PHYSIOLOGY OF PAIN:
NOCICEPTION TO PAIN PERCEPTION



Presented by
Prof. Dr. Farah Naz
Professor
Department of Physiology

CONTENT

- Definition of pain
- History of pain
- Significance of pain
- Common causes of pain
- Common categories of pain
- Definition of nociception
- Physiological stages of pain
- Pain receptor
- Pain fiber
- Dual nature of pain
- Pathway of pain
- Major Neurotransmitters of pain
- Various pain theories
- Take home message

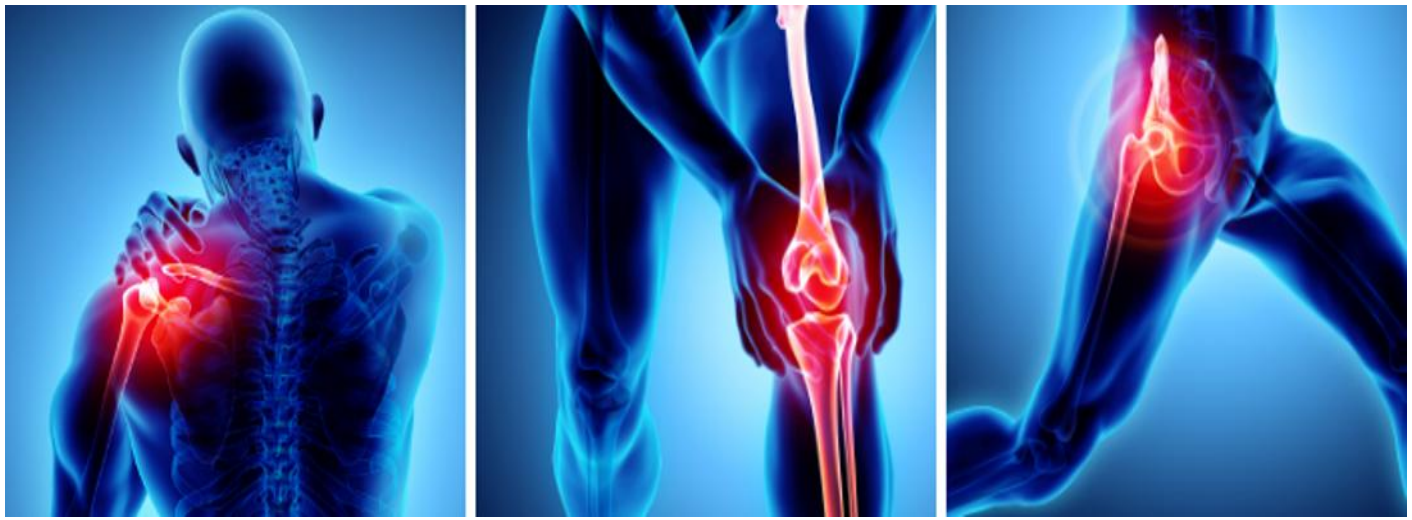




What is pain?

The international Association for the Study of Pain **(IASP)** defined pain as-

"An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage"



History of pain

- Derived from Latin Word "**Poena**" meaning penalty/punishment from God
- **JCAHO** declared pain as "Fifth Vital Sign" (1999)
- **Aristotle** – Considered pain to be the "Passion of the Soul"
- **Plato** – Contented pain and pleasure arose from within the Body



Significance of pain

- Pain gives us warning signal about the problem/injury
- Pain prevents further damage by causing reflex withdrawal of the body from source of injury
- Pain urges the person to take proper treatment to prevent major damage

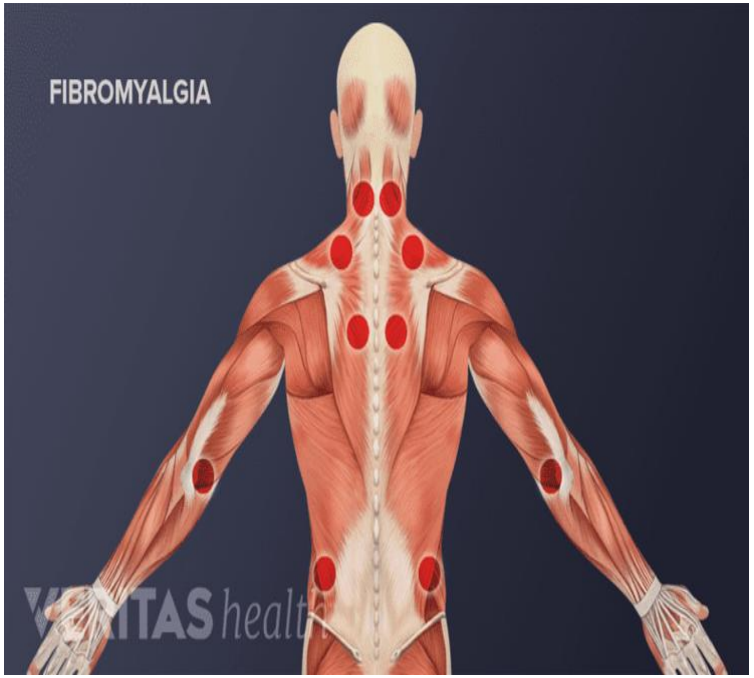


shutterstock.com · 1978317461

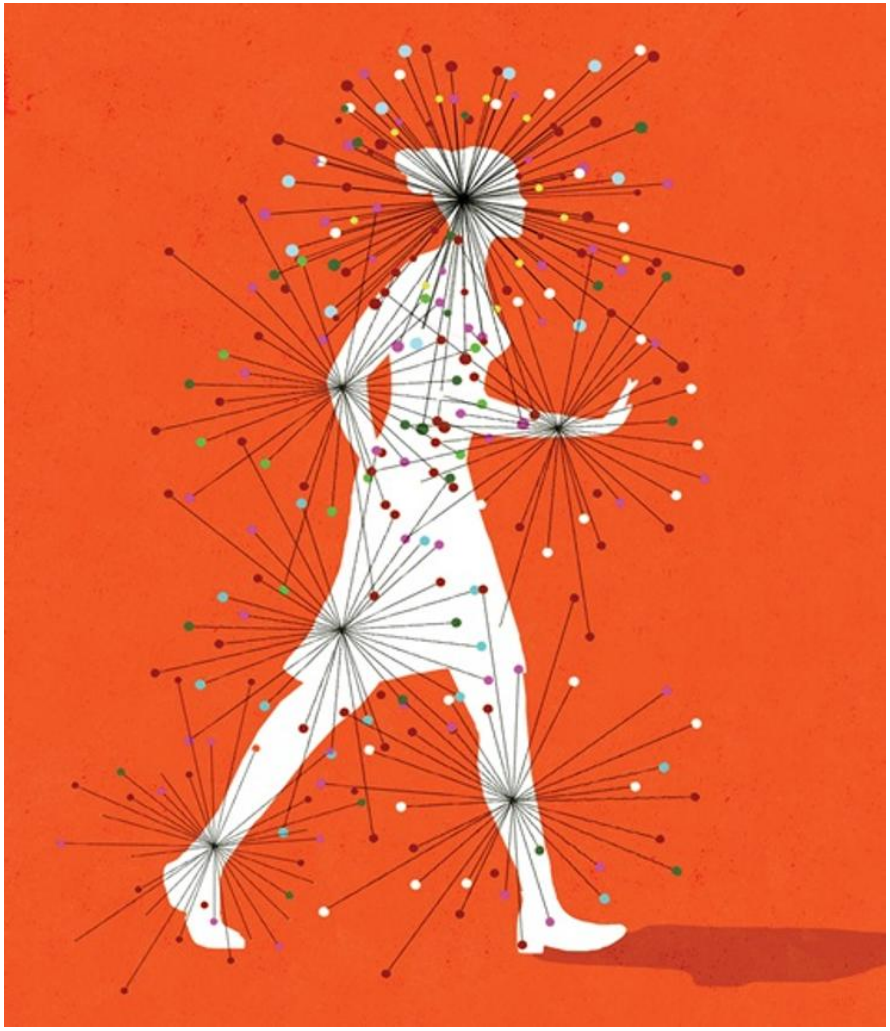
Common causes of pain

- Injuries like strains, sprains, cuts and broken bones
- Inflammation and infections
- Fibromyalgia
- Nerve damage or nervous system dysfunction





Common categories of pain



Acute Pain

- Sudden onset
- Short-term
- Caused by noxious stimulation due to injury, a disease process or abnormal function of muscle or viscera
- Typically, well localized
- usually goes away as the body heals
- Usually resolves within 3 months



shutterstock.com · 476111536



Chronic pain

- Gradual onset
- Long-lasting
- Pain that extends 3-6 months beyond onset, beyond the expected period of healing
- Affect a persons psychological well being and quality of life



Nociceptive pain

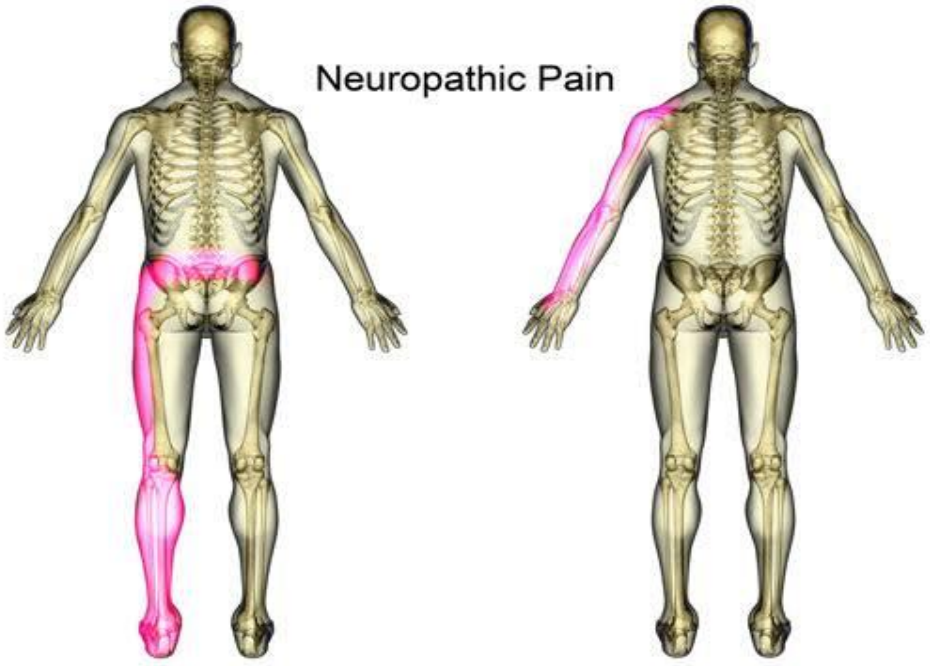
- Caused by activation of nociceptors in response to actual or threatened tissue damage
- It acts as a protective warning system
- Often feels sharp, aching, throbbing, pressure or cramping
- Types-

1) Somatic pain (localize)
   e.g- broken bone, burns or cuts
2) Visceral Pain (hard to localize)
   e.g- appendicitis, IBS, biliary colic



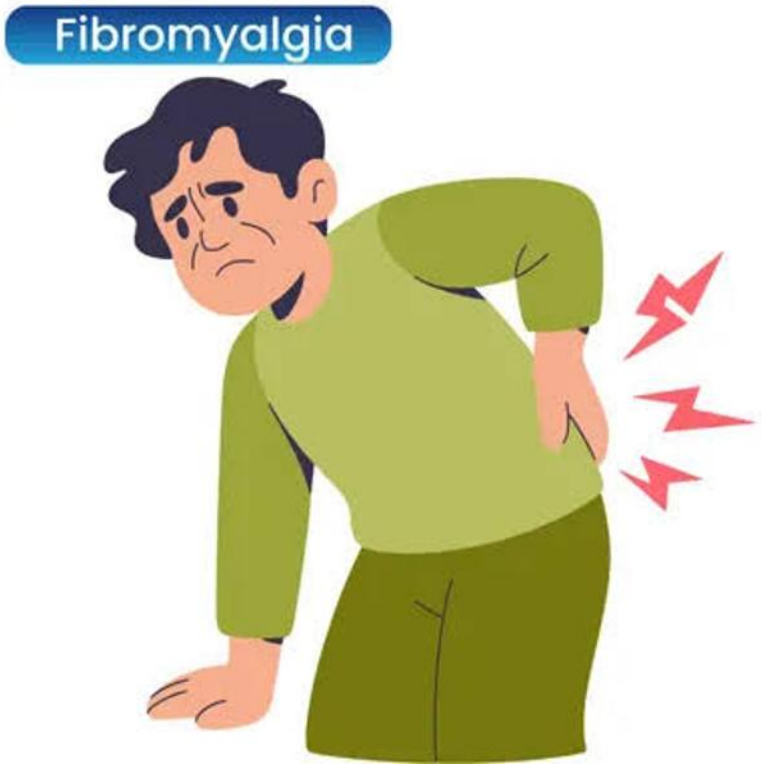
Neuropathic pain

- Arises directly from damage, injury or dysfunction within the PNS or CNS rather than stimulated nociceptors
- Often feels burning, tingling or like electric shock
- e.g- Sciatica, diabetic neuropathy, phantom limb pain



