

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 17th Century

Neuropathic Pain

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

Mixed Pain

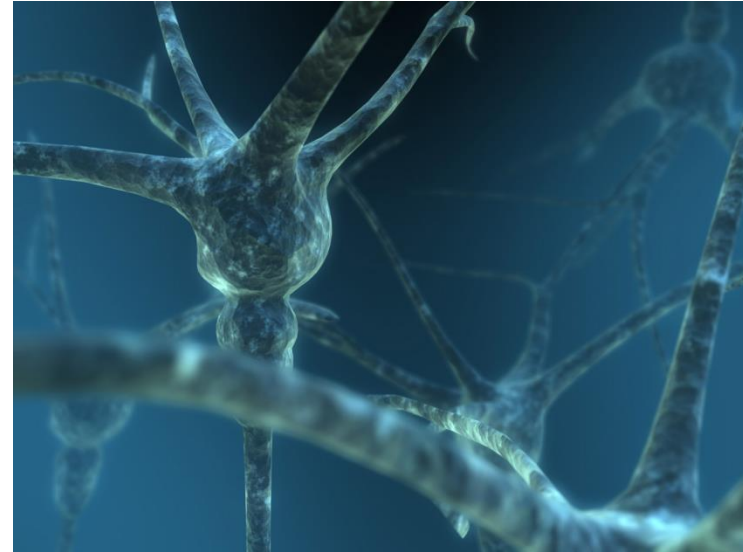
- Both Nociceptive and Neuropathic components

Nociplastic Pain

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

Pain Anatomy

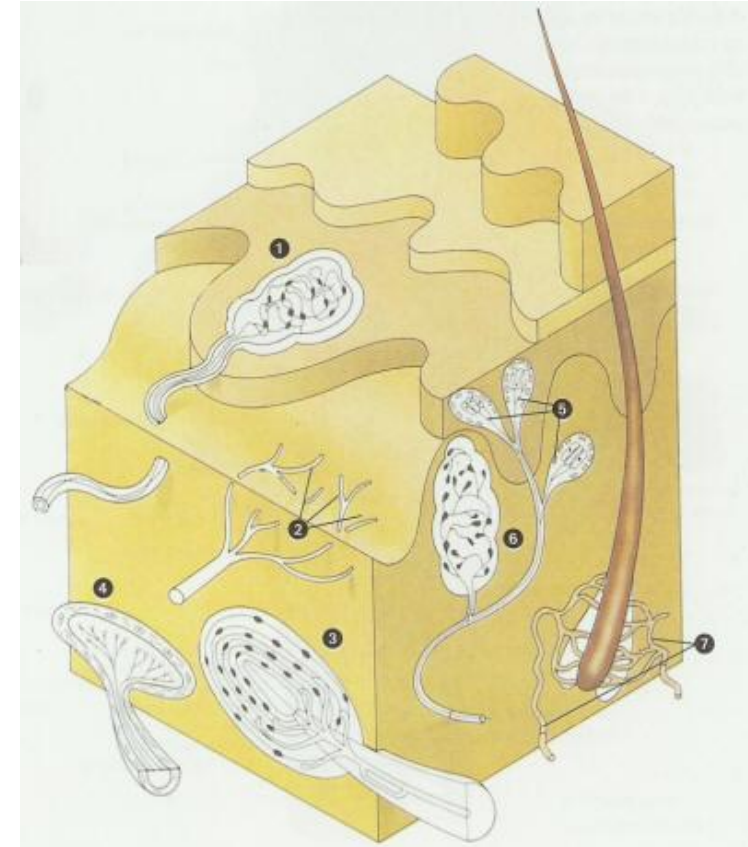
- Receptors
 - Generate Action Potential
- Axons
 - Relay information electrically
- Neurotransmitters
 - Activate nerves and provide interface between nerves



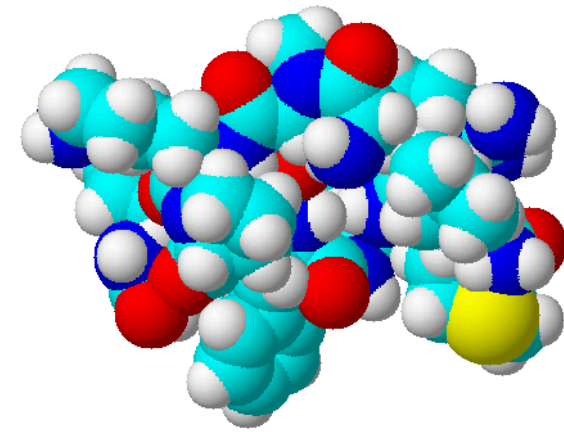
Receptors

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

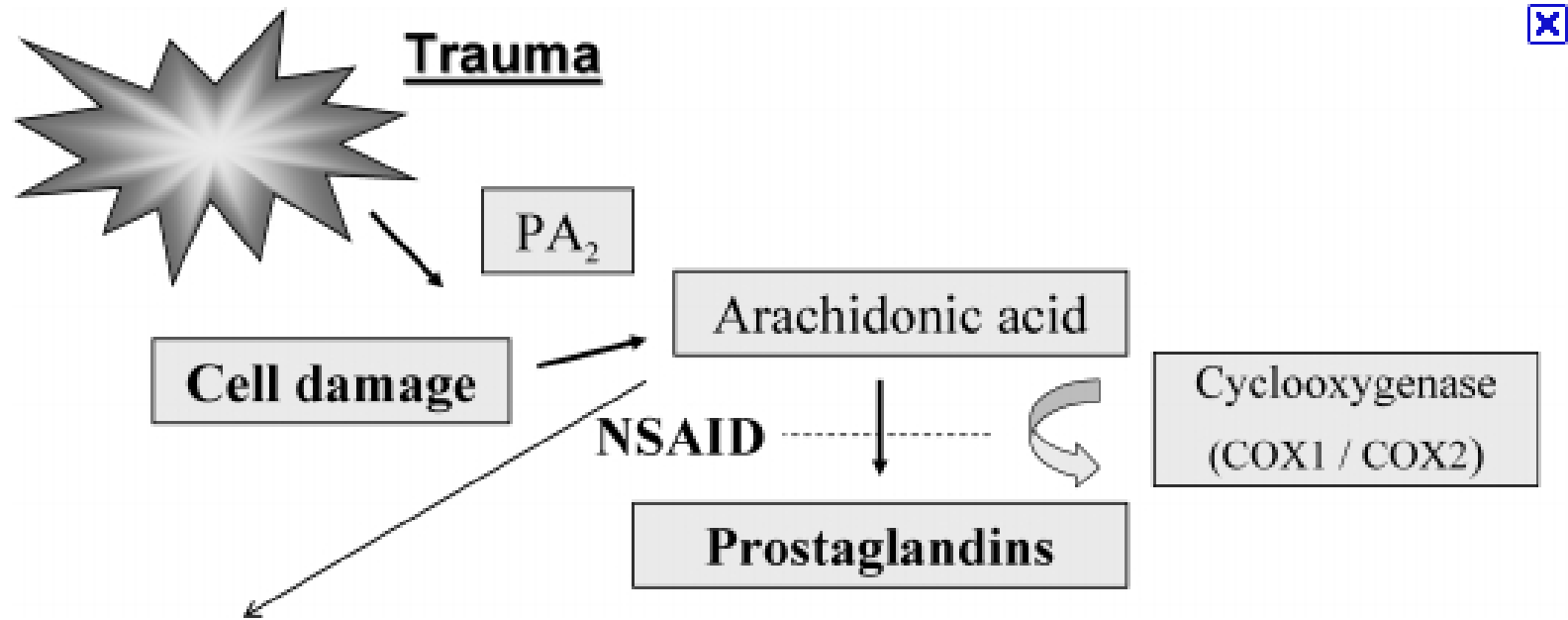
Peripheral Nociception

- 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⁺ Channel Blockers
- Many other compounded substances – peripheral?
 - Ketamine (NMDA)
 - TCAs (5-HT, NE)
 - Gabapentinoids (CA²⁺)

