



Pain Pathophysiology Part I  
Bridging the Mechanism of Action of  
Non-Opioid Medications  
8:30am – 9:30am

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- Review Normal Pain Anatomy and Physiology
- Pathological Pain Pathways
- Targeted Treatments
- Future Developments



Beep Beep – What's the problem?



?



# Basic Wiring

- **Peripheral Nervous System**
  - Gathers information from surroundings
  - Primary afferent neurons
  - Cell bodies located in dorsal root ganglia
- **Central Nervous System**
  - Secondary interneurons
  - Synapse in dorsal horn
  - Information ascends to cerebral cortex
  - Modulating pathways descends back down
- **Autonomic Nervous System**
  - Carries sensory information from viscera

# Nociceptive Pain

- Pain information transmitted from injured tissue (skin, muscle, or viscera) to cerebral cortex
- Protection from tissue damage



Rene Descartes 17<sup>th</sup> Century

# Neuropathic Pain

- Dysfunction within the nervous system
- Not proportional to intensity of stimulus
- Spontaneous
- Quality: Burning, electrical, shooting

# Mixed Pain

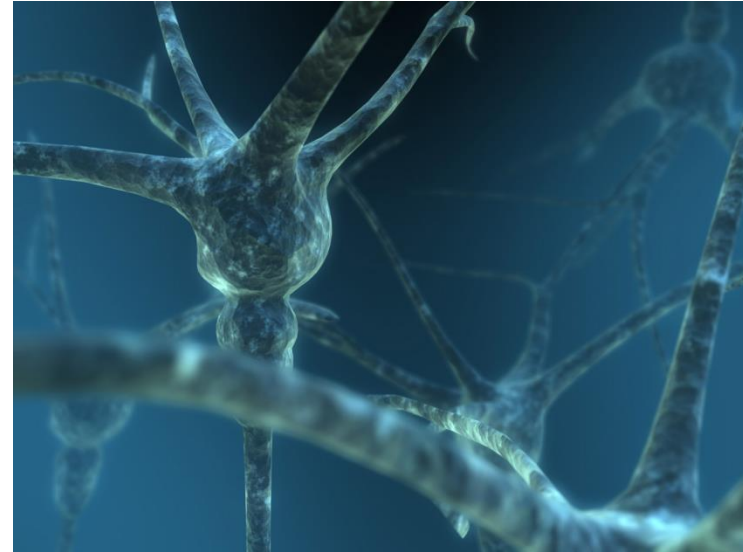
- Both Nociceptive and Neuropathic components

# Nociplastic Pain

- Pain lacking evidence of threatened or actual tissue damage / altered nociception

# Pain Anatomy

- Receptors
  - Generate Action Potential
- Axons
  - Relay information electrically
- Neurotransmitters
  - Activate nerves and provide interface between nerves

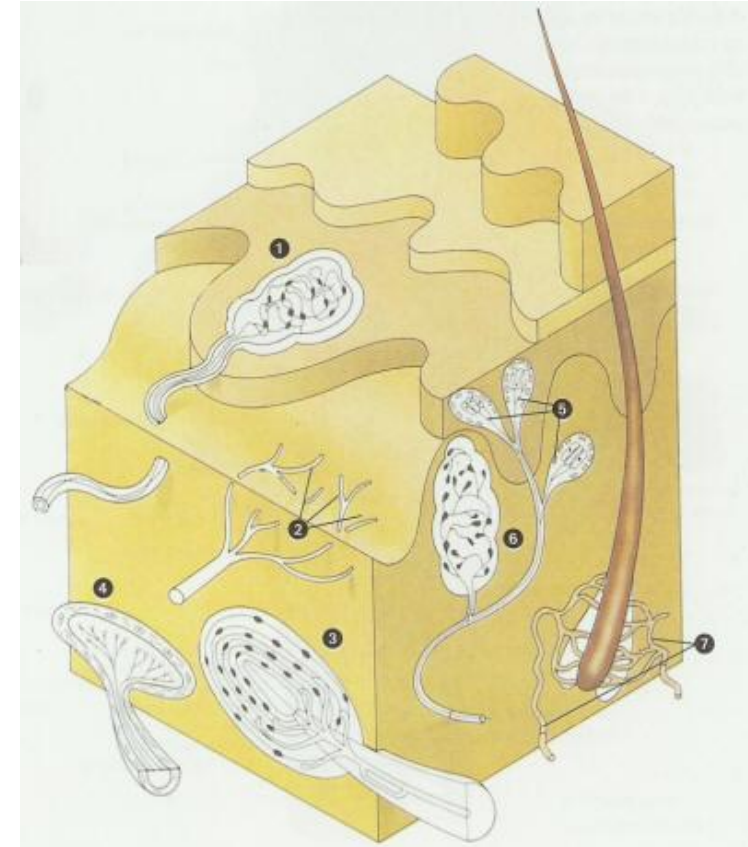




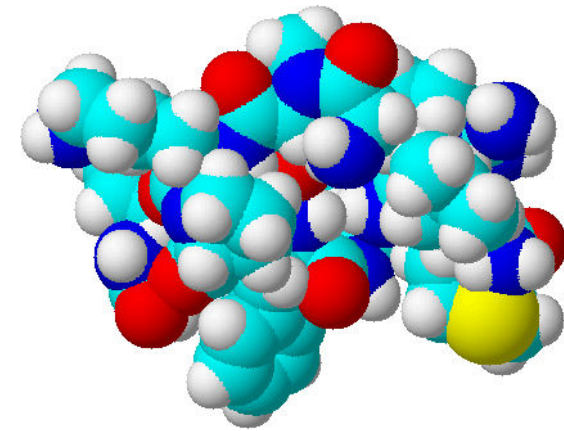
# Receptors

# Peripheral Receptors

- Free nerves – Pain
  - Neurotransmitter Activated
  - Prostaglandin Activated
- Mechanoreceptors
  - Bulbous corpuscle (stretch and slippage)
  - Meissner corpuscle (light touch)
  - Pacinian corpuscle (Vibration)
- Thermal Receptors
  - TRPV1-4
  - Cold, Warm, Warmer, Hot, Painfully Hot
- Chemoreceptors
  - Vanilloid (TRPV 1 – Hot)
  - Camphor



# Neurotransmitters



	Depolarize	Hyperpolarize
Oxytocin	X	
CGRP	X	
Substance P	X	
Somatostatin		X
VIP	X	
CCK	X	
Dynorphin		X
Glutamate	X	
Aspartate	X	
Bombesin		X