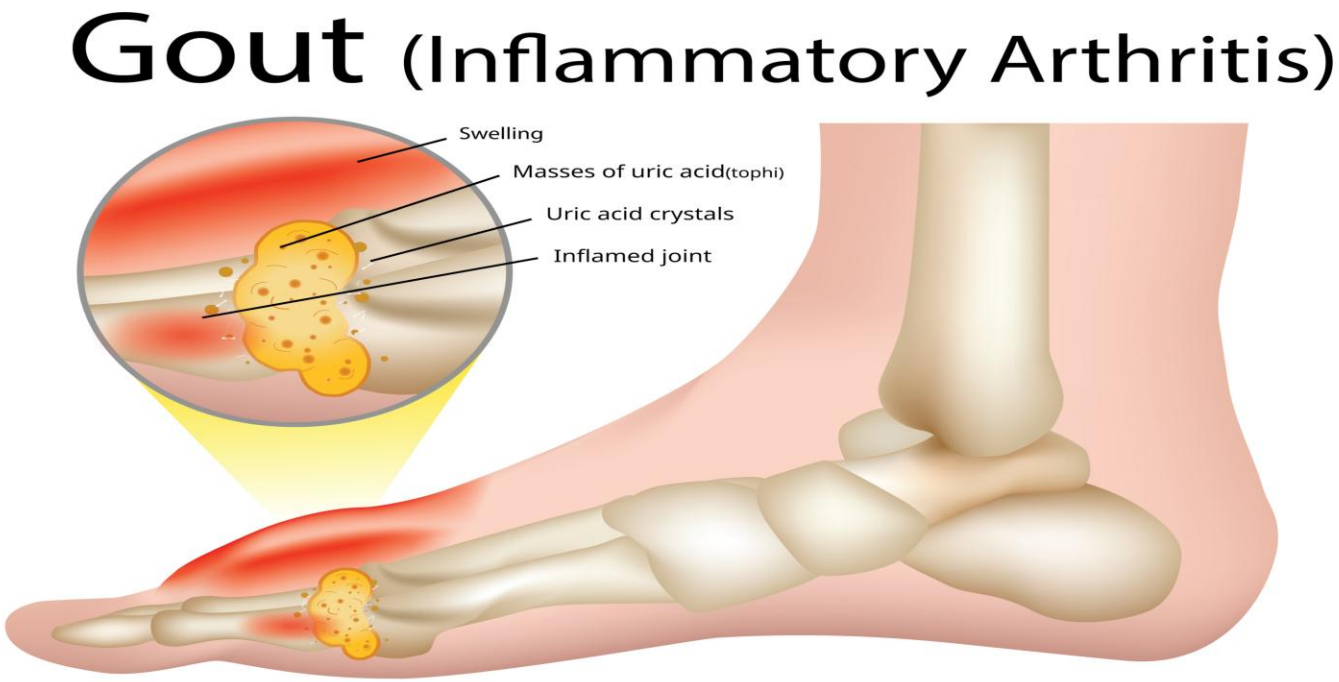
Nociplastic pain

- Arises from altered nociception or CNS processing even when there is no clear evidence of tissue or nerve damage
- e.g- Fibromyalgia



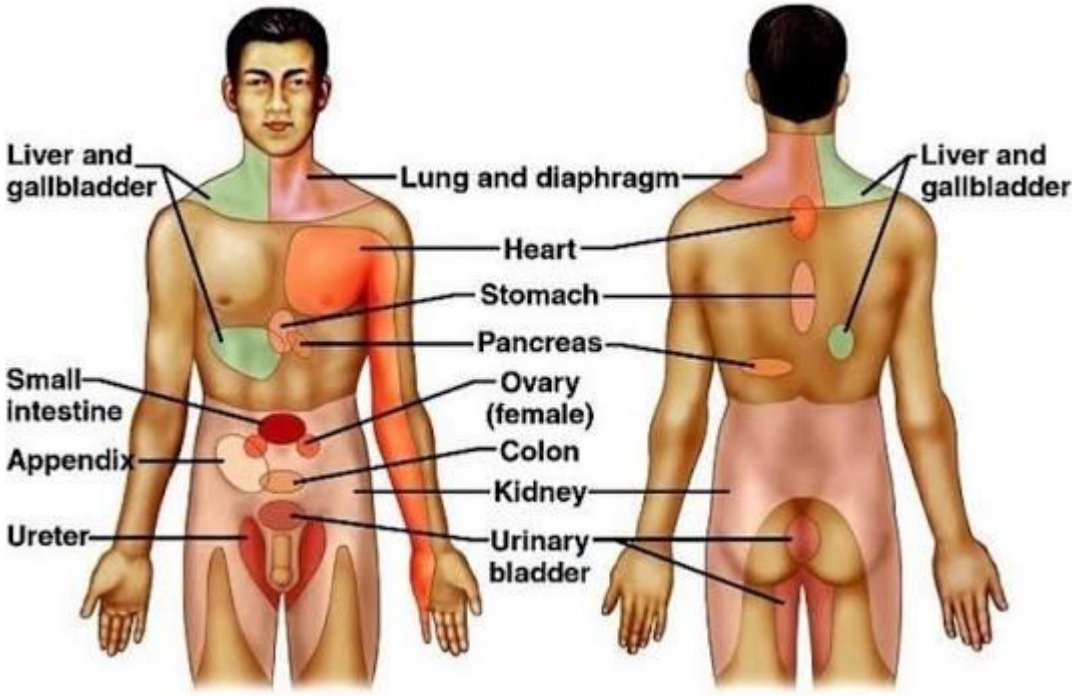
Inflammatory pain

- Triggered by the immune systems response to injury or infection
- e.g- Arthritis or gout



Referred pain

- Perceived in a part of the body separate from the actual source
- Because of shared nerve pathways
- e.g- Left arm pain during a heart attack



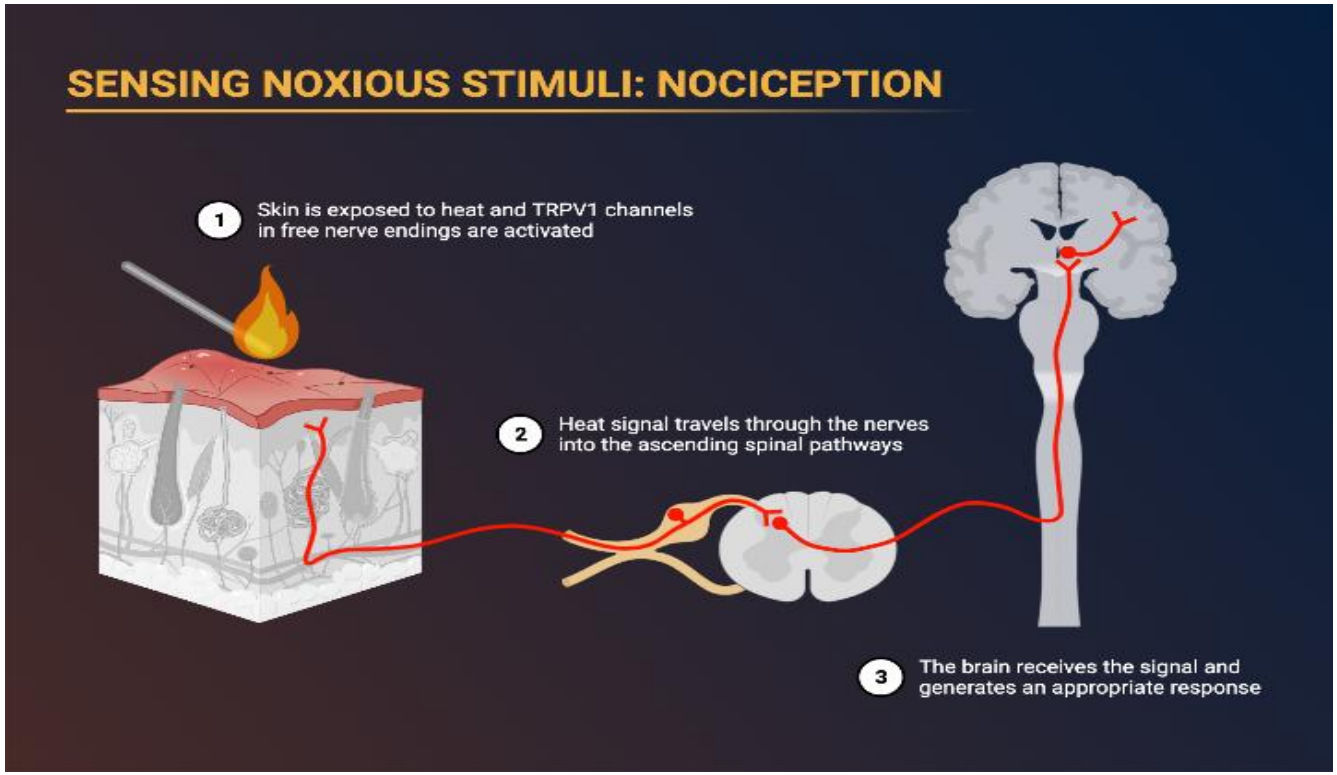
Psychogenic pain

- Physical pain that is started, amplified or prolonged by psychological factors like emotional distress, anxiety or depression



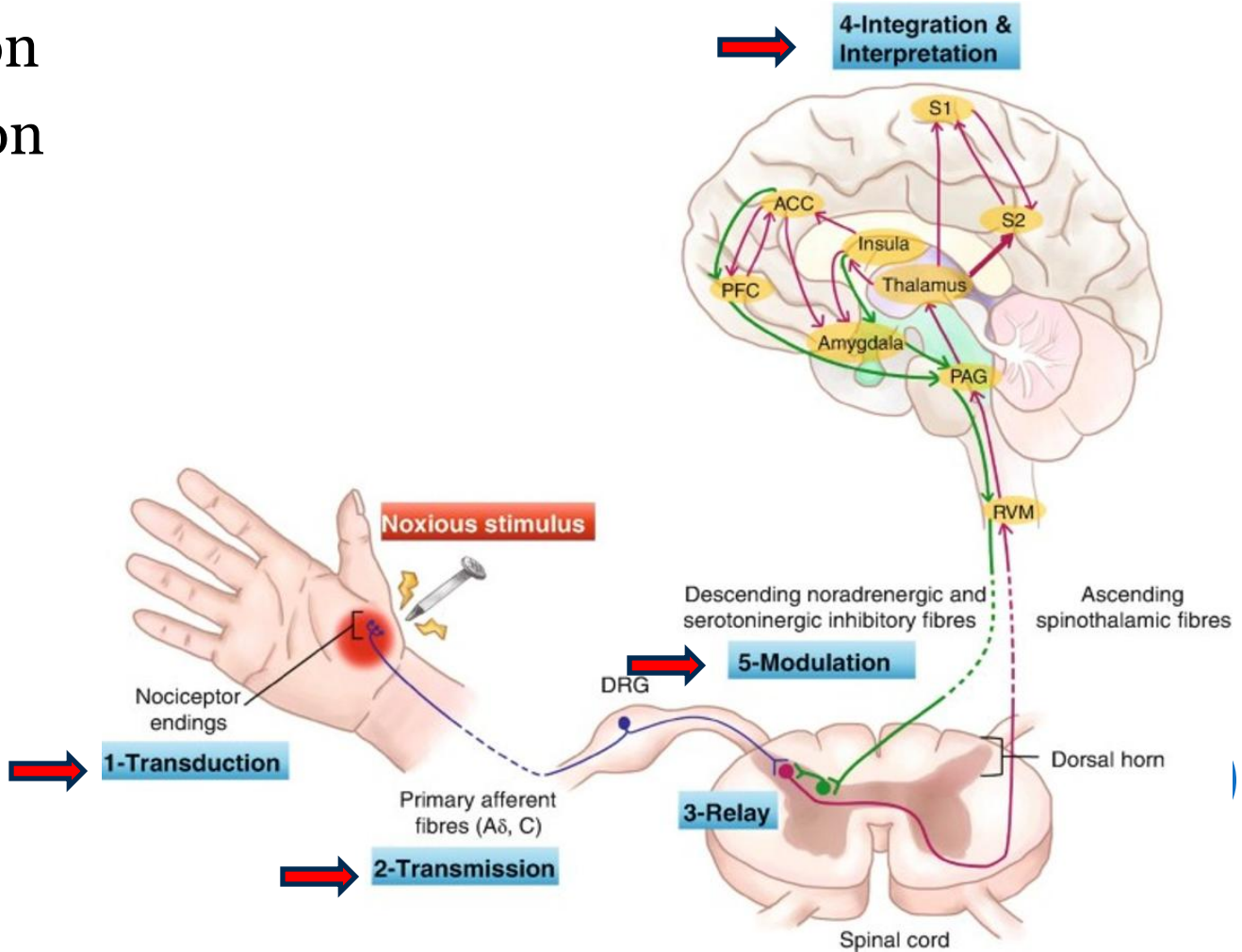
NOCICEPTION

- Is the physiological process by which nervous system detects, relays and interprets harmful or noxious stimuli through four main biological steps



