Anatomy, Physiology, and Pharmacology of Pain

Introduction

Pain

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

Pain

- ✗ 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
- ✗ Chronic post-surgical pain accounts for over 50% of chronic pain
  - Chronic pain is more prevalent than all forms of cancer combined
- ✗ Long term opioid use after surgery is the most common surgical complication
  - 1:10 - 1:15

Anatomy & Physiology

Pain

- ✗ Is an unpleasant sensory and emotional experience associated with actual or potential tissue damage.
  - Transmission
    - Peripheral nerves (1st order neurons)
    - Spine (2nd order neurons)
  - Perception
    - Brain (3rd 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

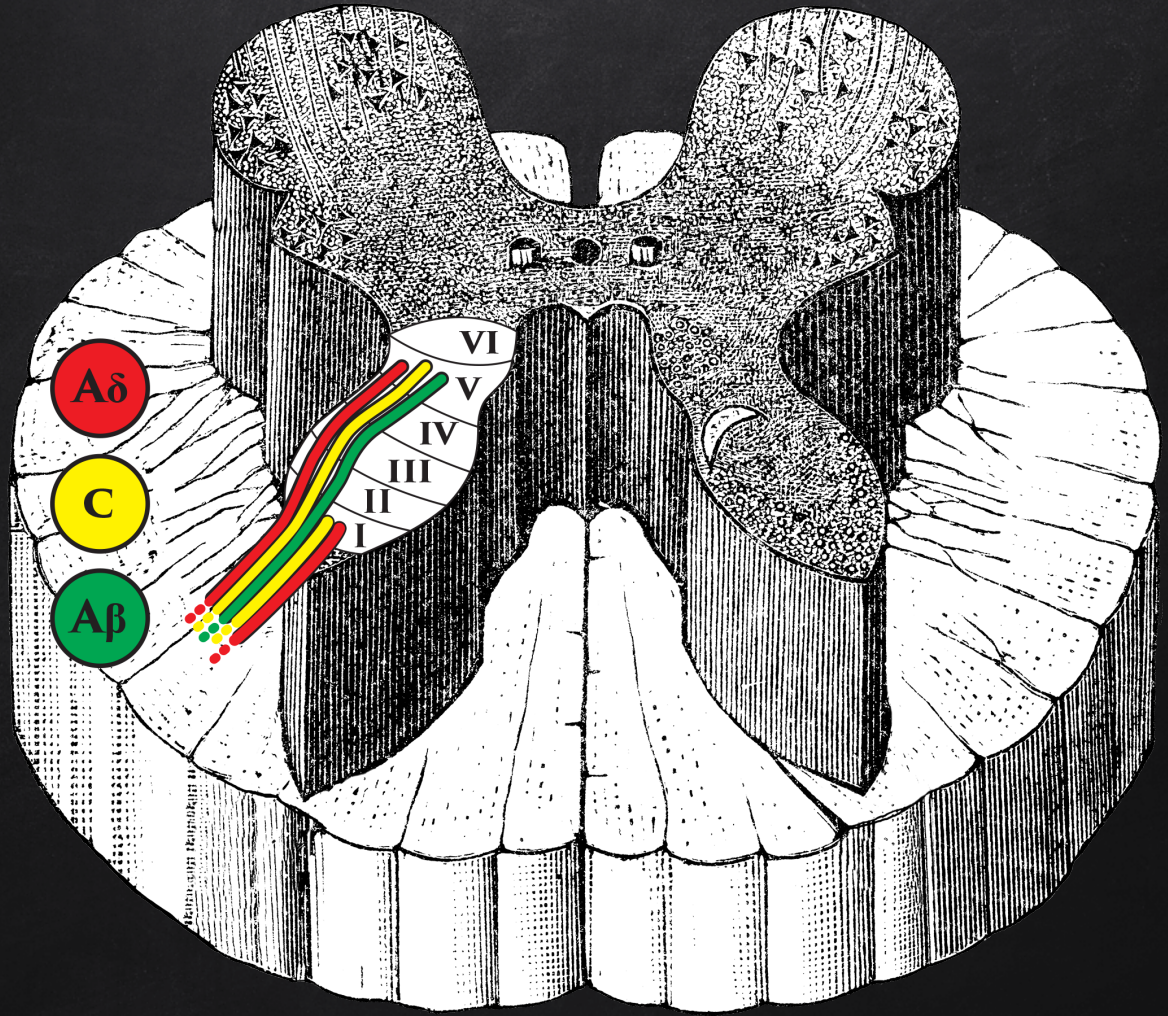
- A Beta
  - Touch and pressure
  - Interneuron
- ADelta
  - First/Fast Pain response
- C
  - Slow/long pain response
  - Mechano/thermal/chemo responsive
  - 15%silent respond only to inflammation