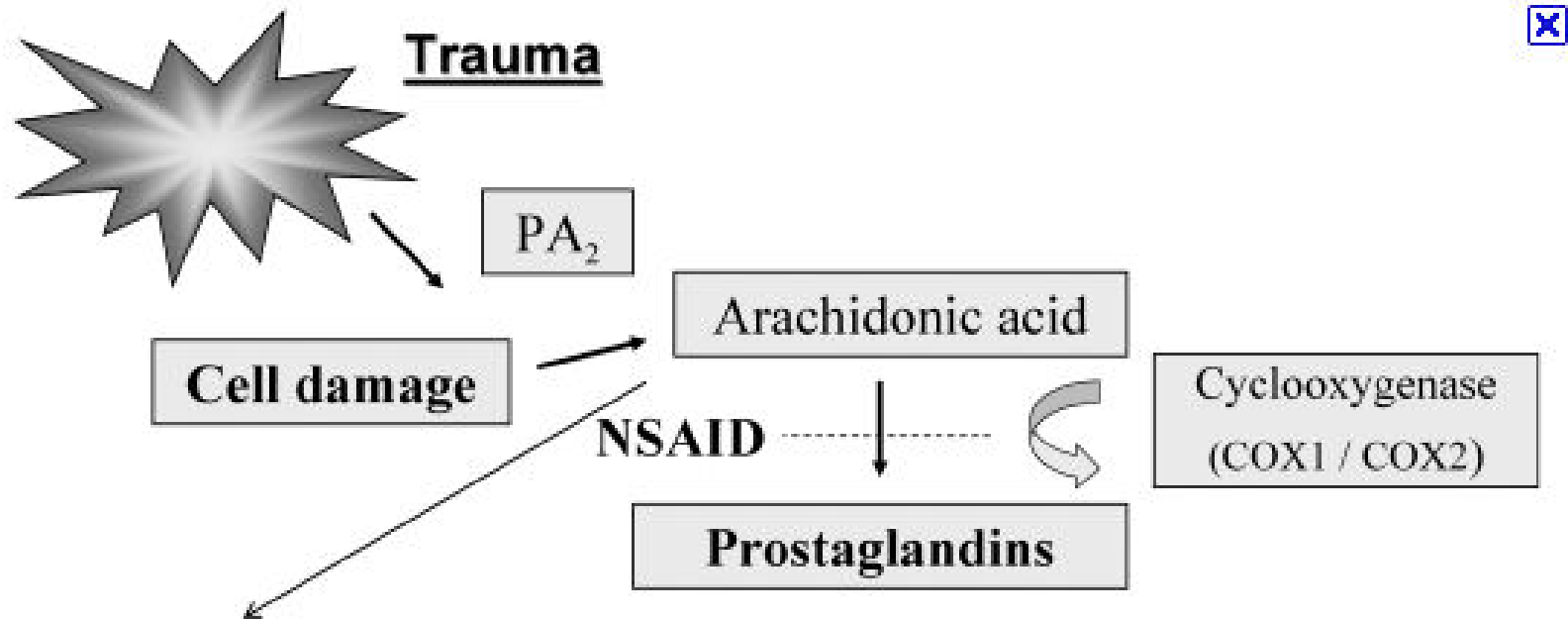
# Peripheral Nociception

- Injury  $\Rightarrow$  Release of peptides (Sp, CGRP)
- Activation of free nerve nociceptors
- $\uparrow$  Vascular permeability and leakage of plasma proteins  $\Rightarrow$  edema
- Injury products released (prostaglandins)
- Inflammation develops
  - *Rubor, Tumor, Calor, Dolor*
- Action potentials transmit pain signal



# Peripheral Targets

# Cyclooxygenase (COX) Inhibitors



- NSAIDs have peripheral anti-inflammatory effects
- Topical preparations as patch, gel or drops
- Repetitive c-fiber activation  $\Rightarrow$  spinal prostaglandin release
- Acetaminophen inhibits COX-3 centrally

# Capsaicin

- Binds Peripheral Vanilloid Receptor
  - Stimulated by heat, abrasion
- Mechanism involves an initial sensitization, followed by desensitization
- Defunctionalization occurs with high potency
- Available as a topical system, patch, and cream



# Other Peripheral Targets

- Opioids
- Na<sup>+</sup> Channel Blockers
- Many other compounded substances – peripheral?
  - Ketamine (NMDA)
  - TCAs (5-HT, NE)
  - Gabapentinoids (CA<sup>2+</sup>)



Axons

# Nerve Axons

- Speed related to diameter

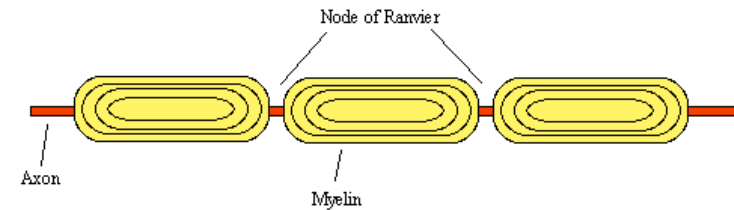
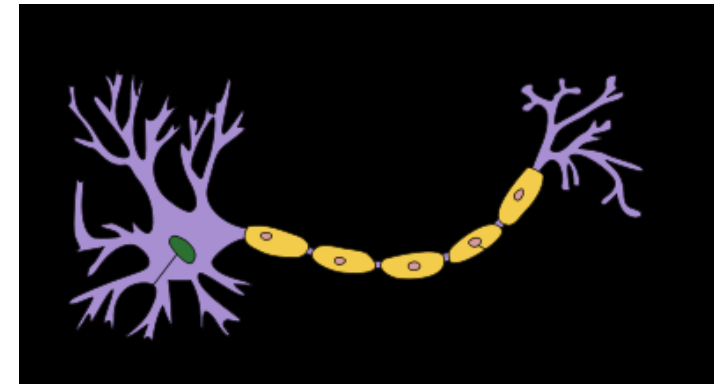
- A $\alpha$ : >60 m/sec
- A $\beta$ : 30 – 60 m/sec
- A $\delta$ : 3 – 30 m/sec
- C-fiber: <2-5 m/sec

- Myelination

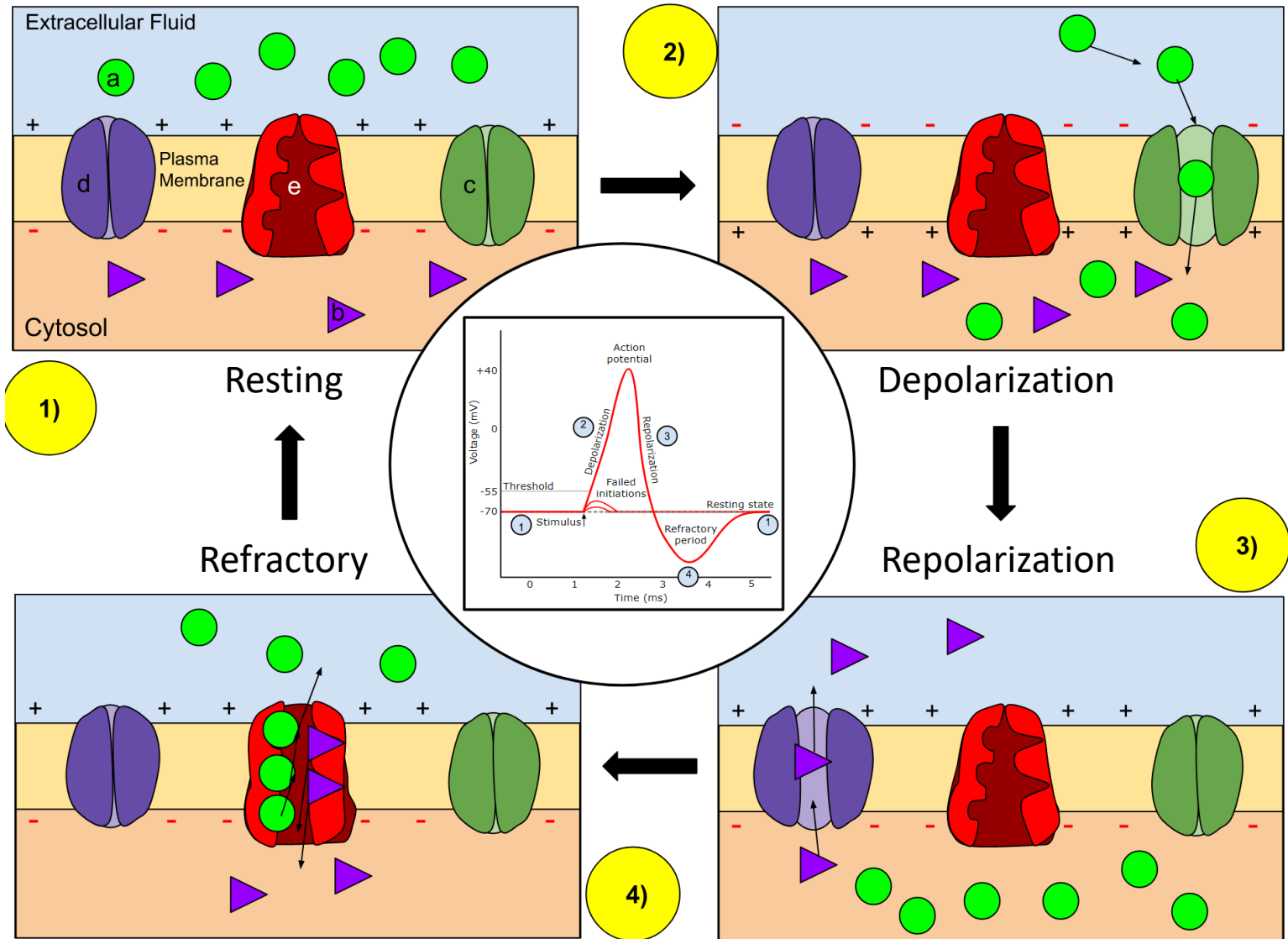
- A-fiber myelinated and fast (avoidance)
- C-fiber unmyelinated and slow (guarding)

