Physiology Team 439

MED439
KING SAUD UNIVERSITY

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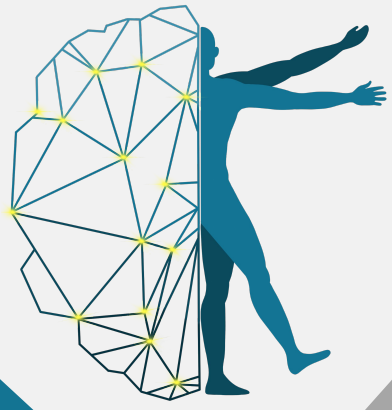


Physiology and Modulation of Pain

Objectives:

- What is pain and its significance.
- Pain receptors and mechanism of stimulation.
- Qualities And types of pain.
- Referred Pain.
- Pathway of pain.
- Role of thalamus and cerebral cortex in pain perception.
- Describe the pain suppression analgesic system.
- A- Spinal modulation (Gate theory of pain control).
  B- Supra spinal modulation (Special analgesic system).
- Pain modulation by opioid neurotransmitters.
- Appreciate that pain can also be facilitated.
- Know the sites & mechanism of pain relief.

Color index:

- Important.
- Girls slide only.
- Boys slide only.
- Dr's note.
- Extra information.

Editing File

Significance of pain: Why do we feel pain?

- It is a protective mechanism meant to make us aware that tissue damage is occurring or is about to occur:-
  - Avoid noxious stimuli.
  - Remove body parts from danger.
  - Promote healing by preventing further damage.
  - Storage of painful experiences in memory to avoid potentially harmful event in the future.
- The sensation of pain may be accompanied by behavioral (motor) responses (withdrawal, defense), emotional responses (crying, anxiety, depression or fear) as well as autonomic reactions (tachycardia, rise in BP, sweating).
- Pain is perceived at both the cortical & thalamic levels. (will be explain)

Reception*

Response of nerve receptors in the skin and tissues to stimuli resulting from actual or potential tissue damage.
(الاستقبال)

Perception*

The process by which pain is recognized and interpreted by the brain. (الإدراك)

Nociception

Refers to the transmission of signals evoked by activation of nociceptors (pain receptors) from periphery to the CNS.

Pain

A perception of unpleasant sensation that originates from a specific body region.
It is an unpleasant sensory and emotional experience associated with actual or potential tissue damage.
emotions might decrease or increase pain

Nociception consists of four basic processes:*

1. **Transduction : nociceptors** (pain receptors) **free nerve endings.**
2. **Transmission.**
3. **Perception of Pain-At cortical Level.**
4. **Modulation of Pain, Changing or inhibiting pain impulses in the descending tract (brain—> spinal cord) [norepinephrine and serotonin].**

Pain Receptors “Nociceptors”

Nociceptors

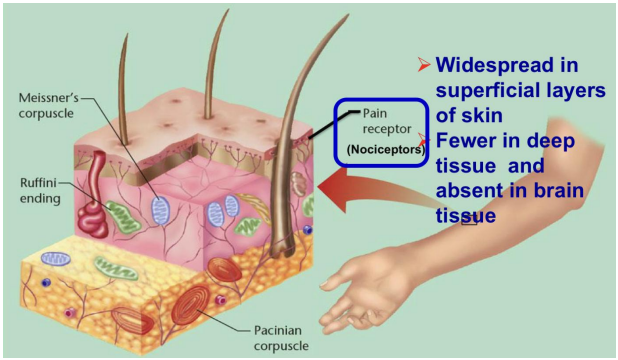
Primary afferent receptors that respond selectively to noxious stimuli.
Special receptors that respond only to noxious (painful) stimuli and generate nerve impulses which the brain interprets as "pain".

What are the Characteristics of Nociceptors?*

- They are the most widely distributed.
- They are specific (have adequate stimulus), pain is not produced by overstimulation of other receptors.
- They are high threshold receptors i.e. painful stimuli must be strong & noxious to produce tissue damage.
- They do not adapt (or very little) to repetitive stimulation (unlike touch receptors)
  Why? it allows the pain to keep the person apprised of a tissue-damaging stimulus as long as it persists.

Distribution of Pain Receptor (Nociceptors)

- Widespread in superficial layers of skin.
- Fewer in deep tissue and absent in brain tissue.
- They are found in largest number & density in skin, periosteum joint surface, arterial wall & duramatar.
- headache is felt by nociceptors in the dura mater and blood vessels but not the brain tissue itself because it lacks nociceptors.