Axons

Nerve Axons

- Speed related to diameter

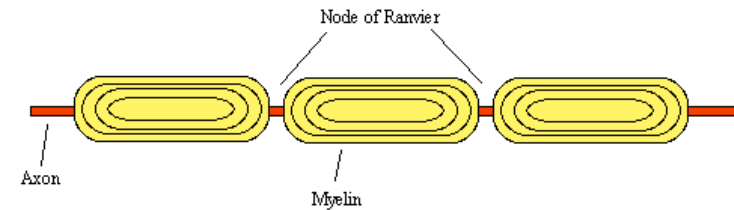
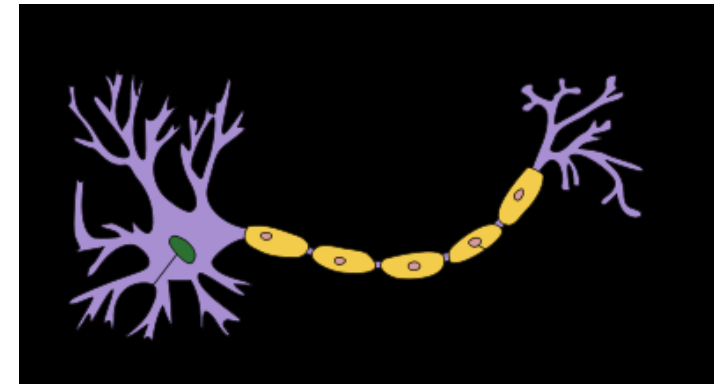
- A α : >60 m/sec
- A β : 30 – 60 m/sec
- A δ : 3 – 30 m/sec
- C-fiber: <2-5 m/sec

- Myelination

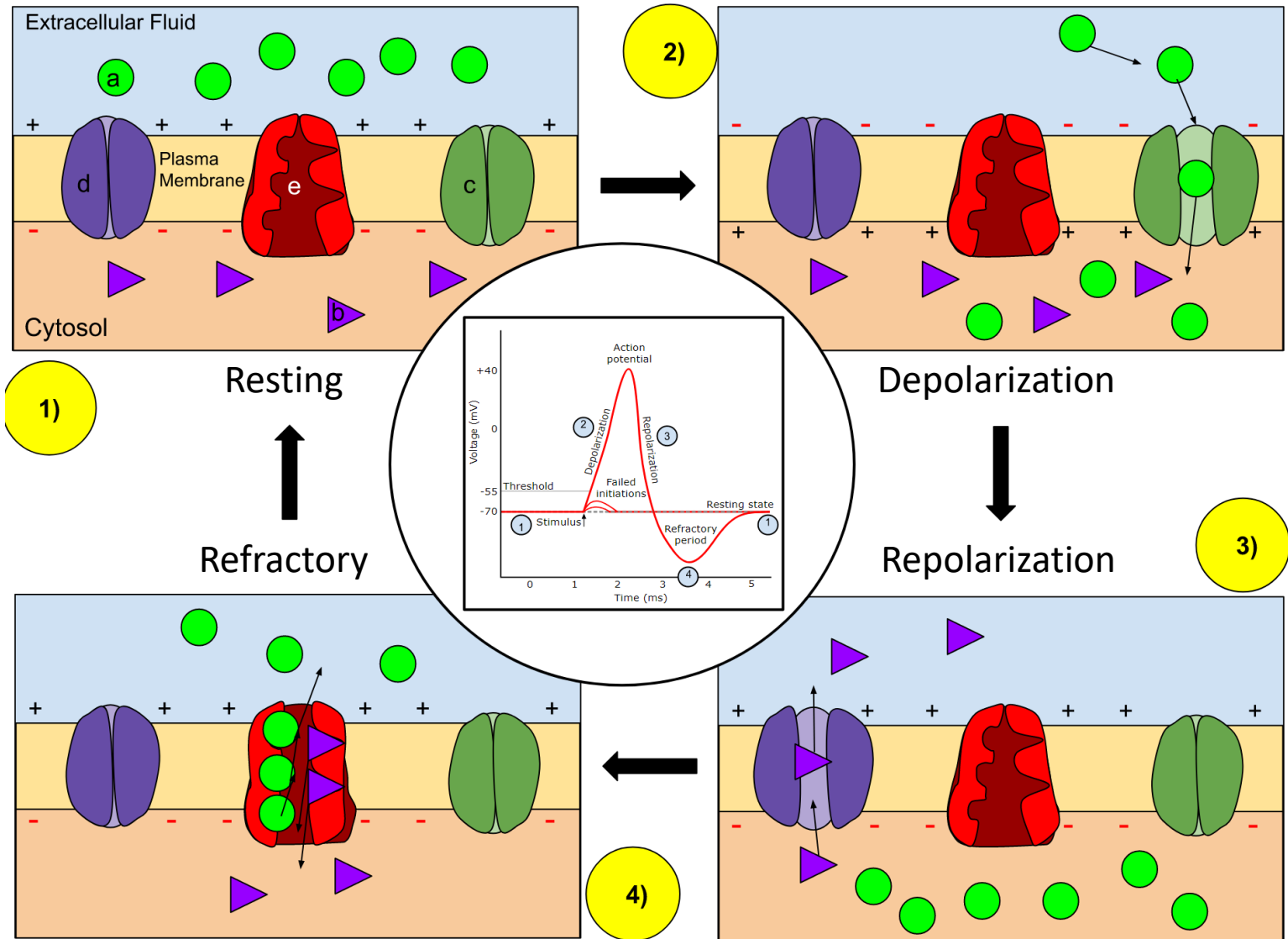
- A-fiber myelinated and fast (avoidance)
- C-fiber unmyelinated and slow (guarding)