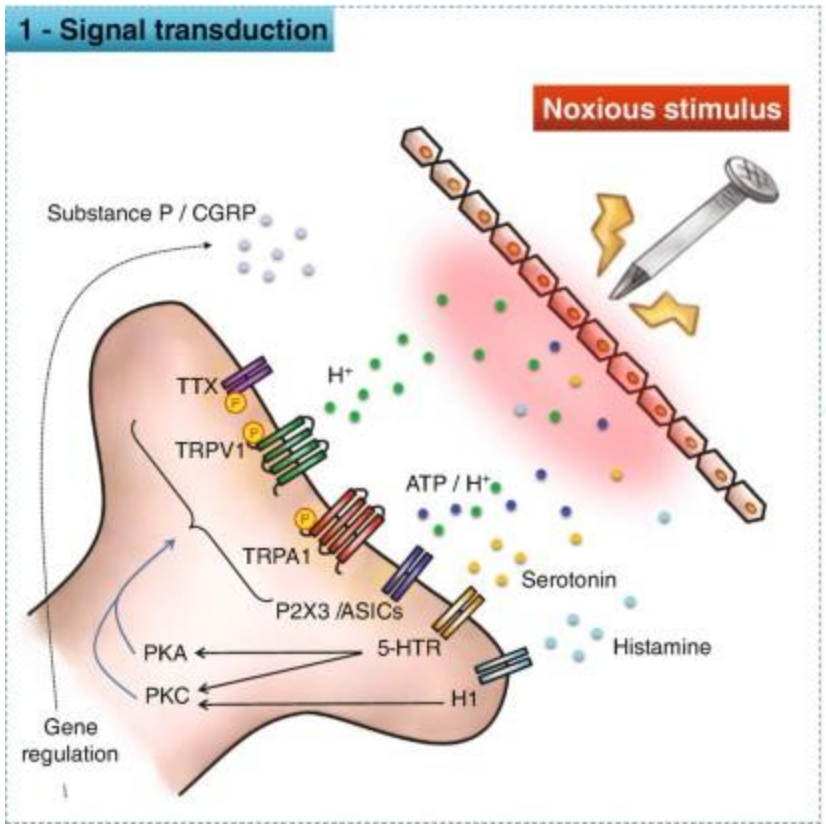
Physiological stages of pain or stages of nociception

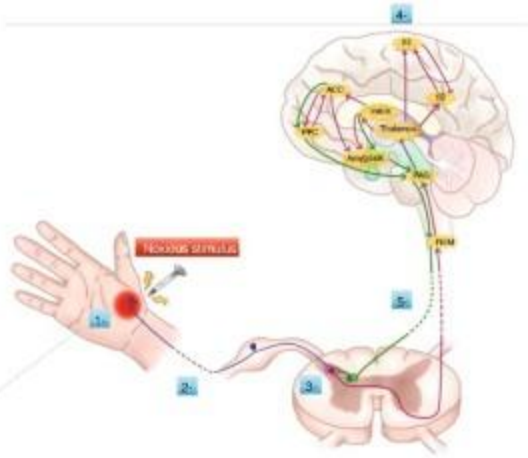
1. Transduction
2. Transmission
3. Perception
4. Modulation



TRANSDUCTION

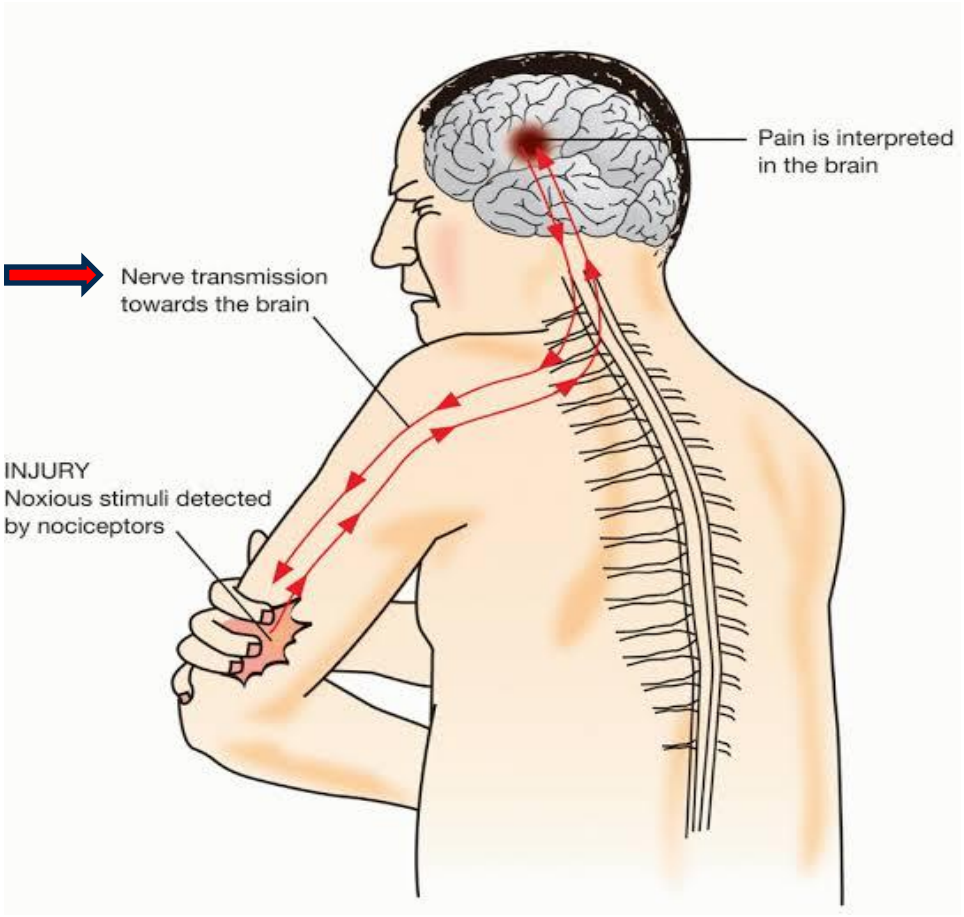
- **What it is:**
  - The process where harmful or noxious stimuli are converted into electrical nerve impulse





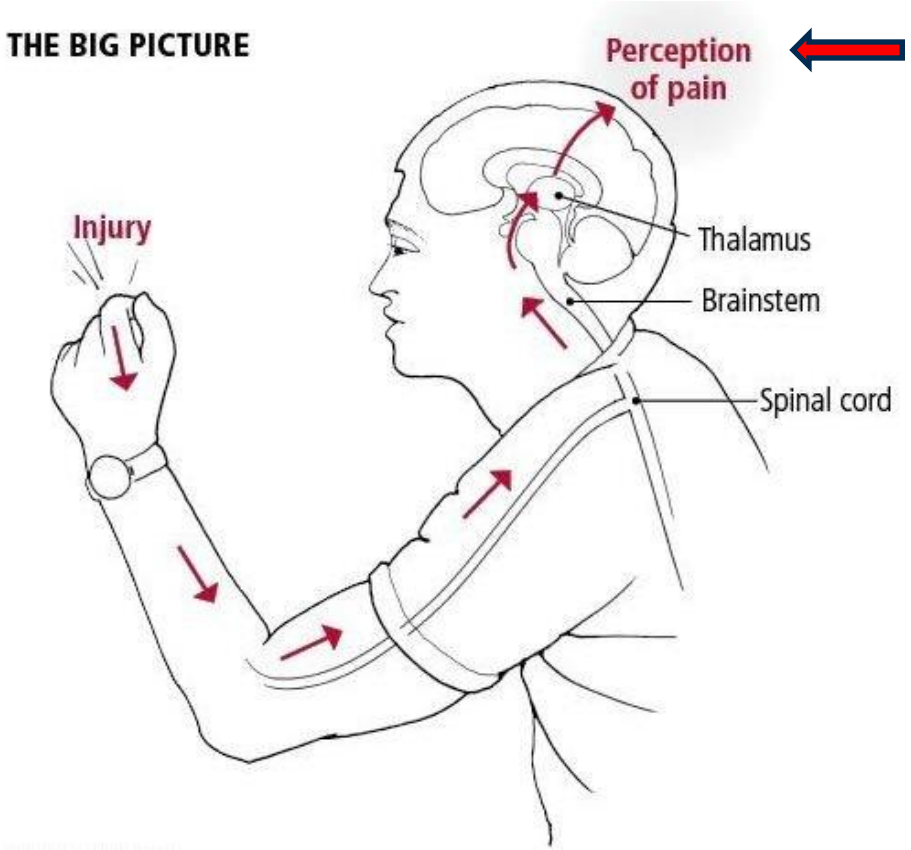
TRANSMISSION

- **What it is:**
  - The movement of the electrical pain signal from the site of injury up to the central nervous system (CNS)



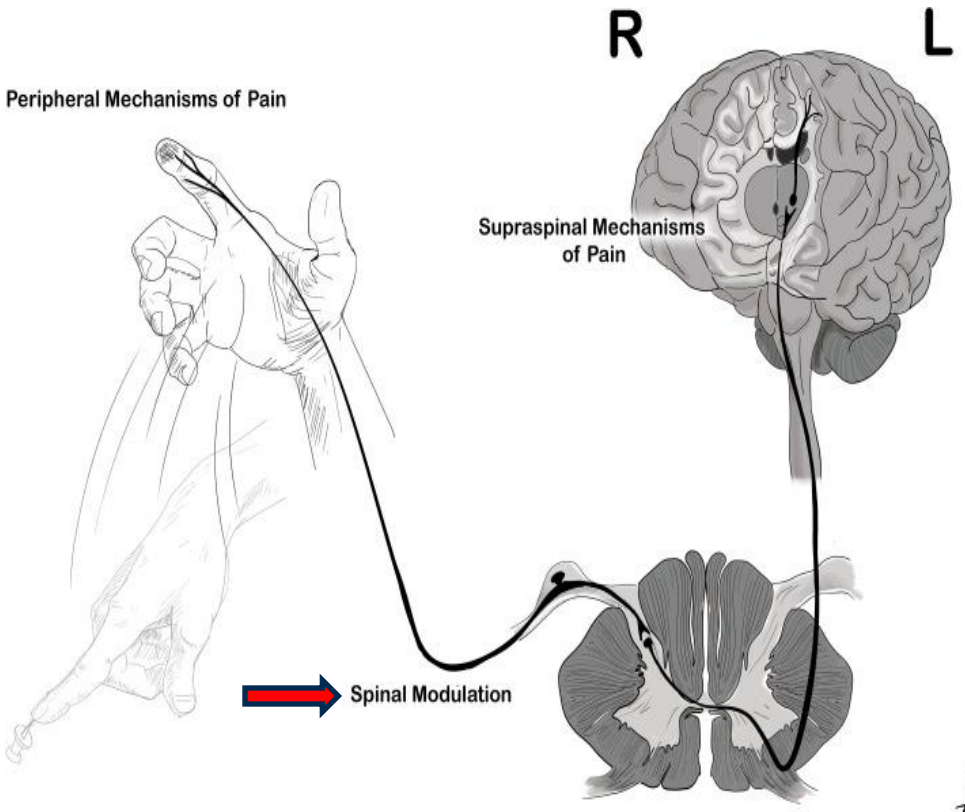
PERCEPTION

- **What it is:**
  - The final conscious, subjective experience of pain after processing the incoming neural signal in the higher region of the brain (Somatosensory cortex & Limbic system)