Classification of Nerve fibres

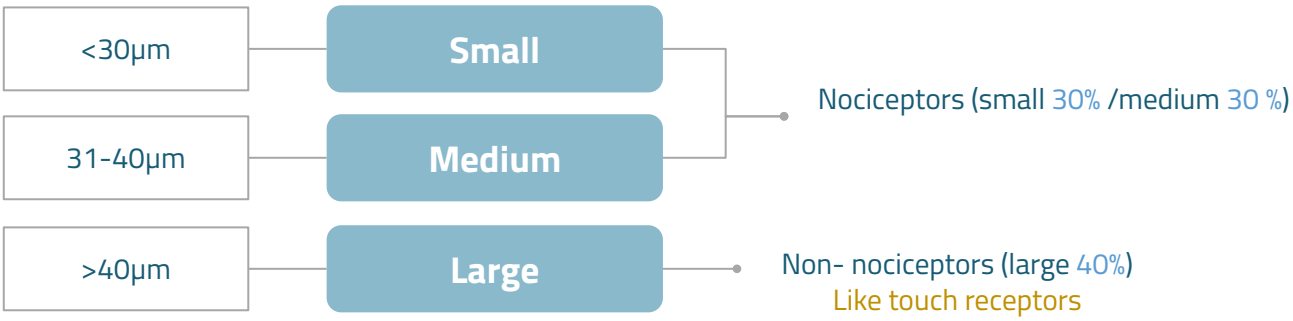
	I Aα*	II Aβ	III Aδ	IV C
myelin Sheath	Myelinated	Myelinated	Myelinated	Unmyelinated
Diameter (μm)*	10-20	5-10	2-5	0.5-2
Conduction Velocity (m/s)*	70-120	30-70	5-30	0.5-2
Function	Motor for skeletal muscles.	carry messages of light touch* Afferent dorsal column system "which carries touch sensation"	sharp Pain* Afferent of nociceptors	dull Pain* Afferent of nociceptors

Decrease in diameter and decrease in velocity

All pain receptors are free nerve endings of:

1. Unmyelinated C fibers (diameter 0.4 – 1.2 μm with conduction velocity 0.5 - 2 m/s.
2. Small diameter myelinated A fibers (diameter fine 2 - 5 μm with conduction velocity 12 - 30 m/sec.

What's the relation between diameter of nerve and velocity of conduction? Diameter and velocity have a direct relationship. ↑diameter ↑ Na+ and Ca++ influx -> ↑ velocity (Rapid depolarization and repolarization)



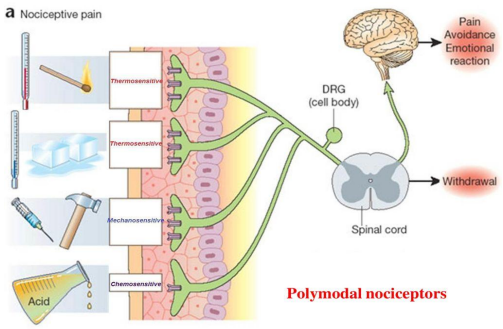
Types of Nociceptors

Types on both slides, but the details are on **boys slide only**.

1- Mechanical nociceptors	They activated by mechanical stimuli and elicit fast pain. Respond to strong pressure (eg, from a sharp object).
2- Thermal nociceptors	- They activated by thermal stimuli and produce fast pain - Activated by skin temperatures above 42°C or by severe cold. - Innocuous cold receptors or cool receptors are on dendritic endings Aδ fibers and C fibers, whereas innocuous warmth receptors are on C fibers. Mapping experiments show that the skin has discrete cold sensitive and heat sensitive spots. There are 4-10 times as many as cold-sensitive as heat sensitive spots.
3- Chemically sensitive nociceptors	- They activated by chemical stimuli. Respond to various chemicals like bradykinin, histamine, high acidity, and environmental irritants. - they produce slow pain. they act slowly from the beginning because chemicals take time to cause tissue damage
4- Polymodal nociceptors	Respond to combinations of these stimuli. Respond to various noxious stimuli.

There are a variety of receptors located on the endings of nociceptive sensory nerves that respond to noxious thermal, mechanical, or chemical stimuli.*

Guyton: In general, fast pain is elicited by the mechanical and thermal types of stimuli, whereas slow pain can be elicited by all three types.