- Schwann Cells

- Produce myelin
- Saltatory Conduction
- Nodes of Ranvier



Action Potential

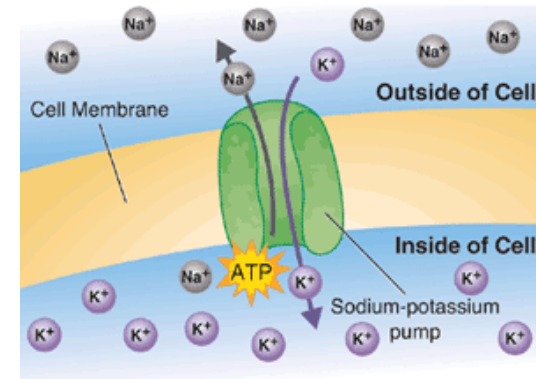


- a) Na^+
- b) K^+
- c) Na^+ Channel
- d) K^+ Channel
- e) Na^+/K^+ Pump

Axonal Targets

Na⁺ Channel Blockers

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



Na⁺ Channel Stabilizers

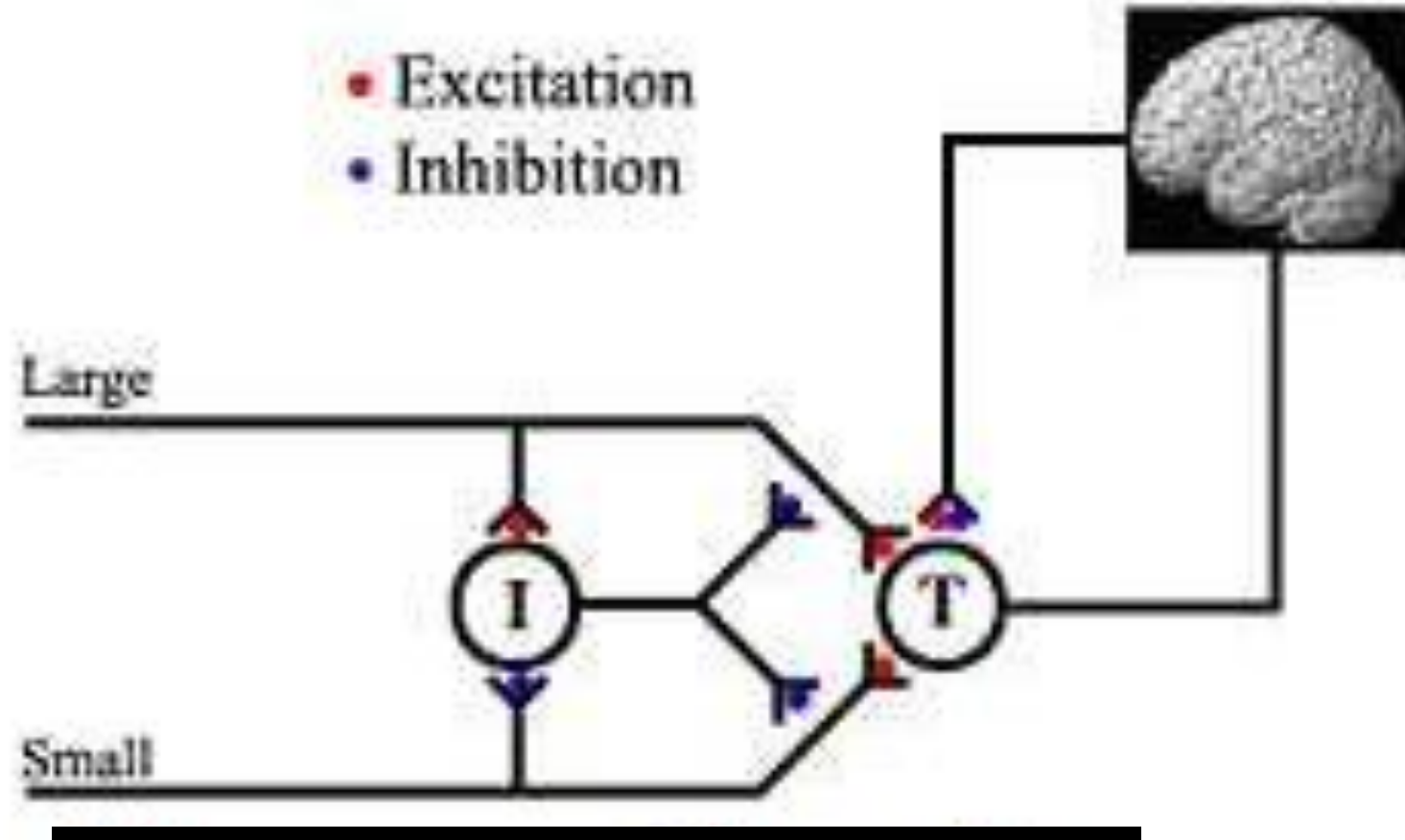
- Carbamazepine
 - Stabilizes Na⁺ channels which suppresses spontaneous A δ and c-fiber activity
- Oxcarbazepine
- Propanolol



Other Axonal Targets

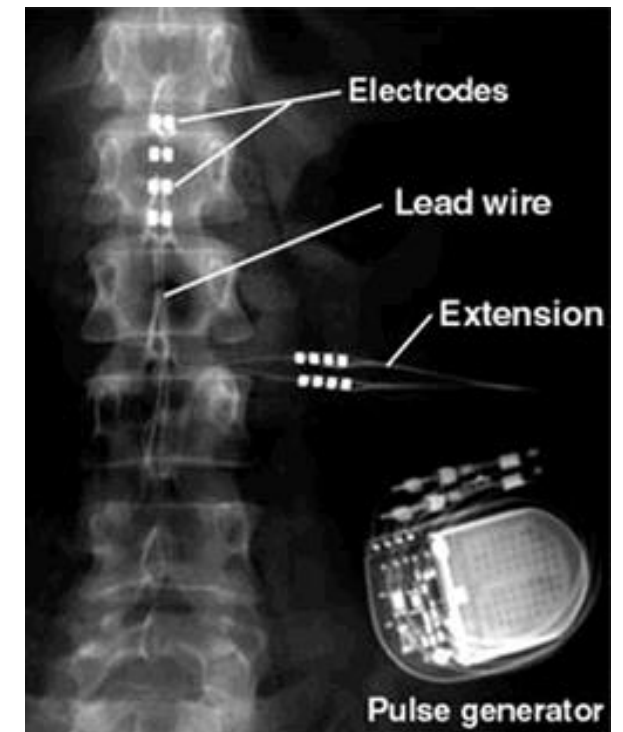
- Lamotrigine
 - Blocks voltage-dependent Na⁺ Channels
 - Inhibits Glutamate release
- Topiramate
 - Na⁺ Channel and Ca²⁺ Channel Antagonist
- Zonisamide
 - Na⁺ Channel and Ca²⁺ Channel Antagonist

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



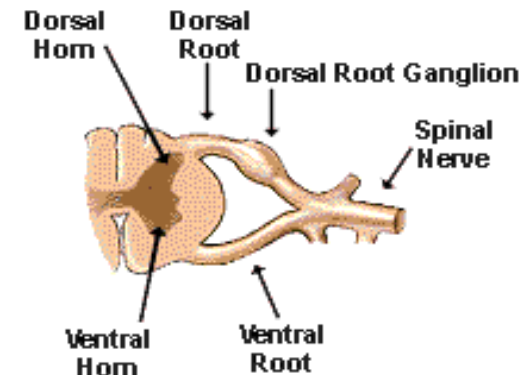
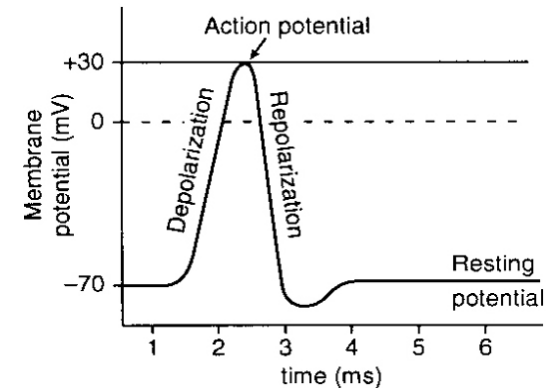
Name that system?

