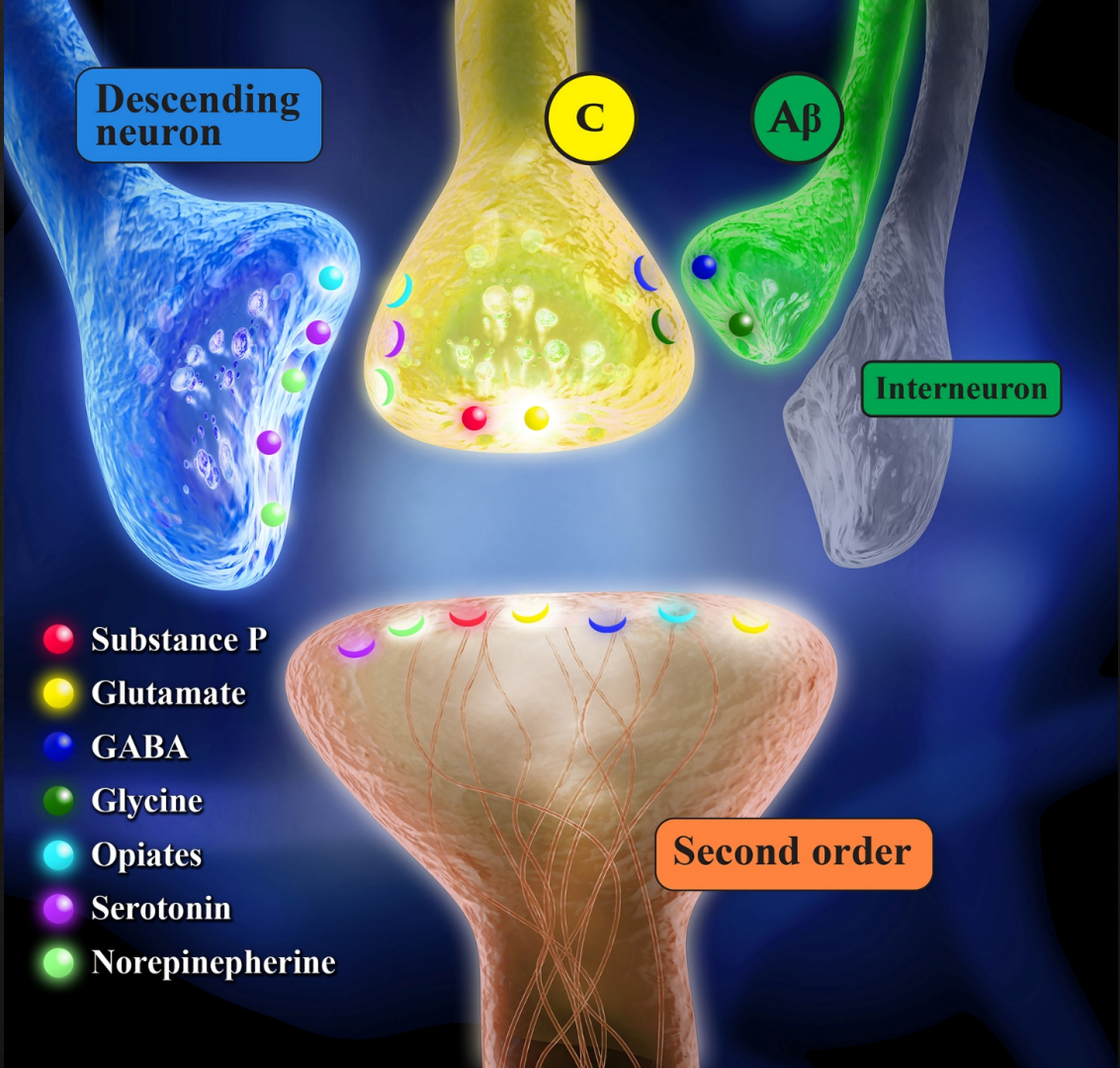
C

A $\beta$

Interneuron

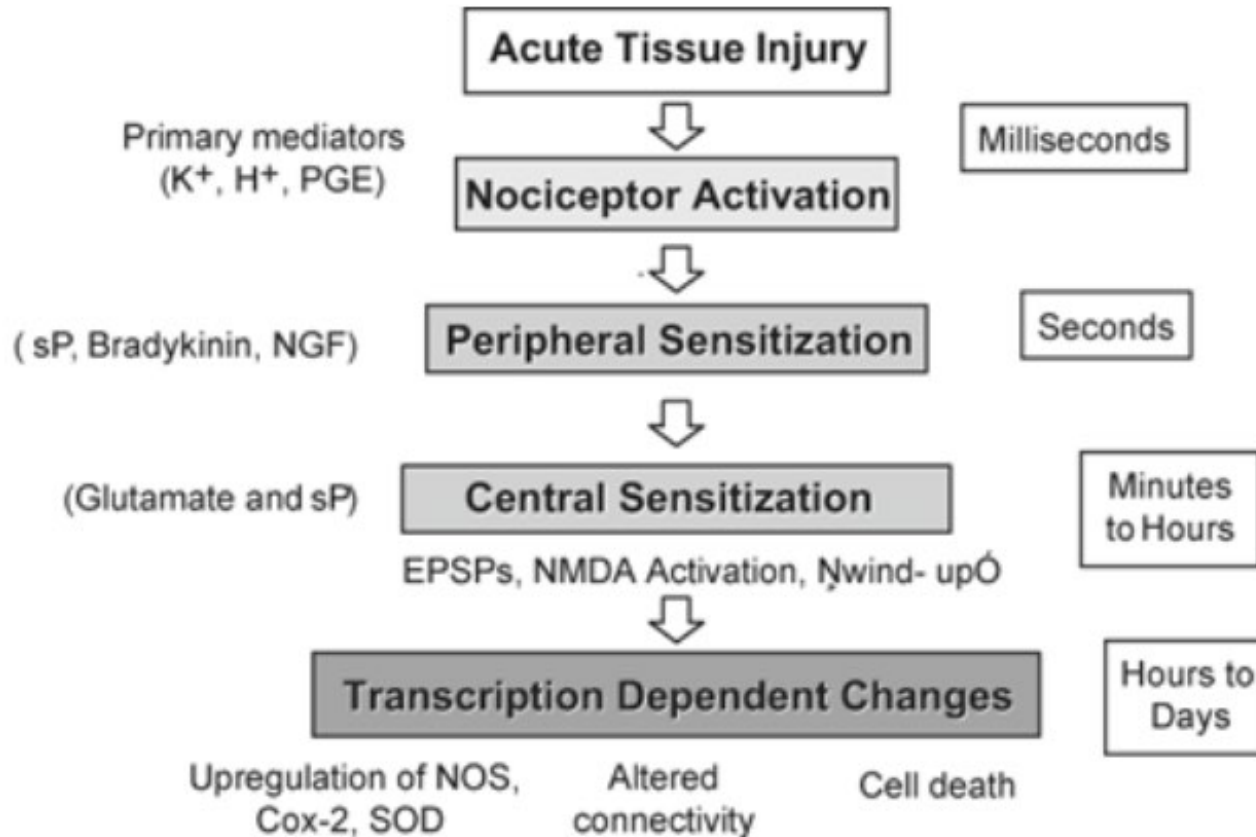
- Substance P
- Glutamate
- GABA
- Glycine
- Opiates
- Serotonin
- Norepinephrine

Second order





# Chronic Post - Surgical Pain



# Chronic Post - Surgical Pain

- X** Pain after the healing is complete
  - 3-6 months
- X** 40% of chronic pain patients
- X** No reliable way to Predict
  - Poorly controlled pain first 48 hours
  - Cause or effect?
- X** Type of surgery
  - Sternotomy
  - Thoracotomy
  - Breast
  - Amputation



# Chronic Post - Surgical Pain

## X Prevention

- Mixed results
  - No silver bullet
  - Combination therapy
    - Regional/neuraxial anesthetic
    - Anti-inflammatories
    - Central antagonists
    - Avoidance opioids