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Many of these are part of a family of nonselective cation channels called transient receptor potential (TRP) channels.

- **TRPV1:** receptors (the V refers to a group of chemicals called vanilloids) that are activated by intense heat, acids, and chemicals such as capsaicin (the active principle of hot peppers is an example of a vanilloid).
- **TRPA1:** Noxious mechanical, cold, and chemical stimuli may activate TRPA1 receptors (A, for ankyrin) on sensory nerve terminals.
- **ASIC:** Sensory nerve endings also have acid sensing ion channel (ASIC) receptors that are activated by pH changes within a physiological range and may be the dominant receptors mediating acid-induced pain.
- **P2X & P2Y:** For example, nociceptive mechanical stimuli cause the release of ATP that acts on purinergic receptors (eg, P2X, an ionotropic receptor and P2Y, a G protein coupled receptor).
- The receptor that is activated by moderate cold is **TRPM8**. The M refers to methanol, the ingredient in mint that gives it its "cool" taste.
- **TRPV4** receptors are activated by by warm temperatures up to 34C; **TRPV3** receptors respond to slightly higher temperature 35-39C

Silent Nociceptors*:

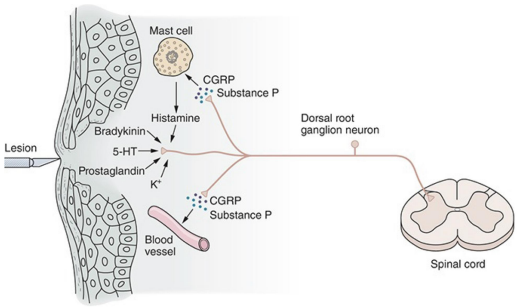
- In the skin and deep tissues there are additional nociceptors called "silent" or "sleep" nociceptors.
- These receptors are normally unresponsive to noxious mechanical stimulation, but become “awakened” (responsive) to mechanical stimulation during inflammation and after tissue injury. One possible explanation of the "awakening" phenomenon is that continuous stimulation from the damaged tissue reduces the threshold of these nociceptors and causes them to begin to respond.
- This activation of silent nociceptors may contribute to the induction of hyperalgesia, central sensitization, and allodynia. Many visceral nociceptors are silent nociceptors.

Mechanism of Stimulation of Nociceptors

- Pain receptors are depolarized either:
  1- Directly (by a stimulus).
  2- Production of pain by producing substances. (inflammatory mediators) **from damaged tissues.**

- E.g. bradykinin, histamine, substance P, calcitonin gene related peptide (CGRP), interleukins, prostaglandins, K+ , Ach, Acids, proteolytic enzymes. pain producers (chemical stimuli). (check the table below)

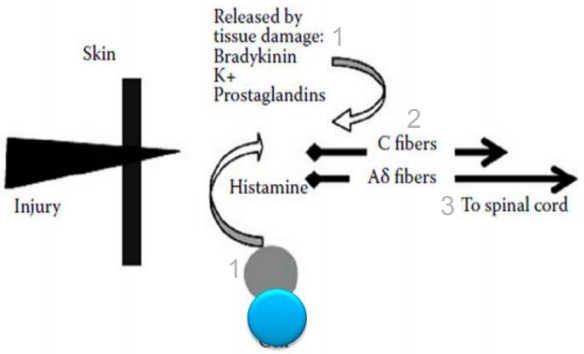
- **PGs & substance-P enhance the sensitivity of pain receptors (Nociceptors)** they might decrease threshold to increase sensitivity to pain.



Chemical Substances Released During Tissue Damage	
Substance	**Source**
Potassium	Damaged cells
Prostaglandins	Damaged cells
Leukotrienes	Damaged cells
Bradykinin	Plasma, mast cells and basophils
Histamine	Mast cell
Serotonin	Platelets
Substance P main pain sensitizer	Primary nerve afferents

Pain Mechanism

1. Damage and inflammation release chemical mediators as cytokines, bradykinin, prostaglandin, Substance P.
2. Activate or sensitize the receptor endings.
3. Transduction and conduction of nerve impulse.