Central Nervous System

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

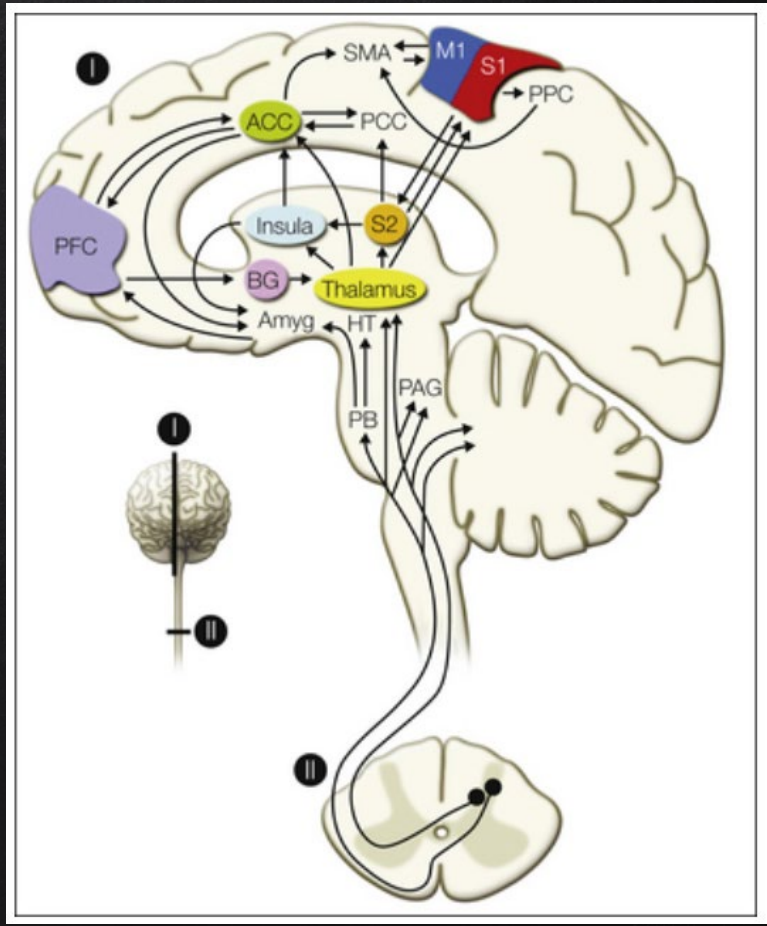
Central Nervous System

- ✗ RexedLamina I
  - ADelta and C fibers
  - Nociceptive specific cells
- ✗ Rexed Lamina V
  - ABeta, ADelta, and C fibers
  - Wide Dynamic Range neurons
- ✗ Others
  - II,III,IV,VI


Aδ
C
Aβ
VI
V
IV
III
II
I

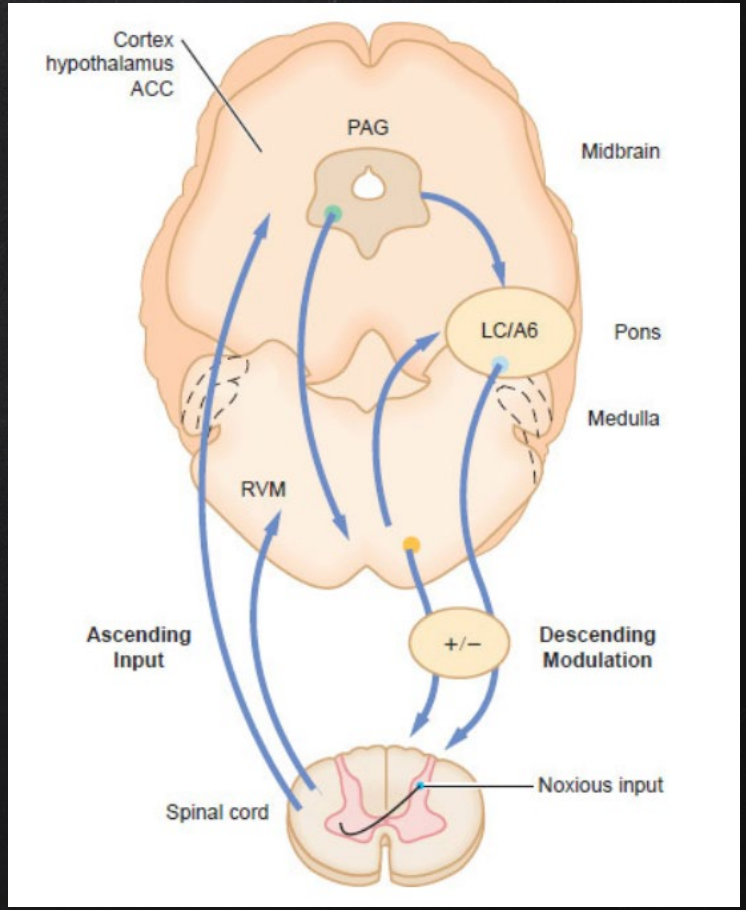
CNS Ascending Tracts

- ✗ Spino-Thalamic Tract
  - Primary Ascending Tract
    - Spino-reticular, spino-mesencephalic, spino-parabrachial
- ✗ Thalamus
  - Somatosensory Cortex
  - Limbic System
  - Prefrontal Cortex



CNS Descending Tracts (DNIC)

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

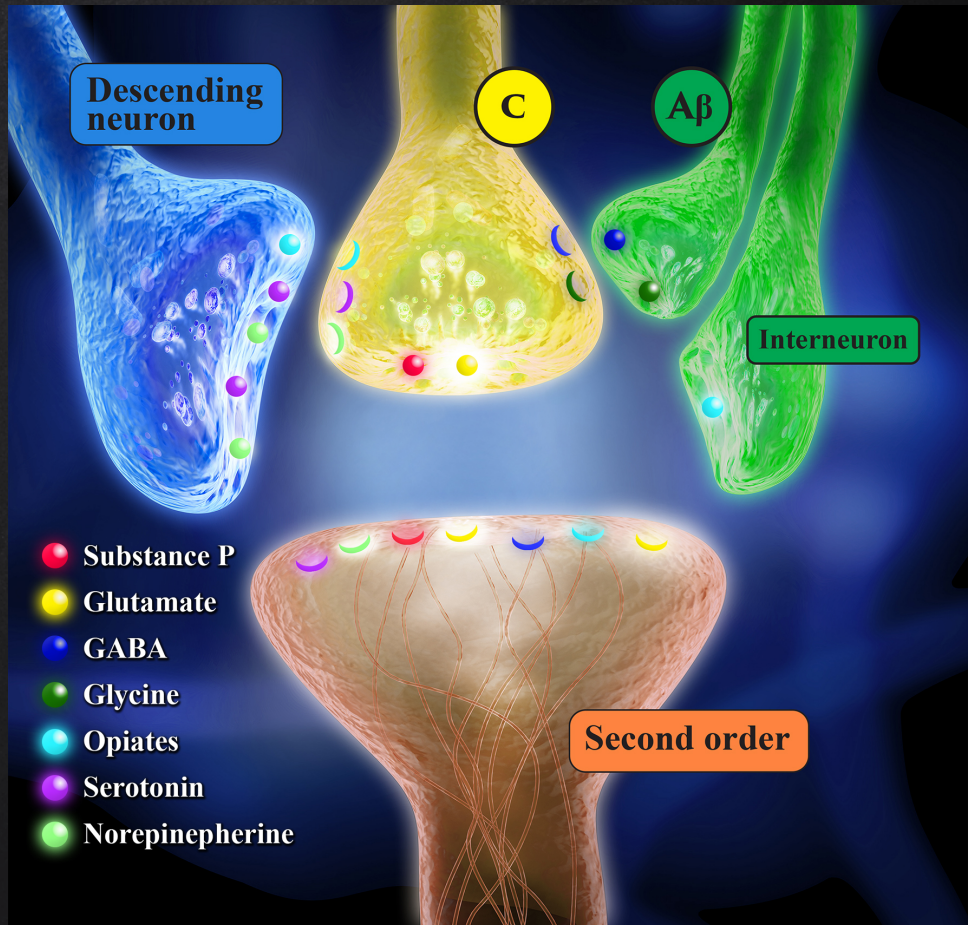


DNIC

- ✗ A Beta
  - Interneuron release GABA, Glycine
  - Inhibits peripheral and spinal neurons
- ✗ Periaqueductal Gray
  - Releases endorphins, dynorphins, enkephalins
  - Activates rostral ventral medial medulla, locus ceurulus
    - Serotonin, norepinephrine
    - Descending pain pathways

