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

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Pacific Pain Medicine Consultants

Encinitas, CA

- 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

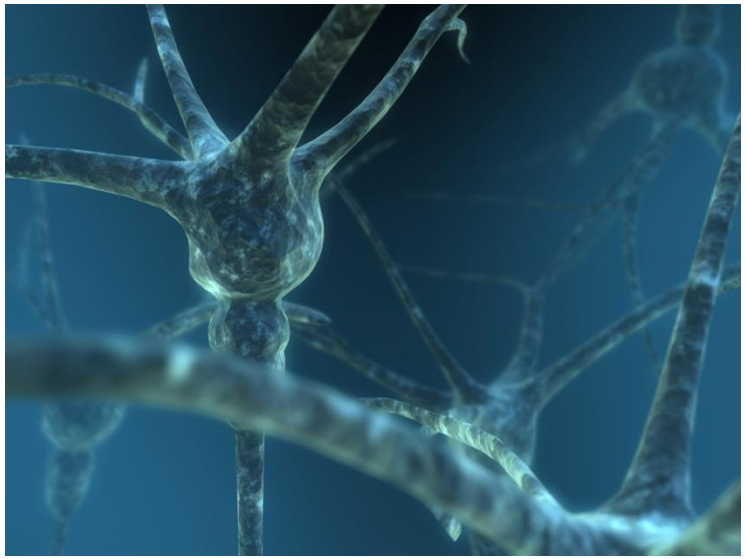
Mixed Pain

- Both Nociceptive and Neuropathic components

Nociplastic Pain

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

Pain Anatomy

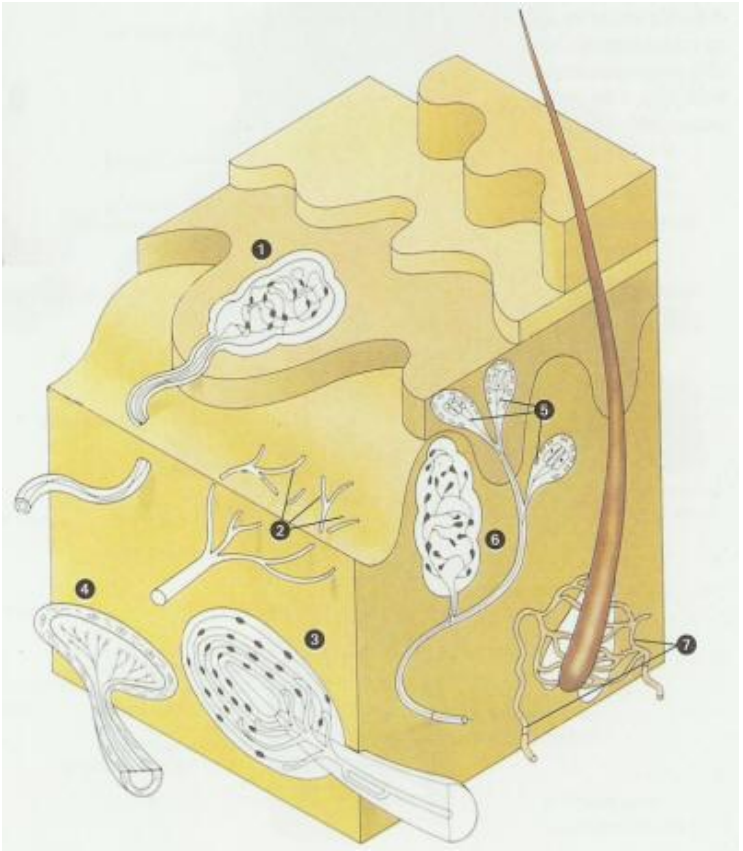


- Receptors
  - Generate Action Potential
- Axons
  - Relay information electrically
- Neurotransmitters
  - Activate nerves and provide interface between nerves

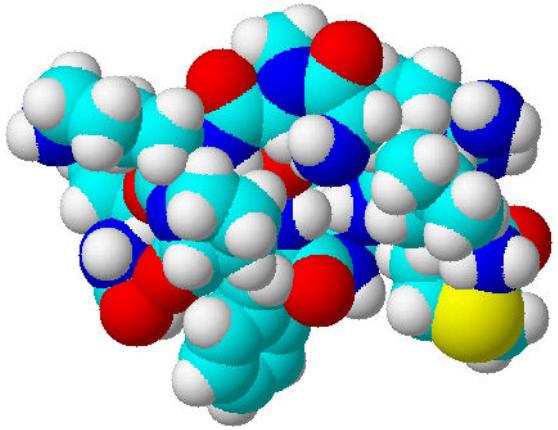
Receptors

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

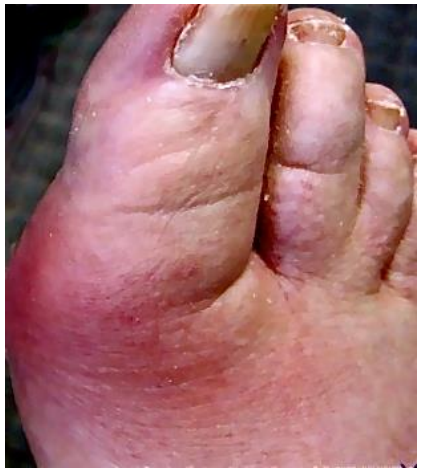


Neurotransmitters



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

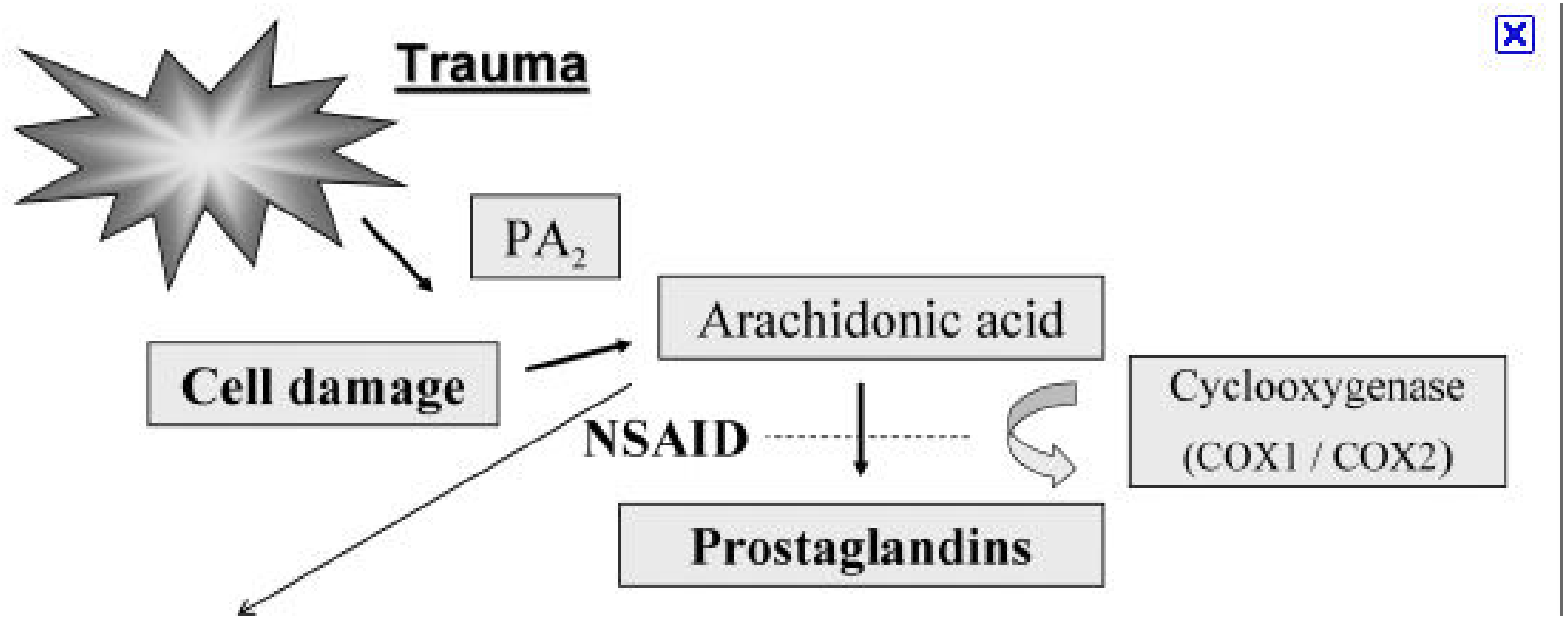
Peripheral Nociception



- Injury ⇨ Release of peptides (Sp, CGRP)
- Activation of free nerve nociceptors
- ⇧ Vascular permeability and leakage of plasma proteins ⇨ 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 ⇨ spinal prostaglandin release
- Acetaminophen inhibits COX-3 centrally