- Schwann Cells

- Produce myelin
- Saltatory Conduction
- Nodes of Ranvier



# Action Potential

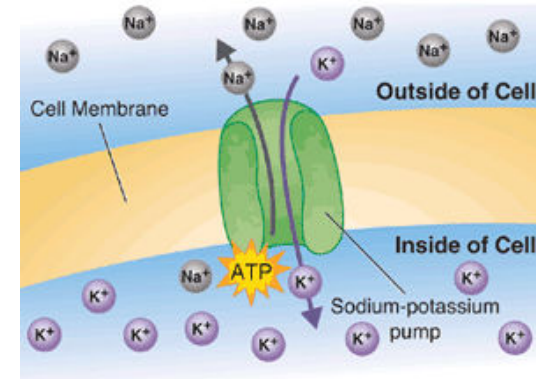


- a) Na<sup>+</sup>
- b) K<sup>+</sup>
- c) Na<sup>+</sup> Channel
- d) K<sup>+</sup> Channel
- e) Na<sup>+</sup>/K<sup>+</sup> Pump

# Axonal Targets

# Na<sup>+</sup> Channel Blockers

- Lidocaine, Bupivacaine
- Na<sup>+</sup> channel functioning essential for nerve conduction
- Block 3 Nodes of Ranvier for complete block
- ↑ Na<sup>+</sup> Channels in nerve damage and inflammation (hyper-excitability)
- Can be injected or applied as patch, EMLA
- Can be compounded into gels/creams



# Na<sup>+</sup> Channel Stabilizers

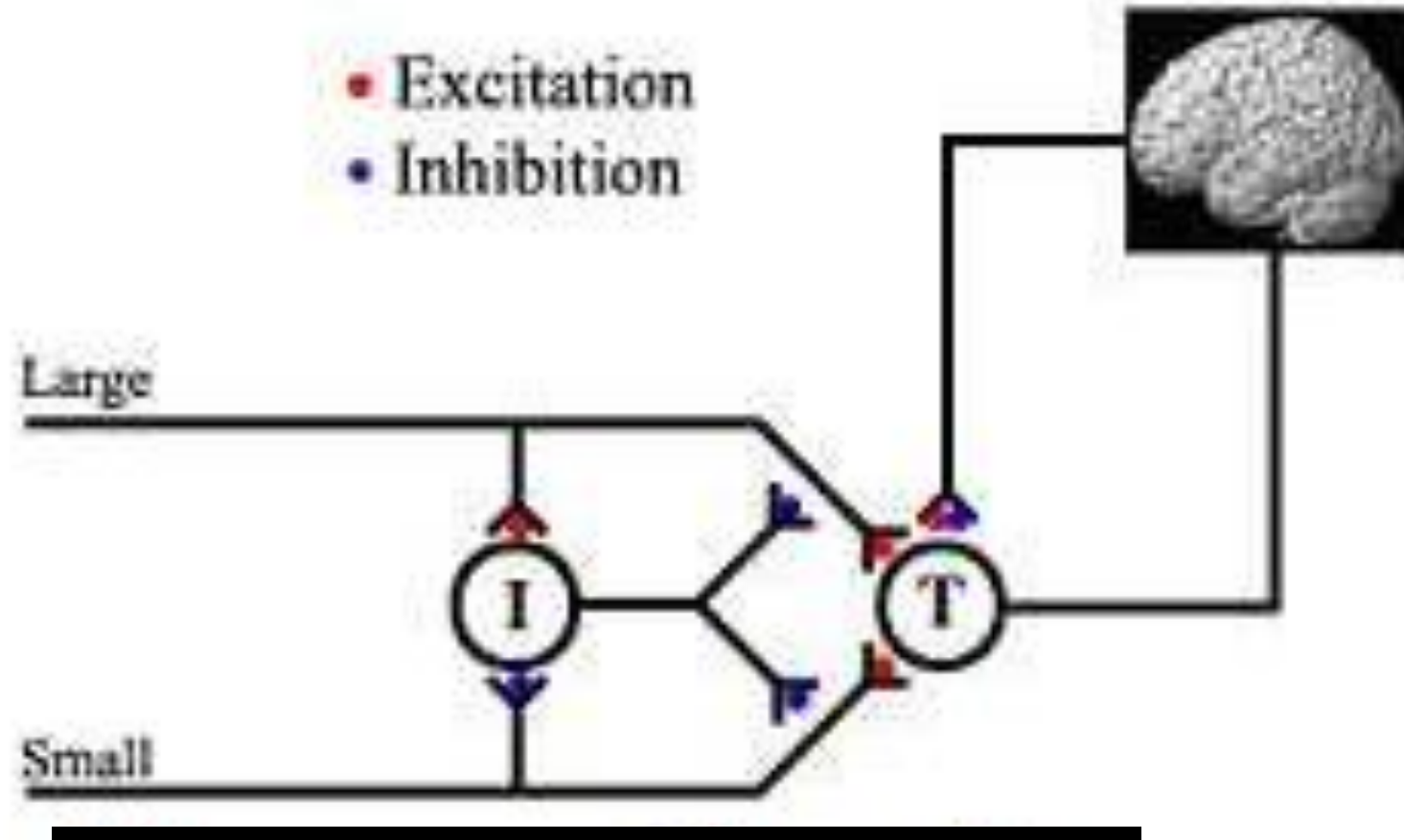
- Carbamazepine
  - Stabilizes Na<sup>+</sup> channels which suppresses spontaneous A $\delta$  and c-fiber activity
- Oxcarbazepine
- Propanolol



# Other Axonal Targets

- Lamotrigine
  - Blocks voltage-dependent Na<sup>+</sup> Channels
  - Inhibits Glutamate release
- Topiramate
  - Na<sup>+</sup> Channel and Ca<sup>2+</sup> Channel Antagonist
- Zonisamide
  - Na<sup>+</sup> Channel and Ca<sup>2+</sup> Channel Antagonist

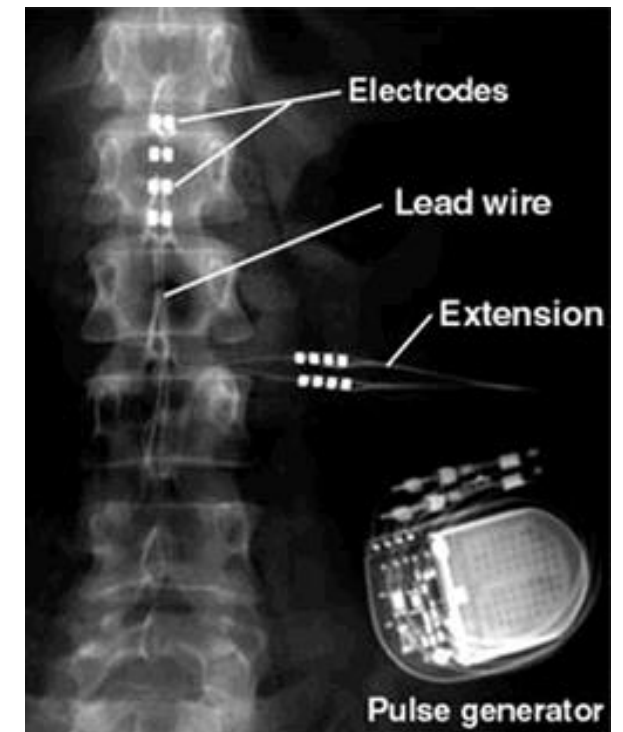
# Gate Control Theory/Modulation





# Neuromodulation

- TENS
  - Closes Gate by activating Large Fiber Receptors
- Spinal Cord/DRG/Peripheral Nerve Stimulation
  - Mechanism Complex
  - Direct electrical block
  - Tonic – Induces GABA-release from inhibitory interneurons
  - Supra-spinal feedback loop may involved 5-HTP
  - HF/Burst – MoA evolving



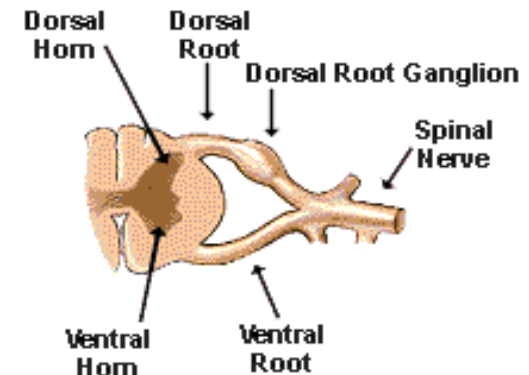
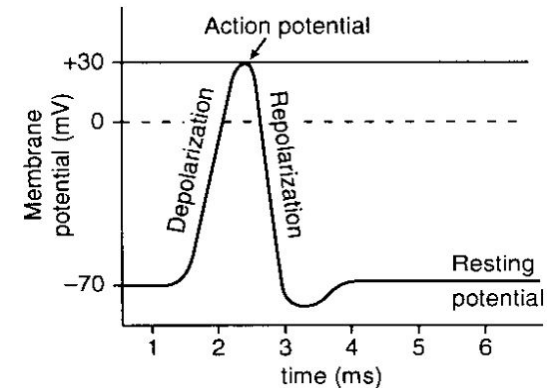
Name that system?