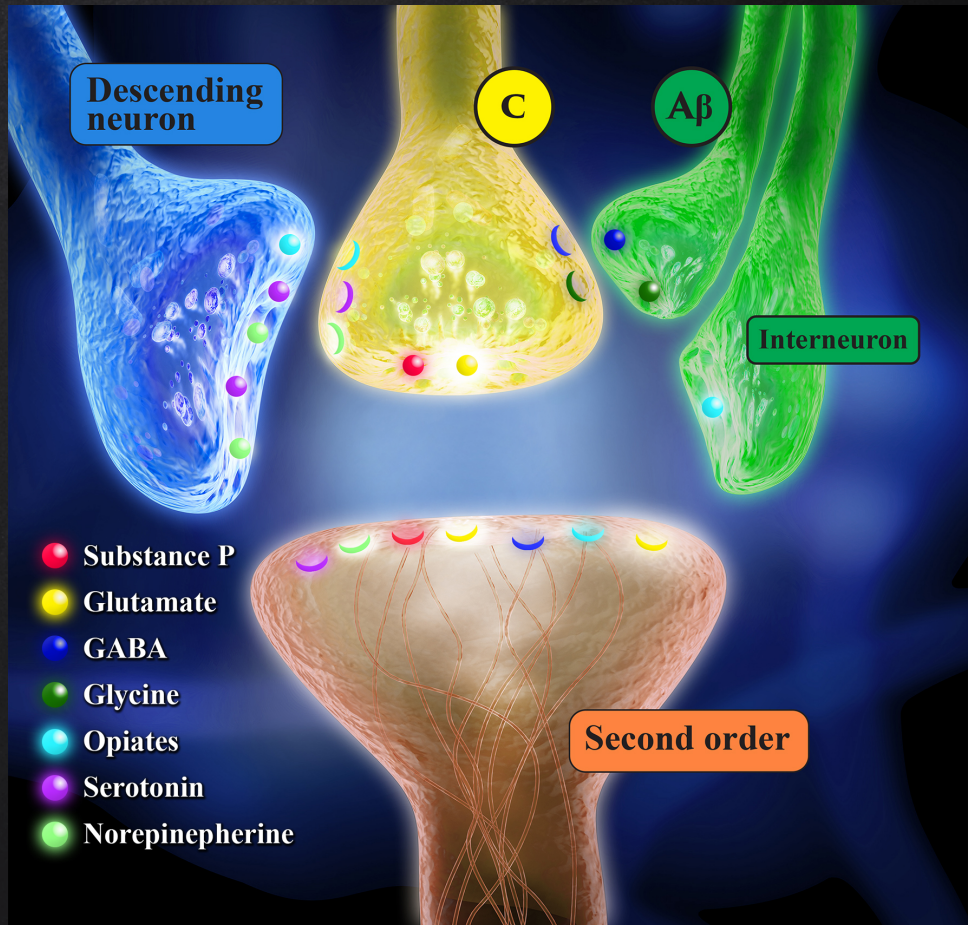
Excitatory Neurotransmitters

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



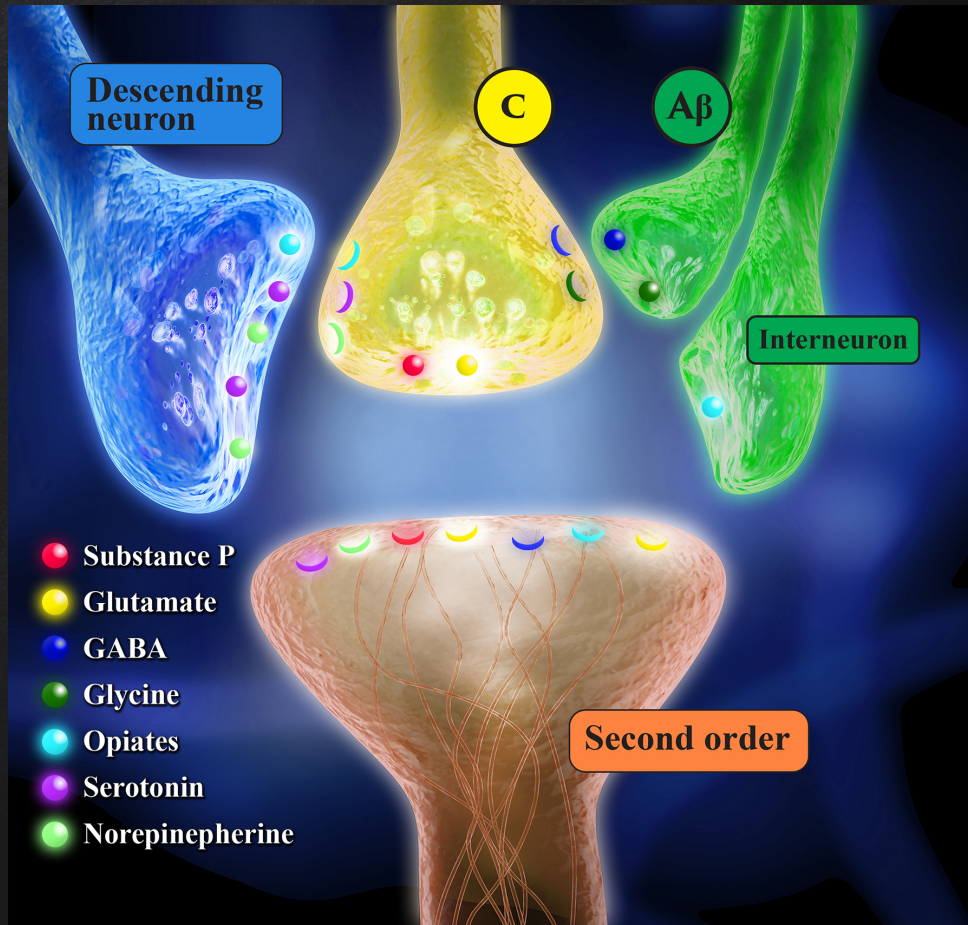
Inhibitory Neurotransmitters

- ✗ GABA
  - GABA A & B receptor
  - Pre & Post synaptic
- ✗ Glycine
  - Strych receptors
  - Pre & Post Synaptic



