

Understanding the Neurophysiology of Pain as a Method to Combat Opioid Abuse

John Maye PhD CRNA
CAPT (Ret) USN

Professor/Pain Management Education
Coordinator

University of South Florida
College of Nursing

Conflict of Interest Disclosure Statement

- I have no financial relationships with any commercial interest related to the content of this activity.

Objectives

- Discuss the current opioid epidemic and its relevance to chronic pain
- Discuss the neurophysiology of pain as it relates to chronic pain pharmacology
- Discuss alternative non-opioid treatments for chronic pain

What is your motivation ?



The story starts with Opium (*papaver somniferum*)

- Friedrich Wilhem Adam Serturner: first isolated morphine from opium in 1804
- Named the compound Morphium after the Greek god of dreams



Opium

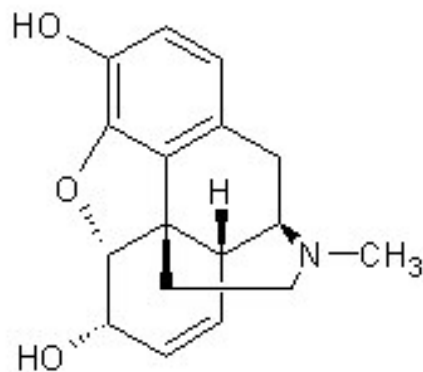
- Opium is acquired from the dried latex of the opium poppy seed
- The unripened pod is slit open and the sap that oozes will dry on the outer surface of the pod
- The dried sap will form a yellow-brown latex which contains varying amount of alkaloids such as morphine, codeine and papaverine



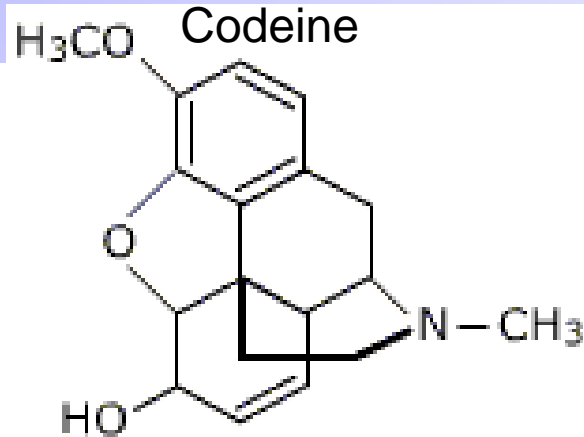
Semisynthetic Opioids

- Semisynthetic opioids result from relatively simple modification of the morphine molecule (codeine, heroin)

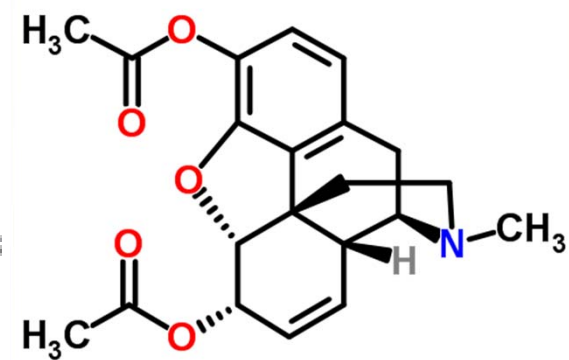
Morphine



Codeine



Heroin



Heroin

- Heroin first synthesized in 1874
- Originally marketed as a pain reliever “without the addictive side effects of morphine”
- The St James Society sent free samples of heroin through the mail to people addicted to morphine.



History of Regulations

- Opium Exclusion Act of 1909 becomes the nations first drug prohibition law barring the importation of opium for smoking that was favored by Chinese immigrants —not the medicinal opium that white Americans commonly kept in their household medicine cabinets
- Most Americans are unaware that there was once a time when people were free to buy any drug, including opium, cocaine, and cannabis, at the pharmacy

History of Regulations

- State Department calls on Congress to pass legislation that would ban the importation of smoking opium, thereby creating the first illegal drug.
- California, at the forefront of the war on Chinese smoking opium, went beyond the federal ban on importation by outlawing simple possession as well, thereby inventing a new class of criminals,
- The illegal drug consumer

- 1906 Pure Food and Drug Act
- 1909 Smoking Opium Exclusion Act
- 1914 Harrison Act
- 1919 Harrison Act Ratified
- 1924 Heroin Act
- 1922 Narcotic Drug Import and Export Act
- 1932 Uniform State Narcotic Act
- 1938 Food, Drug, and Cosmetic Act
- 1951 Boggs Act
- 1956 Narcotics Control Act
- 1965 Drug Abuse Control Amendment
- 1970 Controlled Substances Act
- 1973 DEA
- 1974 Narcotic Addict Treatment Act
- 1986 & 1988 Anti-Drug Abuse Act
- 2000 The Drug Addiction Treatment Act (DATA 2000)
- 2016 Comprehensive Addiction and Recovery Act (CARA)

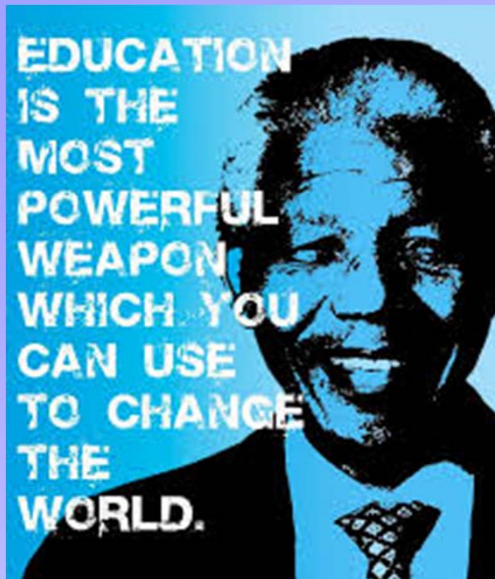


Current Opioid Epidemic

- 1980 The One Hundred Word Letter: New England Journal of Medicine reports that less than 1% of patients who received narcotics while hospitalized at Boston Hospital become addicted
- 2001, the Joint Commission instructed hospitals to measure pain and prioritize treatment. Based upon the consensus guidelines of organizations heavily funded by the pharmaceutical companies.



Education Challenges



- Across health care and society there are major gaps in knowledge about pain
- Educating health professionals about how to better understand pain and what causes pain will help bridge these gaps
- To improve understanding of pain, federal agencies and other stakeholders should redesign education programs

The Institute of Medicine of the National Academies:
Relieving Pain in America: A Blueprint for Transforming
Prevention, Care, Education, and Research. June 2011.

How much do we know about pain?



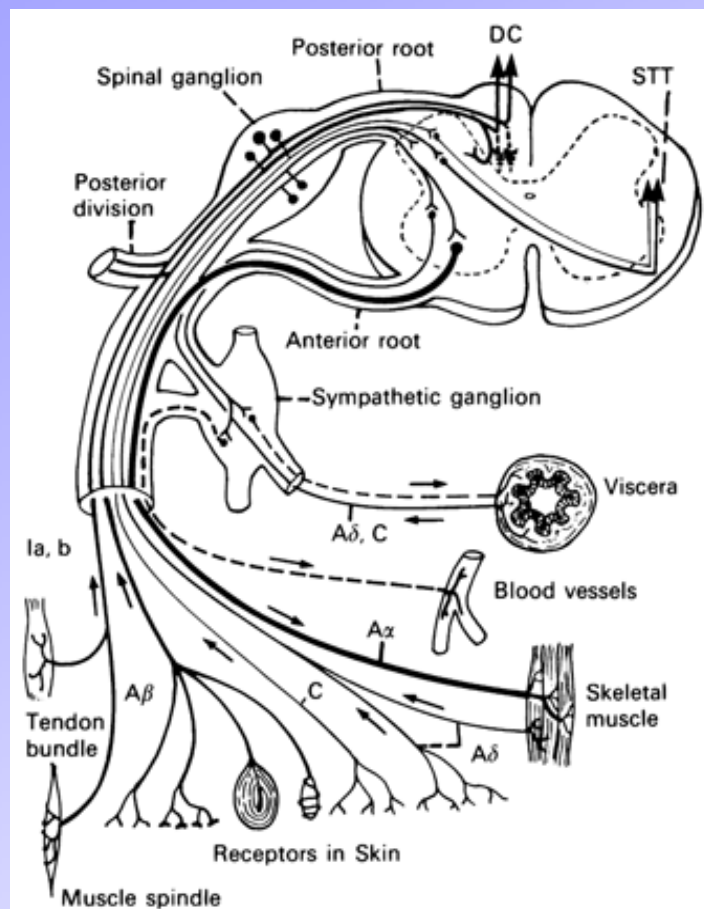
- What is your understanding of pain and pain treatments?
- Do you understand the complex physiologic and psychological mechanisms that are involved when a patient is experiencing pain?
- How do opioids work?
- What accounts for the variability of patient requirements for opioids?