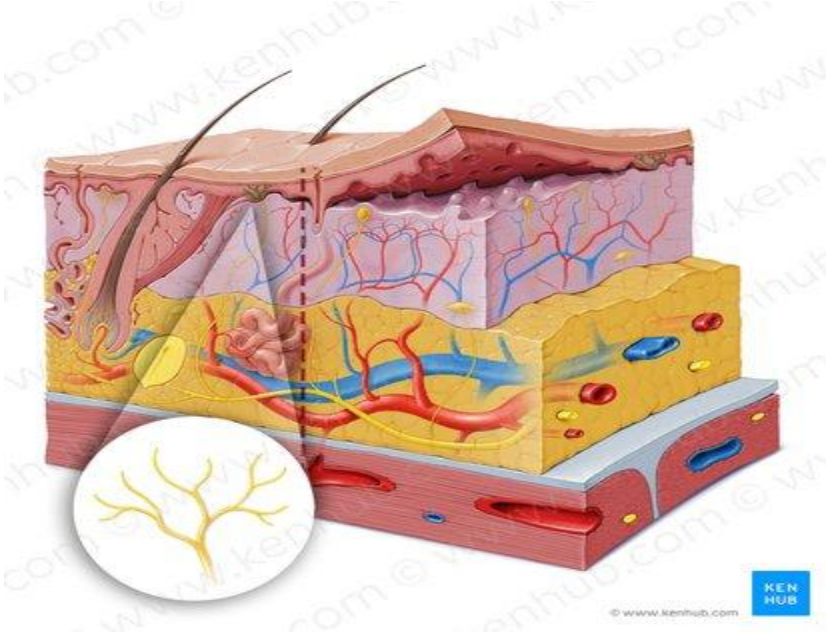
MODULATION

- **What it is:**
  - Pain modulation is the natural process by which the CNS changes, reduces or increases pain signals as they travel along the nervous pathway



Pain receptor

- The receptors which mediate pain is called **nociceptors**
- These are specialized free nerve endings
- Detect potentially damaging thermal, mechanical or chemical stimuli
- Very slowly adapting type of receptor
- Distributed in skin, dental pulp, periosteum, meninges



Classification of pain receptor on the basis of type of stimuli

- Mechanical nociceptor → Respond to intense pressure, sharp objects, cutting, stretching
- Thermal nociceptor → Activated by heat above 45° C or noxious cold below 15° C
- Chemical nociceptor → Respond to irritating chemicals, acids, inflammatory molecules like histamine or bradykinin
- Polymodal nociceptor → Respond to combination of high intensity mechanical, thermal & chemical stimuli

Pain fiber

- Specialized nerve fiber that send pain signals from nociceptors to spinal cord and brain

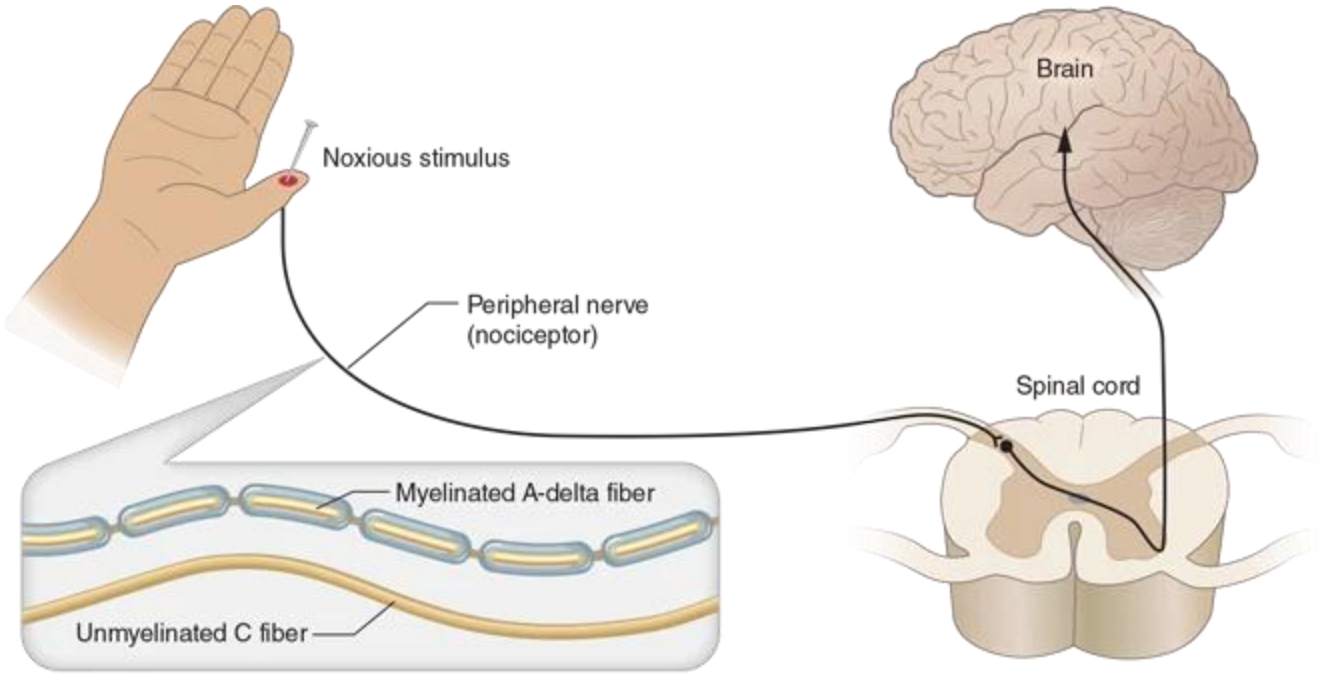


FIGURE 8.1 When a pain-inducing stimulus is applied, the signal is transmitted to the brain by nociceptors (A-delta fibers and C-fibers) through the spinal cord to the brain.

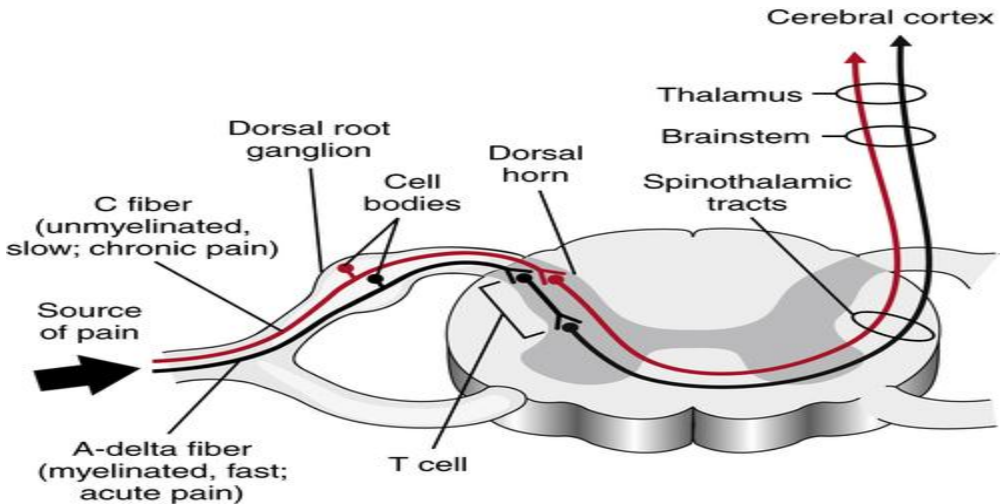
Types of pain fiber according to dual nature of pain

A-delta fibers for Fast Pain

- Myelinated fibers
- Conduct fast signals
- Cause the initial sharp pain of an injury
- Diameter: 1-5µm
- Speed: fast 5-30m/sec

C- fibers for Slow Pain

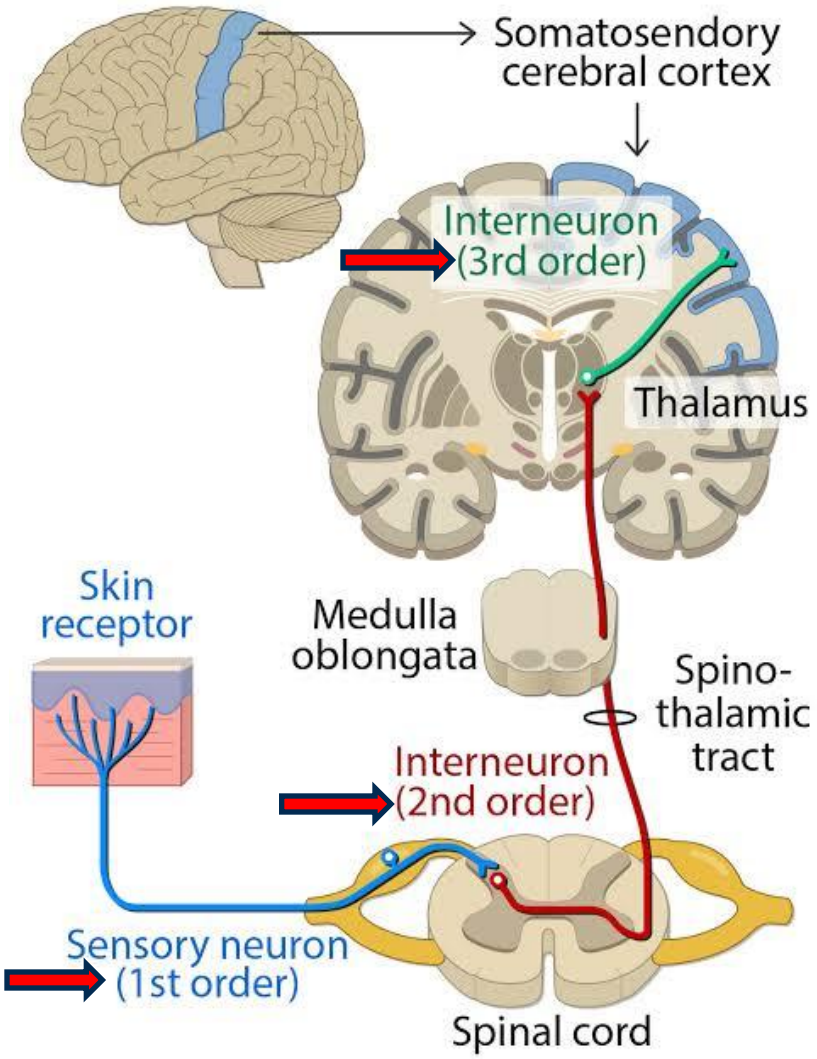
- Unmyelinated fibers
- Conduct slow signals
- Cause a dull, long-lasting, aching pain
- Diameter: 0.25-1.5µm
- Speed: slow 0.5-2m/sec



Pathway of pain

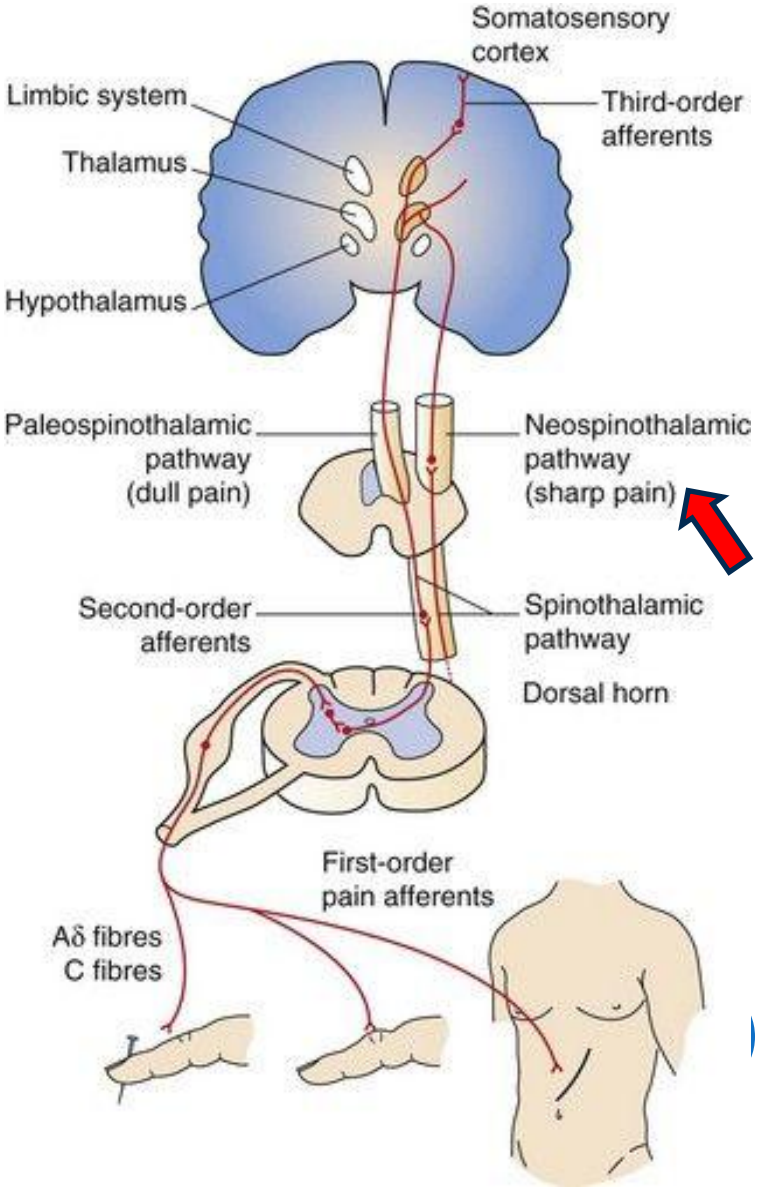
Dual Pain Pathways in the Cord and Brain Stem