Classification of Pain

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- **Pain classified by duration**
  - Acute
  - Chronic
- **Pain classified by nature**
  - Nociceptive
    - Visceral
    - Somatic
  - Non-nociceptive
    - Neuropathic
      - Central NP- Damage of CNS.
      - Peripheral NP- Damage to PNS.
    - Sympathetic

Differences Between Nociception and Neuropathic pain:

Nociception Pain	Neuropathic Pain (non-Nociception)
It is caused by the presence of a painful stimulus on nociceptors	**Occurs as a result of damage to the nerve fibers with the pain impulse emanating from the nerve itself** (Pain caused by a primary lesion or dysfunction in the nervous system)*
Nociceptive pain is detected by specialized transducers connected to A-delta and C-fibers (stimuli from somatic and visceral structures)*	Neuropathic pain damage to nerves (trigeminal neuralgia, postherpetic pain, diabetic neuropathy and after chemotherapy. Hyperalgesia, allodynia and spontaneous pain.*
Sustained primarily by the nociceptive system	Sustained by aberrant processes in PNC or CNS
Proportionate to stimulation of the nociceptors when acute	Disproportionate to stimulation of the nociceptors
Serve as a protective function, normal pain when acute	Serve no protective function
Pathological when chronic	Pathological pain
Respond to common analgesics	Resistant to common analgesics. Can persist for years.
E.g.: acute burn, bone fracture and other similar somatic & visceral pain	E.g.: painful diabetic & peripheral neuropathies, sympathetic-mediated pain, nerve inflammation, compression, post herpetic neuralgia, diabetic neuropathy and after chemotherapy.

Idiopathic Pain : No underlying lesion found yet, disproportionate to the degree of clinically discernible tissue injury. *

Mixed Pain: Eg; Failed low back surgery syndrome and complex regional pain syndrome. *

Qualities of Pain
(Phenomenon of double-pain)

Fast/immediate (1st) pain epicritic Pain	slow/delayed (2nd) pain
Sharp, intense, pricking, well localized e.g. pricking, cut with knife	Burning, aching, throbbing "unbearable" diffuse, dull, chronic pain, poorly localized
Felt within 0.1 sec on stimulation of Mechanical & Thermal nociceptors skin or superficial stimuli	Felt after 1 sec or more on stimulation of Polymodal receptors
Associated with reflex withdrawal*	Associated with destruction of tissue*
Usually somatic not visceral*	Can occur in skin or internal organ/tissue*
Transmitted by **Aδ- fibers** in the peripheral nerves & centrally by **Neospinothalamic Tract**	Transmitted by **C fibers** peripherally & centrally by **paleospinothalamic Tract**
Terminate at I and V laminas lamina marginalis	Terminate at II and III laminas (substantia gelatinous)
Neurotransmitter – Glutamate	Neurotransmitter – Substance-P
20% pain conduction	80% of pain conduction

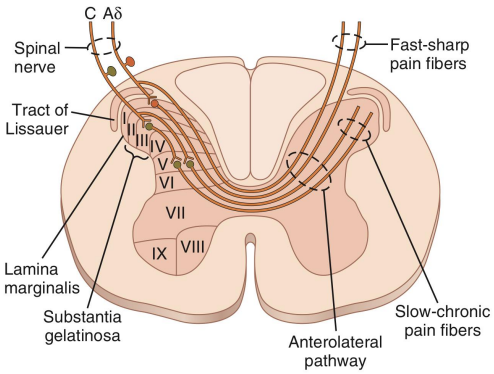
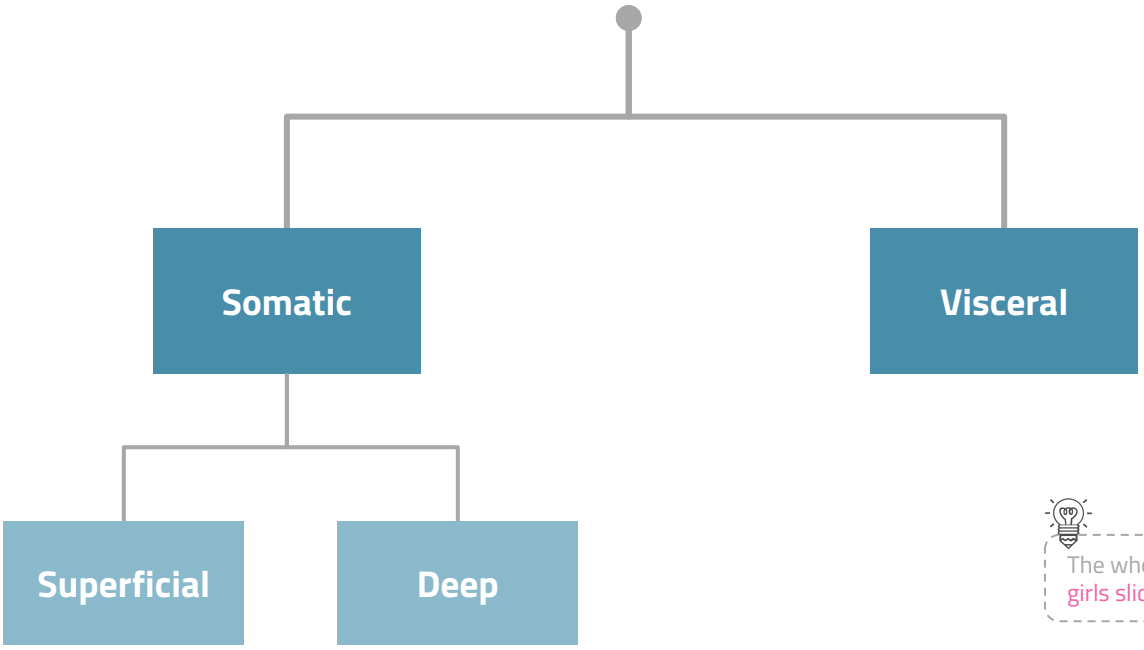