Capsaicin

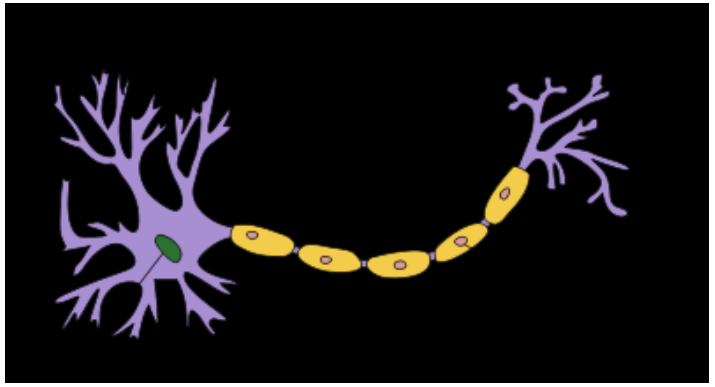
- Binds Peripheral Vanilloid Receptor
  - Stimulated by heat, abrasion
- Mechanism involves an initial sensitization, followed by desensitization
- Defunctionalization occurs with high potency
- Available as a topical system, patch, and cream

Other Peripheral Targets

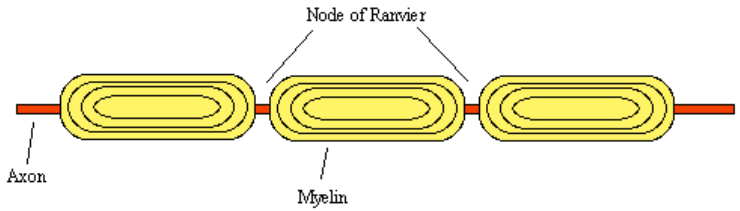
- Opioids
- Na^+ Channel Blockers
- Many other compounded substances – peripheral?
    - Ketamine (NMDA)
    - TCAs (5-HT, NE)
    - Gabapentinoids (CA^{2+})

Axons

Nerve Axons

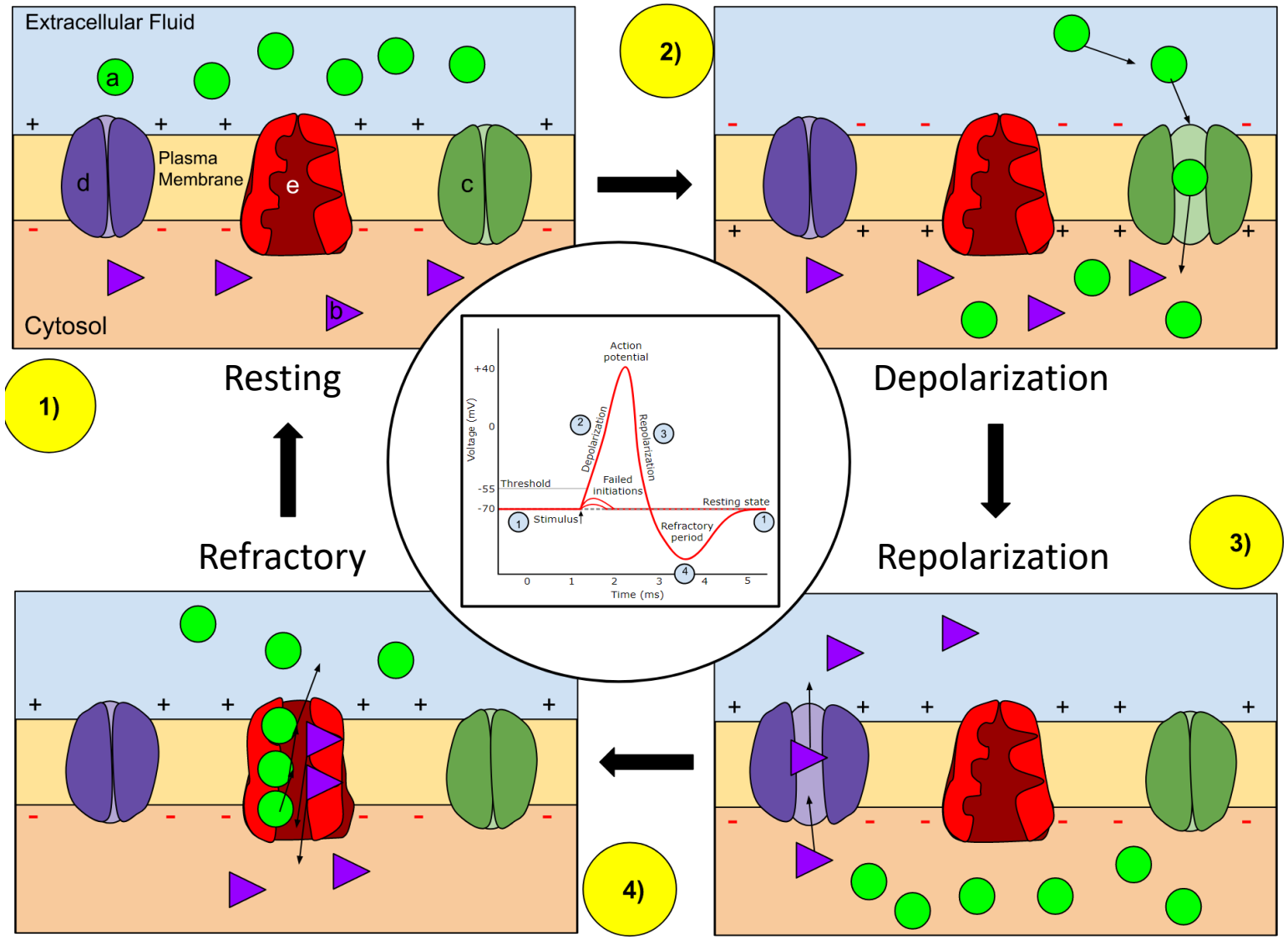


- Speed related to diameter
  - Aα: >60 m/sec
  - Aβ: 30 – 60 m/sec
  - Aδ : 3 – 30 m/sec
  - C-fiber: <2-5 m/sec



- Myelination
  - A-fiber myelinated and fast (avoidance)
  - C-fiber unmyelinated and slow (guarding)
- Schwann Cells
  - Produce myelin
  - Saltatory Conduction
  - Nodes of Ranvier