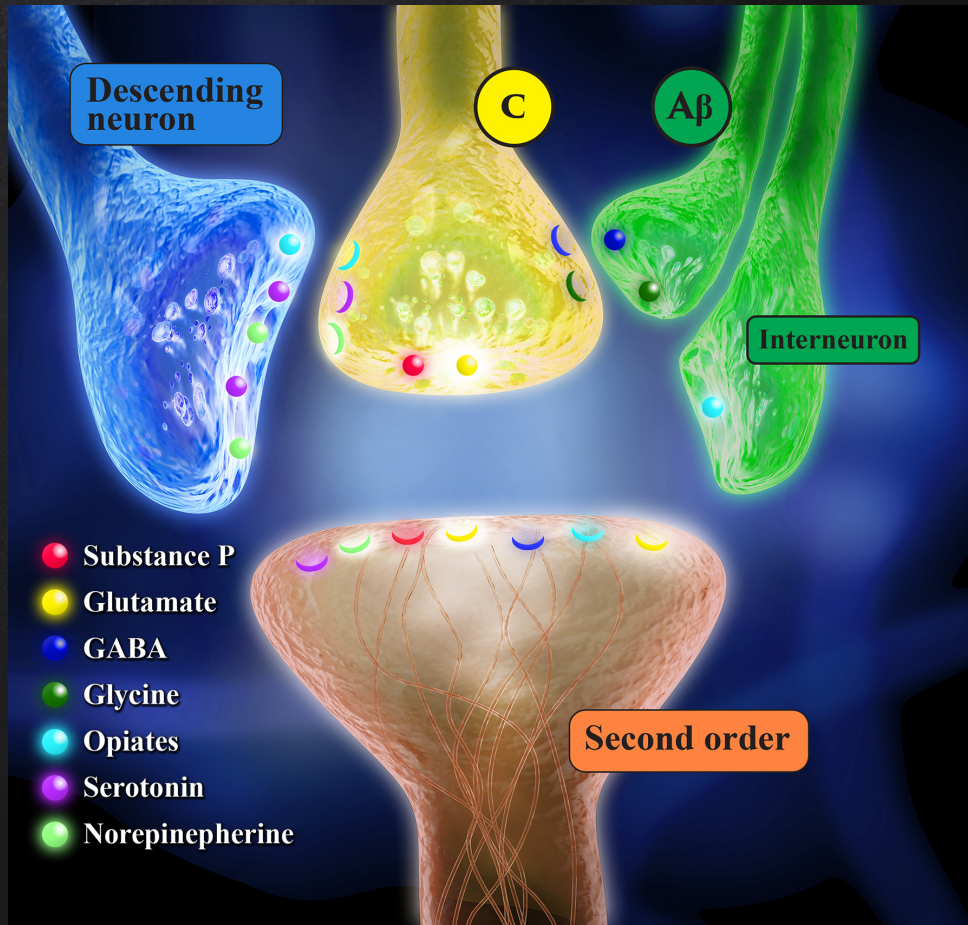
Inhibitory Neurotransmitters

- ✗ Norepinephrine
  - Alpha 2 receptor
  - Pre &Post Synaptic
- ✗ Serotonin
  - 5HT2 receptor
  - Post-synaptic



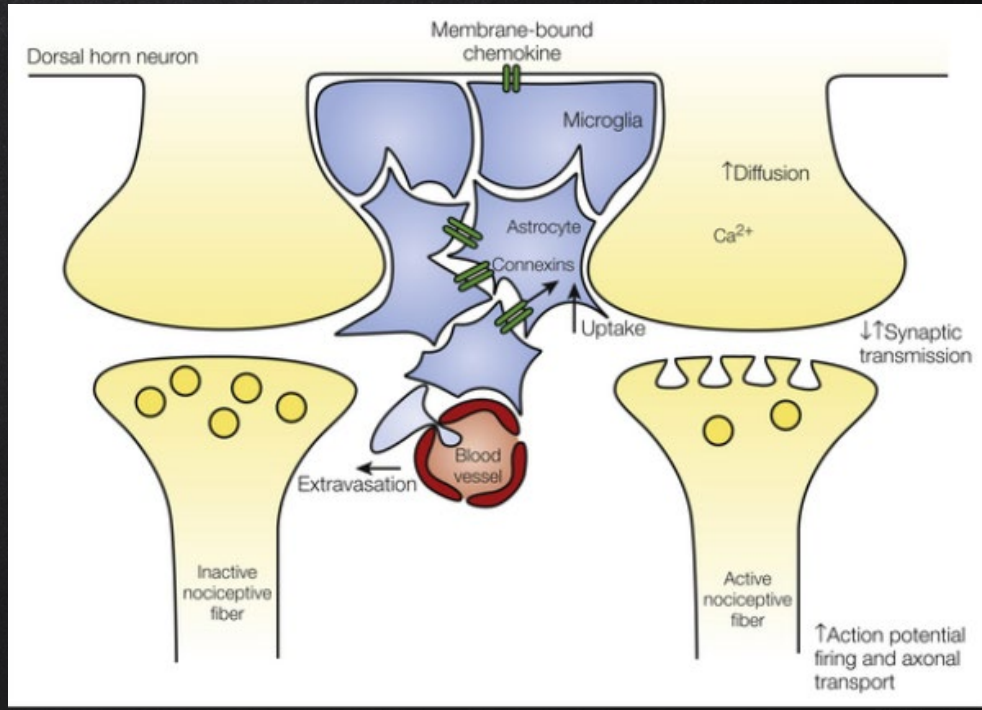
Inhibitory Neurotransmitters

- ✗ Endorphin, dynorphin, enkephalin
  - Mu, Kappa, Delta
  - Pre & Post Synaptic
  - Inhibit Ca & K ion channels