# Peripheral/Central Interface

# Dorsal Root Ganglia and Dorsal Horn

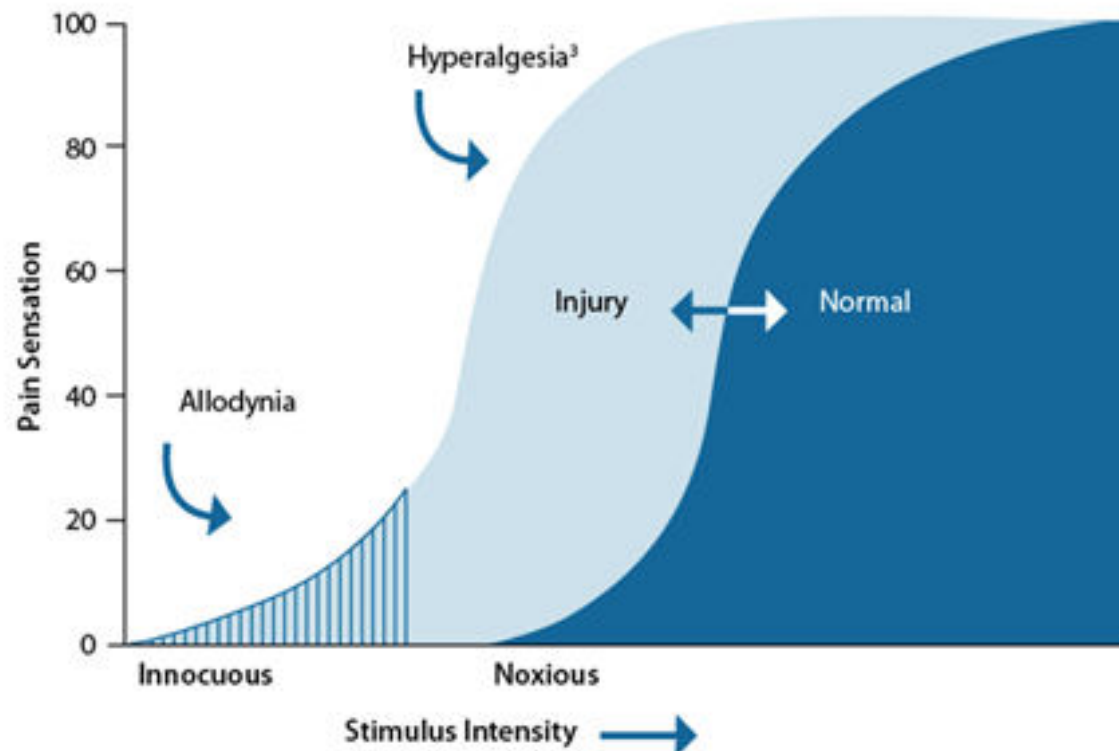
- DRG contains cell bodies for peripheral nerves
- Dorsal Horn contains many receptors:

	Depolarize	Hyperpolarize
GABA-A		X
GABA-B		X
$\alpha_1$ adrenergic	X	
$\alpha_2$ adrenergic		X
Opioid		X
Histamine	X	
Muscarinic		X
Nicotinic	X	
Glutamate (non-NDMA)	X	
Glutamate (NDMA)	X	
5HT2/3	X	



# Sensitization

- Repeated c-fiber activation results in amplification of pain transmission
- Involves Glutamate and NMDA receptors



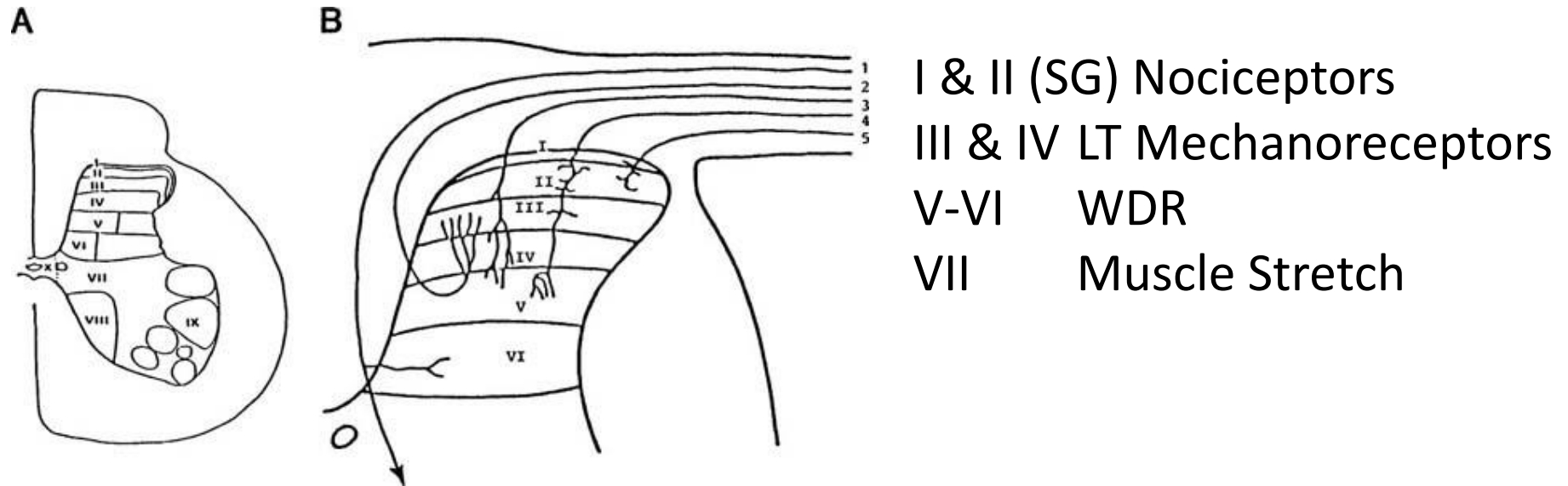
# NMDA Antagonists

- Receptor Blockers
  - Ketamine
  - Dextromethorphan
  - Memantine
  - Methadone
- Minimal data on efficacy/safety



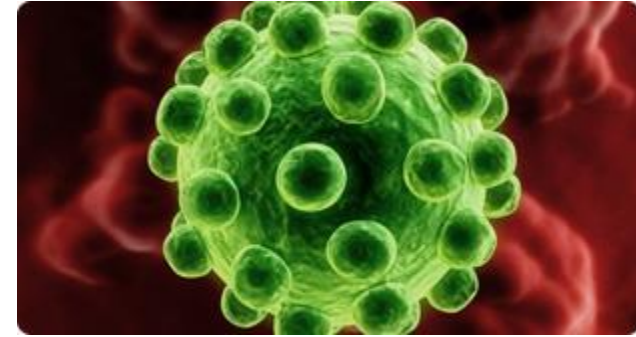
# Dorsal Horn of Spinal Cord

- Primary afferent neurons project into dorsal horn lamina



- Convergence (especially viscera) may explain “referred pain”