- **The Neospinothalamic tract** — for Fast Pain
- **The Paleospinothalamic tract** — for Slow Pain



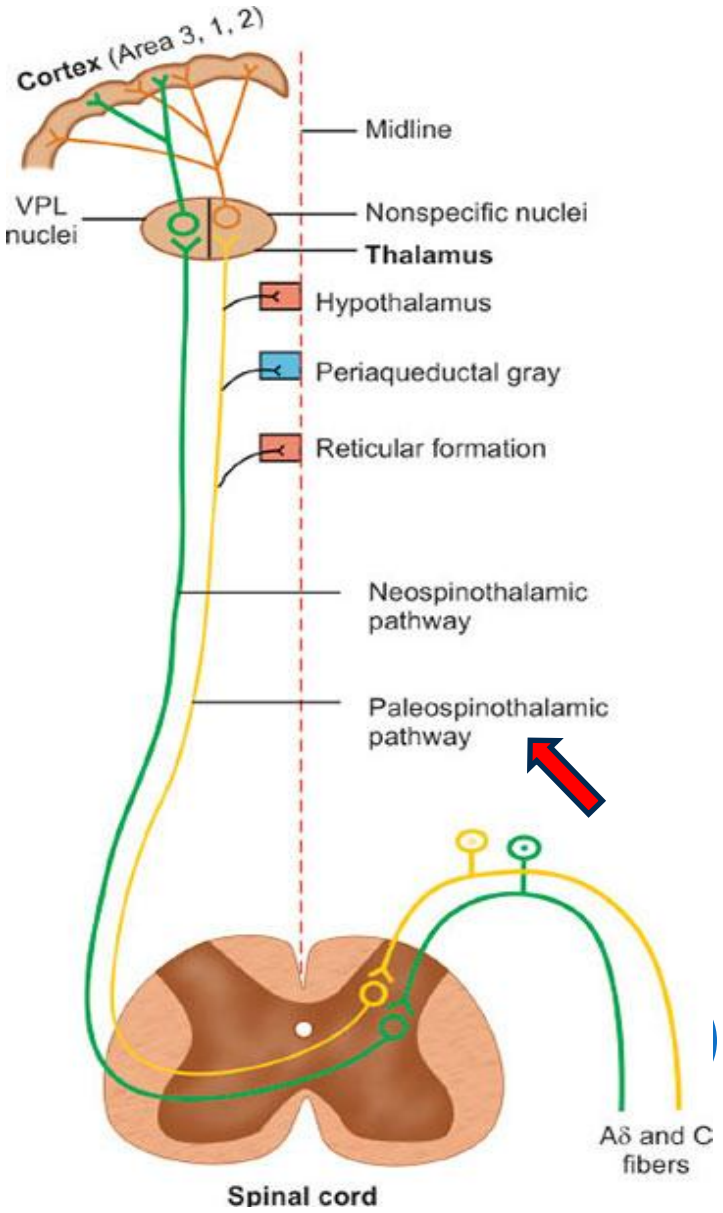
Neospinothalamic pathway

- Pain receptor (free nerve ending)
- Peripheral fibers (A-δ pain fibers)
- Dorsal root ganglia (1st order neuron)
- Spinal cord, lamina I-lamina marginalis (2nd order neuron)
- Cross to opposite side
- Neospinothalamic tract
- Thalamus- ventrobasal complex, Reticular formation (3rd order neuron)
- Somatosensory cortex



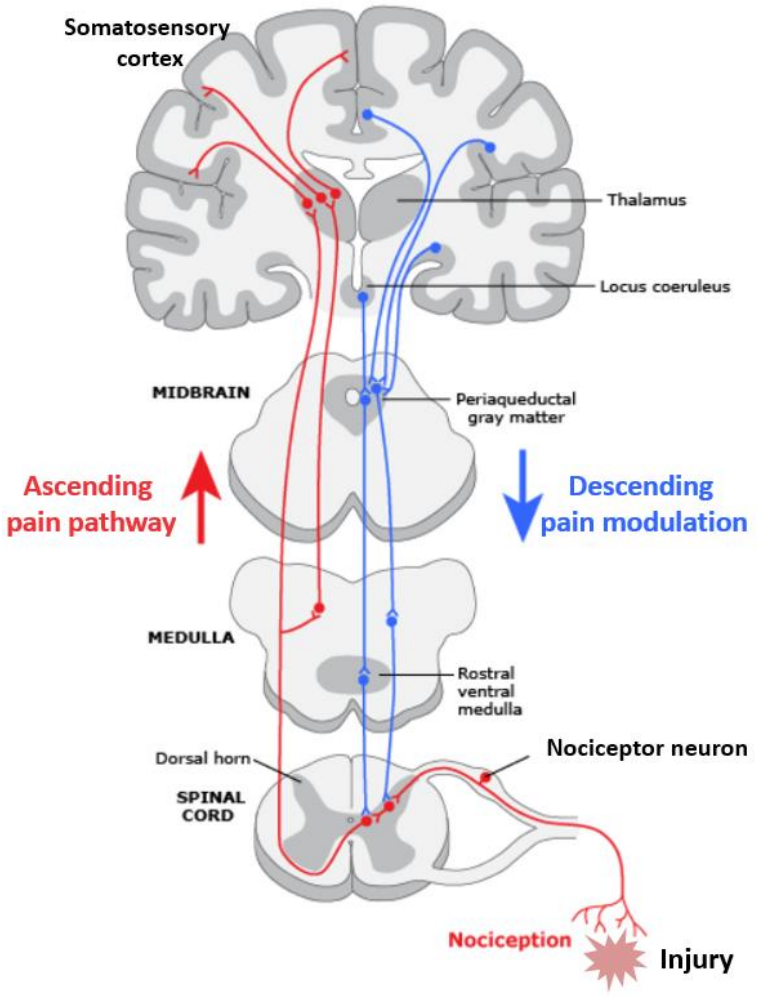
Paleospinothalamic pathway

- Pain receptor (Free nerve ending)
- Peripheral fibers (C fibers)
- Dorsal root ganglia (1st order neuron)
- Spinal cord, lamina II & III- substantia gelatinosa (2nd order neuron)
- Cross to opposite side
- Paleospinothalamic tract
- Reticular nuclei, Tectal area & periaqueductal grey region
- Intralaminar & ventrolateral nuclei of Thalamus (3rd order neuron), Hypothalamus, other basal region of brain
- Somatosensory cortex



Descending pain pathway

- Is a “top-down” neural circuit in the CNS
- Originates in the brain
- Travels down to the spinal cord
- Regulates & modifies pain signals



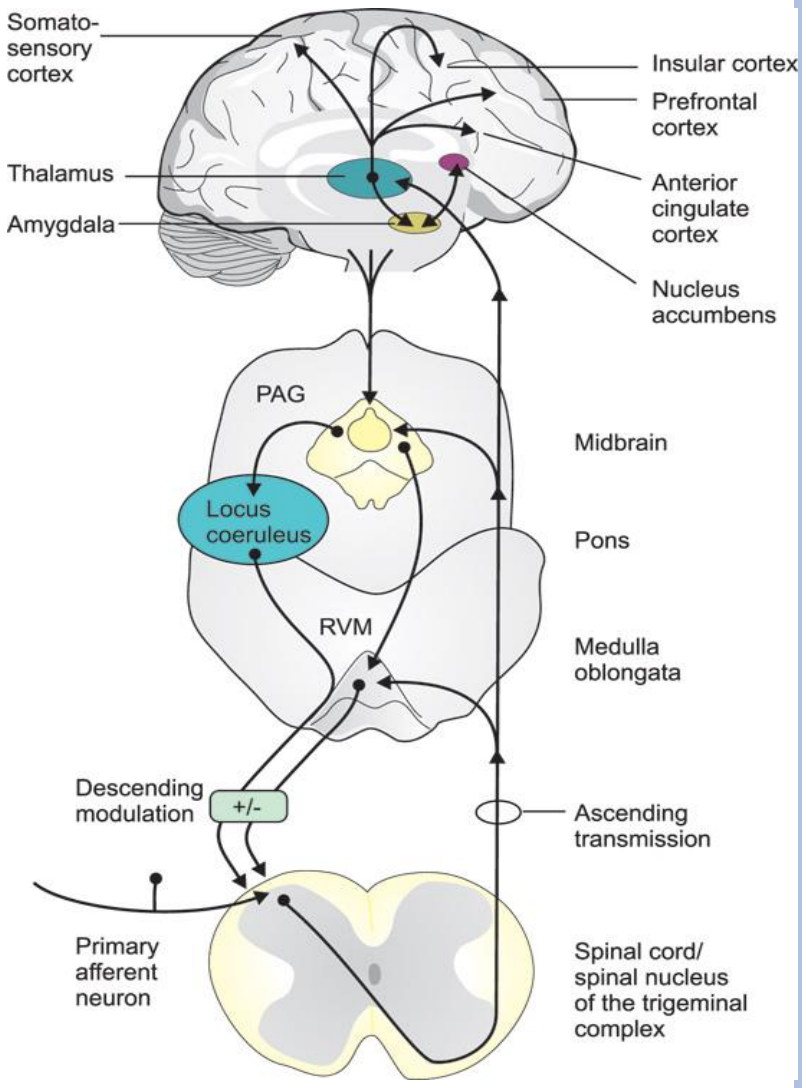
Descending pain pathway

Higher cortical & Limbic centers (somatosensory cortex, prefrontal cortex, amygdala, hypothalamus)

Periaqueductal Gray (PAG) in midbrain

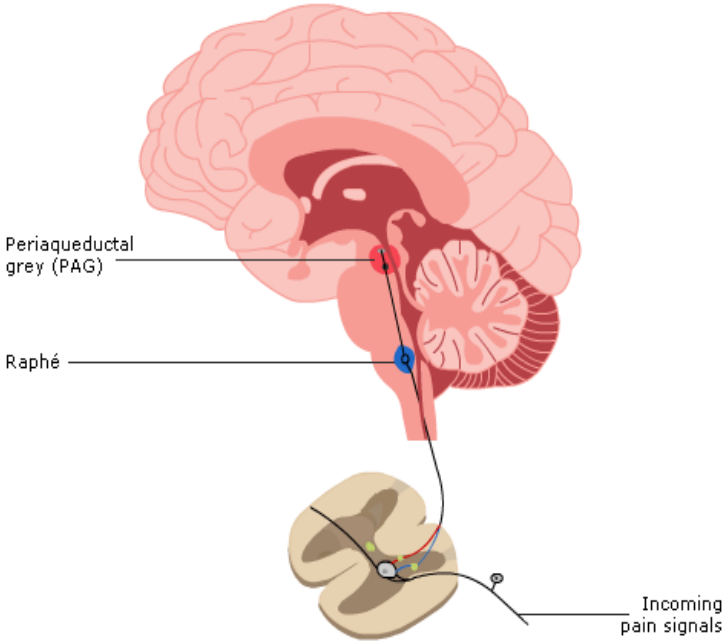
Rostral Ventromedial Medulla (RVM) & Brainstem nuclei (nucleus raphe magnus and locus coeruleus)