Figure 49-2. Transmission of both "fast-sharp" and "slow-chronic" pain signals into and through the spinal cord on their way to the brain. Aδ fibers transmit fast-sharp pain, and C fibers transmit slow-chronic pain.

Types of Pain:

- Pain can be classified **according to the site of stimulation** into:-



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Superficial: vs. Deep:

- Arises from skin or other superficial structures.
- Occurs in 2 phase (fast pricking , slow burning pain).
- Can be well localized.
- Associated with motor, autonomic, emotional reactions.

- Arises from muscles, joints, periosteum, tendons & ligaments.
- Diffuse, slow prolonged conducted by type C fibers.
- May be referred , initiate reflex contraction of nearby muscles.
- Caused by: trauma, bone fracture, inflammation, arthritis, muscle spasm & ischemia.

Visceral Pain

- There are few pain receptors in most viscera.
- Some viscera are pain insensitive e.g. liver parenchyma, lung alveoli, brain tissue, visceral layer of peritoneum, pleura and pericardium.

Characteristics:

1	Gradual onset, Slow, diffuse, poorly localized. Conducted by C fibers.
2	Pain arising from parietal peritoneum,pleura and pericardium is sharp and pricking.*
3	often referred ; associated with rigidity of nearby muscles, autonomic reactions/disturbance like nausea and diaphoresis.

** **N.B: Cutting and crushing are not painful when applied to viscera.**

Causes of Visceral Pain

- **distension** of a hollow organ
- **ischemia** (e.g. pain due to myocardial ischemia)
- **inflammation of an organ**

Summary

Pain can be classified **according to the site of stimulation**	**1. Somatic:**		**2. Visceral**
	Superficial	**Deep**	
Localization	Well localized	less localized than superficial but better than visceral	Poorly localized
Referred pain +/-	-	+ (excluding bone)	+
Conducting fibers	**Double phenomenon** Aδ fiber pathway, followed by C fiber pathway	Type C fibers	Type C fibers

Referred Pain

- Pain that is not felt in the diseased structure itself, but at another place in the body far away from the site of origin.
- Referred pain can be felt away from its original site.
- Frequent with visceral , deep somatic pain (are often referred), but **Cutaneous / superficial pain is not referred.**
- when the pain is both localized/migrates and referred it is called radiating pain.

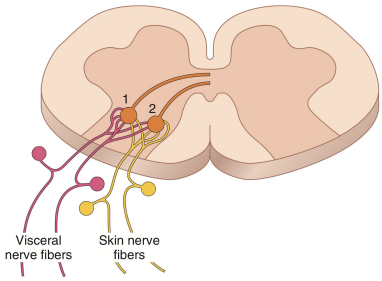


Figure 49-5. Mechanism of referred pain and referred hyperalgesia. Neurons 1 and 2 receive pain signals from the skin as well as from the viscera.