TABLE 3-2. Classification of opioid receptors

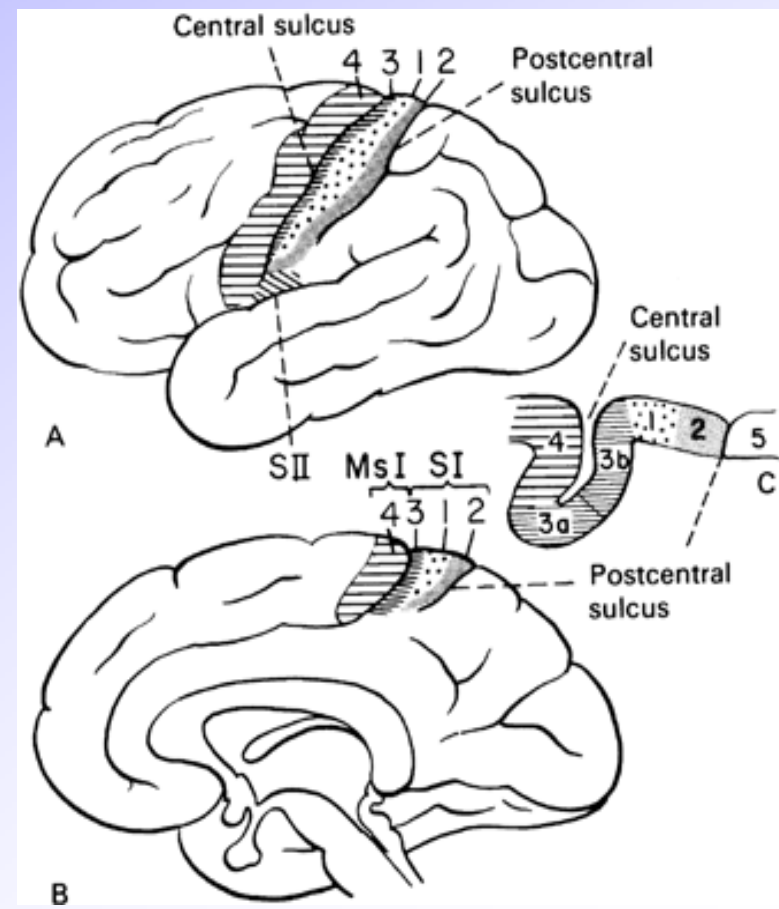
	Mu ₁	Mu ₂	Kappa	Delta
Effect	Analgesia (supraspinal, spinal)	Analgesia (spinal)	Analgesia (supraspinal, spinal)	Analgesia (supraspinal, spinal)
	Euphoria		Dysphoria, sedation	
		Depression of ventilation		Depression of ventilation
	Low abuse potential	Physical dependence	Low abuse potential	Physical dependence
	Miosis	Constipation (marked)	Miosis	Constipation (minimal)
	Bradycardia			
	Hypothermia			
	Urinary retention		Diuresis	Urinary retention
Agonists	Endorphins*	Endorphins*	Dynorphins	Enkephalins
	Morphine	Morphine		
	Synthetic opioids	Synthetic opioids		
Antagonists	Naloxone	Naloxone	Naloxone	Naloxone
	Naltrexone	Naltrexone	Naltrexone	Naltrexone
	Nalmefene	Nalmefene	Nalmefene	Nalmefene

MAPQUEST

From:



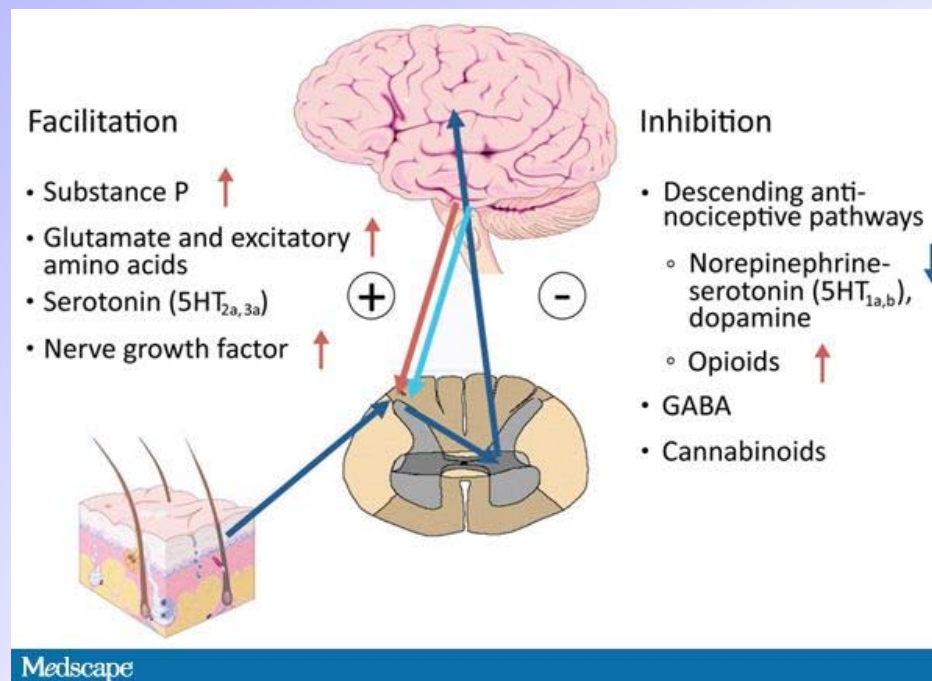
To:



Definitions

- Facilitation:

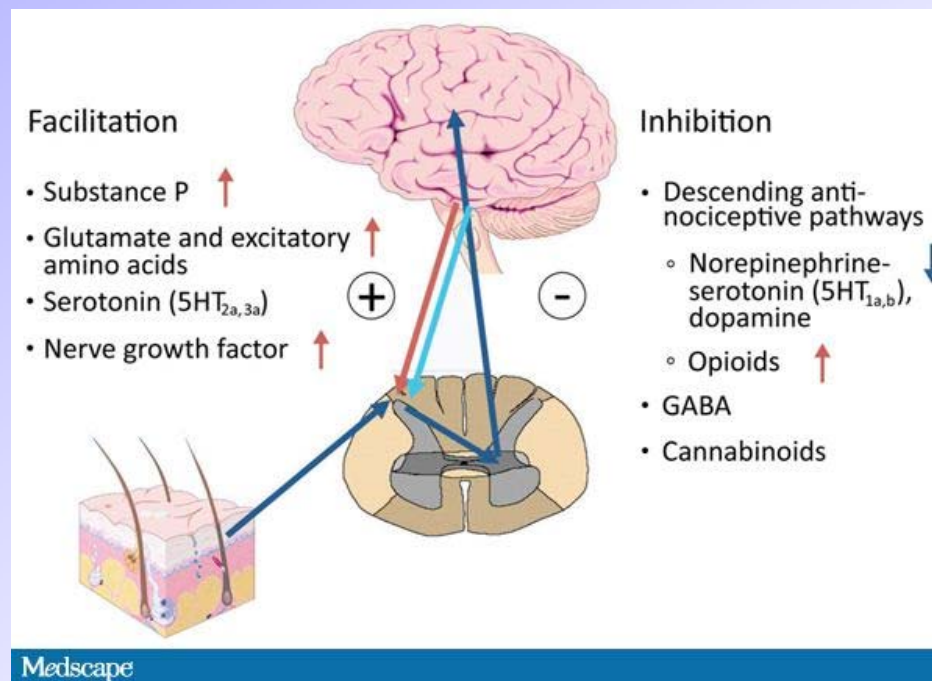
The excitatory process by which a neurotransmitter released by one nerve causes the second nerve to release a greater than normal amount of neurotransmitter