Inhibitory Neurotransmitters

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



Pathophysiology

Acute Surgical Pain

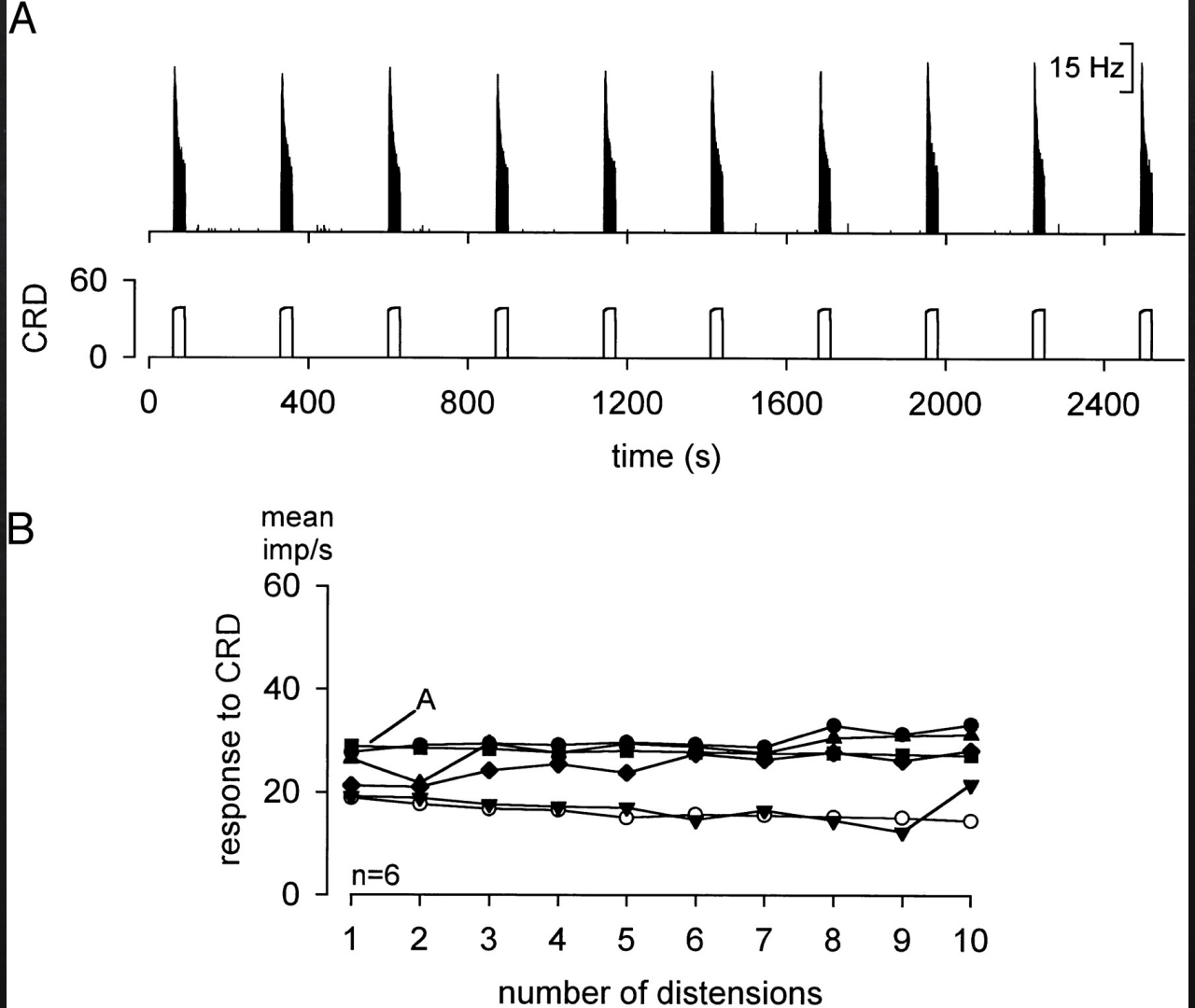
- ✗ Pathophysiologic process
  - Pain without stimulation
  - Hyperalgesia
- ✗ Changes to function and structure of the nerves
  - Peripheral sensitization
  - Central sensitization
  - Inflammation induced central sensitization
  - Allodynia

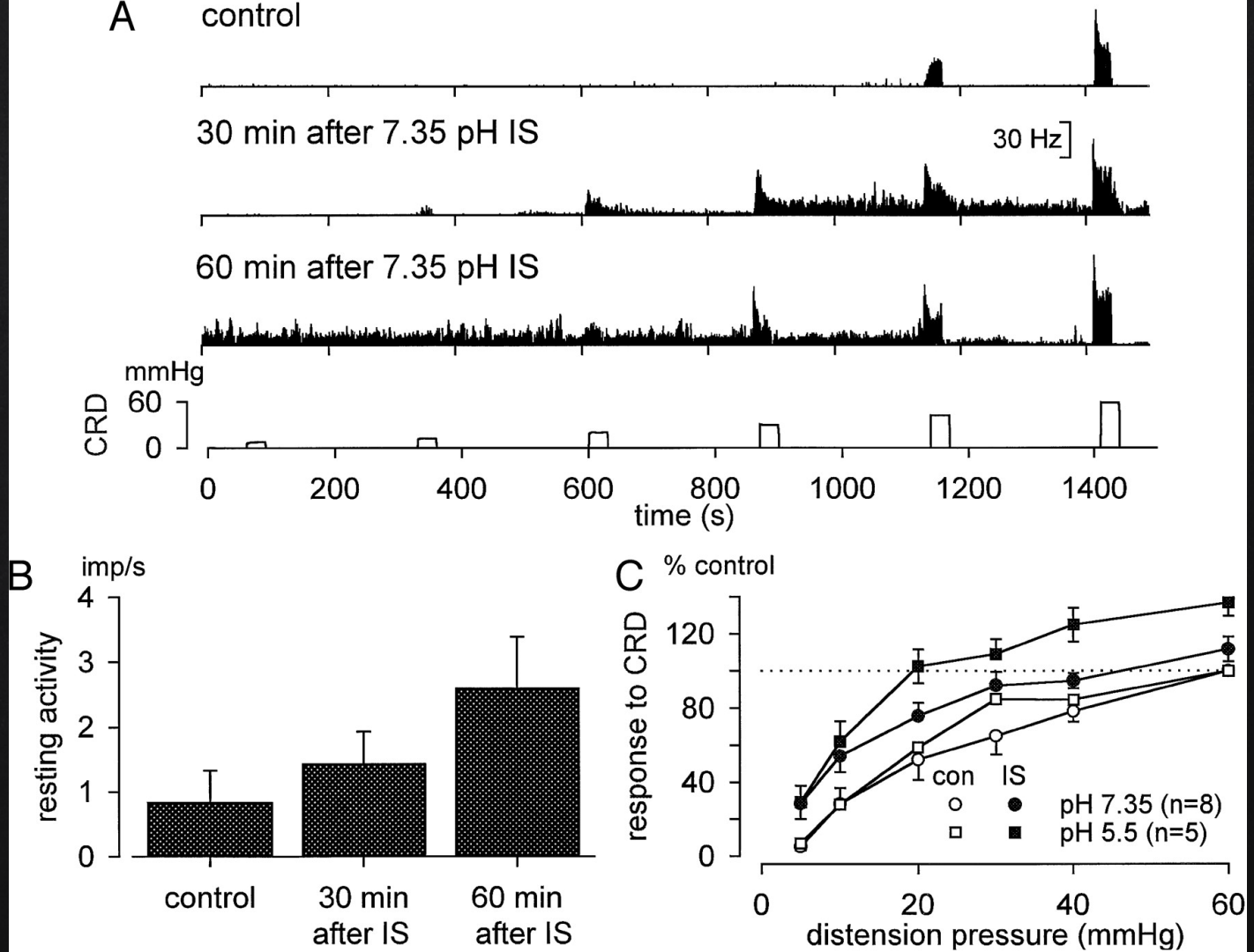
Peripheral Sensitization
(primary Hyperalgesia)