Action Potential

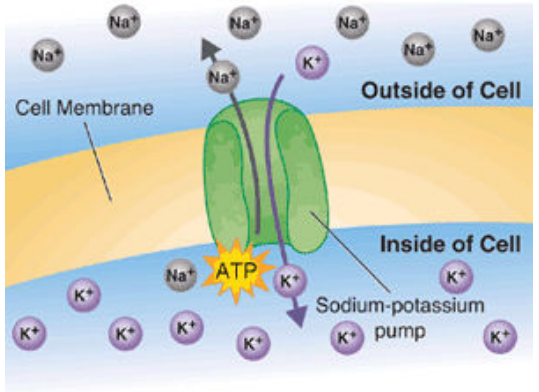


a) Na^+
b) K^+
c) Na^+ Channel
d) K^+ Channel
e) Na^+/K^+ Pump

https://en.wikipedia.org/wiki/Action_potential

Axonal Targets

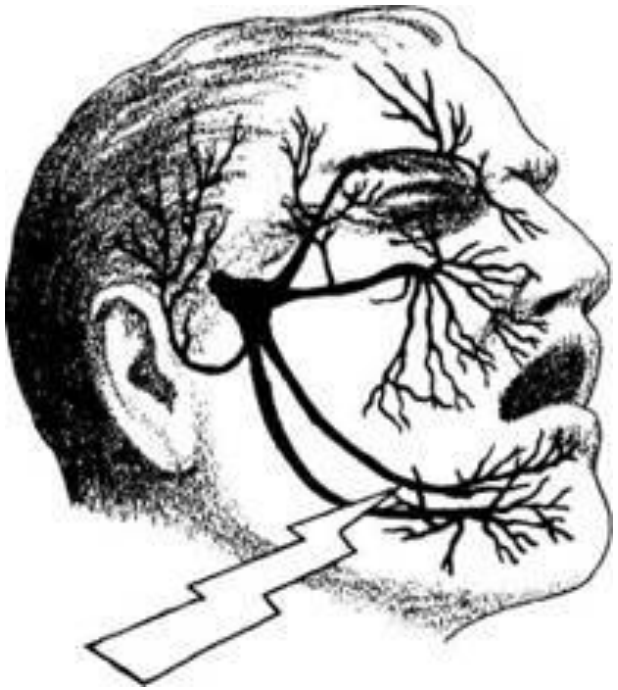
Na^+ Channel Blockers



- 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-excitabilty)
- Can be injected or applied as patch, EMLA
- Can be compounded into gels/creams

Na^+ Channel Stabilizers

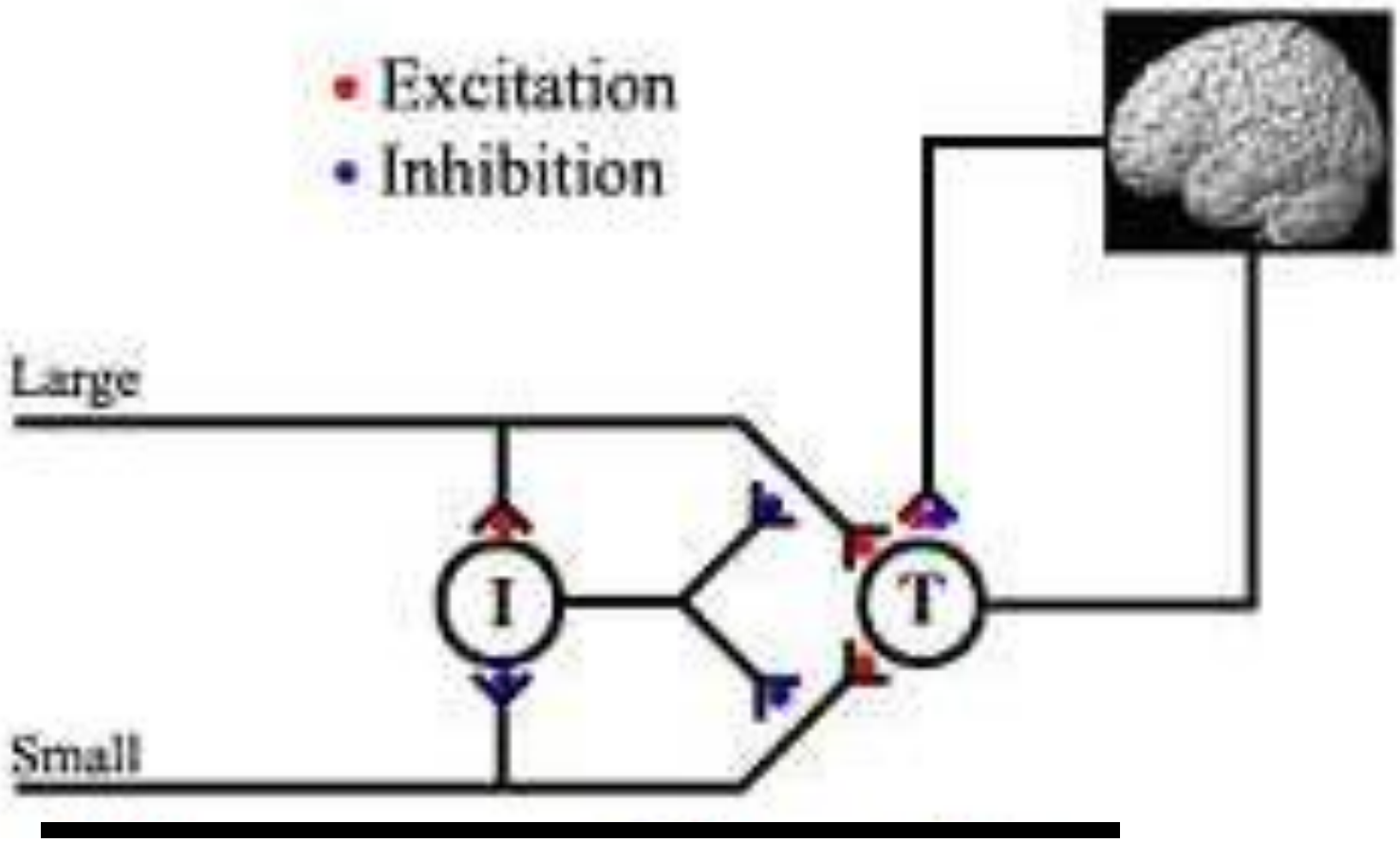
- Carbamazepine
  - Stabilizes Na^+ channels which suppresses spontaneous Aδ and c-fiber activity
- Oxcarbazepine
- Propanolol



Other Axonal Targets

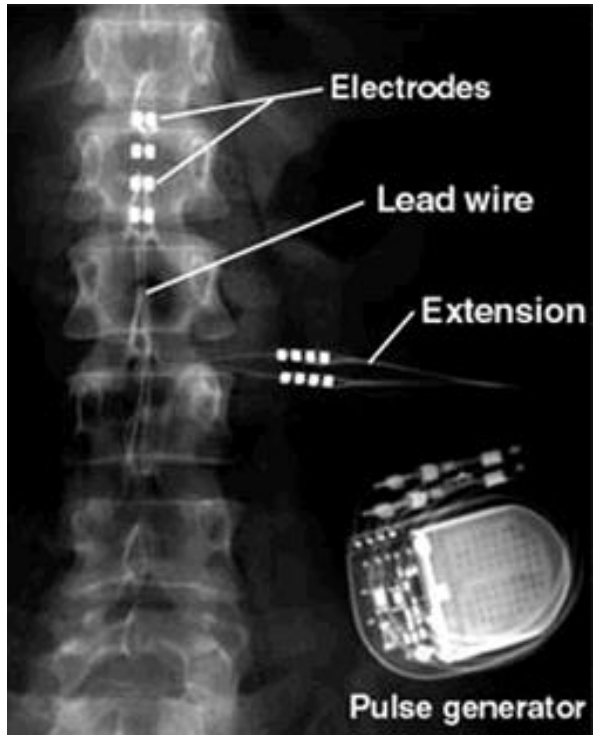
- Lamotrigine
  - Blocks voltage-dependent Na^+ Channels
  - Inhibits Glutamate release
- Topiramate
  - Na^+ Channel and Ca^{2+} Channel Antagonist
- Zonisamide
  - Na^+ Channel and Ca^{2+} Channel Antagonist

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



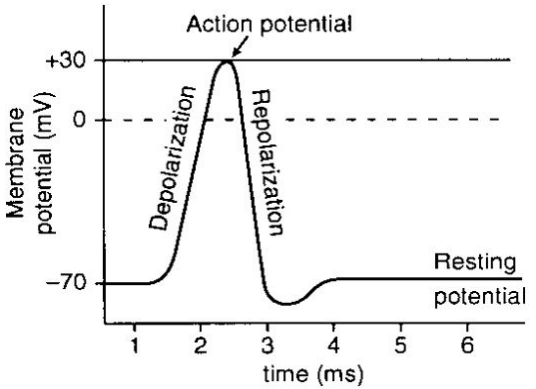
Name that system?