Definitions

- Inhibition:

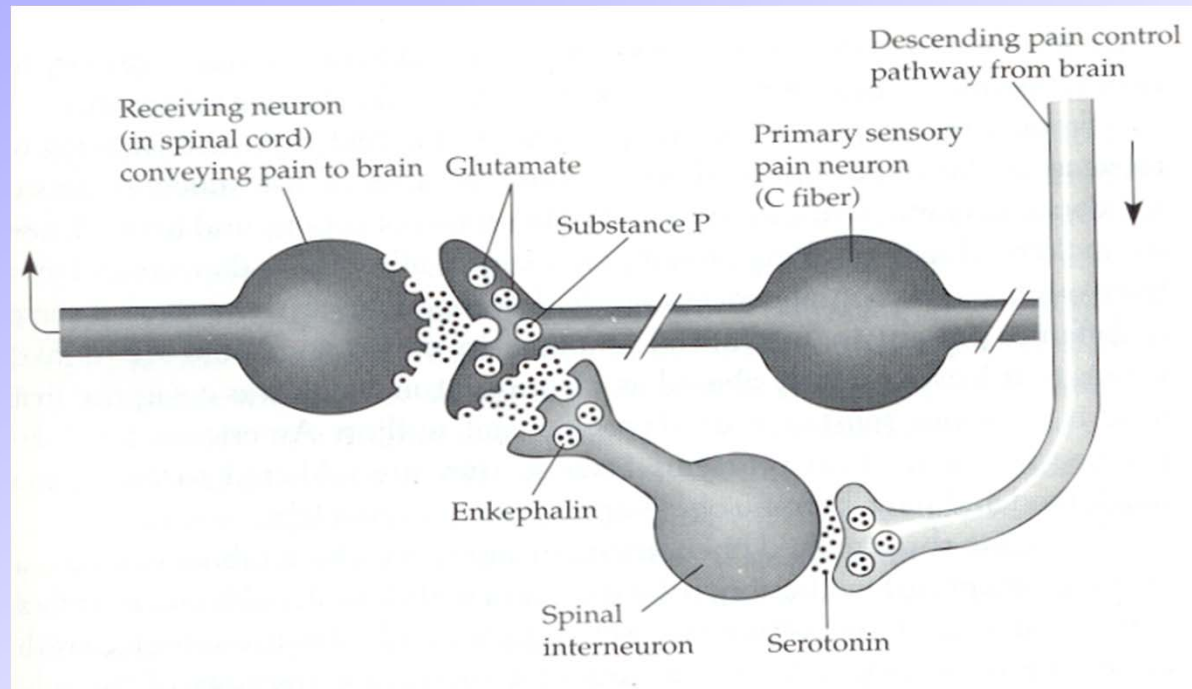
The inhibitory process by which a neurotransmitter released by one nerve causes the second nerve to release a lower than normal amount of neurotransmitter



Definitions

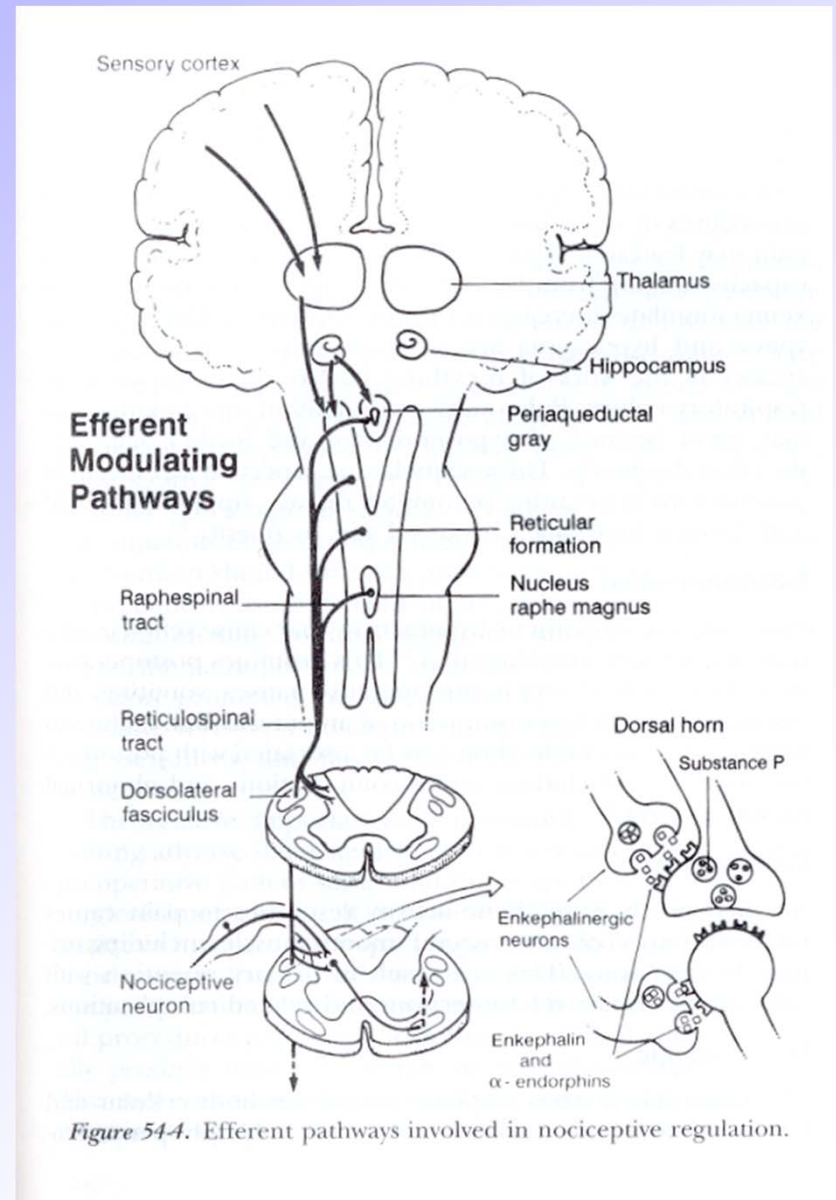
- Modulation:

Long lasting changes in the electrical potential of a nerve that alter the flow of ions across the cell membrane.