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

Peripheral Sensitization
(primary Hyperalgesia)

- ✗ 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/thermos/chemo specificity
  - Nerve memory
    - Repeat exposure within 21 days leads to more severe changes
    - Can lead to permanent changes in nerve function


A
15 Hz
CRD
60
0
0
400
800
1200
1600
2000
2400
time (s)
B
mean
imp/s
60
40
20
0
response to CRD
A
n=6
1
2
3
4
5
6
7
8
9
10
number of distensions

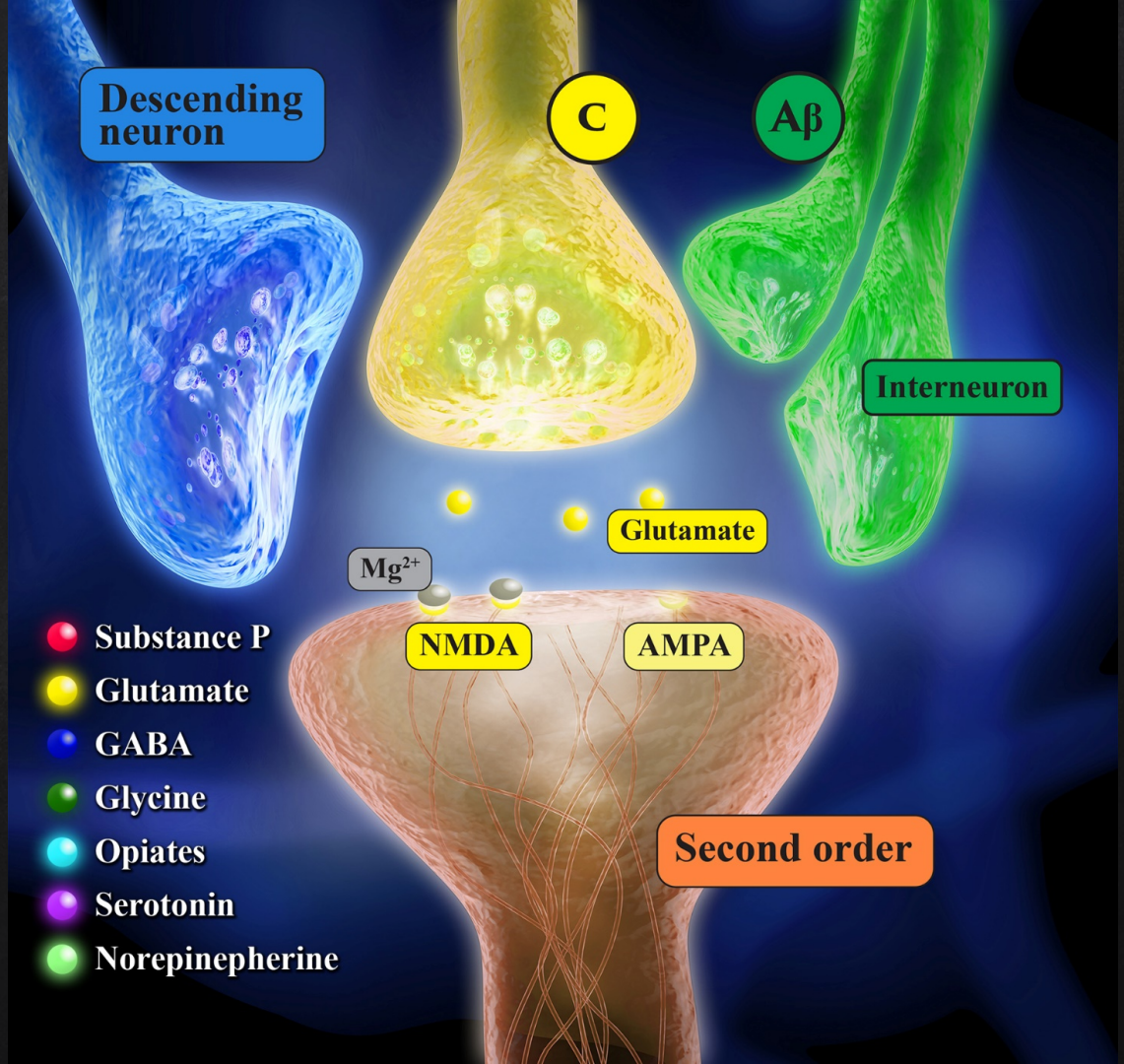

A
control
30 min after 7.35 pH IS
30 Hz
60 min after 7.35 pH IS
mmHg
60
0
CRD
0
200
400
600
800
1000
1200
1400
time (s)
B
imp/s
resting activity
4
3
2
1
0
control
30 min after IS
60 min after IS
C
% control
response to CRD
120
80
40
0
con
IS
pH 7.35 (n=8)
pH 5.5 (n=5)
0
20
40
60
distension pressure (mmHg)