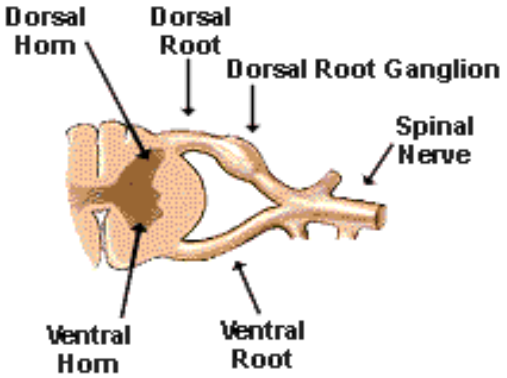
Peripheral/Central Interface

Dorsal Root Ganglia and Doral Horn

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

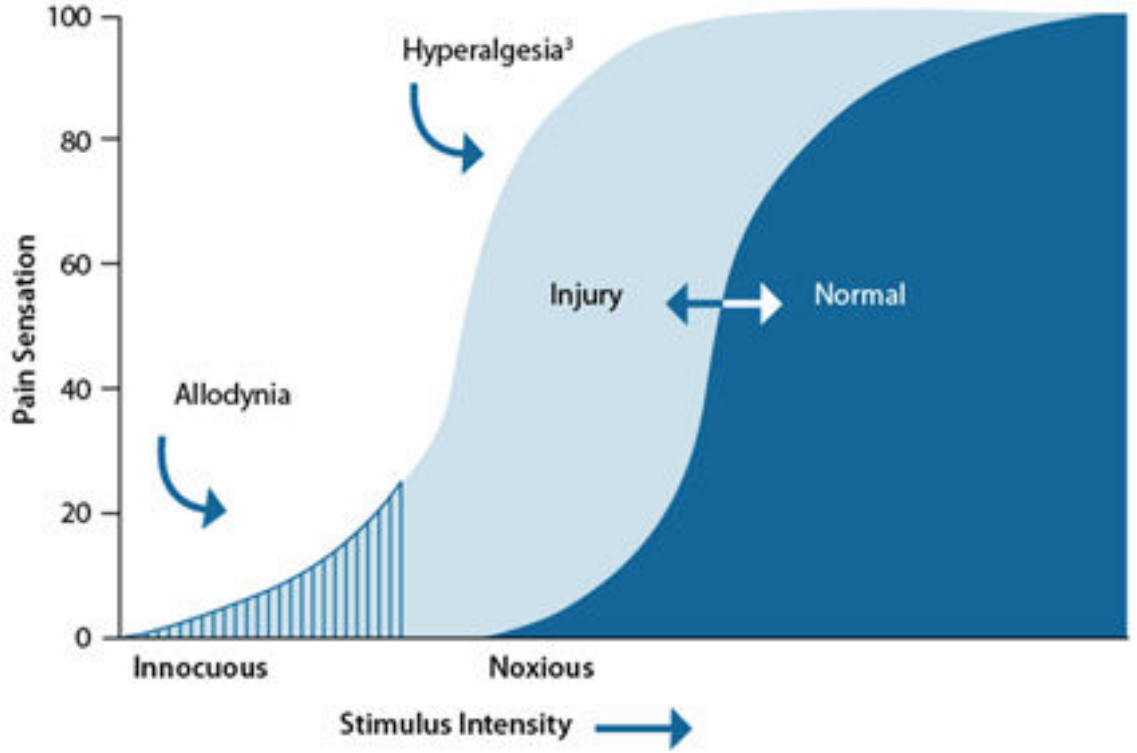
	Depolarize	Hyperpolarize
GABA-A		X
GABA-B		X
α_1 adrenergic	X	
α_2 adrenergic		X
Opioid		X
Histamine	X	
Muscarinic		X
Nicotinic	X	
Glutamate (non-NDMA)	X	
Glutamate (NDMA)	X	
5HT2/3	X	





Sensitization

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

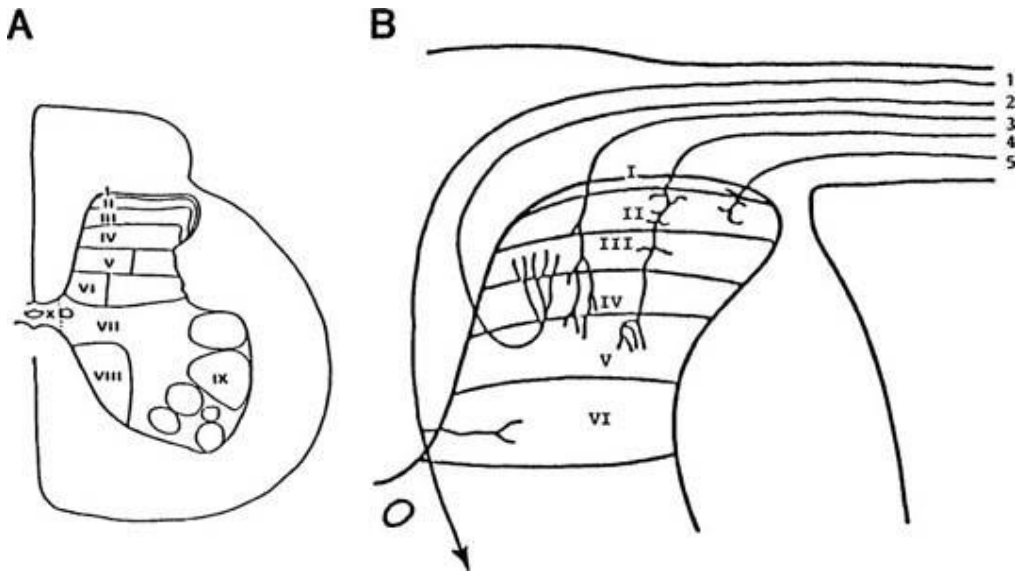


NMDA Antagonists

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

Dorsal Horn of Spinal Cord

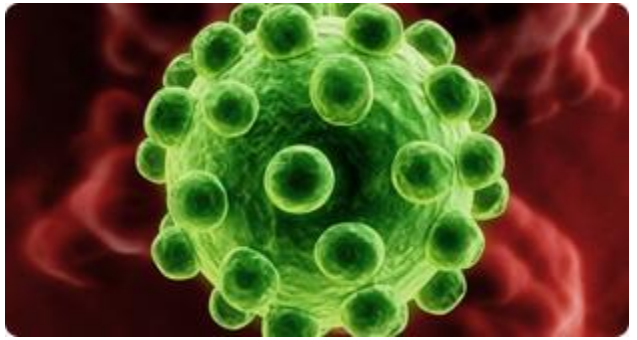
- Primary afferent neurons project into dorsal horn lamina