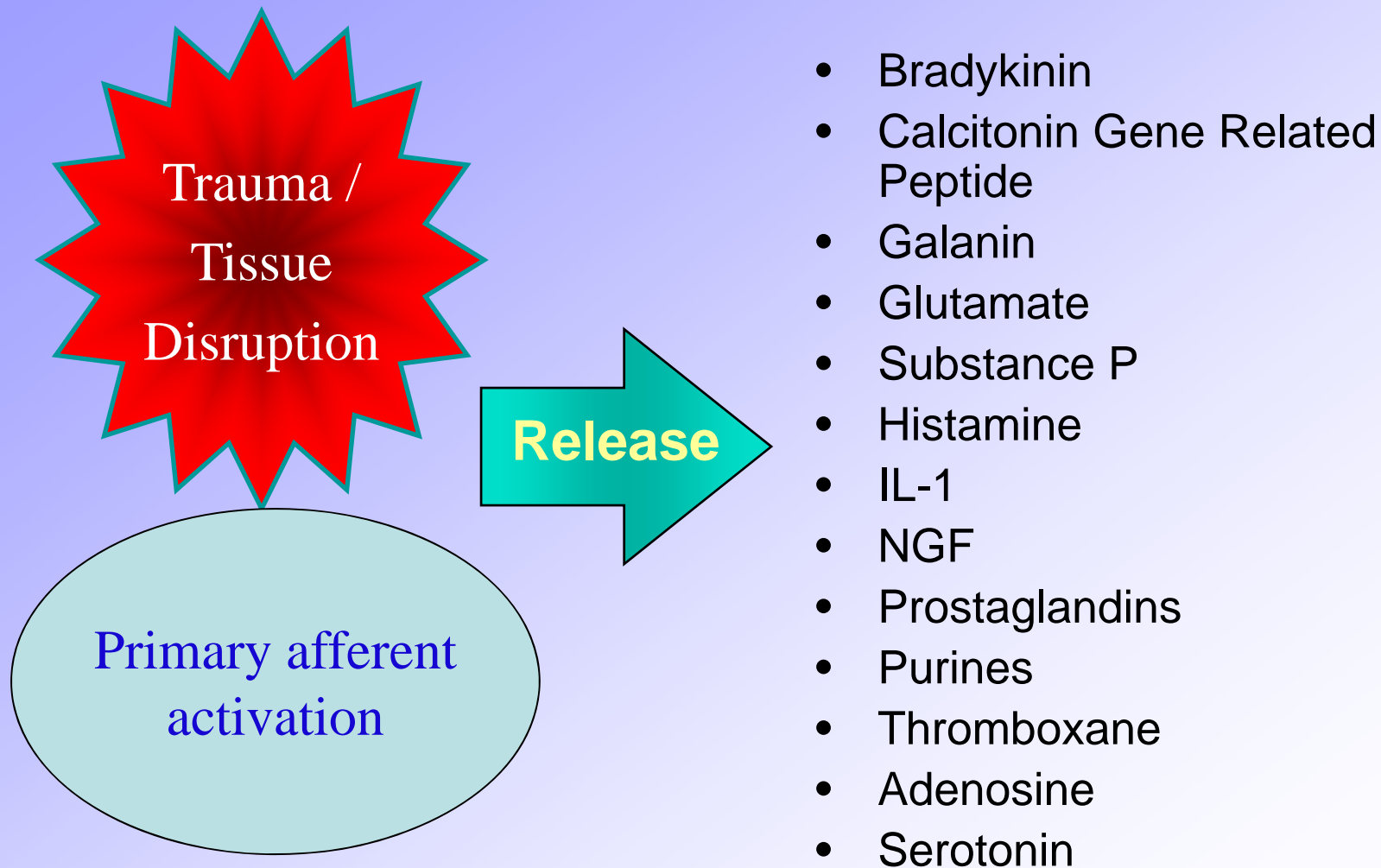


Descending Modulation

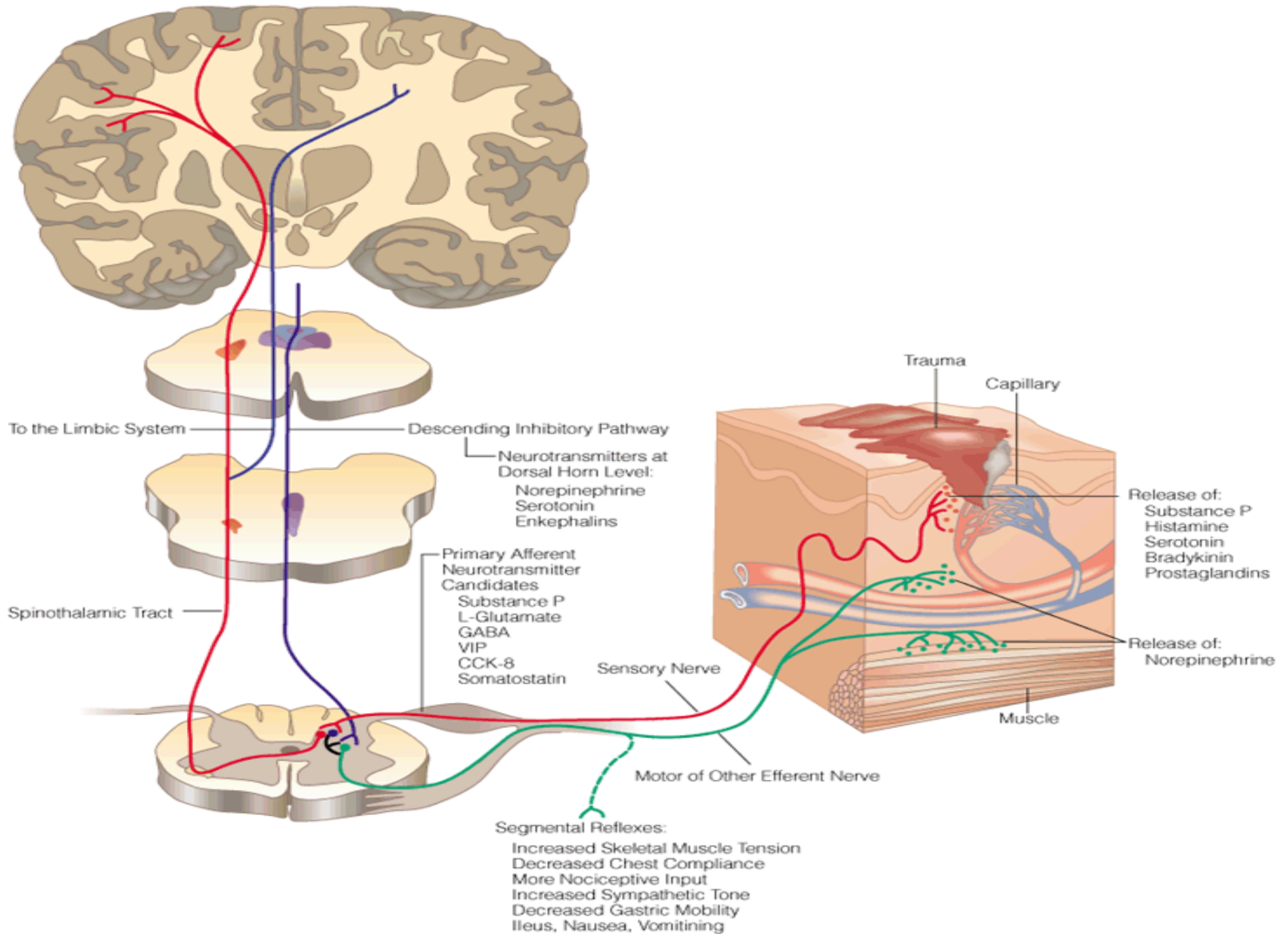
- Descending inhibitory tracts originate in the periaqueductal gray, reticular formation, and nucleus raphe magnus
- Descend in the dorsolateral fasciculus



Peripheral Inflammation



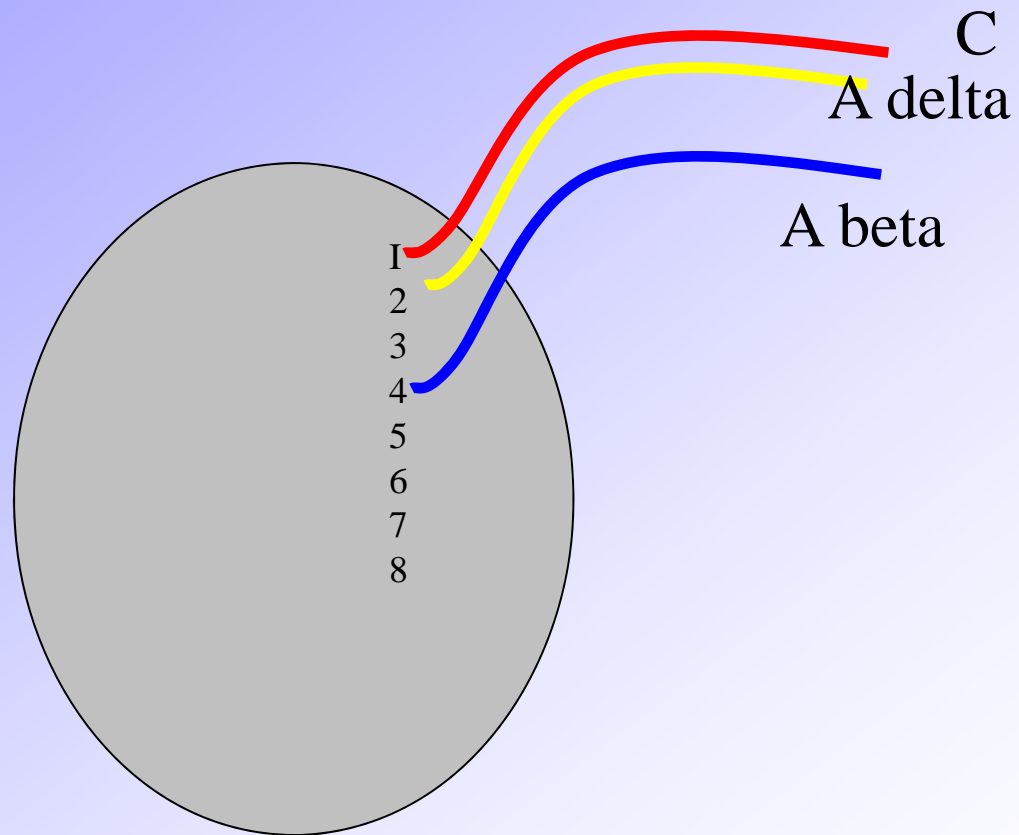
Perception of Pain



Peripheral Sensitization

- Due to release of inflammatory mediators
- Causes changes in peripheral nerves and receptors making them more sensitive
- Receptors easier to excite and lowers thresholds (hyperalgesia)