Peripheral/Central Interface

Dorsal Root Ganglia and Dorsal Horn

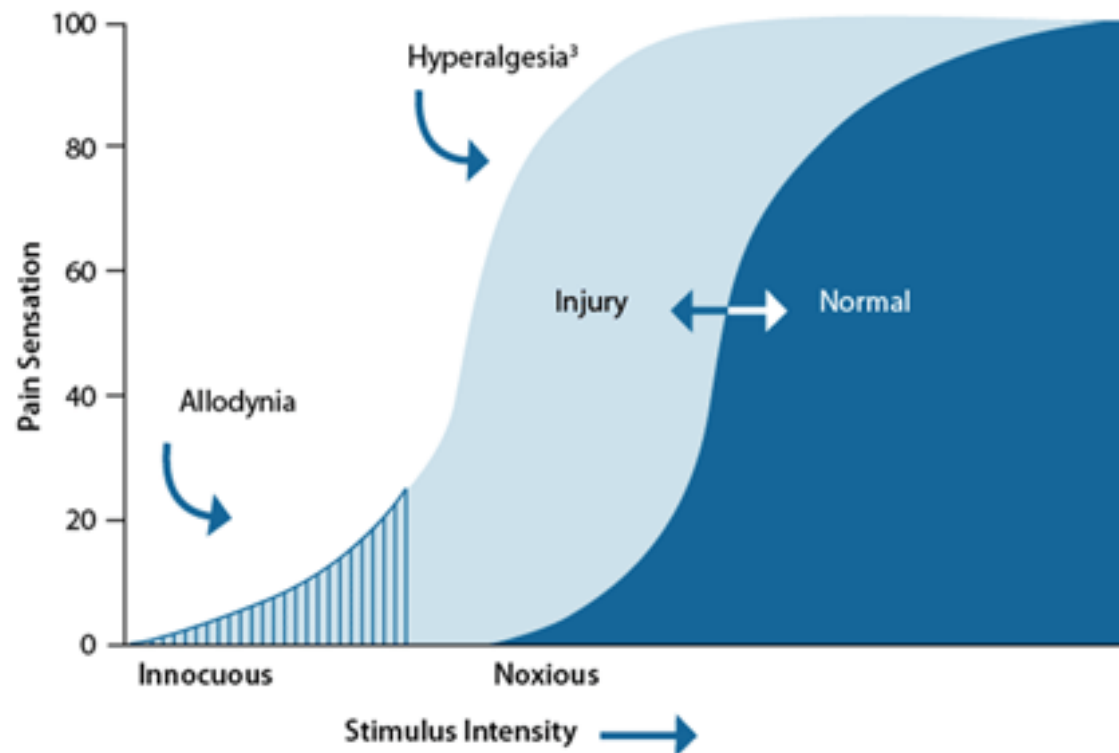
- DRG contains cell bodies for peripheral nerves
- Dorsal Horn contains many receptors:

	Depolarize	Hyperpolarize
GABA-A		X
GABA-B		X
α_1 adrenergic	X	
α_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