Spinal cord dorsal horn (lamina I, II & IV-VII)



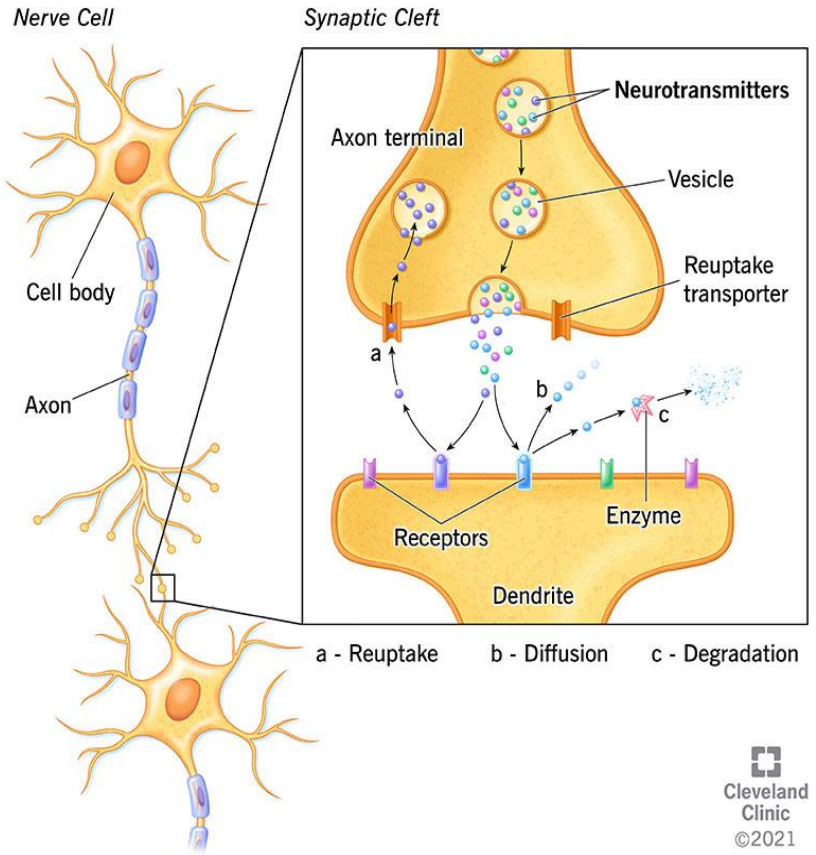
Modification of pain signal by Descending pain pathway

- Periaqueductal Gray Area (PGA)
  - release Enkephalins
- Nucleus Raphe Magnus (NRM)
  - release Serotonin
- The release of these neurotransmitters inhibit ascending neurons
- Endogenous opioid peptides causes Analgesia (loss of sensitivity to painful stimuli



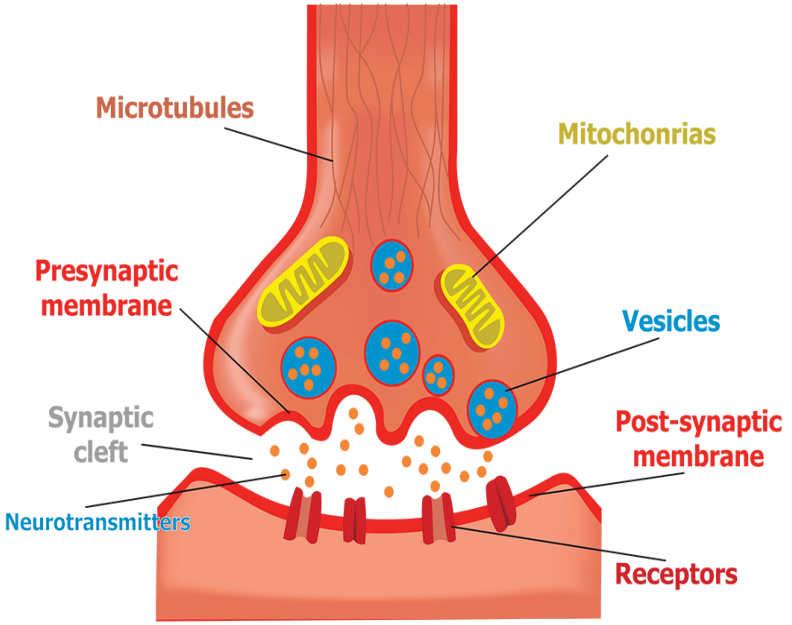
Major pain neurotransmitters

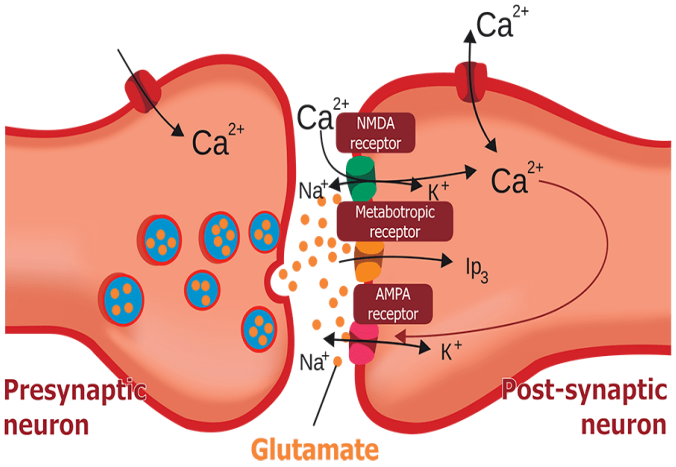
- **Excitatory :**
  - Glutamate
  - Substance P
- **Inhibitory :**
  - GABA
  - Glycine
- **Modulatory :**
  - Endogenous opioids
  - Serotonin
  - Norepinephrine



Major excitatory pain neurotransmitter

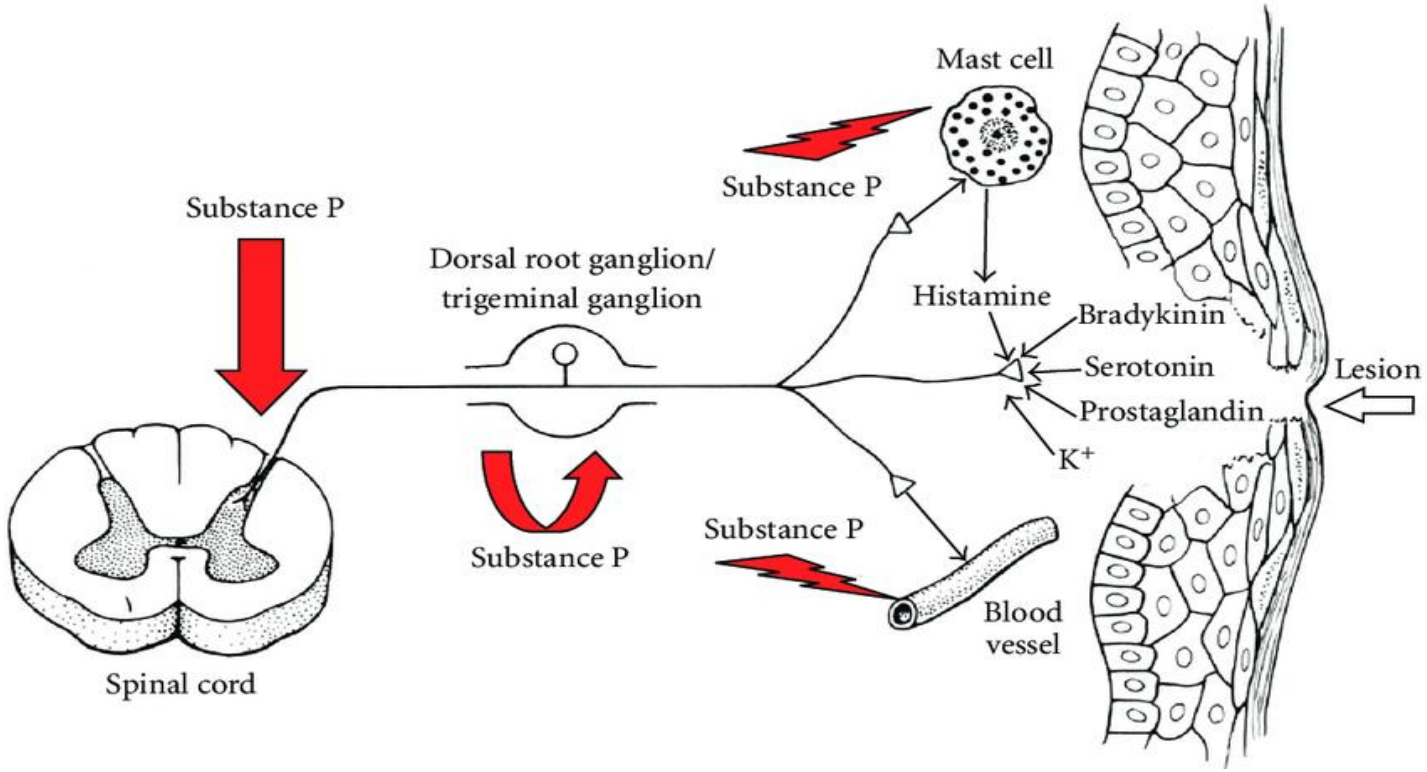
- **Glutamate:**
  - The main fast acting excitatory neurotransmitter
  - It triggers quick, sharp pain signal from A-delta fibers





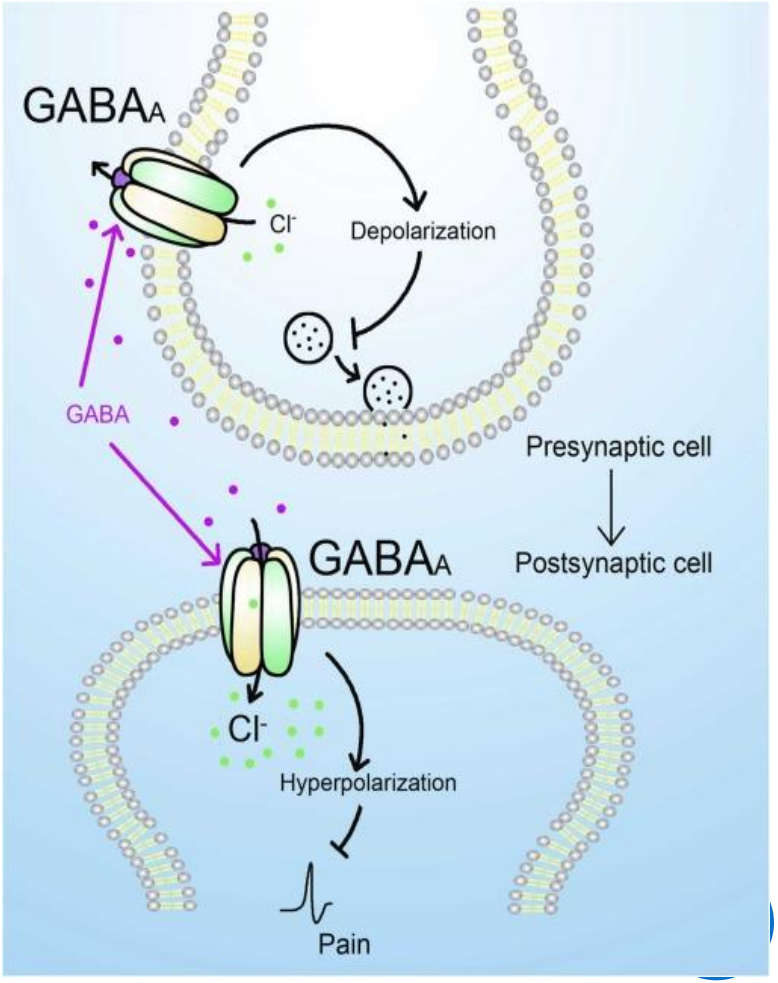
Major excitatory pain neurotransmitter

- **Substance P:**
- A neuropeptide released by slow pain fibers (C- fibers)
- It promotes prolonged pain transmission & CNS sensitization