Structural Changes

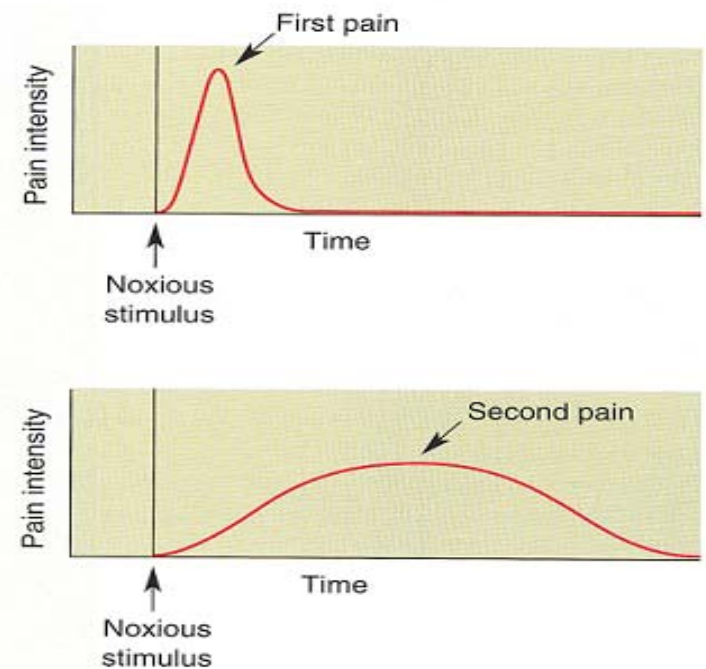
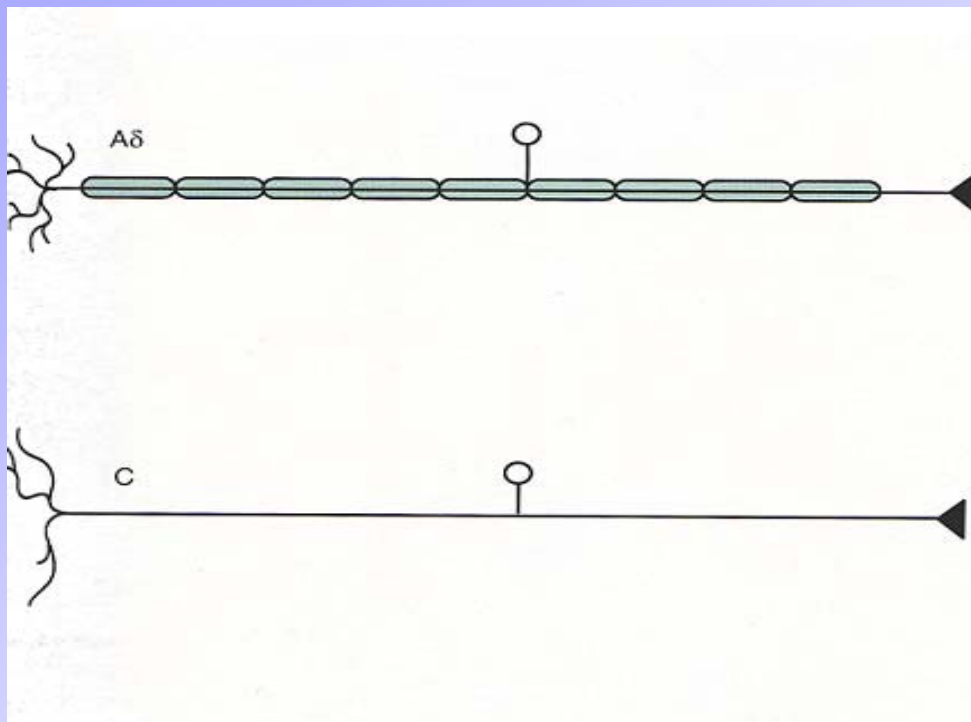


Central Sensitization

- **Allodynia:** pain to a stimulus that does not normally produce pain
- **Hyperalgesia:** An exaggerated pain response to a normally painful stimulus
- **Receptive Field Expansion:** An expansion of the area of skin innervated by the A-delta and C-fibers

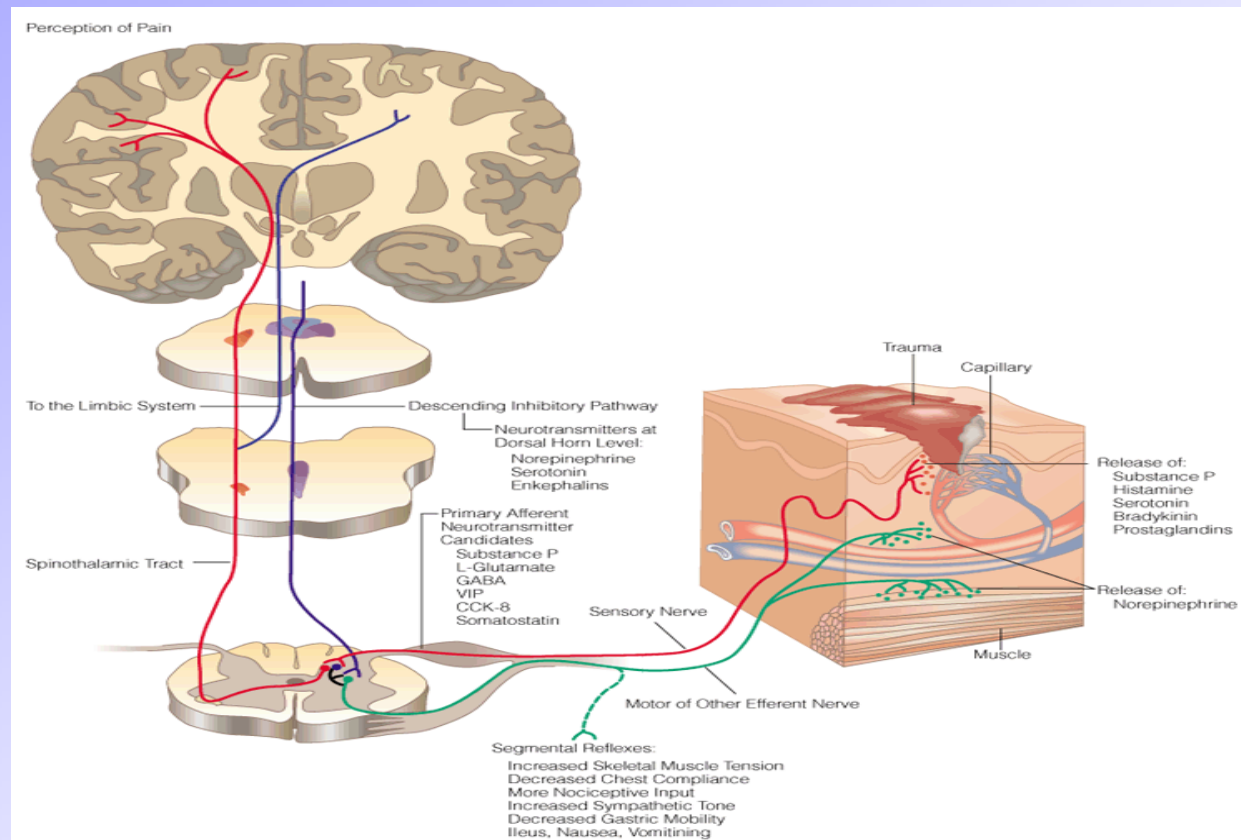


At what point does acute pain become chronic pain ?