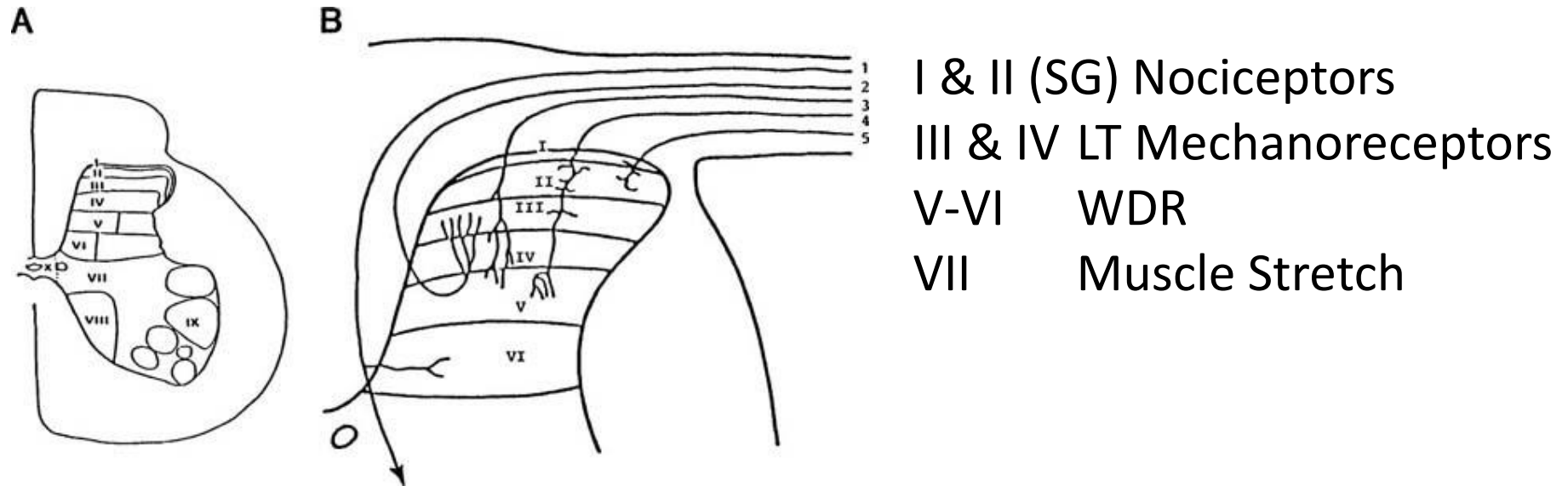
NMDA Antagonists

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



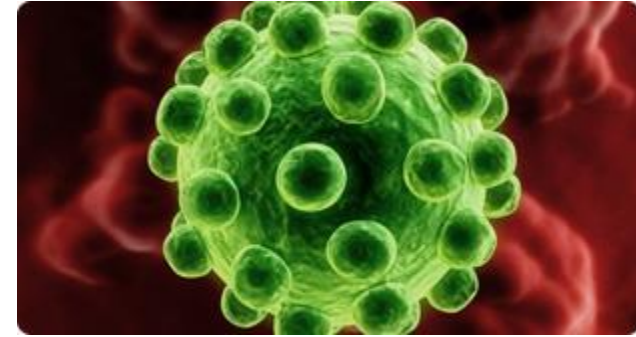
Dorsal Horn of Spinal Cord

- Primary afferent neurons project into dorsal horn lamina



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

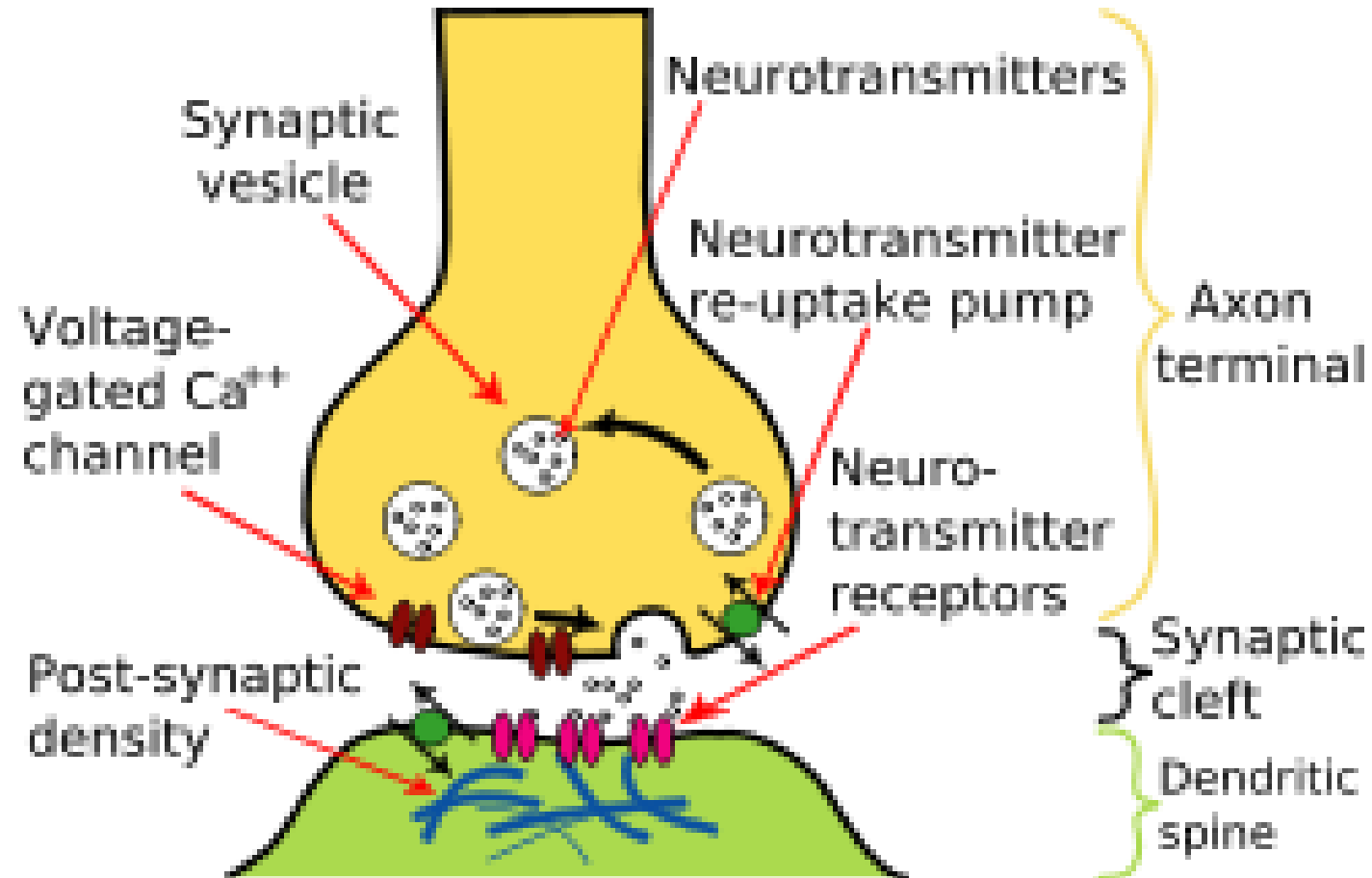
Post-herpetic Neuralgia



- Herpes Zoster Virus activation
- Loss of C-fiber density and dorsal horn cells
- Loss of superficial lamina terminals
- A β 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

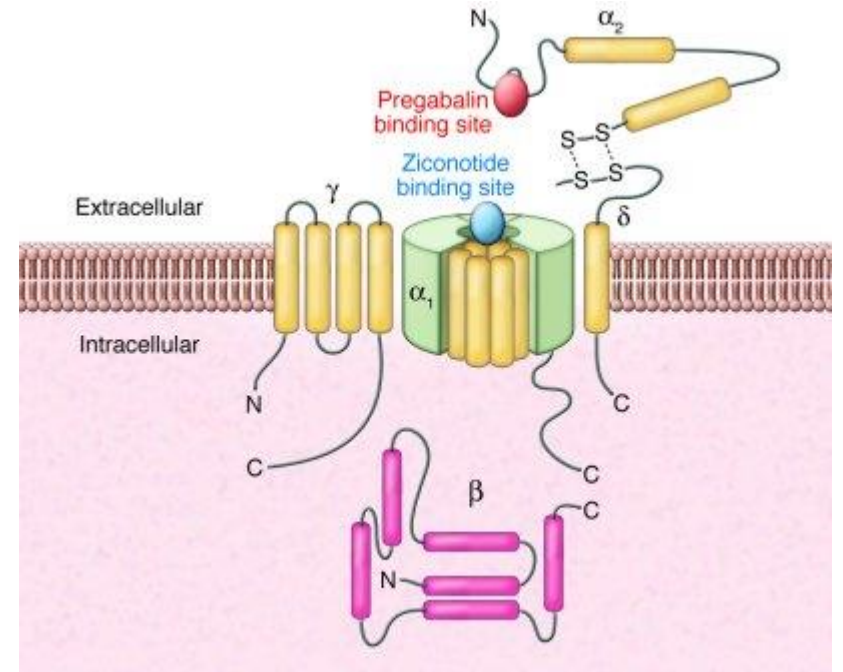
- Primary Afferent Nociceptors synapse with secondary interneurons



Dorsal Horn Targets

Ca²⁺ Channel (N-type) Drugs

- Modulators
 - Gabapentinoids
 - Bind $\alpha_2\delta$ subunit of Ca²⁺
 - Gabapentin, Pregabalin
- Blockers
 - Physically Block Channel
 - Ziconotide
- Reduce Neurotransmitter Release



