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# Anatomy and Physiology of Surgical Pain


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## Conclusion

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




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## Introduction

- 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




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## Peripheral Nervous System

- A Beta
  - Touch & pressure
  - Thick, myelinated
  - Low threshold
  - Interneuron
- A Delta
  - First/Fast pain response
  - Mechanical & thermal
  - Well localized
  - Thick, myelinated
  - High threshold fibers




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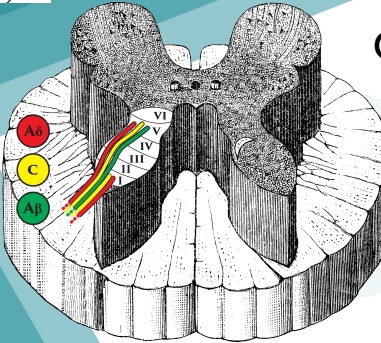


## Peripheral Nervous System

- C
- Majority of pain fibers
- Slow, long-lasting pain
- Not well localized
- Mechanical, thermal, chemical, or inflammatory
- Thin, unmyelinated



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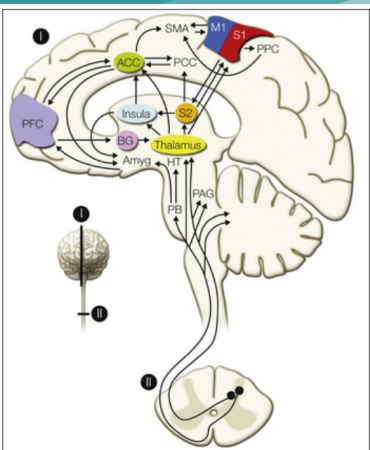



## Central Nervous System

- Rexed Lamina I
  - Nociceptive specific cells
  - A Delta & C
- Rexed Lamina V
  - Wide Dynamic Range Neurons
  - A Beta, A Delta, C
- II, III, IV, VI



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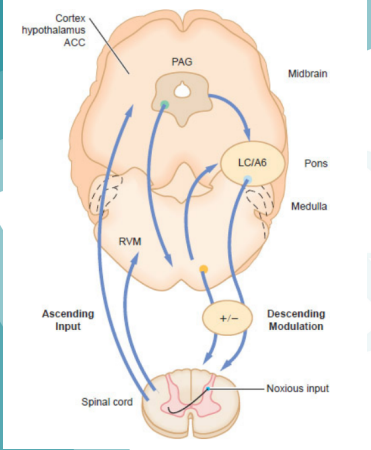


## CNS Ascending Tracts

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



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## CNS Descending Tracts

- Periaqueductal Gray
  - Endorphins, dynorphins, enkephalins
- Rostral Ventral medial Medulla, Locus Ceruleus
  - Norepinephrine, Serotonin, Descending pain pathways


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## Diffuse Noxious Inhibitory Control (DNIC)

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

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## Neurotransmitters Excitatory

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

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## Neurotransmitters Inhibitory

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

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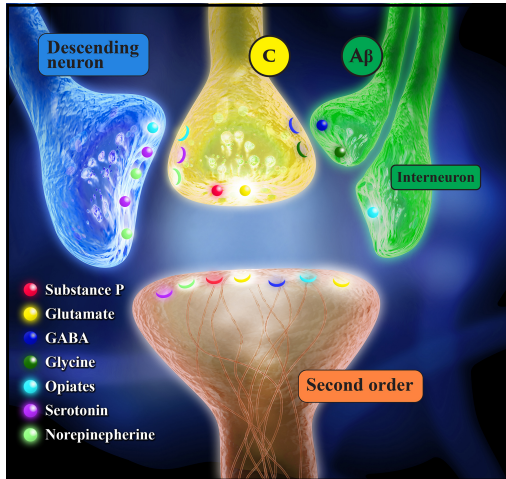
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## Neurotransmitters Inhibitory

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

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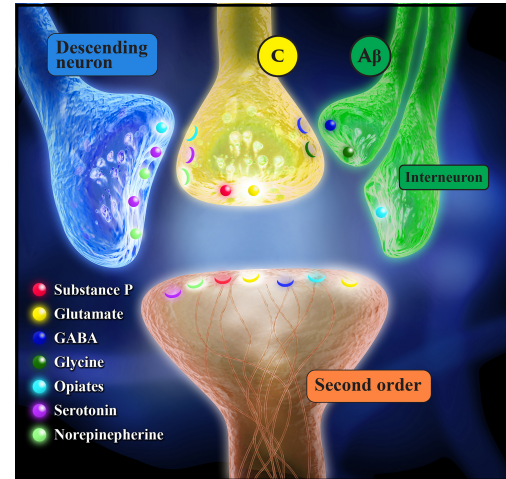