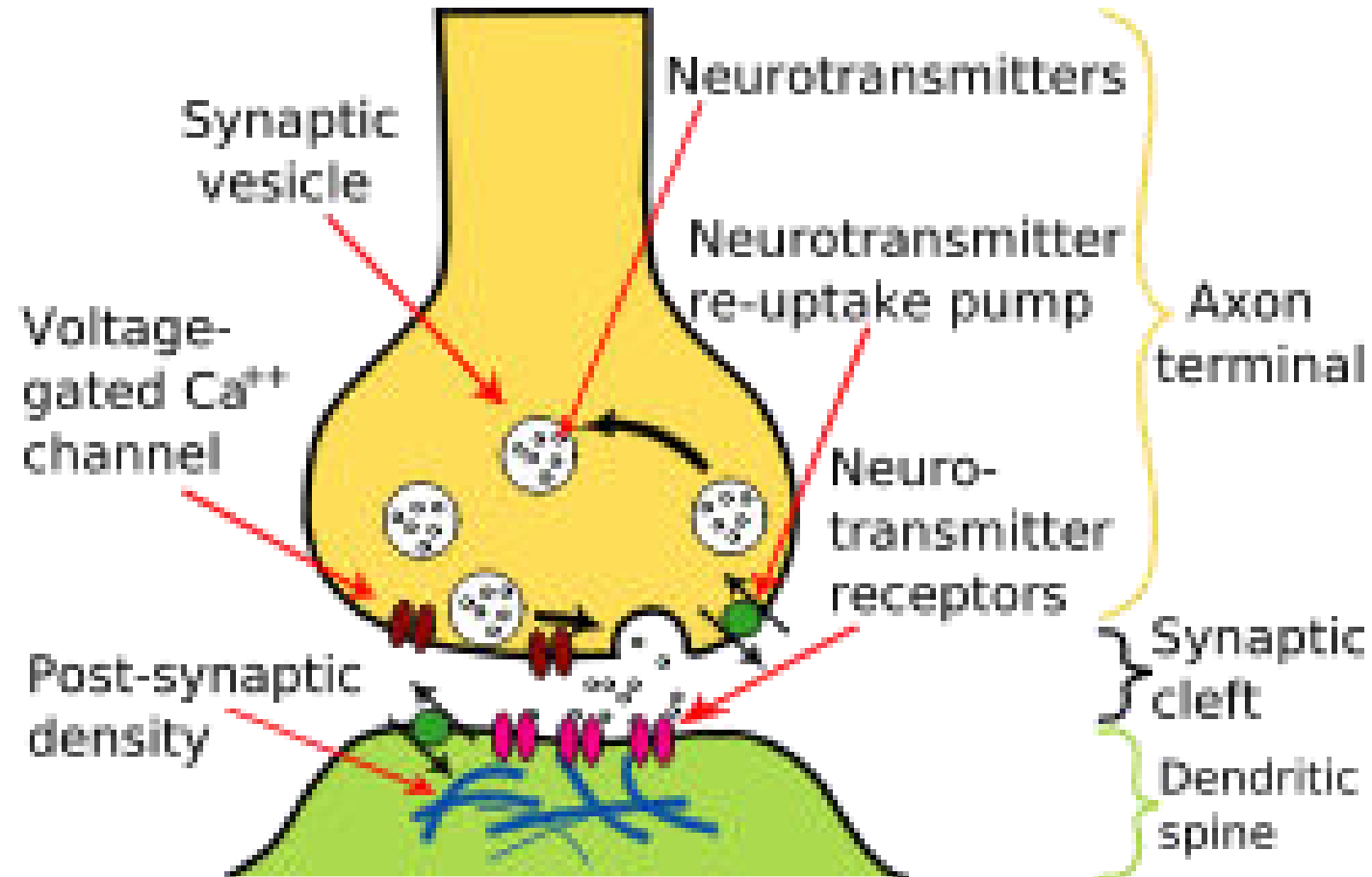
# Post-herpetic Neuralgia



- Herpes Zoster Virus activation
- Loss of C-fiber density and dorsal horn cells
- Loss of superficial lamina terminals
- A $\beta$  fibers sprout into superficial terminals
  - Express glutamate (depolarizes) and creates allodynia
  - Start expressing Substance P
- Not *sensitization*, rather change in “wiring”
- Neural Plasticity = Disease?
- Anti-NGF?

# Synaptic Cleft in Dorsal Horn

- Primary Afferent Nociceptors synapse with secondary interneurons

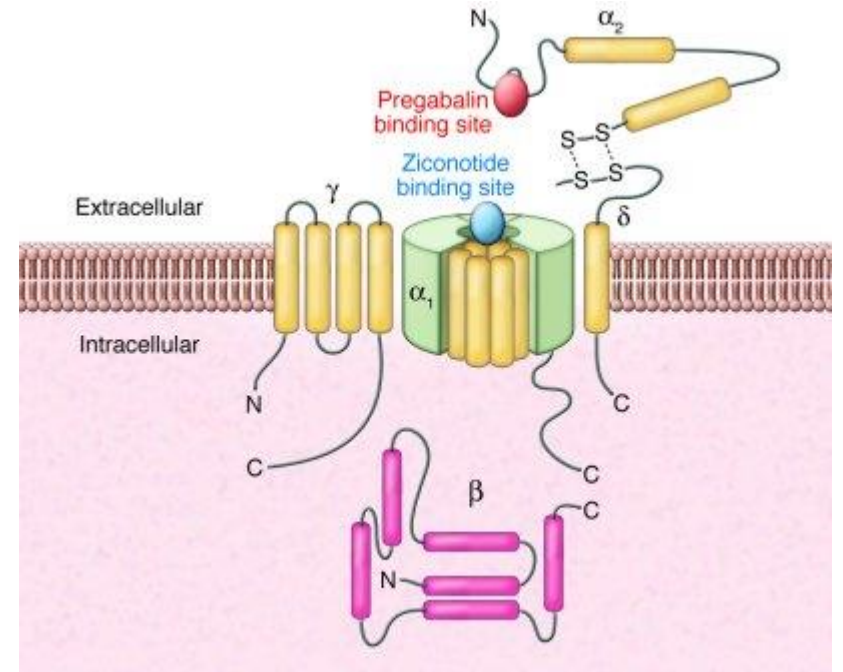




# Dorsal Horn Targets

# Ca<sup>2+</sup> Channel (N-type) Drugs

- Modulators
  - Gabapentinoids
  - Bind  $\alpha_2\delta$  subunit of Ca<sup>2+</sup>
  - Gabapentin, Pregabalin
- Blockers
  - Physically Block Channel
  - Ziconotide
- Reduce Neurotransmitter Release



# Ca<sup>2+</sup> Channel Modulators

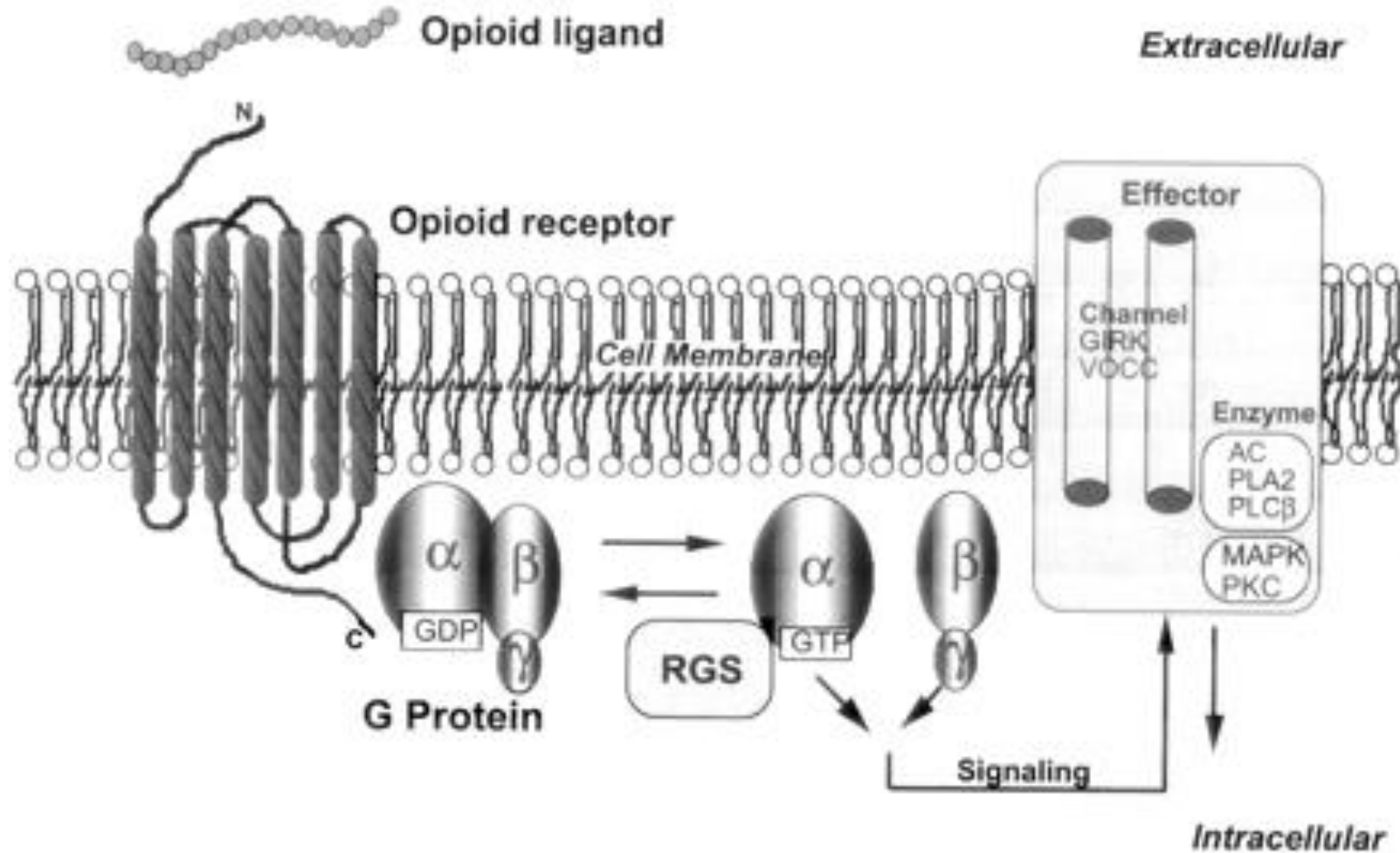
- Pregabalin (Lyrica)
  - New indication:
    - Management of Neuropathic Pain Associated with Spinal Cord Injury
    - Fibromyalgia
    - Post-herpetic neuralgia
    - Painful Diabetic Nerve Pain
- Gastroretentive Gabapentin (Gralise)
  - Once-daily for post-herpetic neuralgia
- Gabapentin enacarbil (Horizant)
  - New indication:
    - Management of post-herpetic neuralgia in adults
  - Prodrug of gabapentin