Ca²⁺ Channel Modulators

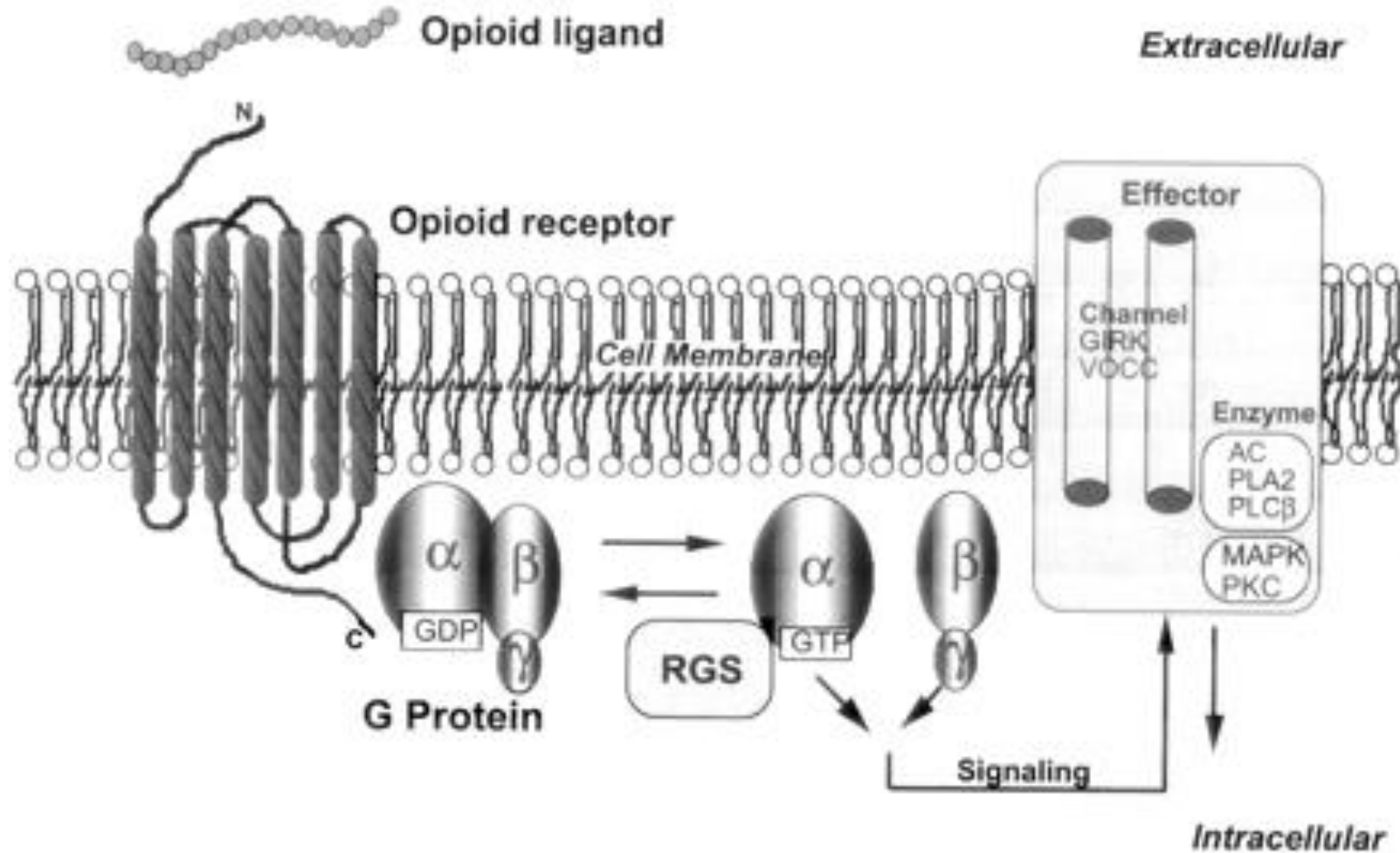
- Pregabalin (Lyrica)
 - New indication:
 - Management of Neuropathic Pain Associated with Spinal Cord Injury
 - Fibromyalgia
 - Post-herpetic neuralgia
 - Painful Diabetic Nerve Pain
- Gastroretentive Gabapentin (Gralise)
 - Once-daily for post-herpetic neuralgia
- Gabapentin enacarbil (Horizant)
 -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

conopeptides

- N-type 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

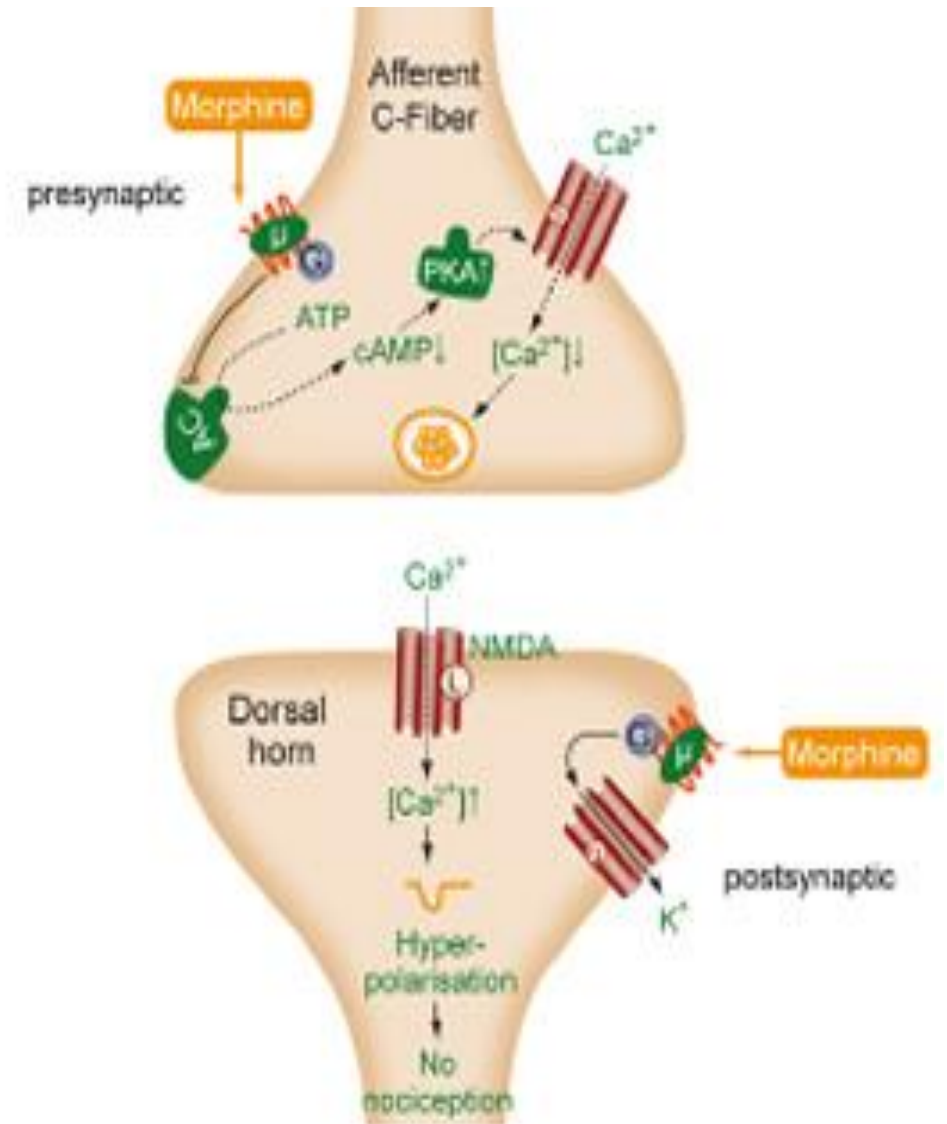


Opioid Receptors



Dorsal Horn Opioids

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



GABA Agonists

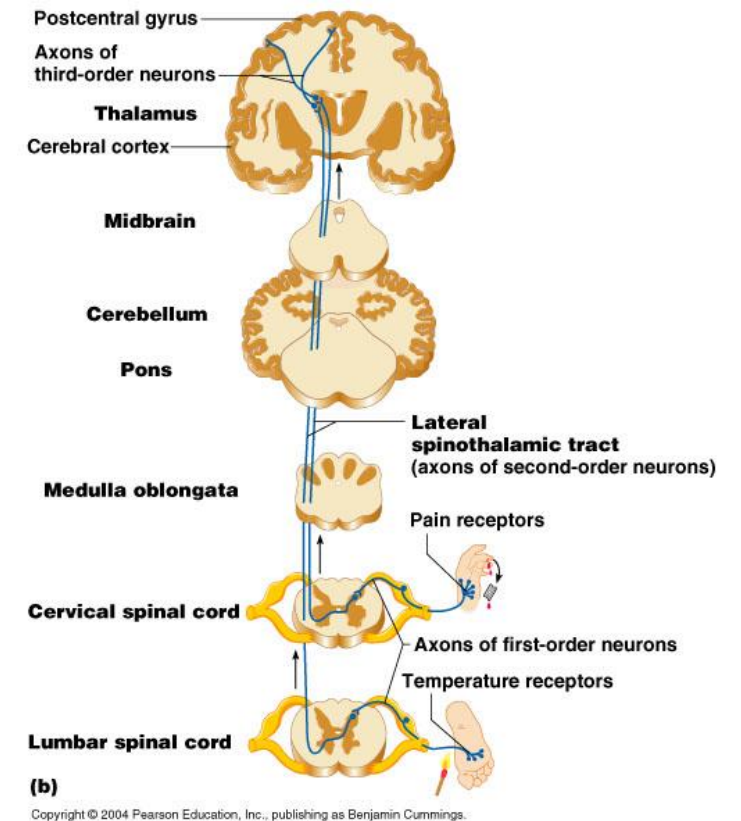
- GABA: Primary inhibitory neurotransmitter ⇒ Hyperpolarization
- Regulates muscle tone
- GABA-A agonists: Benzodiazepines
- GABA-B agonists: Baclofen