### Neurotransmitters Inhibitory

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

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### Neurotransmitters Inhibitory

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

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### 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

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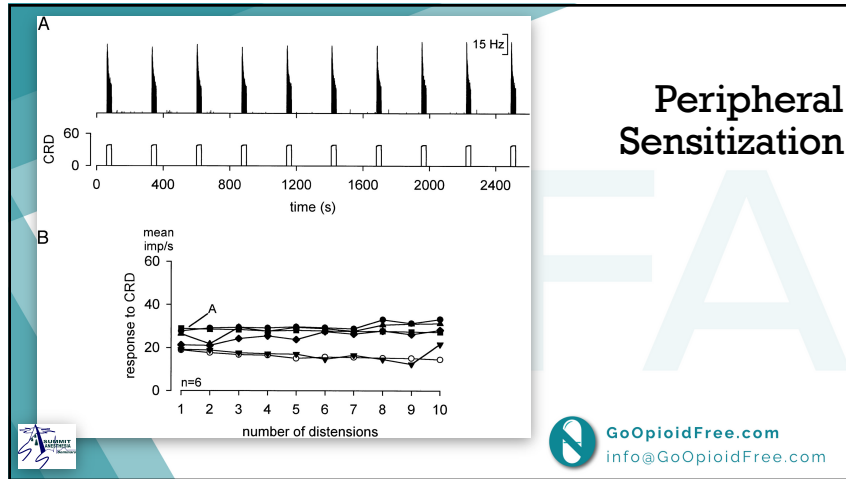
### Peripheral Sensitization

- Primary Hyperalgesia
  - Tissue damage leads to release of inflammatory mediators (sensitizing soup)
    - Bradykinin, substance P, histamine, leukotrienes
- C nerve fibers
  - Activation of inflammatory fibers
  - High threshold to low
  - Stronger response to same stimulation
  - Continue firing after stimulation has stopped
  - Lose specificity
  - 21-day memory

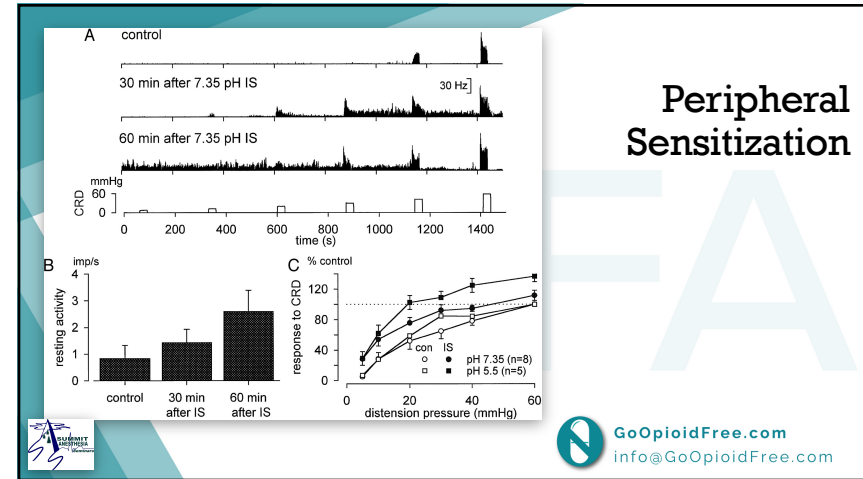
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**Inflammation induced Central Sensitization**

- 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

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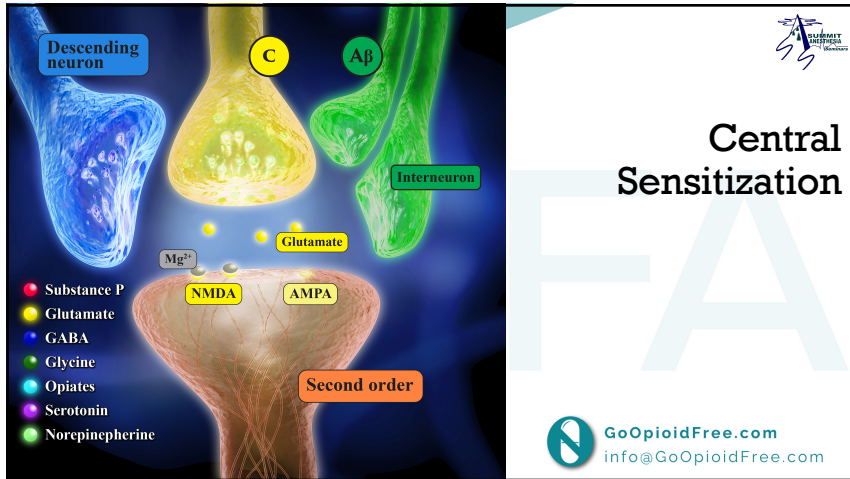
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**Central Sensitization**