I & II (SG) Nociceptors
III & IV LT Mechanoreceptors
V-VI WDR
VII Muscle Stretch

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

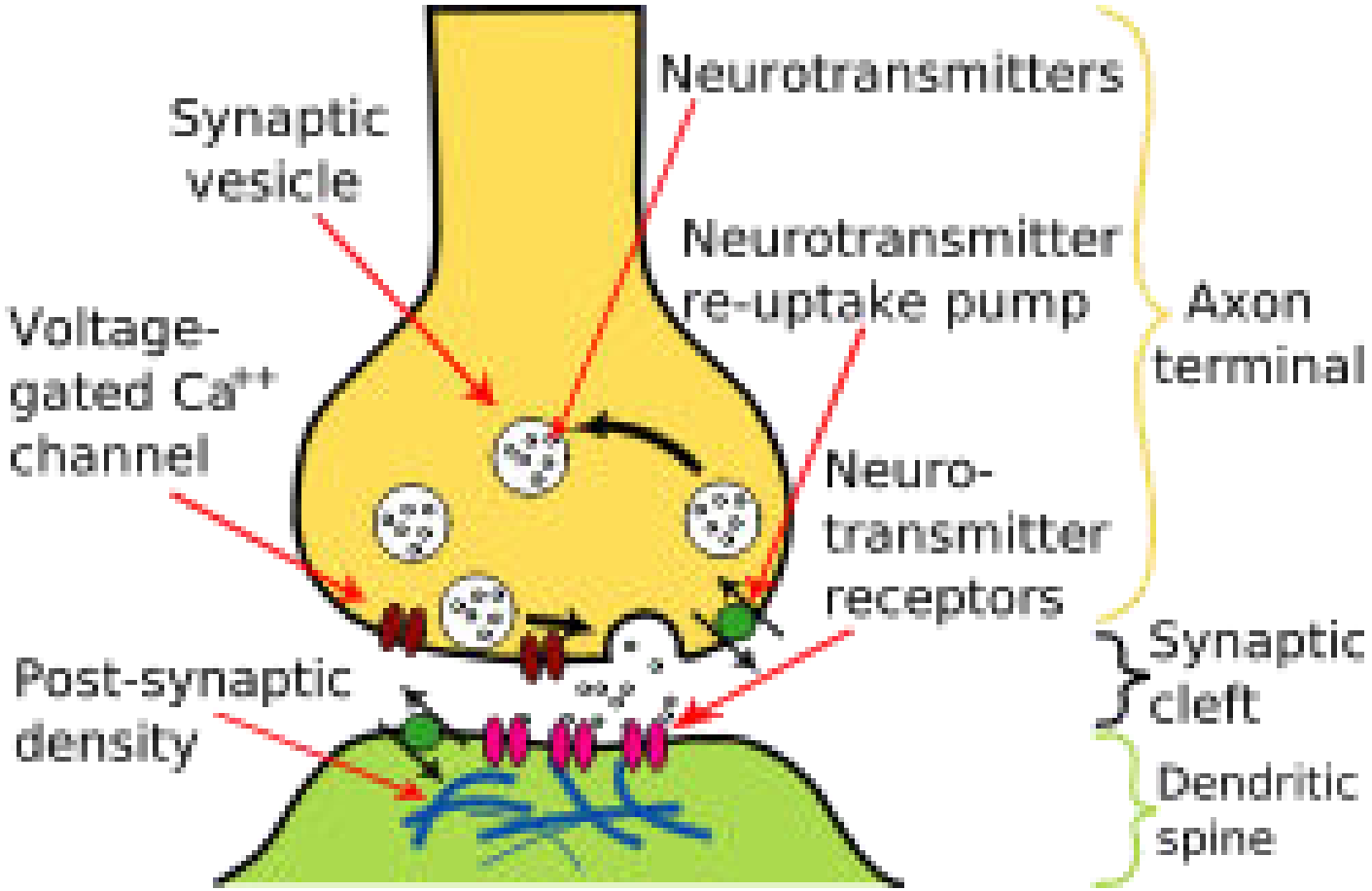
Post-herpetic Neuralgia



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

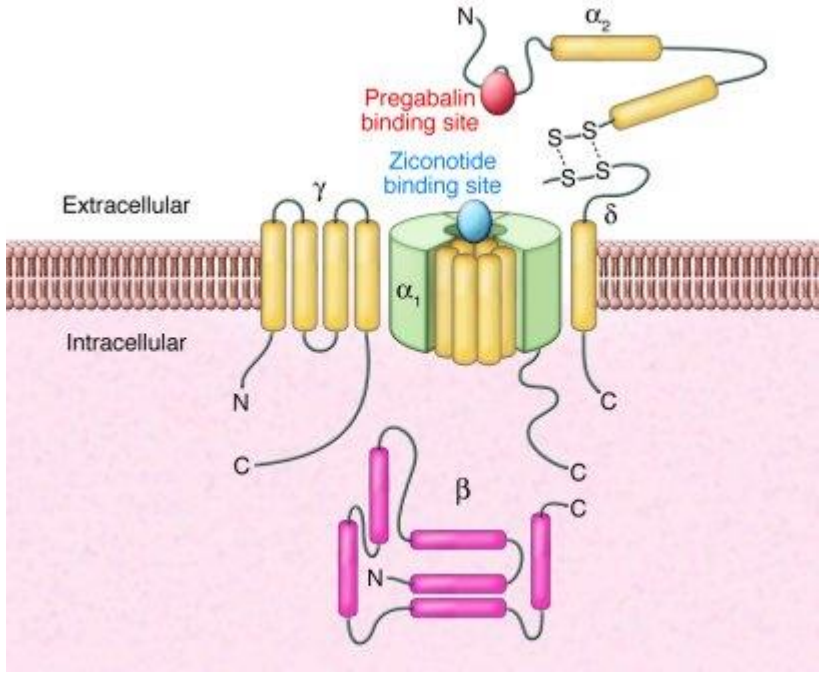
- Primary Afferent Nociceptors synapse with secondary interneurons



Dorsal Horn Targets

Ca^{2+} Channel (N-type) Drugs

- Modulators
  - Gabapentinoids
  - Bind $\alpha_2\delta$ subunit of Ca^{2+}
  - Gabapentin, Pregabalin
- Blockers
  - Physically Block Channel
  - Ziconotide
- Reduce Neurotransmitter Release