Pain is referred according to the dermatomal rule:

- When visceral pain is referred to the surface of the body, the person generally localizes it in the dermatomal segment from which the visceral organ originated in the embryo, not necessarily where the visceral organ now lies. Figure 49-6
- Localization of Visceral Pain "Visceral" and the "Parietal" Pain Transmission Pathways. Figure 49-7

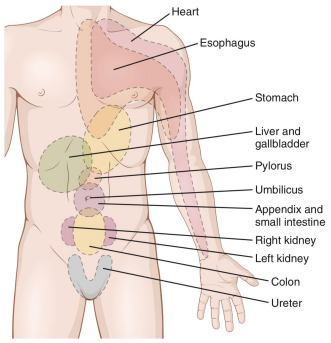


Figure 49-6. Surface areas of referred pain from different visceral organs.

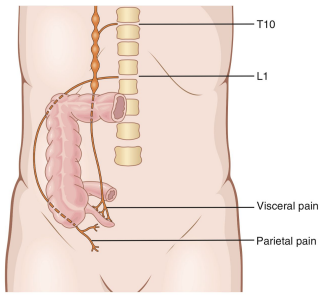
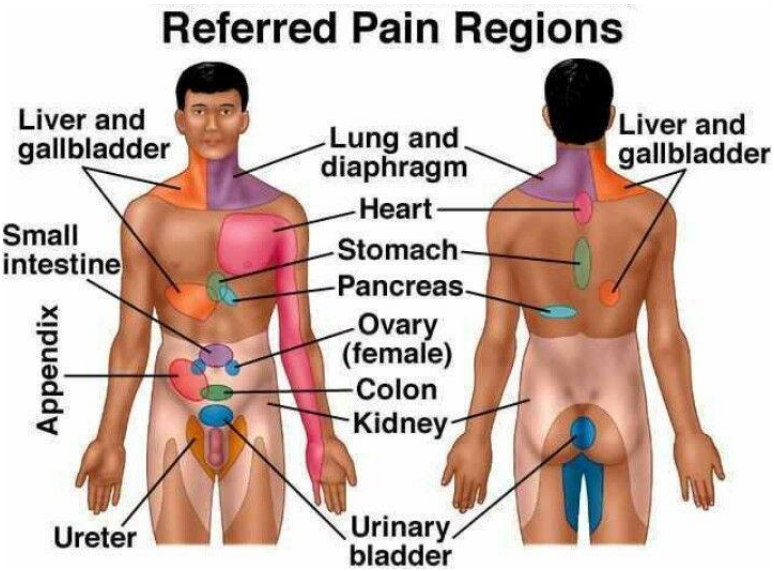


Figure 49-7. Visceral and parietal transmission of pain signals from the appendix.

Examples of referred pain

cardiac pain	Is referred to the jaw, left shoulder & inner side of the left arm
pain of appendicitis	referred to the periumbilical region
pain of ureter	referred to testicular region



Referred Pain Regions *

Organ	Site of referred pain
meninges	Back of head and neck
Heart	central chest,left arm
Diaphragm	Shoulder tip
Esophagus	behind sternum
Stomach, duodenum	Epigastrium
Small bowel, pancreas	Around umbilicus
Large bowel, bladder	Lower abdomen
Kidney	Loin
Ureter	Testicles
Trigon of bladder	Tip of penis
Hip	Knee
Appendix	Umbilicus
Uterus	Low back

Mechanism of Referred Pain

1 Convergence theory :

- Convergence of peripheral & visceral pain on the same second order neuron that project to brain.
- Branches of visceral pain fibers synapse in the spinal cord on the same second-order Neurons that receive pain signals from the skin.
- Afferent pain fibers from skin area & diseased viscera that develop from same embryonic segment converge on the same 2nd order neuron and finally stimulate the same cortical neuron.
- The brain interprets the information coming from visceral nociceptors as having arisen from cutaneous nociceptors, because this is where the nociceptive stimuli originates more frequently.