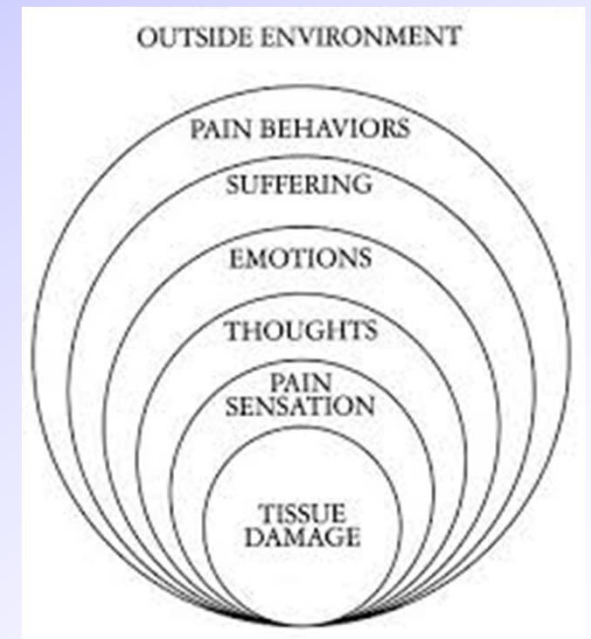
Research and Scholarship

- The concept of pain should expand beyond the traditional views of interpretation and modulation of nociceptive impulses

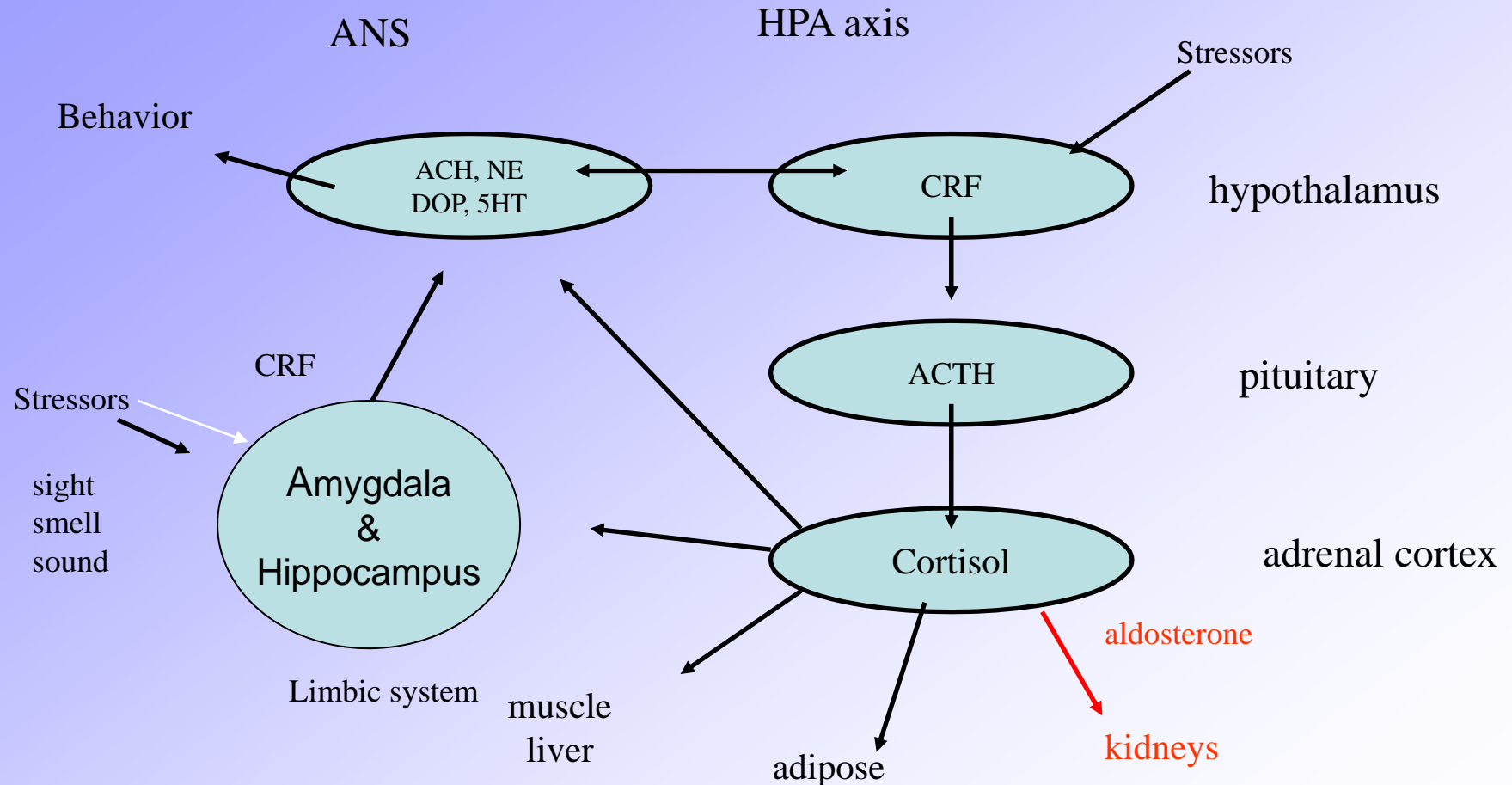


Concepts of Pain

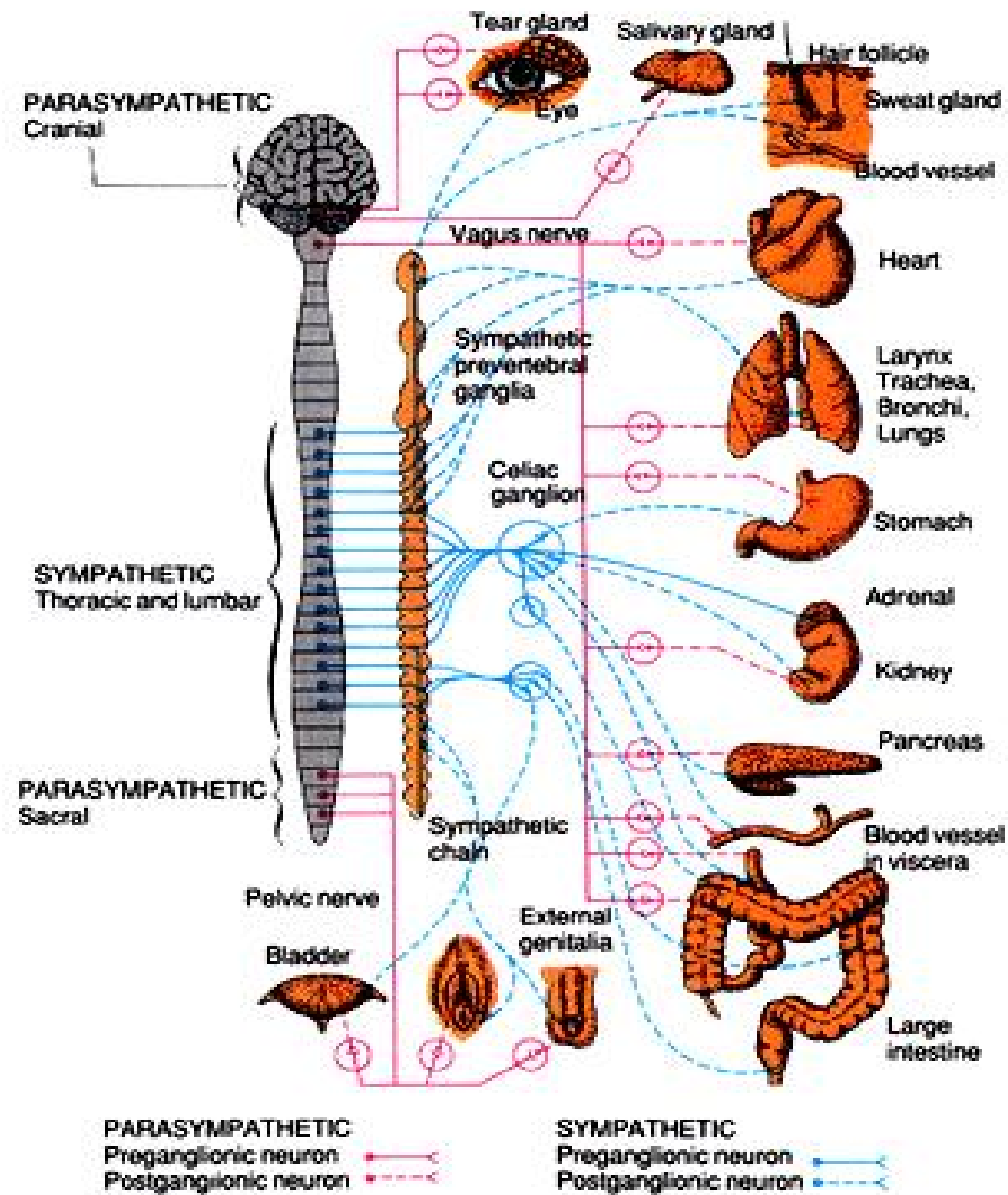
- Pain experience expands to encompass stress and emotional responses that exacerbate pain perception
- The perception of pain can be modified by emotional and social factors and is often accompanied by neuroplastic changes in the peripheral and central nervous system (Neugebauer, Weidong, Bird, & Han 2004).