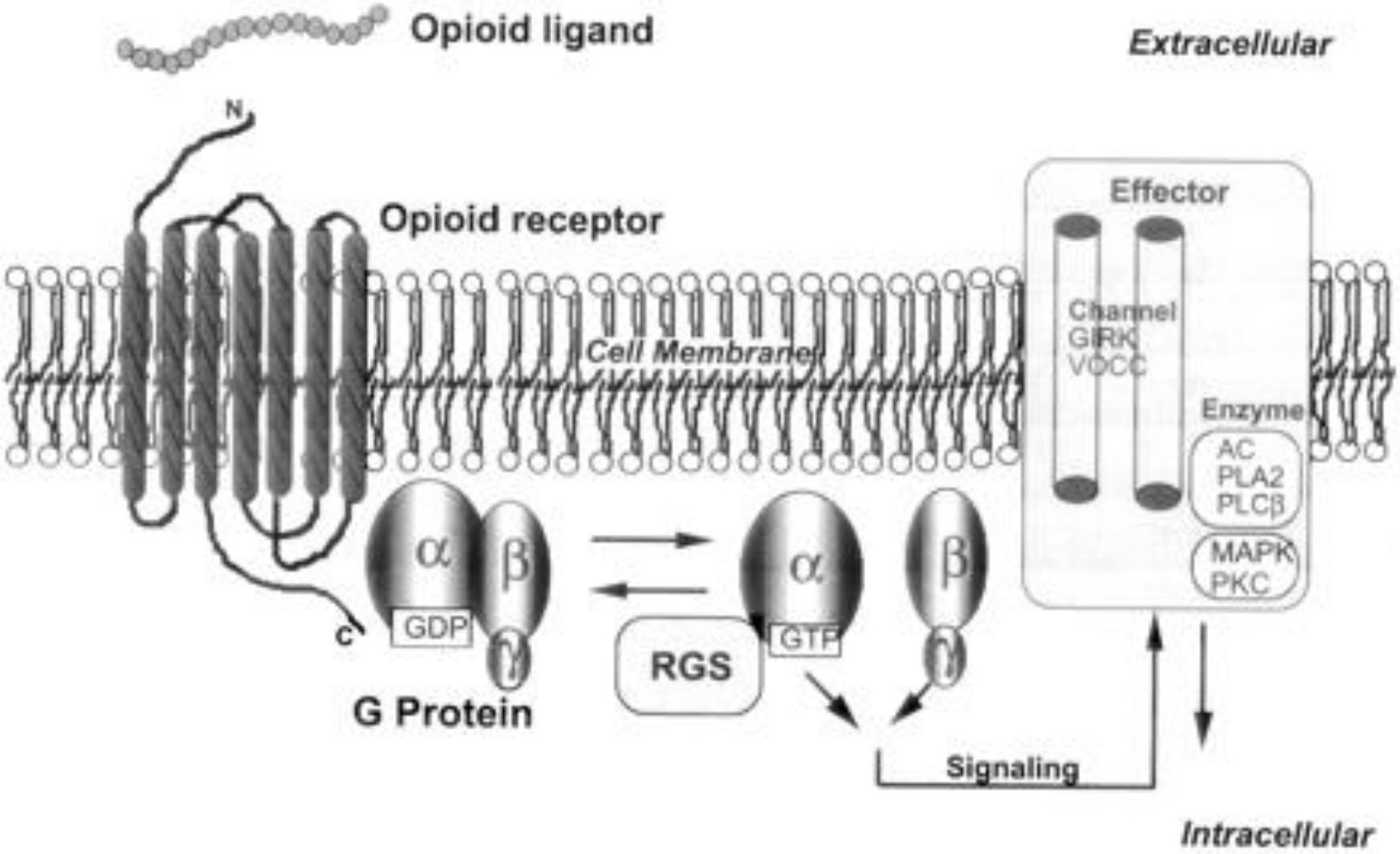
Ca^{2+} Channel Modulators

- 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

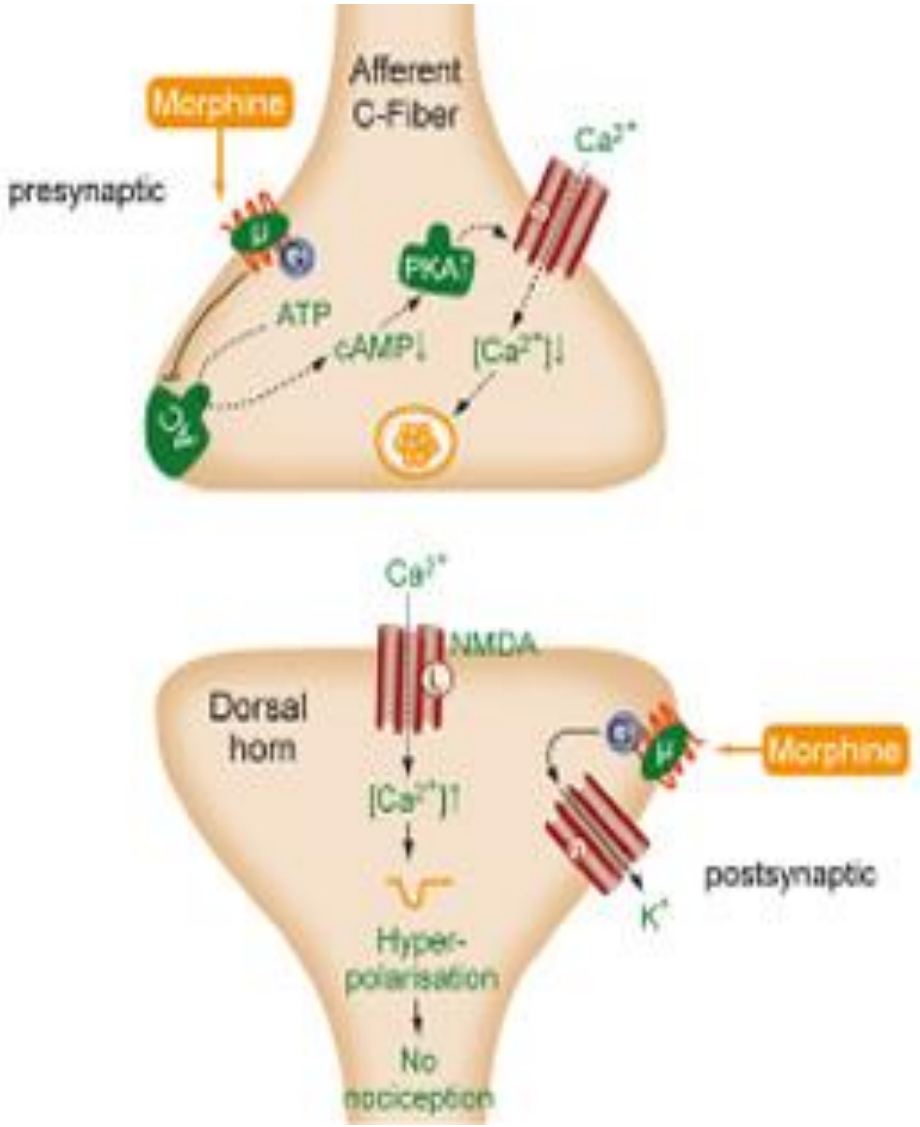
- N-type Ca^{2+} Channel Blocker
- Ziconotide (Prialt)
  - *Conus Magus* Snail
  - For management of severe chronic pain when IT therapy warranted and intolerant or refractory to other treatment, such as systemic analgesics, adjunctive therapies or IT morphine
  - 1000x more potent than morphine
- Other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

Opioid Receptors



Dorsal Horn Opioids

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



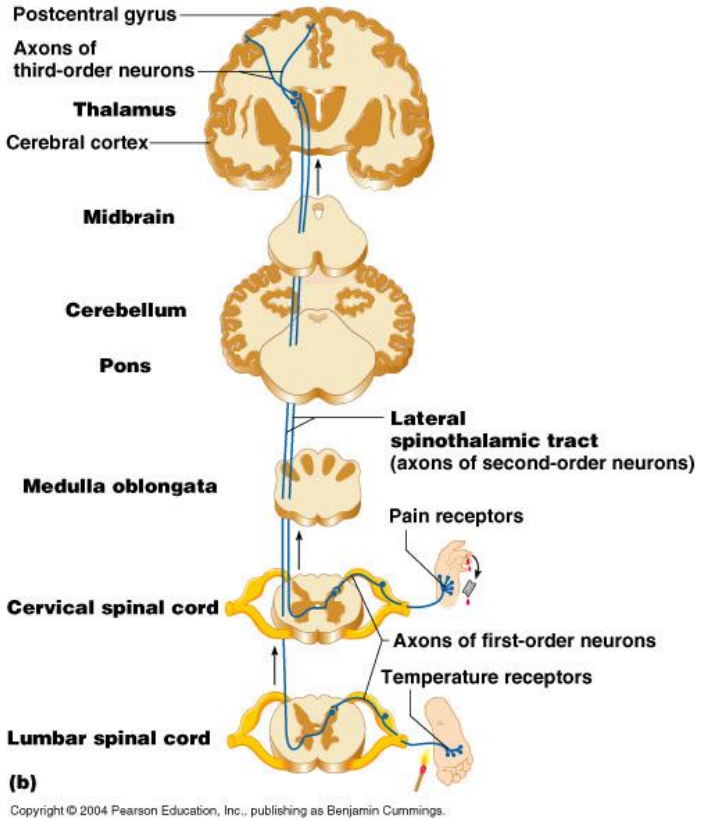
GABA Agonists

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

Ascending Pathways

Ascending Projection Systems

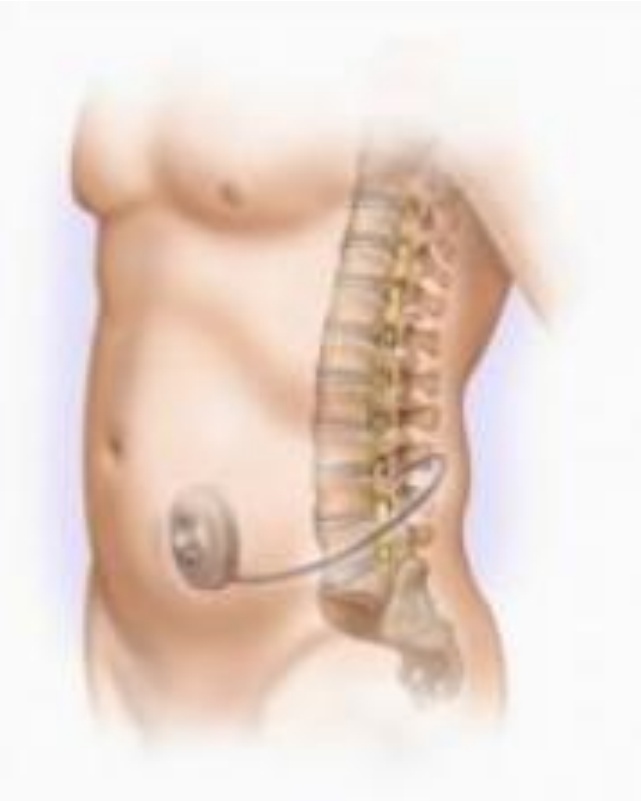
- Bring spinal cord information to brain
- Several nociceptive pathways
  - Spinothalamic Tract
  - Quality, location, duration, intensity of sensation
  - Spinoreticular Tract
  - Spinomesencephalic Tract
- Many cross and ascend on contralateral side
- Reflex motor activity