# conopeptides

- N-type  $\text{Ca}^{2+}$  Channel Blocker
- Ziconotide (Prialt)
  - *Conus Magus* Snail
  - For management of severe chronic pain when IT therapy warranted and intolerant or refractory to other treatment, such as systemic analgesics, adjunctive therapies or IT morphine
  - 1000x more potent than morphine
- Other conopeptides in development
  - 1000s small stable proteins in venom

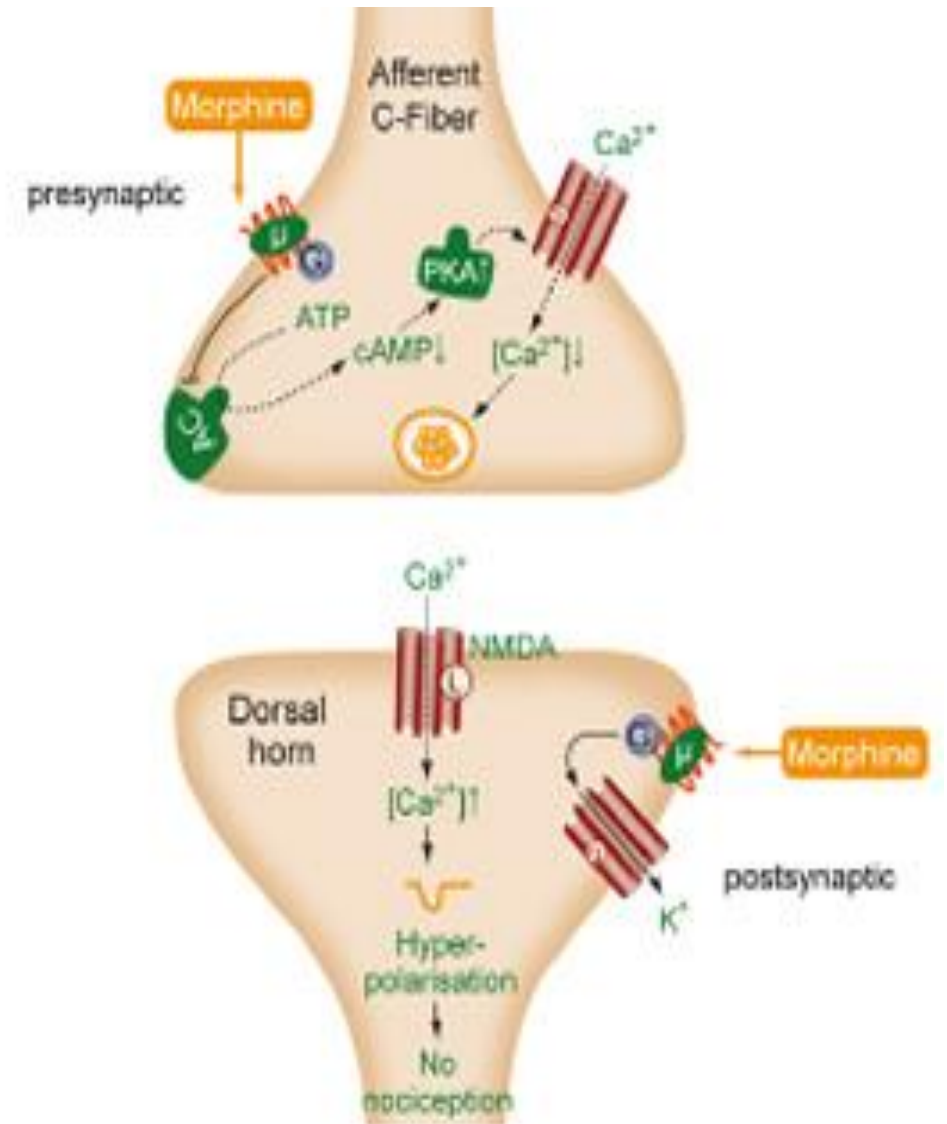


# Opioid Receptors



# Dorsal Horn Opioids

- Presynaptic Binding  $\Rightarrow$ 
  - $\text{Ca}^{2+}$  channel inhibition
  - G-protein linked
- Postsynaptic Binding  $\Rightarrow$ 
  - Membrane Hyper-
  - polarization by opening
  - $\text{K}^+$  channels



# GABA Agonists

- GABA: Primary inhibitory neurotransmitter ⇒ Hyperpolarization
- Regulates muscle tone
- GABA-A agonists: Benzodiazepines
- GABA-B agonists: Baclofen

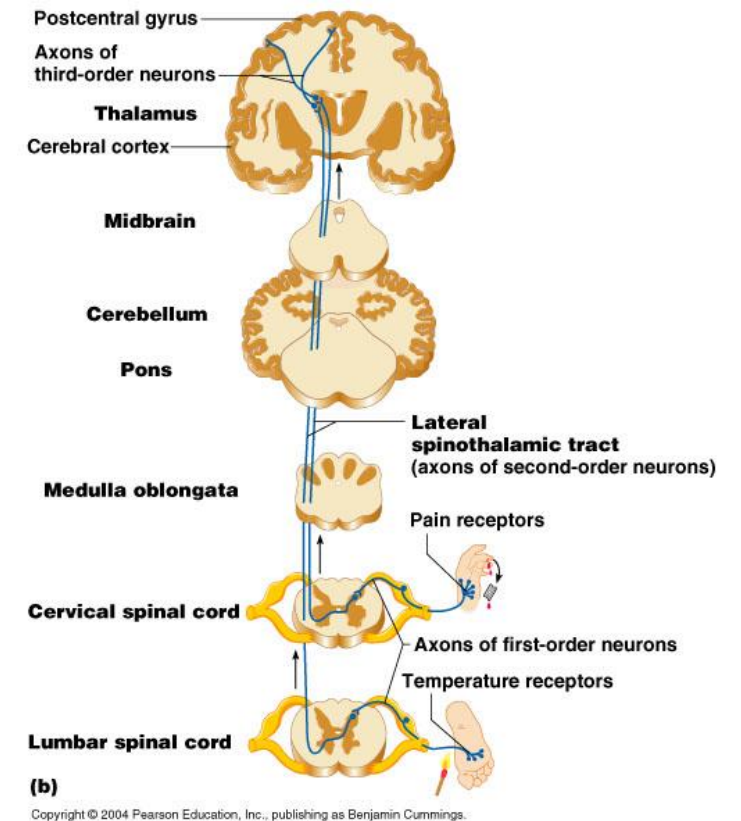


# Ascending Pathways



# Ascending Projection Systems

- Bring spinal cord information to brain
- Several nociceptive pathways
  - Spinothalamic Tract
  - Quality, location, duration, intensity of sensation
  - Spinoreticular Tract
  - Spinomesencephalic Tract
- Many cross and ascend on contralateral side
- Reflex motor activity