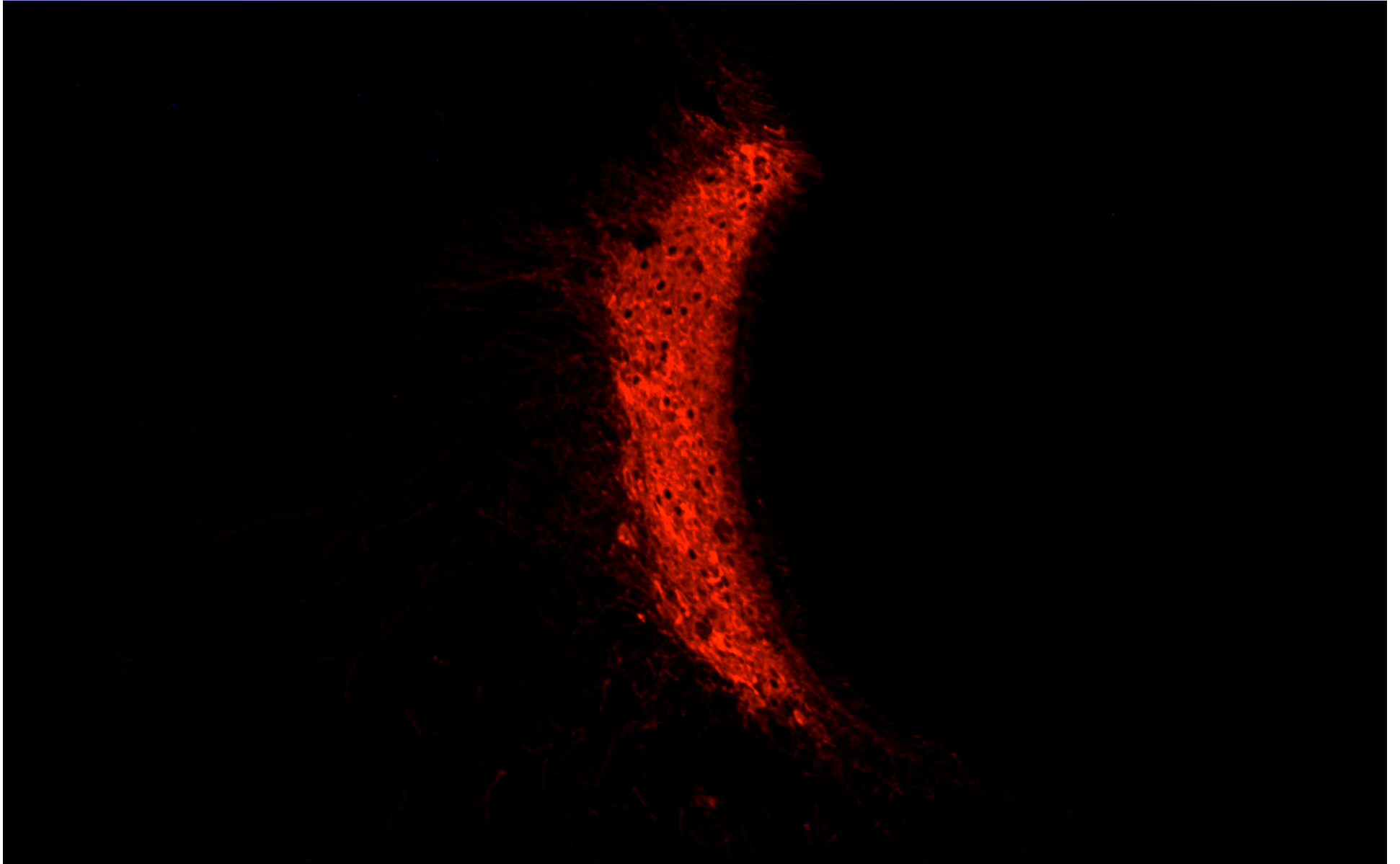
Stress Physiology



► The Autonomic Nervous System



Locus Coeruleus







Alternative Approaches

- Discuss alternative non-opioid treatments for chronic pain



Anticonvulsants
acts on a Selective Molecular Target



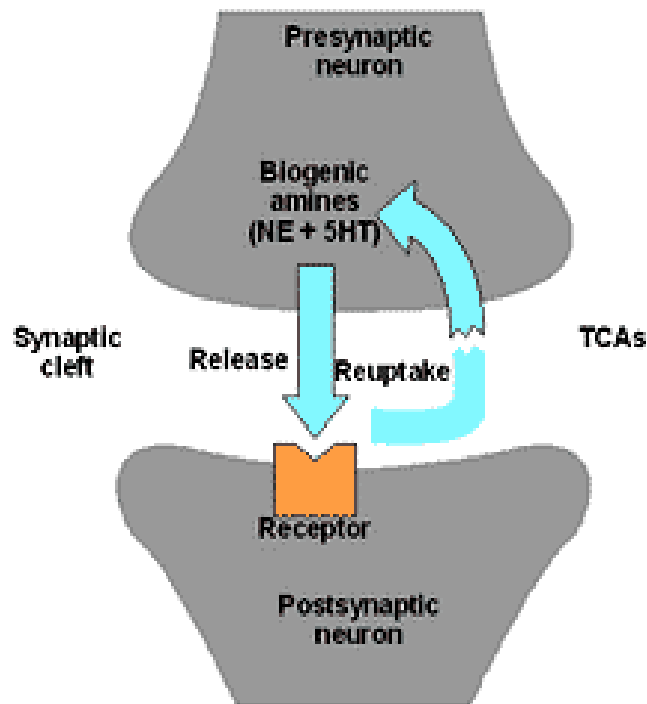
Basic Characteristics of Antidepressant Analgesics

- Serotonergic effect
- Noradrenergic effect
- Opioidergic effect
- N-methyl-D-Aspartate Receptor (NMDA) effect
- Adenosine Receptor effect
- Sodium Channel effect
- Calcium Channel effect
- Other effects