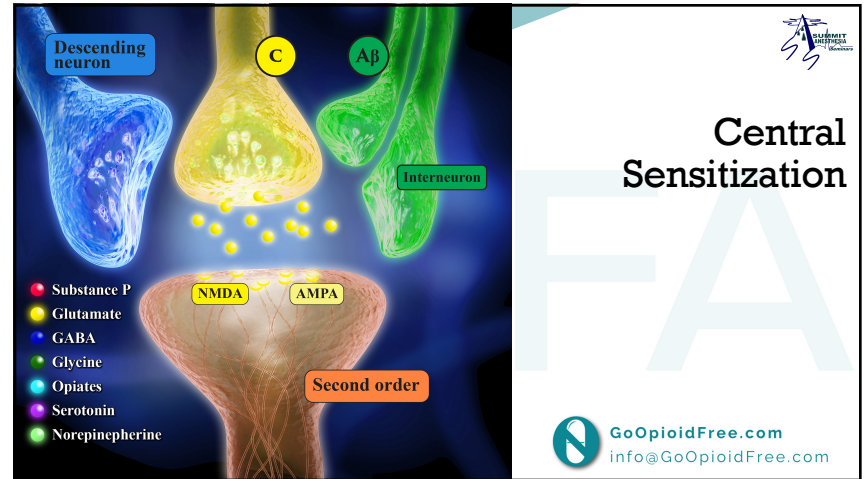
- Secondary Hyperalgesia (Wind-up)
  - Peripherally sensitized C nerve fibers release excess glutamate
  - Creation of more AMPA receptors/Na channels
  - Loss of Mg plug from NMDA receptors/Ca channel
  - Starts within minutes

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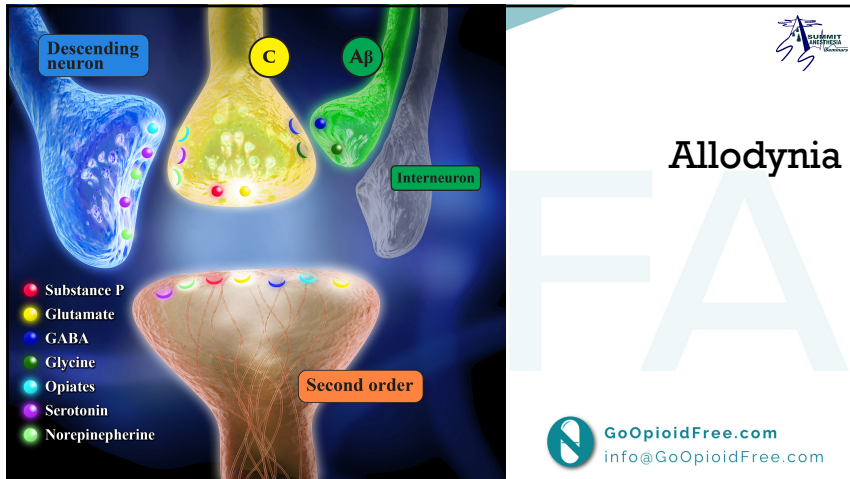
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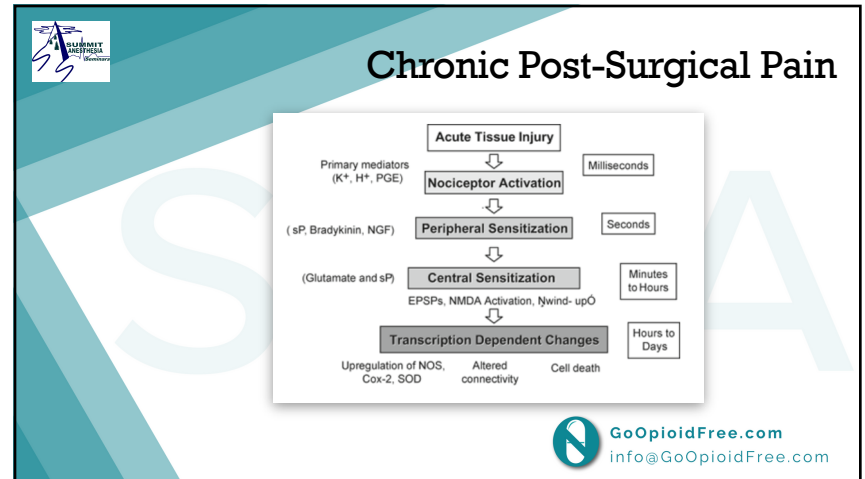
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## Chronic Post-Surgical Pain