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

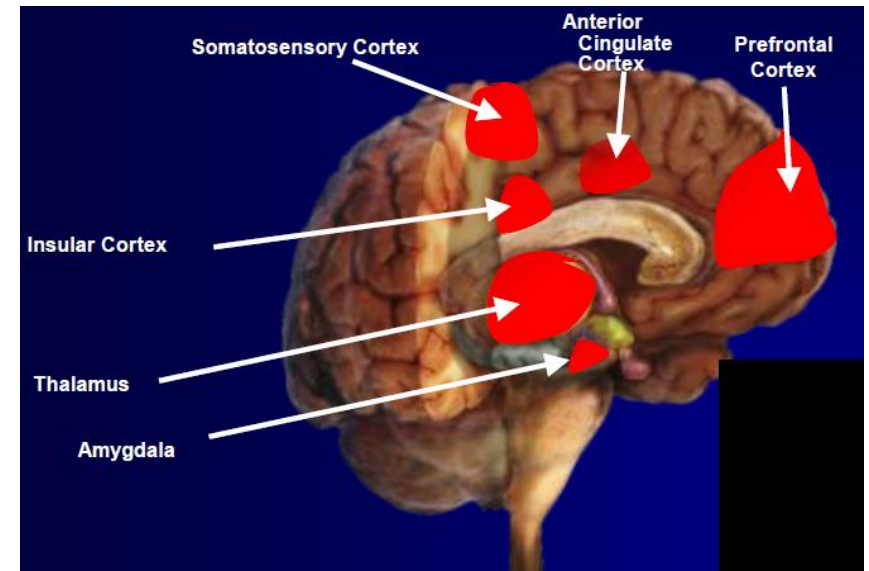
- Intra-spinal Na⁺ Blockers (Bupivacaine)
- Spinal Cord Stimulation (Descending as well)



Cerebral Cortex

Central Projections

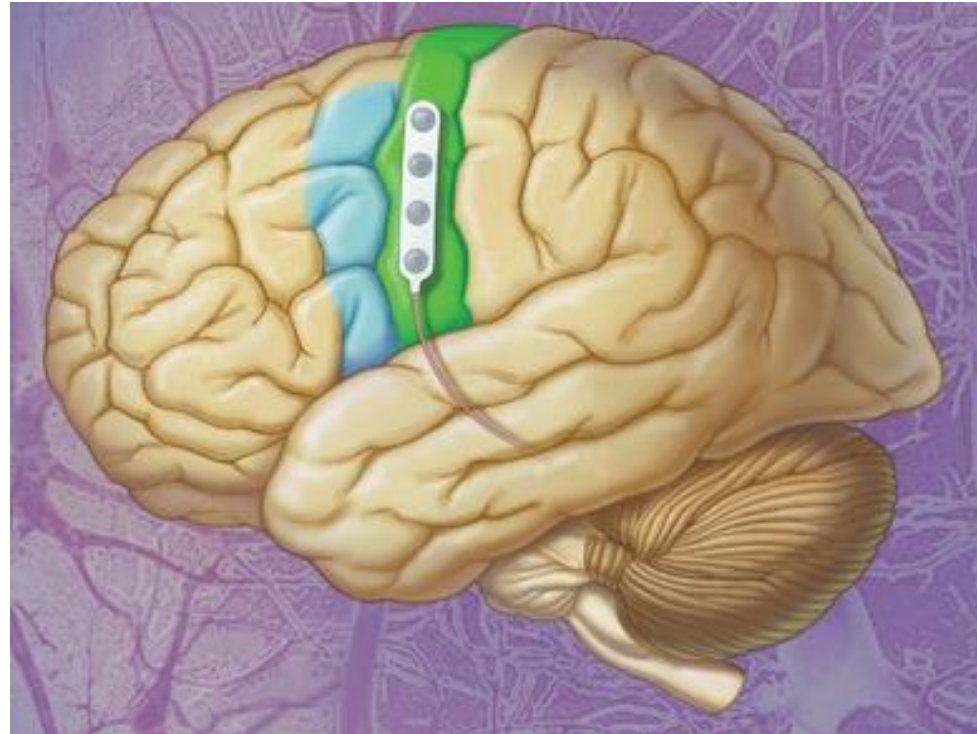
- Thalamus projects to many areas in brain
- Sensory-discriminative System
- Motivational-Affective System
- Pain Perception and interpretation
 - Primary Somatosensory
 - Secondary Somatosensory
 - Anterior Cingulate
 - Anterior Insula Frontal
 - Basal Ganglia
- Future Modulation



Central Targets

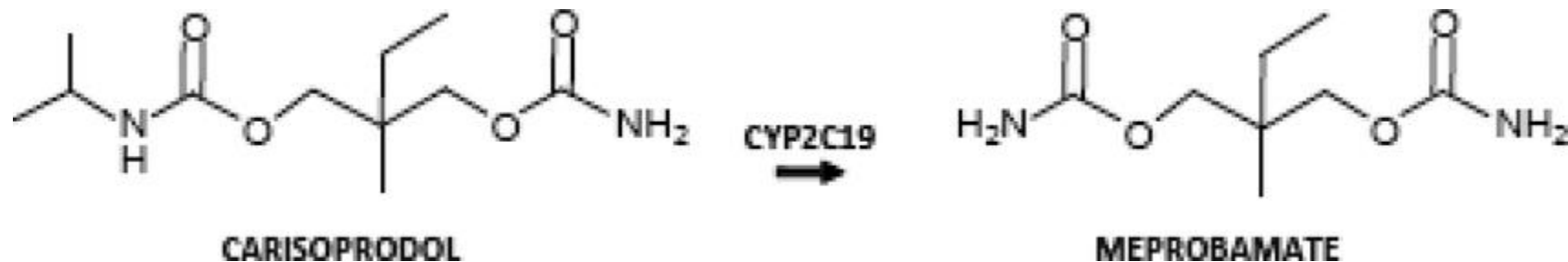
Motor Cortex Stimulation

- 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 α_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-HT₂, 5-HT₃, 5-HT₄ subtypes)
- Secondary pathways:
 - Opioid receptors interaction (stimulate endogenous opioid release)
 - Ion channel blocking (Ca²⁺, Na⁺, K⁺)
 - NMDA antagonism
 - Histamine blocking
 - Cholinergic receptor inhibition (α_1 , α_2 , β)