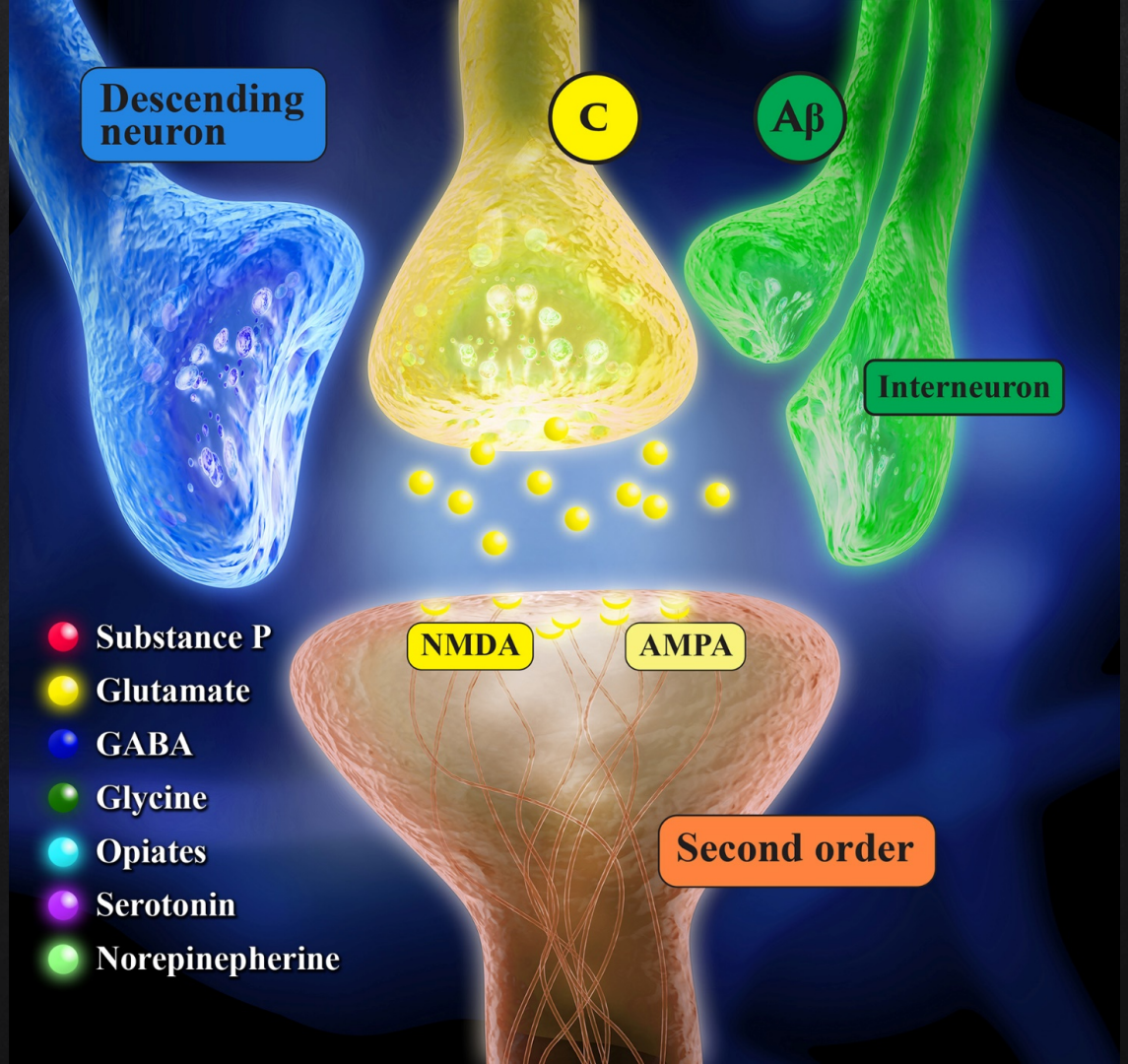
Inflammation Induced Central Sensitization

- ✗ Peripheral Nerve Injury activates microglial cells
- ✗ Microglia release inflammatory mediators that bind to receptors on spinal nerve fibers causing sensitization
- ✗ 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)

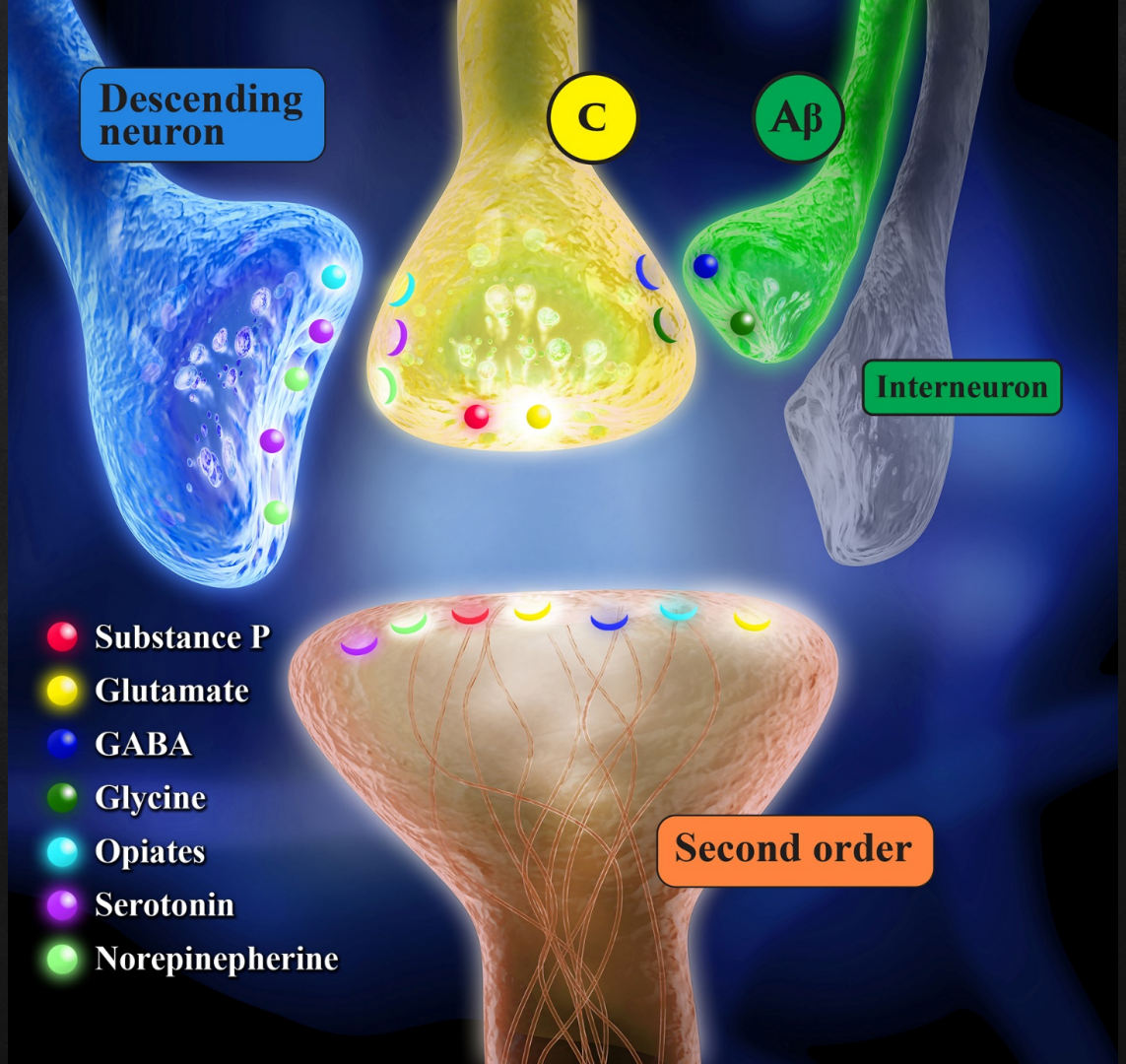
- ✗ Wind Up
  - Peripherally sensitized C fibers release excess glutamate into synaptic cleft
  - Mg plug blocking Ca channel is lost
  - Body creates more AMPA receptors
  - Starts in minutes