- Upregulating of neurotransmitters and receptors
- Arborization of peripheral nerves into rexed lamina
- Dark Neurons = cell death of inhibitory neurons




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## Chronic Post-Surgical Pain

- Pain after the healing is complete
  - 3-6 months
- 40% of chronic pain patients
- No reliable way to predict




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## Risk Factors

- Poorly controlled pain first 48 hours
  - Cause or effect?
- Type of surgery
  - Sternotomy
  - Thoracotomy
  - Breast
  - Amputation



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## Risk Factors

- Pre-operative catastrophizing
  - Highest reliability
- Pre-operative opioid use
- Age
  - Young > Old
- Length
  - > 3 hours
- Genetics




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## Prevention

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


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## Fibromyalgia

- Multiple conditions
  - Similar pathophysiology
- Diagnosis
  - Widespread pain index >7
  - Symptom severity score >5
  - >3 months
  - Not explained by any other condition


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## Fibromyalgia

- Multiple conditions
  - Similar pathophysiology
- Diagnosis
  - Widespread pain index >7
  - Symptom severity score >5
  - >3 months
  - Not explained by any other condition
- Fibromyalgia-ness score
  - Predictive of post-operative pain and opioid requirements


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## Fibromyalgia

- Symptoms
  - Magnified sensory transmission
    - “volume knob concept”
    - Pain, allodynia (tender points), heat & cold, auditory, and visual stimuli
  - +/- inflammation
  - Sleep disruption
  - Memory problems
  - Poor exercise tolerance
  - Depression

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## Fibromyalgia

- Treatment
  - Aerobic exercise
  - Cognitive behavioral therapy
- Medical
  - Anti-depressants
    - TCA Amitriptyline
    - SSRI/SSNI Duloxetine
  - Gabapentinoid
    - Gabapentin/Pregabalin


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## Fibromyalgia

- Treatment
  - Tizanidine
    - Muscle relaxant with A2 agonist activity
  - Tramadol/Tapentadol
    - Opioid with SSRI activity
- Unsuccessful
  - Opioids
    - Overproduction of endogenous opioids
  - Acetaminophen/NSAIDS


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## Opioid Tolerant

- Long term opioid therapy
- Illicit opioid use
- Medication assisted therapy
  - Methadone
  - Buprenorphine
    - Suboxone
    - Subutex
  - Naltrexone (Vivitrol)


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## Opioid Tolerant

- Methadone
  - Broad spectrum opioid
    - Mu, Delta, Kappa, and NMDA receptor
    - Blocks opioid tolerance and hyperalgesia
  - 6-8-hour alpha phase elimination
    - 400% inter-patient variability
    - Respiratory depression can outlast analgesia
  - Prolongs QT interval


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## Opioid Tolerant

- Buprenorphine
  - Partial agonist Mu receptor
    - Less sedation, nausea, pruritis, respiratory depression, urinary retention
  - Higher affinity/slower disassociation than full Mu agonist
- Subutex
  - Buprenorphine
  - Higher abuse risk
- Suboxone
  - Buprenorphine + Naloxone




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## Opioid Tolerant

- Naltrexone (Vivitrol)
  - Antagonist Mu receptor
  - Can't start until withdrawal
  - Monthly injection
  - Least potential for abuse




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## Opioid Tolerant

- Methadone
  - Continue
- Buprenorphine or Naltrexone
  - Minor surgery continue
  - Major surgery wean vs continue
    - Can we control pain?
    - Is there a plan?
    - Wean
      - 3-day Buprenorphine
      - 28 days Naltrexone




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## Pain management

- Regional technique
  - PNB
    - single shot vs catheter
  - Epidural catheter
    - Local vs A2 agonist
- Post-operative Infusions
  - Lidocaine
  - Ketamine
  - Dexmedetomidine




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## Pain management

- Opioids
  - Not helpful, but if on chronic opioids don't stop them
- Central acting medications
  - Gabapentin/Pregabalin
    - Consider 1-week Pre/Post
  - Tizanidine
    - If muscle spasm
- SSRI/SSNI
  - Duloxetine or Tramadol/Tapentadol
- Scheduled non-opioid analgesics
  - Acetaminophen
  - Nsaid/Coxib



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