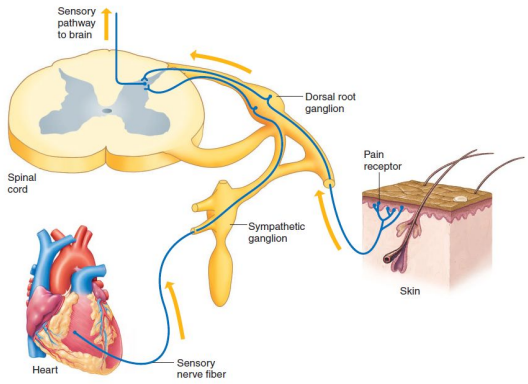
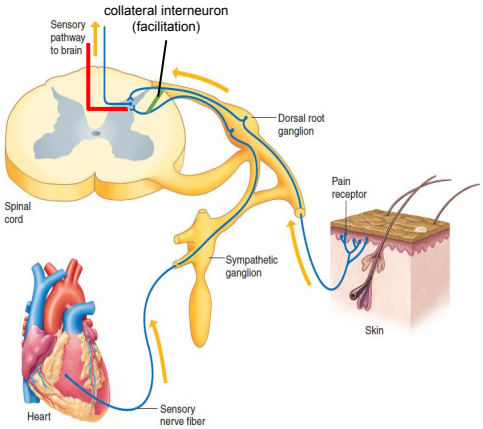


Figure 7.17 Convergence of visceral and somatic afferent neurons onto ascending pathways produces the phenomenon of referred pain.

2 afferent from viscera and skin converge on the same spinothalamic neurons
skin يفسرها من ال Brain وال

2 Facilitation theory :

- Pain fiber from skin are always carrying impulses, not enough to produce pain though.
- Impulses from diseased viscus pass through afferents which give collaterals to ST neurons receiving pain fibers from skin.
- As a result, ST neurons' excitability is raised (facilitated) to reach a threshold level.
- The signals reaching the brain are projected to skin area and pain is felt in skin dermatome.



2 separate pathways to the brain, afferent from viscera will facilitate the afferent from the skin>
skin يفسرها من ال Brain وال

Pathway of Pain

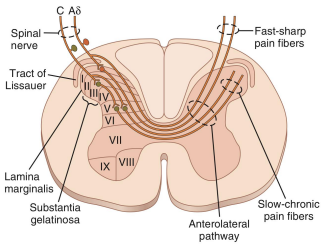
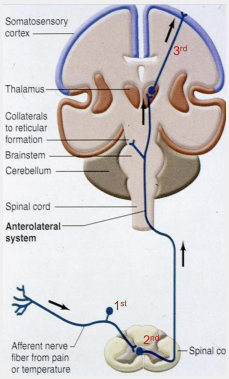


Figure 49-2. Transmission of both "fast-sharp" and "slow-chronic" pain signals into and through the spinal cord on their way to the brain. Aδ fibers transmit fast-sharp pain, and C fibers transmit slow-chronic pain.

Pain sensation is carried by **lateral spinothalamic tracts** which includes 2 separate pathways:-

A) The neospinothalamic pathway:



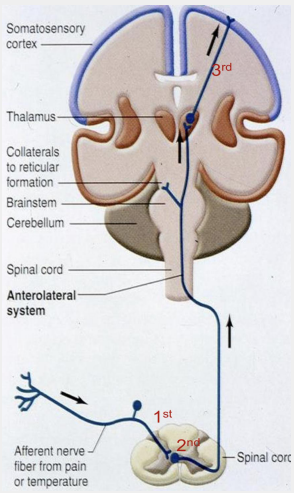
- **20% of pain conduction.**
- **Transmits fast pain (epicritic pain).**
- **Occurs First** upon stimulation of Mechanical and Thermal nociceptors

- **1st order neurons** : mainly **A δ (delta)** afferent fibers in the peripheral nerves and they terminate at lamina I (lamina marginalis) & lamina V.

- **2nd order neurons**: the tract starts at the dorsal horn then they cross to the opposite side and ascend in the lateral column, then they ascend to the brain stem to terminate in ventrobasal complex of thalamus (most pass all the way to the thalamus without interruption).

- **3rd order neurons**: most fibers project from(start) the thalamus to the somatosensory cortex (rest to basal areas of the brain and somatosensory cortex).

B) The paleospinothalamic pathway:



- **80% of pain conduction.**
- **Transmits slow pain sensation.**
- **Occurs second** upon stimulation of Polymodal receptors.
- Poor localization.

- **1st order neurons**: type C fibers. they enter the spinal cord via dorsal roots and terminate at substantia gelatinosa (laminae II & III).

- **2nd order neurons**: they start at SGR, cross to opposite side in front of the central canal, ascend in lateral column and terminate at:
  - reticular formation of brain stem.
  - intralaminar nuclei of thalamus.
  - hypothalamus and adjacent region of basal brain.

  impulses arriving these regions have strong arousal effects & can be perceived.
- **3rd order neurons**: these start at the thalamus and only few fibers project to cerebral cortex.
- 1/10 to 1/4 of the fibers pass all the way to the thalamus.
- Most terminate reticular nuclei the tectal area & periaqueductal gray region for feeling the suffering types of pain.