# Ascending Path Targets

# Spinal Ascending Modulation

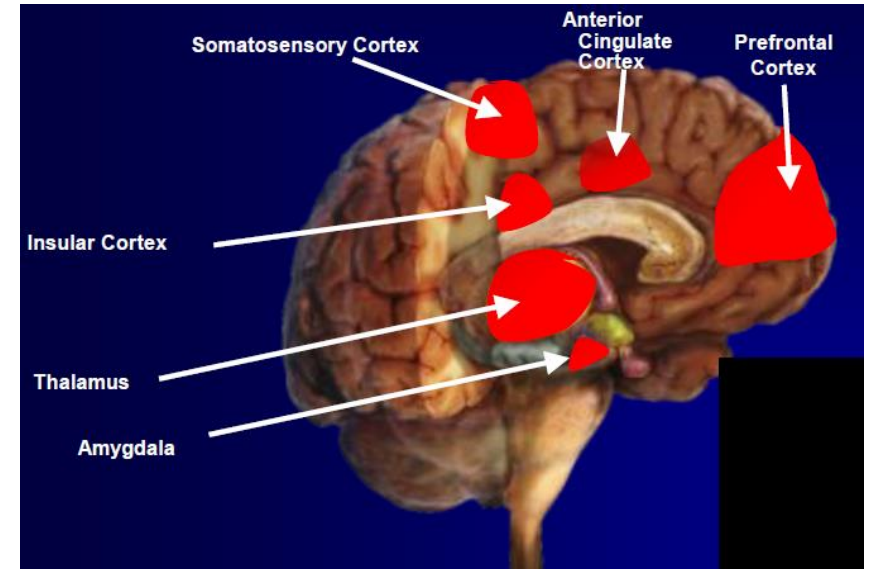
- Intra-spinal Na<sup>+</sup> Blockers (Bupivacaine)
- Spinal Cord Stimulation (Descending as well)



# Cerebral Cortex

# Central Projections

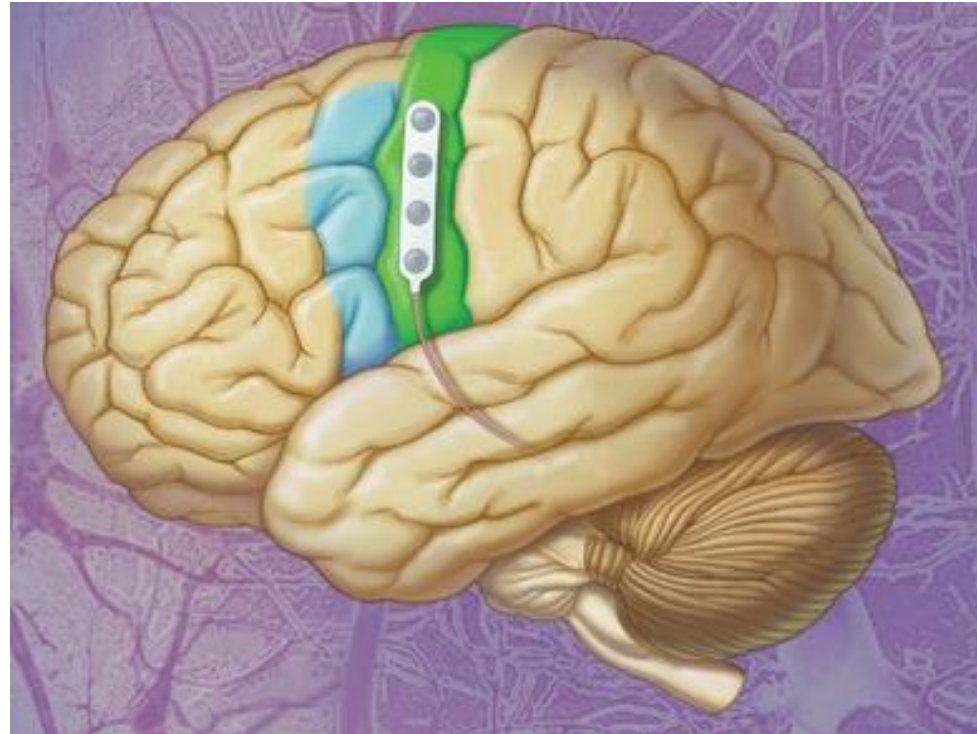
- Thalamus projects to many areas in brain
- Sensory-discriminative System
- Motivational-Affective System
- Pain Perception and interpretation
  - Primary Somatosensory
  - Secondary Somatosensory
  - Anterior Cingulate
  - Anterior Insula Frontal
  - Basal Ganglia
- Future Modulation



# Central Targets

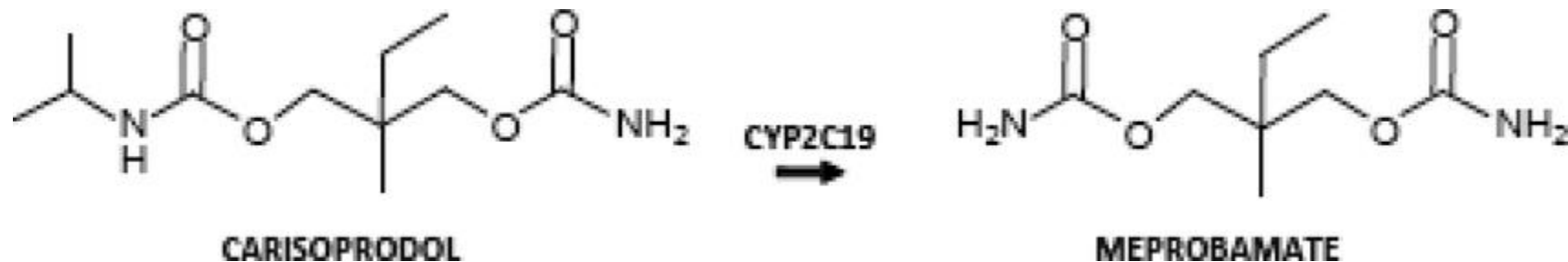
# Motor Cortex Stimulation

- Evolving technique
- Stimulate Motor Cortex
- Facial and Central Pain
- Craniotomy



# Muscle Relaxants

- Unclear mechanism, but may have central effects
  - Methocarbamol
  - Cyclobenzaprine
  - Others
- Carisprodol → Meprobamate (GABA modulator)





# Descending Pathways

# Descending Projections

- Endogenous Analgesia System
- Raphespinal Pathways
  - Antinociceptive Effects through Serotonin
- Catecholaminergic Pathways
  - Norepinephrine release inhibits  $\alpha_2$  adrenergic receptors
- Reticulospinal Tracts
- Periaqueductal Gray
  - Antinociceptive through endogenous opioids, serotonin, norepinephrine, GABA and glycine
- Anterior Pretectal Nucleus
- Ventrobasal Thalamus
- Motor Cortex

# Descending Pathway Targets

# Antidepressants for Pain

- Analgesia primary through block of 5-HT and NE reuptake (5-HT<sub>2</sub>, 5-HT<sub>3</sub>, 5-HT<sub>4</sub> subtypes)
- Secondary pathways:
  - Opioid receptors interaction (stimulate endogenous opioid release)
  - Ion channel blocking (Ca<sup>2+</sup>, Na<sup>+</sup>, K<sup>+</sup>)
  - NMDA antagonism
  - Histamine blocking
  - Cholinergic receptor inhibition ( $\alpha_1$ ,  $\alpha_2$ ,  $\beta$ )

# Serotonin Reuptake Inhibitors (SSRIs)

- Weak anti-nociceptive effects in animals
- Some data for diabetic neuropathy, rheumatoid arthritis and migraine headache

# Serotonin/Norepinephrine Reuptake Inhibitors (SNRIs)

- TCAs

- Tertiary TCAs (Balanced 5HT and NE reuptake) – Generally better analgesia
  - Imipramine (1960 for TN), amitriptyline, doxepin
- Secondary TCAs (More NE reuptake) – Generally better tolerated
  - Desipramine, nortriptyline, maprotiline

- Selective SNRIs

- Generally better tolerated than TCAs
- Venlafaxine reduced neuropathic pain following breast cancer treatment
- Duloxetine approved for a variety of pain conditions (OA, Back Pain, DPN, FMS)

# Norepinephrine Reuptake Inhibitors

- Milnacipran approved for Fibromyalgia pain

# Norepinephrine/Dopamine Reuptake Inhibitors

- Bupropion reduces thermal nociception

# Multimodal Analgesics

- Tramadol

- Racemic, synthetic analog of codeine

Tramadol (+) Enantiomer	Tramadol (-) Enantiomer
Weak $\mu$ -receptor agonist	Inhibits NE reuptake
Blocks 5-HT reuptake and inhibits 5-HT release	

- Heavily metabolized (CYP2d6) – active M1

M1 (+) Enantiomer	M1(-) Enantiomer
200 X $\mu$ binding	Inactive
6 X Analgesic Potency	

- 5-15% of white population unable to metabolize to M1
- Pharmacology changes over time as metabolized



# Multimodal Analgesics

- Tapentadol
  - Opioid receptor agonist and NE reuptake inhibitor
  - No active metabolites
  - No P450 Drug Drug Interactions
  - Non-racemic