Major inhibitory pain neurotransmitter

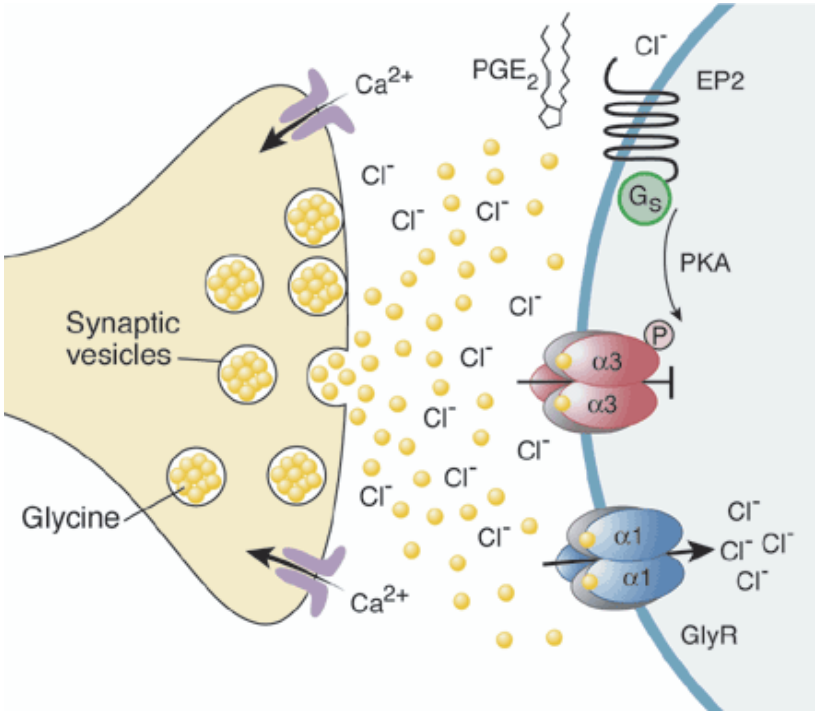
- **GABA :**
  - Primary inhibitory neurotransmitter in the CNS
  - Playing a vital role in dampening pain transmission
  - maintaining the balance between excitation and inhibition



Major inhibitory pain neurotransmitter

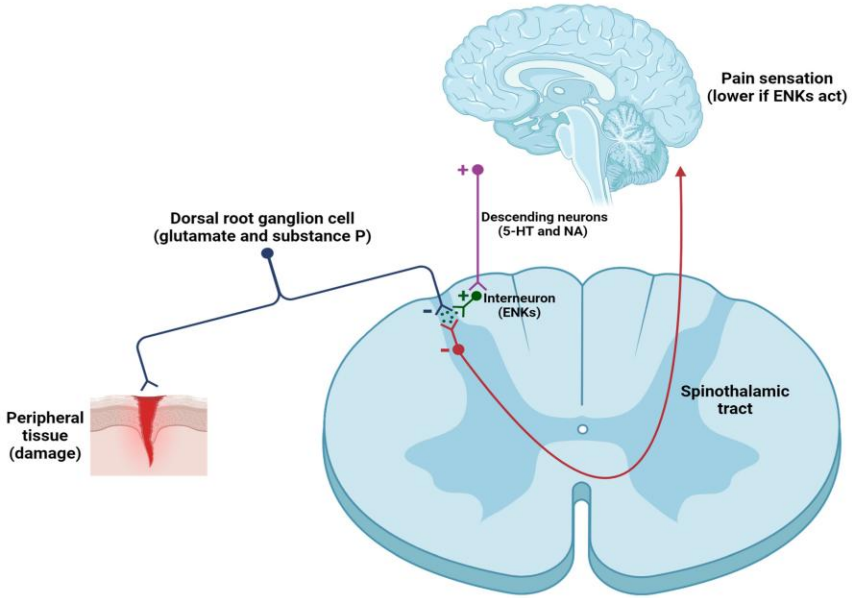
- **Glycine :**

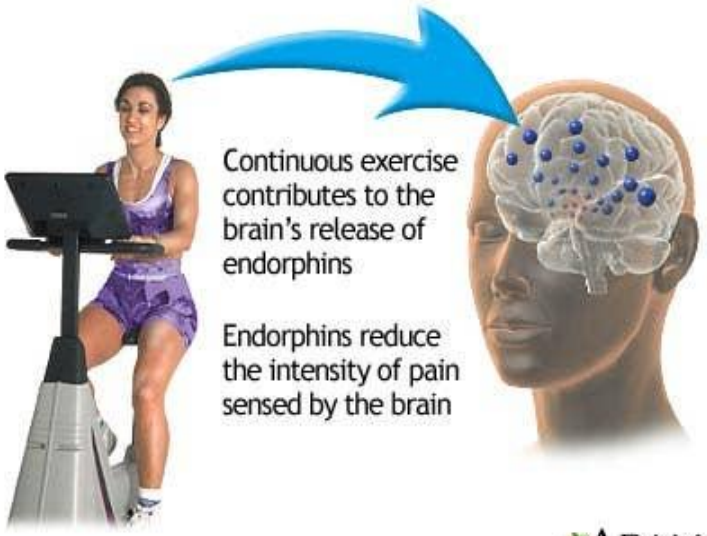
- Plays a dual & critical role in pain physiology
- Acting as a primary inhibitory neurotransmitter in the spinal cord
- Also act as a co-agonist at excitatory NMDA (N-methyl-D-aspartate) receptors



Major modulatory pain neurotransmitter

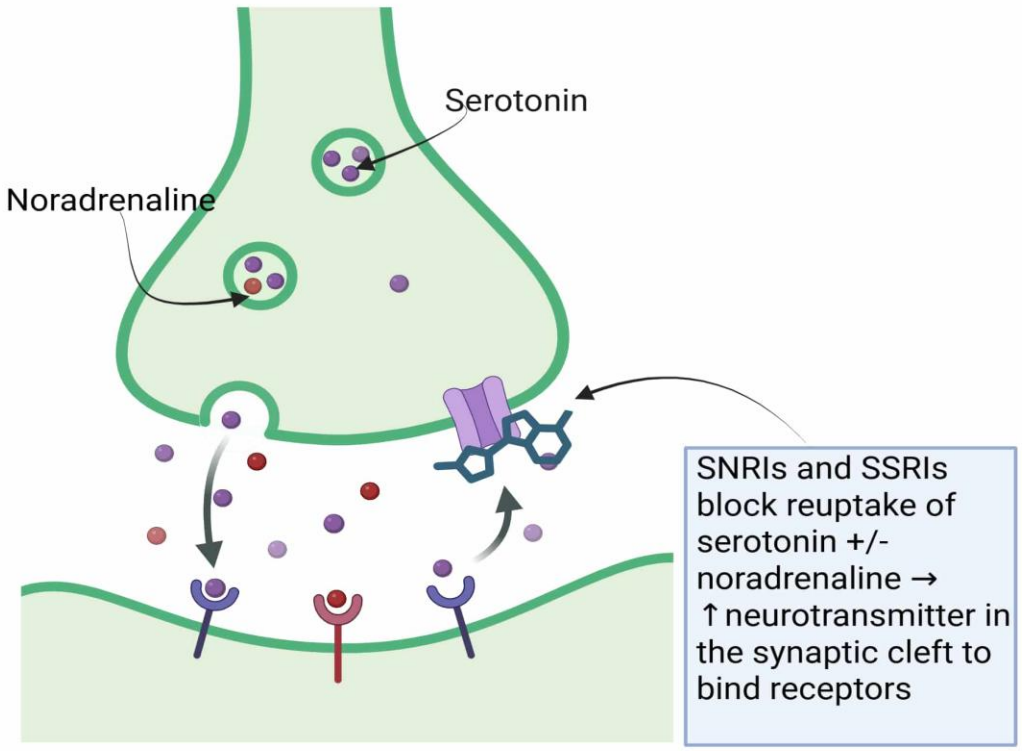
- **Endogenous Opioids (Enkephalin & Endorphin):**
  - Both are inhibitory neurotransmitters, act as natural pain killer in the spinal cord to block pain signals
  - Endorphin binds to opioid receptors in the CNS & PNS, which blocks pain signals by blocking the release of substance P





Major modulatory pain neurotransmitter

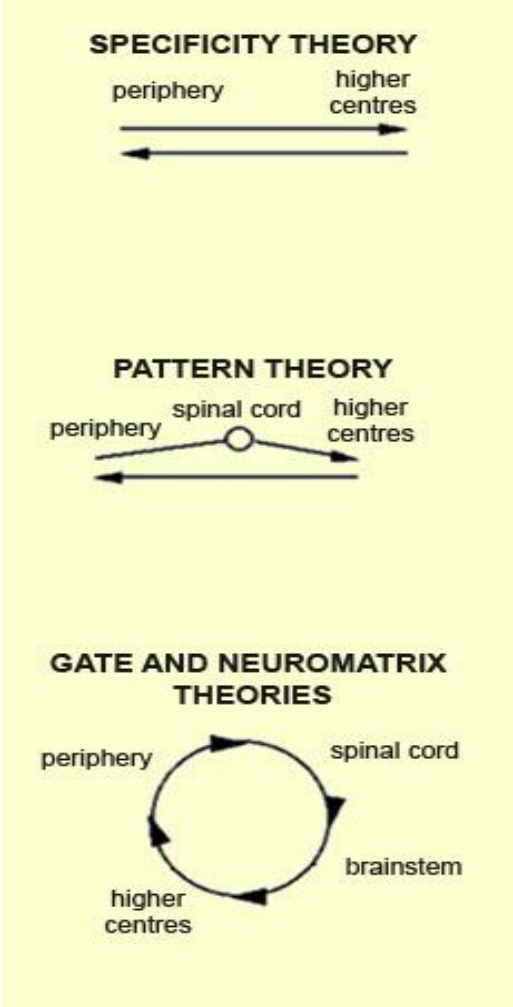
- **Serotonin & Norepinephrine:**
- Monoamine neurotransmitters
- Involved in descending pain modulation
- Can suppress or reduce pain perception



Various pain theories

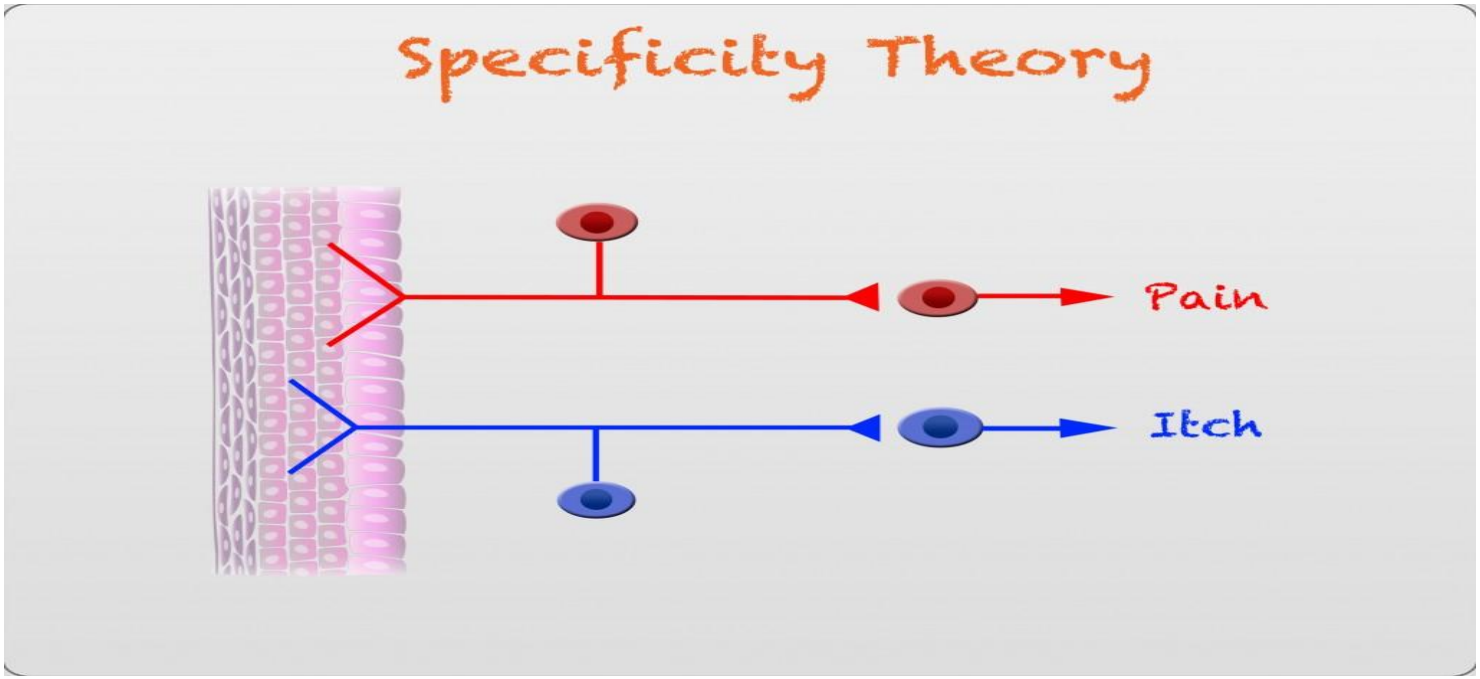
- Pain theories are proposed to offer the possible physiologic mechanisms involved in pain
- They are as follows-