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 μ -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 μ 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

α -Adrenergic Active Drugs

- α -Antagonists

- Phentolamine
- Sympathetic Blockade

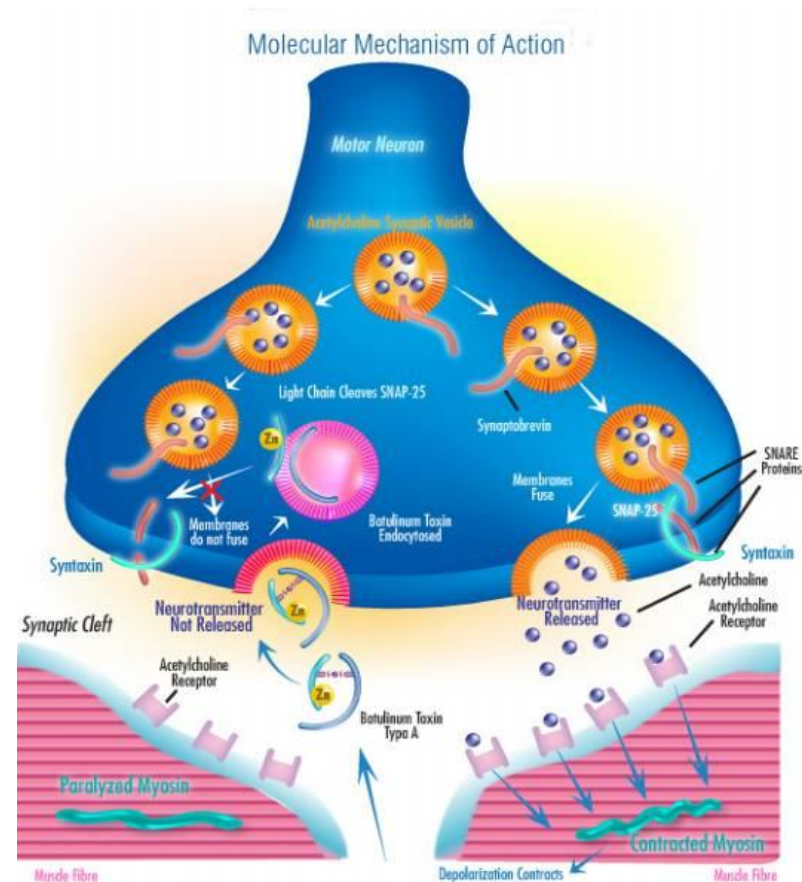
- α_2 -Agonists - Central

- 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



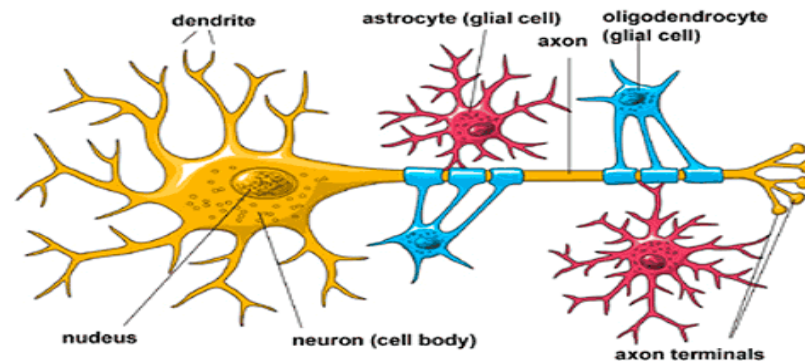
Future Targets

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 (CB₁, CB₂)
 - Endogenous cannabinoids
- Conopeptides
 - Ziconotide approved, others in clinical trials
- Targeted cerebral sites
- Gene Therapy
- ???

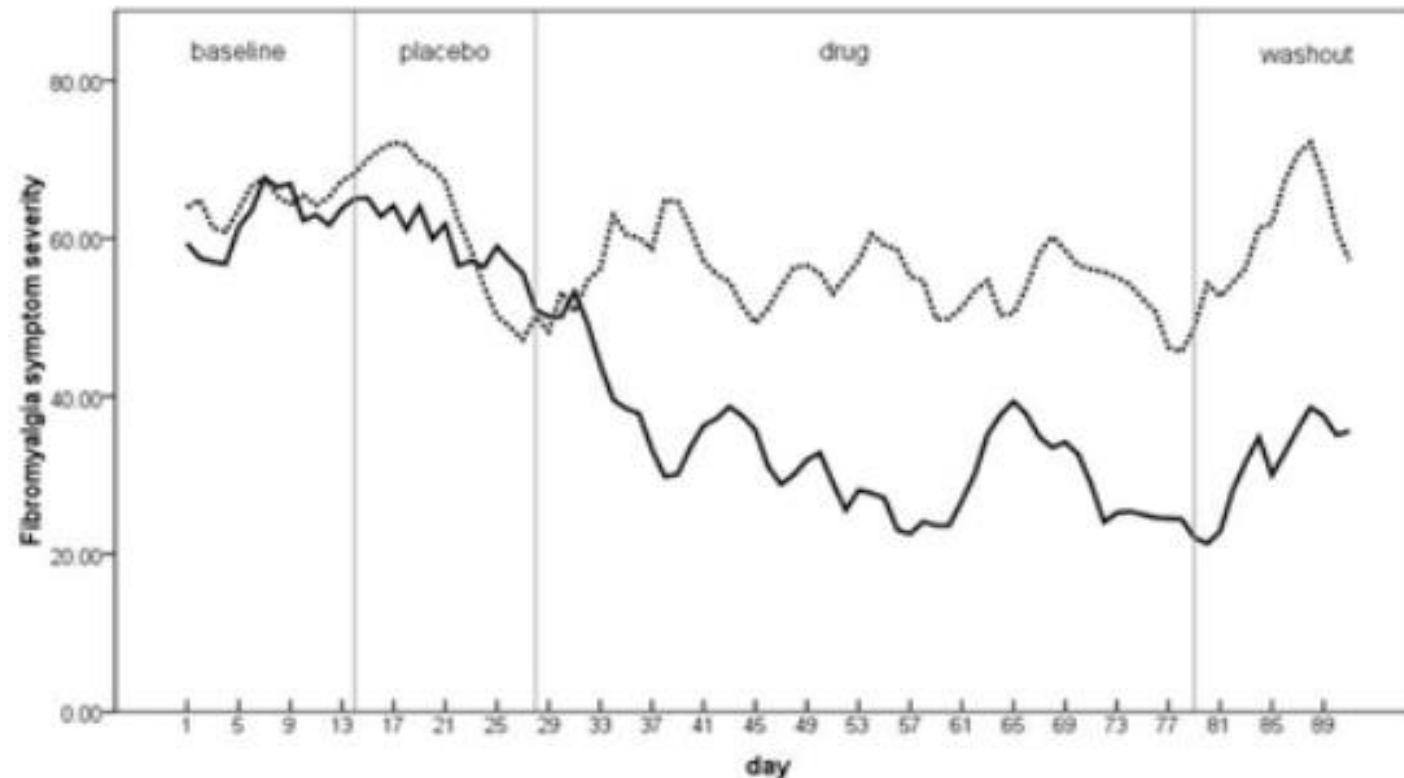
Glial Cell Activation

- 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