# Miscellaneous Targets

# $\alpha$ -Adrenergic Active Drugs

- $\alpha$ -Antagonists

- Phentolamine
- Sympathetic Blockade

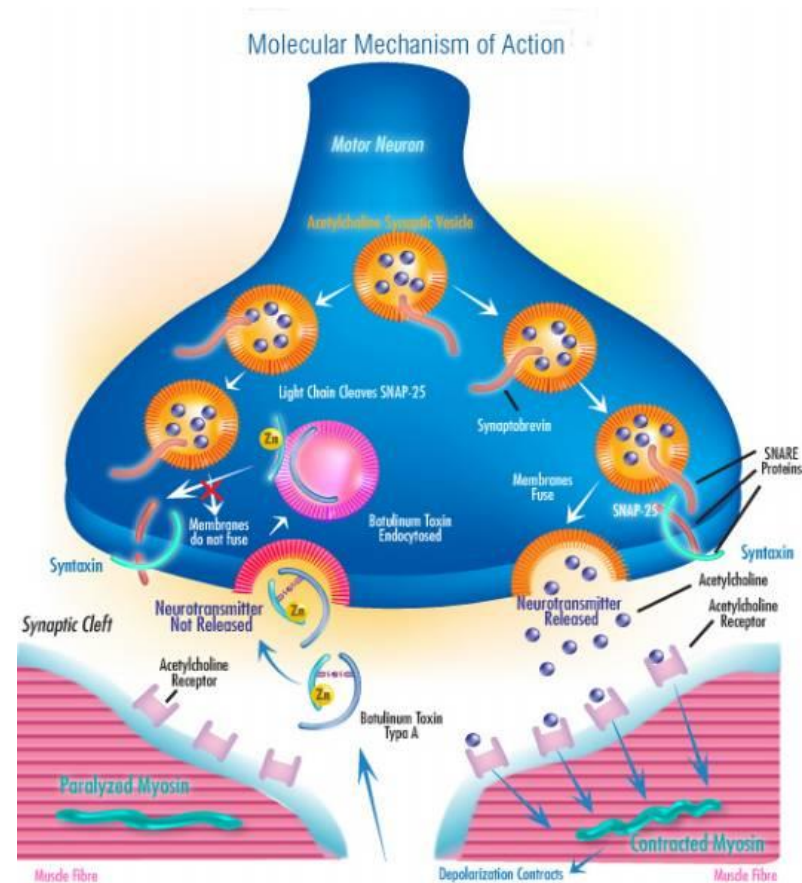
- $\alpha_2$ -Agonists - Central

- Clonidine – Sympathetic Blockade
- Tizanidine – Anti-spasmodic



# Botulism Toxin

- Blocks binding of Acetylcholine containing vesicle and subsequent release
- Can be used for migraine headache treatment
- Myofascial Pain



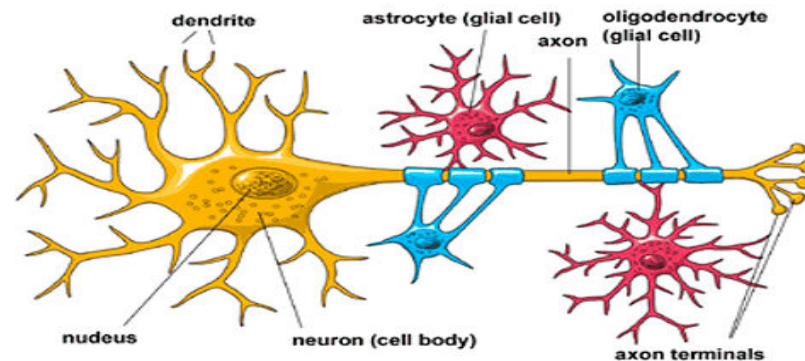
# Future Targets

# Future Targets and Treatments

- Glia Cell Activation Modulators
  - Glia maintain increased nociception in response to nerve injury
  - Opioids induce glia cell activation may limit analgesia
- Nerve Growth Factor Modulators
- Cannabinoids
  - Receptors (CB<sub>1</sub>, CB<sub>2</sub>)
  - Endogenous cannabinoids
- Conopeptides
  - Ziconotide approved, others in clinical trials
- Targeted cerebral sites
- Gene Therapy
- ???

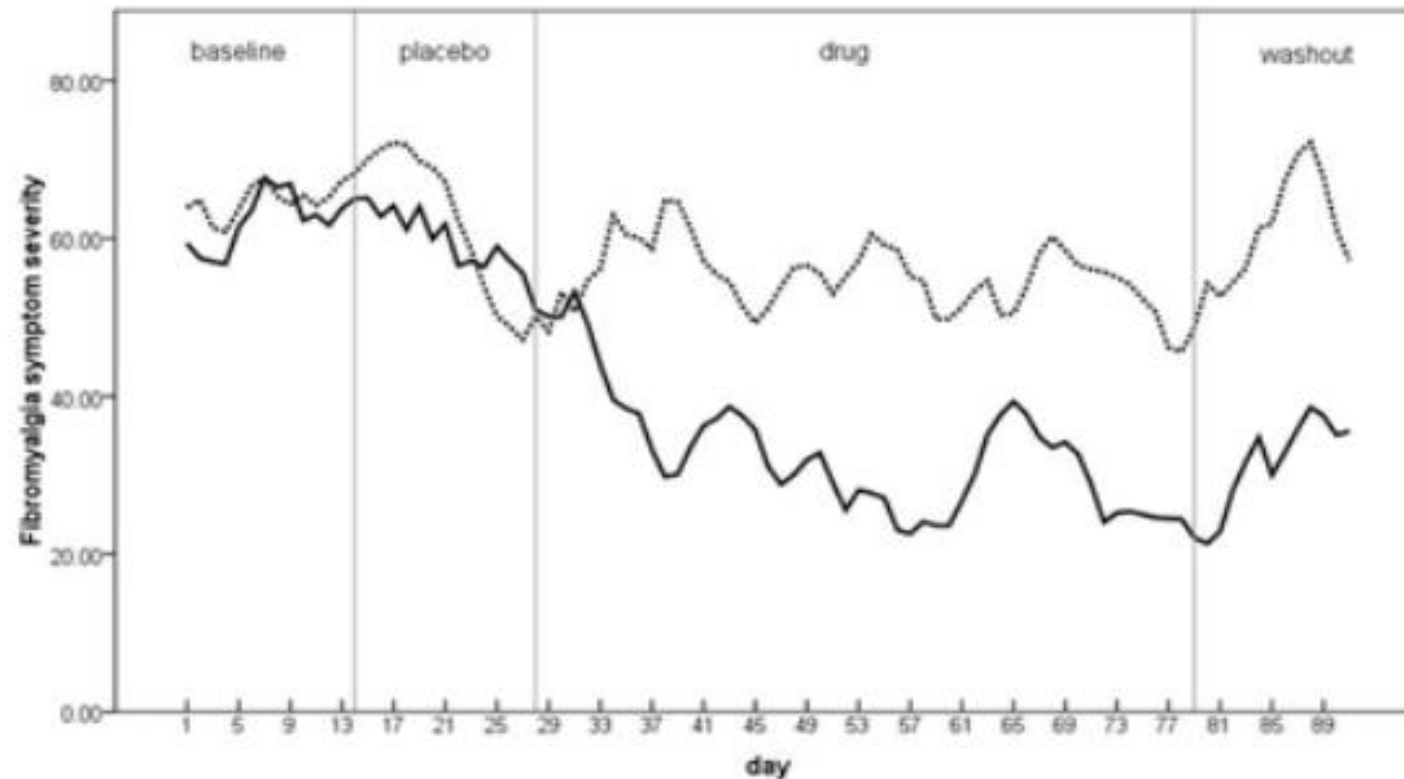
# Glial Cell Activation

- Glia have role in initiating and maintaining pain in peripheral nerve injury (neuroexcitatory substances)
- Glia activation has been demonstrated in multiple pain states (nerve injury, bone cancer, MS, radiculopathy, etc.)
- Suppressing Glia (or it's proinflammatory cytokines) returns pain to normal
  - Suppress tolerance, dependence, reward, respiratory depression and constipation
  - Enhance analgesia



# Fibromyalgia (Stanford Idn study)

- Glia cell antagonist: naltrexone
- Low dose <5 mg (study used 4.5mg daily)





# Conclusions

# Conclusions

- Anatomy and Physiology of pain is complex
- Multiple therapeutic targets currently exist
- Understanding pathophysiology and treatment mechanisms can lead to more thoughtful and successful treatments
- Expansion of the understanding of pathophysiology will lead to novel and more selective therapeutic options