1. Specificity theory
2. Pattern theory
3. Gate control theory
4. Neuromatrix theory



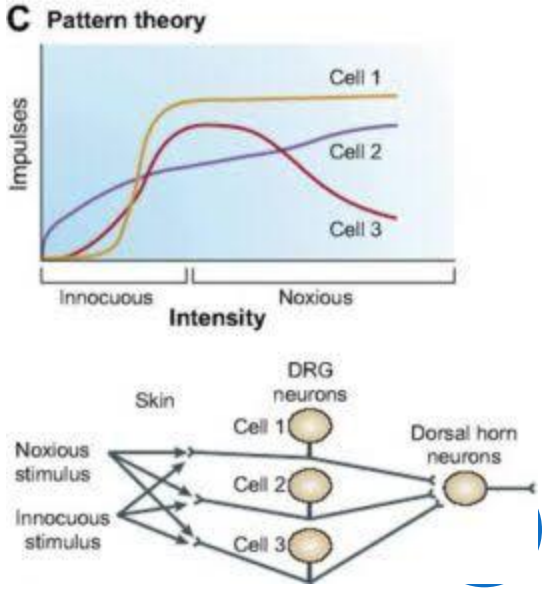
Specificity theory

- Proposed by Von Frey, 1895
- States pain as separate modality evoked by specific receptors
- That transmit information to pain centers or regions in the forebrain where pain is experienced



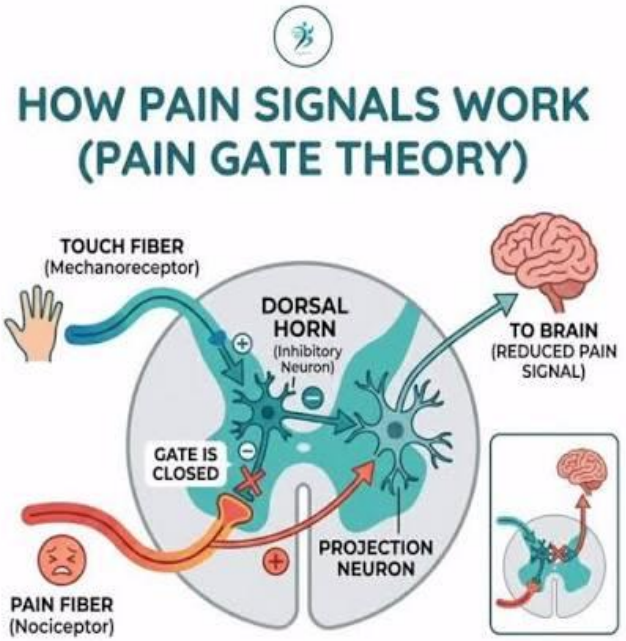
Pattern theory

- Proposed by Goldschneider, 1920
- Pain receptors share endings or pathways with other sensory modalities
- But different patterns of activity of the same neurons can be used to signal painful & non painful stimuli
- e.g-
  - Light touch applied to skin would produce the sensation to touch
  - But intense pressure would produce pain through high frequency firing of the same receptor



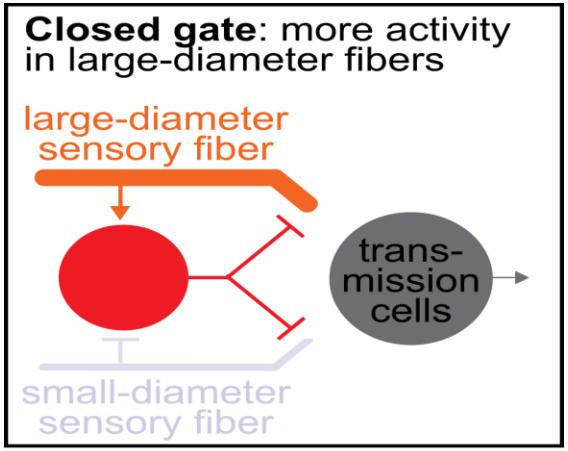
Gate control theory

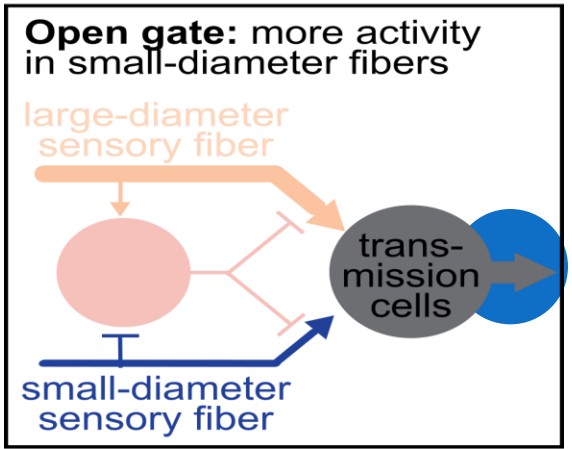
- Proposed by RONALD MELZACK & PATRICK WALL in 1965
- This theory states that non-painful input closes the “gates” to painful input
- “Gate” is located at the posterior gray horn of spinal cord
- There is an interaction between pain fibers (A-δ & C) and touch fibers (A-β) input at the spinal cord level in the form of “gating mechanism”



Gate control theory

- When pain fiber is stimulated, gate will be opened and pain felt
- When pain & touch fibers are stimulated together, gate will be closed and pain is not felt

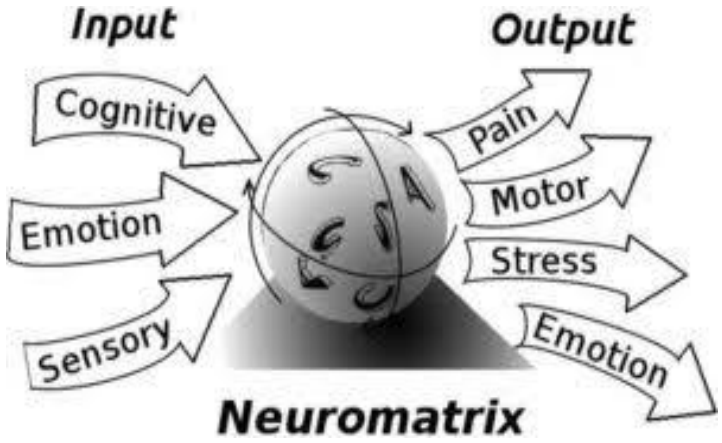




- **This theory provided basis for various methods of pain relief-**
  - Massaging a painful area
  - Applying irritating substances to a painful area (counter-irritation)
  - TENS (transcutaneous electrical nerve stimulation)
  - Acupuncture

Neuromatrix theory

- This theory was put forward by RONALD MELZACK, 1990
- States that pain is not a simple, passive “alarm signal” sent from the damaged tissue to the brain
- Instead, pain is a complex, multidimensional experience actively generated by a widely distributed neural network in the brain called the body self “Neutomatrix”
- That contains Somatosensory, Limbic & Thalamocortical components



Take home message

- Pain is bad but not feeling pain is even worst
- Pain is a protector, not just a detector
- Pain is influenced by individual's thoughts, emotions & environment
- Pain is an active process involving specialized sensory pathways, the spinal cord & extensive brain networks that amplify or dampen the sensation
- Chemicals play an important role in causing pain as well as in reducing pain



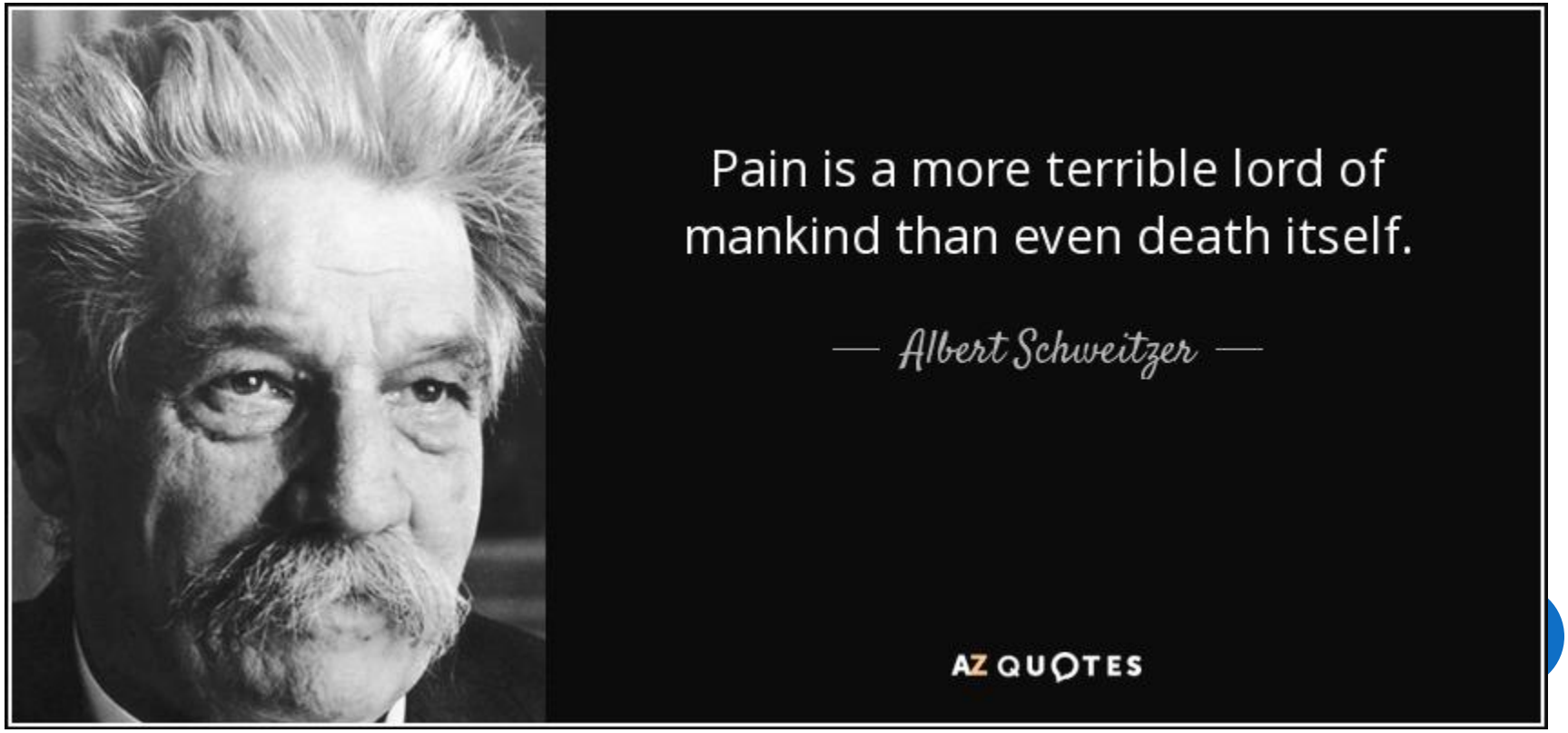
REFERENCES

- Guyton and Hall – Textbook of medical physiology
- K. Sembulingam – Essentials of medical physiology
- Indu Khurana - Textbook of human physiology
- S Chand – Textbook of human physiology
- Chaudhuri – Consice Medical Physiology

Articles

- Anatomy, physiology & pharmacology of pain- Ryan Moffat, Colin P.Rae anesthesia & intensive care medicine; 2010; 12(1)
- Case report study on Brown Sequard syndrome – Ponachi et.al Neurology Asia 2007; 12; 65-67
- Determination of painful experience during dental treatment- Ruth Suzanne et.al Rev.Dor 2012;13(4)
- Gilron, Ian. (2000). Neural Blockade in the Evaluation and Management of Chronic Pain: An Overview. Pain Research and Management. 5. 93-100. 10.1155/2000/546792.
- Bader MS. Herpes zoster: diagnostic, therapeutic and preventive approaches. Postgrad Med. 2013 Sep;125(5):78-91. doi: 10.3810/pgm.2013.09.2703. PMID: 24113666.

Thank you


Pain is a more terrible lord of mankind than even death itself.
— Albert Schweitzer —
AZ QUOTES