Ascending Path Targets

Spinal Ascending Modulation

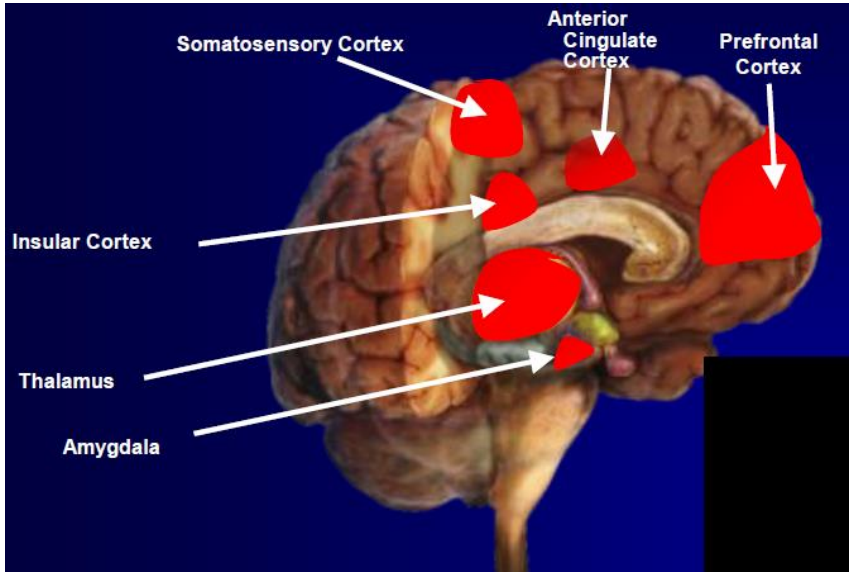
- Intra-spinal Na^+ Blockers (Bupivacaine)
- Spinal Cord Stimulation (Descending as well)



Cerebral Cortex

Central Projections

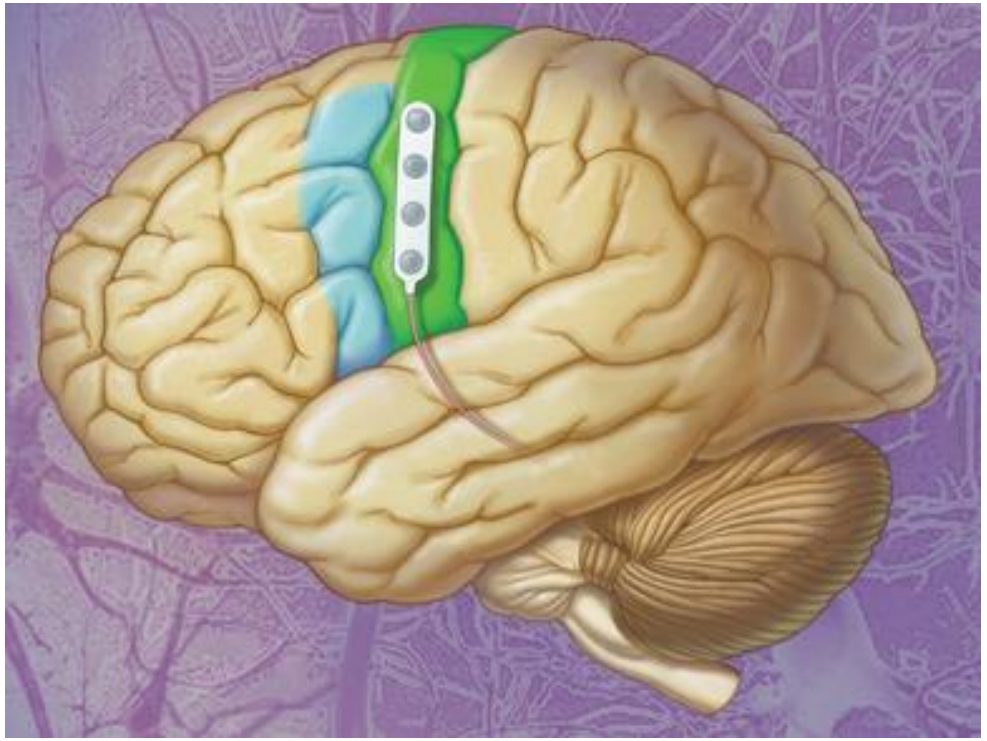
- Thalamus projects to many areas in brain
- Sensory-discriminative System
- Motivational-Affective System
- Pain Perception and interpretation
  - Primary Somatosensory
  - Secondary Somatosensory
  - Anterior Cingulate
  - Anterior Insula Frontal
  - Basal Ganglia
- Future Modulation



Central Targets

Motor Cortex Stimulation

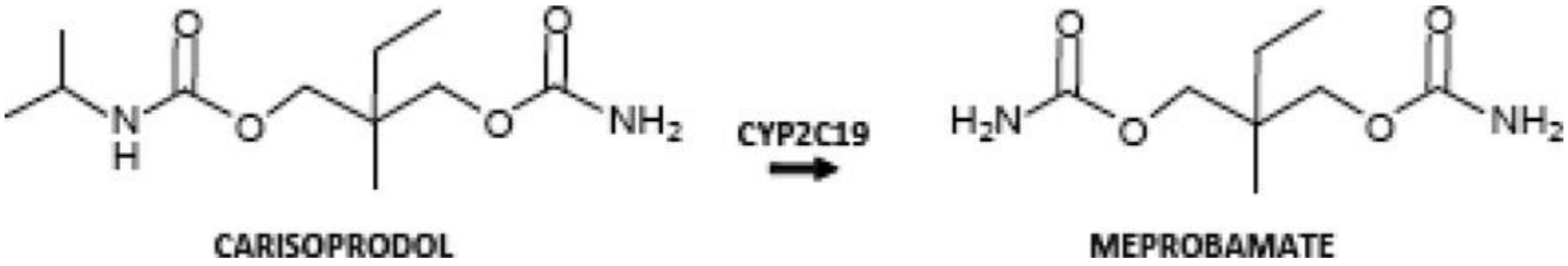
- Evolving technique
- Stimulate Motor Cortex
- Facial and Central Pain
- Craniotomy



Muscle Relaxants

- Unclear mechanism, but may have central effects
  - Methocarbamol
  - Cyclobenzaprine
  - Others

- Carisprodol -→ Meprobamate (GABA modulator)



CARISOPRODOL MEPROBAMATE

Descending Pathways

Descending Projections

- Endogenous Analgesia System
- Raphespinal Pathways
  - Antinociceptive Effects through Serotonin
- Catecholaminergic Pathways
  - Norepinephrine release inhibits α_2 adrenergic receptors
- Reticulospinal Tracts
- Peraqueductal 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 (Ca^{2+}, 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