Descending neuron
C
Aβ
Interneuron
Glutamate
Mg2+
NMDA
AMPA
Second order
Substance P
Glutamate
GABA
Glycine
Opiates
Serotonin
Norepinepherine

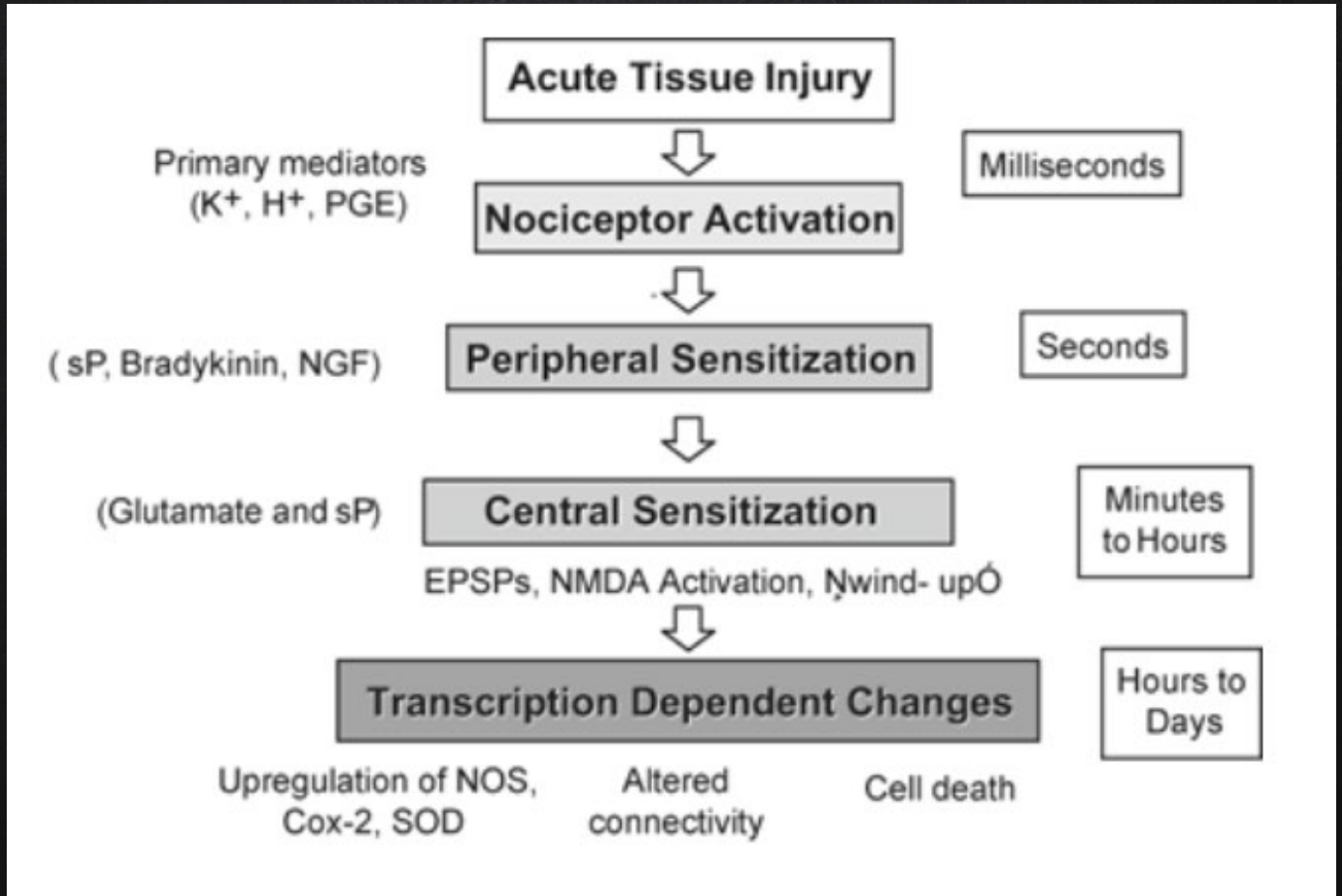

Descending neuron
C
Aβ
Interneuron
Substance P
Glutamate
GABA
Glycine
Opiates
Serotonin
Norepinepherine
NMDA
AMPA
Second order

Allodynia

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


Descending neuron
C
Aβ
Interneuron
Substance P
Glutamate
GABA
Glycine
Opiates
Serotonin
Norepinepherine
Second order

Chronic Post - Surgical Pain



Chronic Post - Surgical Pain

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

Chronic Post - Surgical Pain

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