Mechanism of Action Antidepressant Analgesics

Mechanism of action of tricyclic antidepressants



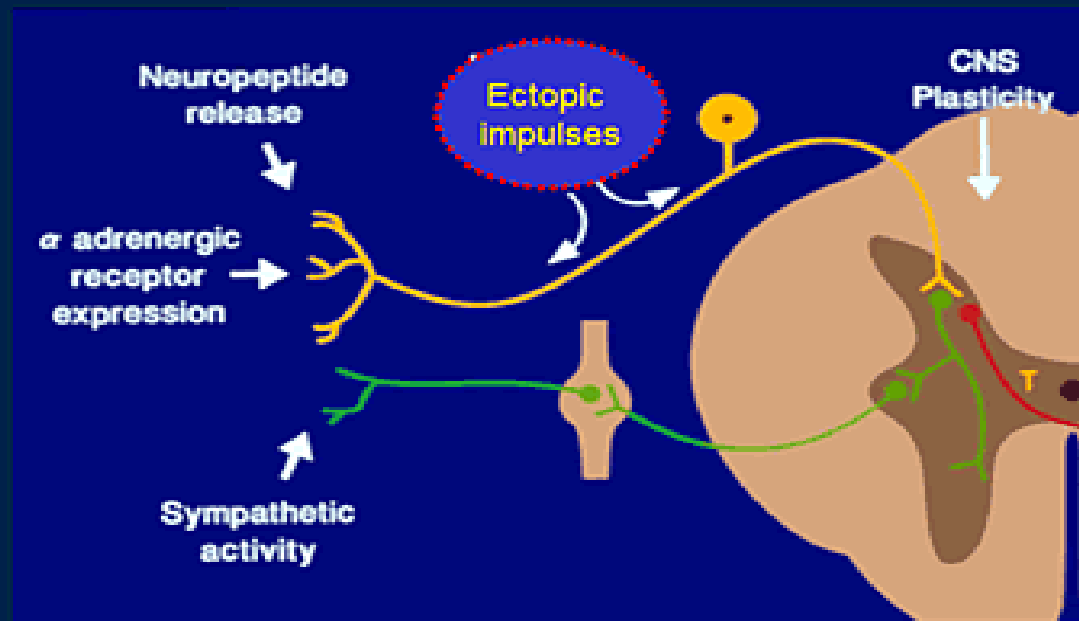
Basic Characteristics of Anticonvulsant Analgesics

- Neuronal membrane stabilizers:
- Inhibition of voltage gated sodium channels
- Inhibition of voltage gated calcium channels



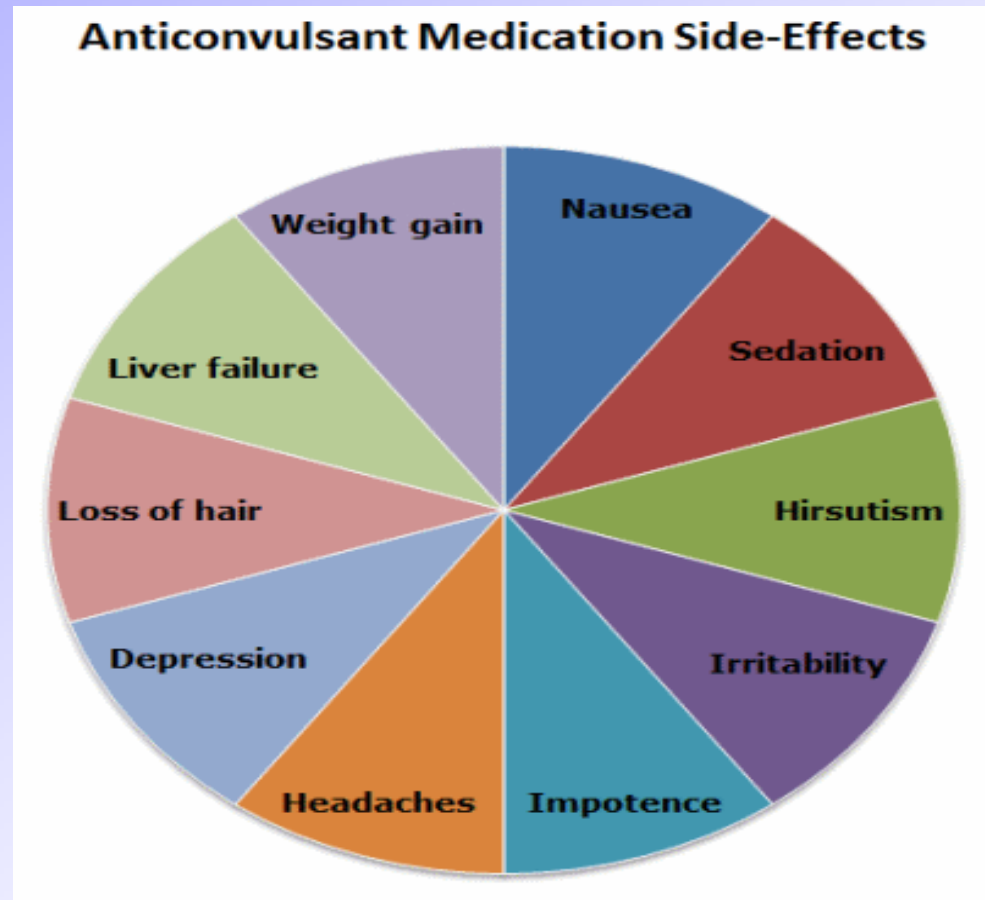
Mechanism of Action Anticonvulsant Analgesics

Peripheral Mechanisms of Nociceptor Hyperexcitability



Anticonvulsant Analgesics

- Carbamazepine
- Oxcarbazepine
- Phenytoin
- Gabapentin
- Lamotrigine
- Pregabalin
- Levetiracetam
- Sodium Valproate



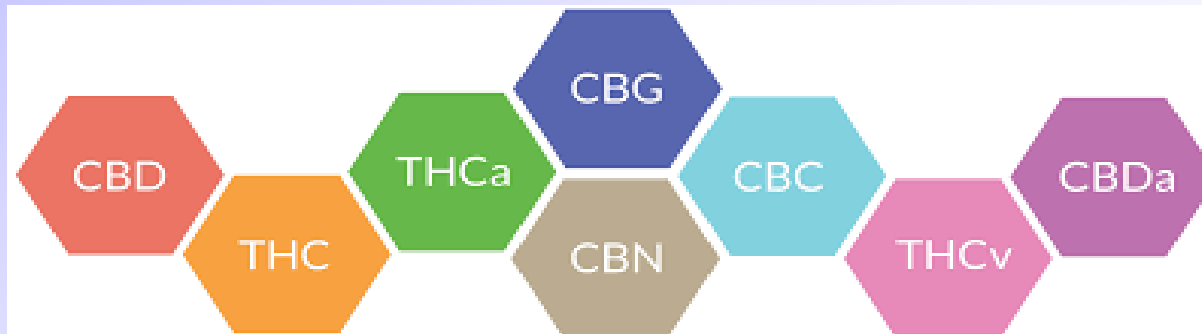
Serotonin-Norepinephrine Reuptake Inhibitor Antidepressant Analgesics

- Duloxetine (Cymbalta)
- Venlafaxine (Effexor)



Cannabinoids

- A class of diverse chemical compounds that act on cannabinoid receptors in cells that alter neurotransmitter release
- Phytocannabinoids found in cannabis
- Synthetic cannabinoids (manufactured artificially)
- At least 113 different cannabinoids isolated from cannabis which exhibit varied effects



Cannabinoids

- Tetrahydrocannabinol (THC) the most notable cannabinoid and the primary psychoactive component in cannabis.
- Potency has increased over the years: The highest tested sample had 27.30% THC (nondomestic).
- In comparison, the national average of Marijuana THC content in 1978 was 1.37%, in 1988 it was 3.59%, in 1998 4.43%, and in 2008 8.49%.



Cannabidiol (CBD)

- CBD is a major phytocannabinoid and accounts for about 40% of the plants extract
- Minimal if any intoxicating effects
- May have a down-regulating impact on disordered thinking and anxiety
- Considered a schedule I drug under the controlled substance act



Cannabidiol (CBD)

- 17 states have passed laws to allow for the use of CBD products (not exceeding a specified concentration of THC) for the treatment of certain medical conditions (seizure disorders, addiction treatments)
- Demonstrates potential as a new class of anti-inflammatory agents against a number of inflammatory and autoimmune diseases that are primarily triggered by activated T cells or other cellular immune components.

QUESTIONS?