- Buproprion 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

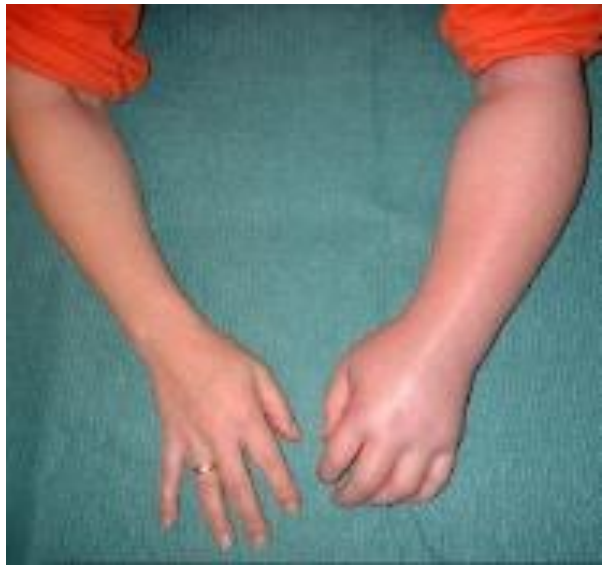
Multimodal Analgesics

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

Miscellaneous Targets

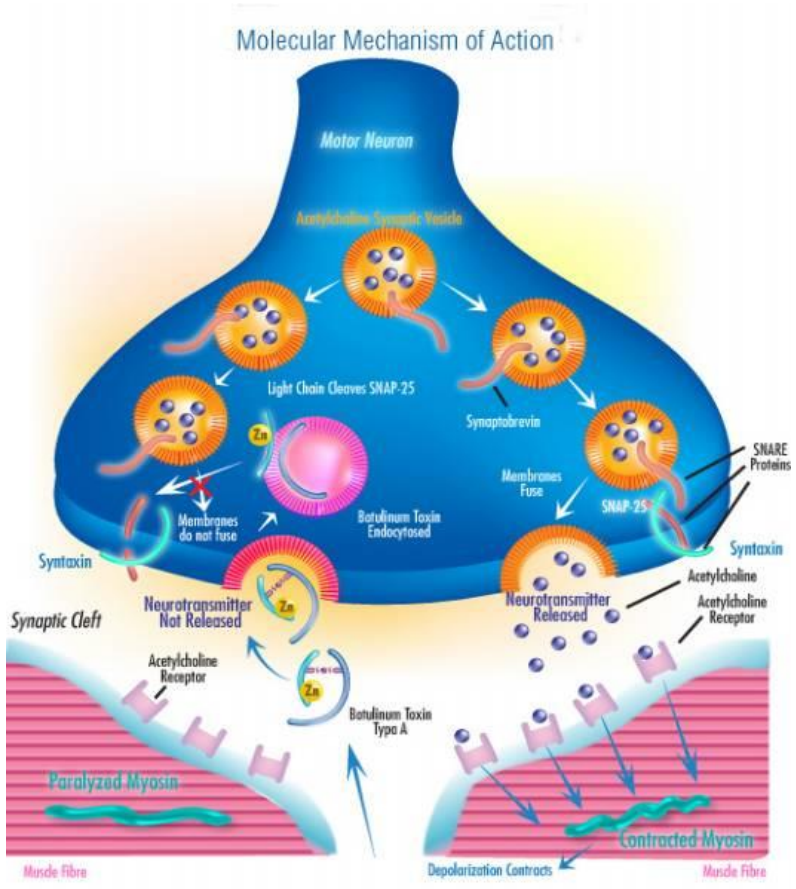
α-Adrenergic Active Drugs

- α-Antagonists
  - Phentolamine
  - Sympathetic Blockade
- α_2-Agonists - Central
  - Clonidine – Sympathetic Blockade
  - Tizanidine – Anti-spasmotic



Botulism Toxin

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



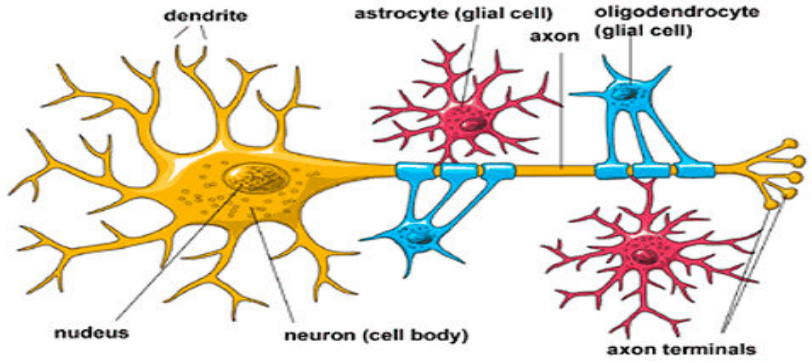
Future Targets

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_1, CB_2)
  - Endogenous cannabinoids
- Conopeptides
  - Ziconotide approved, others in clinical trials
- Targeted cerebral sites
- Gene Therapy
- ???

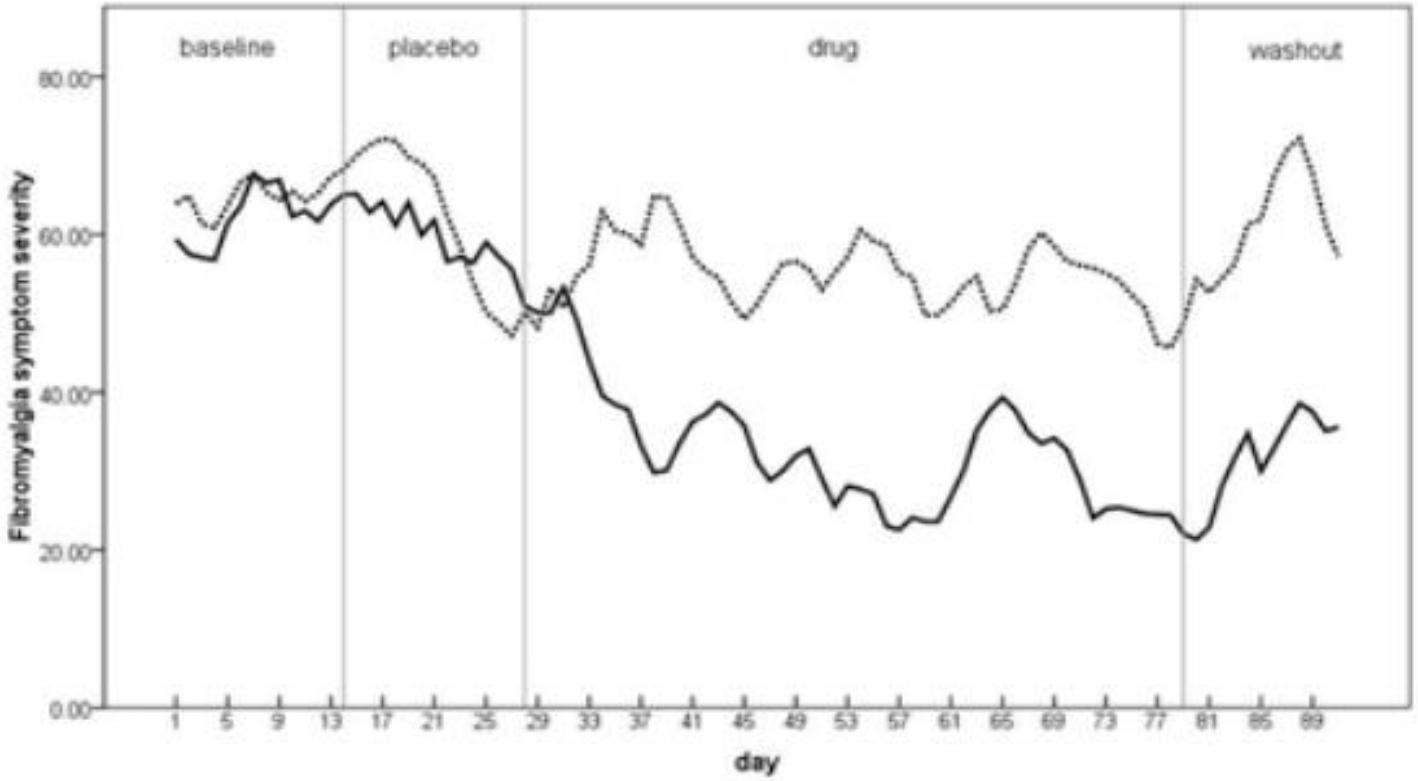
Glial Cell Activation

- 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 analgeisa



Fibromyalgia (Stanford ldn study)

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



http://snapl.stanford.edu/research/ldn.html

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