Role of Cerebral Cortex in Pain Perception*

- Full perception of pain occurs when signals enter RF of brain stem, thalamus & basal regions.
- Somatosensory cortex plays an important role in topognosis (**localization & interpretation of pain quality**).
- Fast pain (neospinothalamic) is localized better than slow pain(paleospinothalamic) because the neospinothalamic tract reaches the somatosensory cortex while only a small portion of the paleospinothalamic pathway gets there.

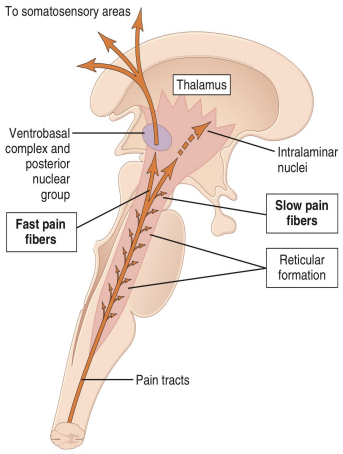


Figure 49-3. Transmission of pain signals into the brain stem, thalamus, and cerebral cortex by way of the *fast pricking pain pathway* and the *slow burning pain pathway.*

"AROUSAL SYSTEM"*

Reticular areas of the brain stem and in the intralaminar nuclei of the thalamus

Pain Modulation*

Definition

It means pain perception variability (the degree to which a person reacts to pain).
i.e. A decrease or an increase in the sensation of pain caused by inhibition or facilitation of pain signals.

Inhibition

- Spinal (segmental) inhibition: Gate control theory.

- Supraspinal (descending) inhibition .
Brain , brain stem

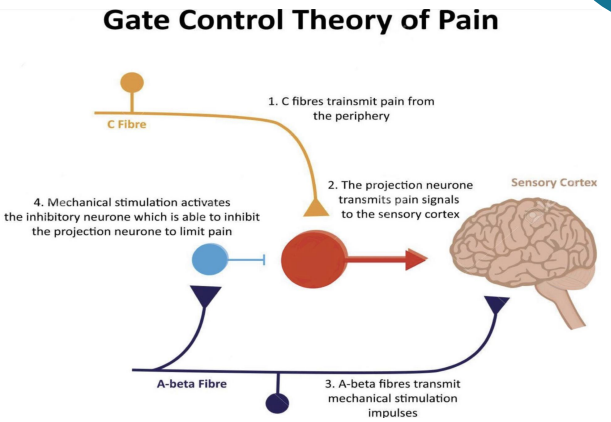
Facilitation

- Peripheral sensitization (release of chemicals after tissue injury).

- Central sensitization (Dis-inhibition).

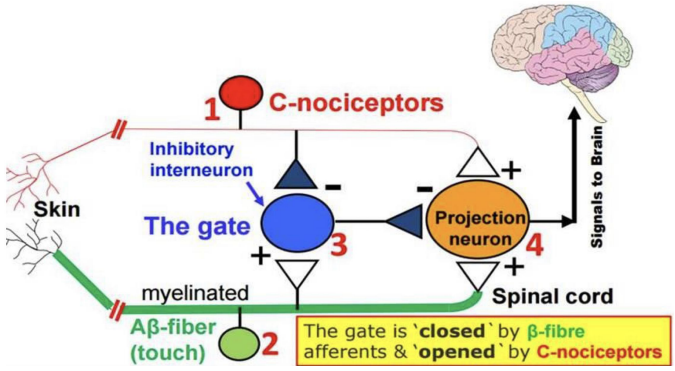
Gate Control Theory of Pain:

- Special neurons in the the dorsal horn of spinal cord SGR (Substantia gelatinosa of Rolando, second order neurons of Paleospinothalamic pathway) form the gate through which pain impulses must pass to reach brain.
- It Is based on the premise that the gate, located in the dorsal horn of the spinal cord, modulates the afferent nerve impulses.



Four Variables Control This Gate:

1. Type C- fibers (slow pain).	**2. Type A-β fibers (Light touch).**
3. Inhibitory Interneurons.	**4. Projection neuron.**



Gate Opened Or Closed By Three Factors:

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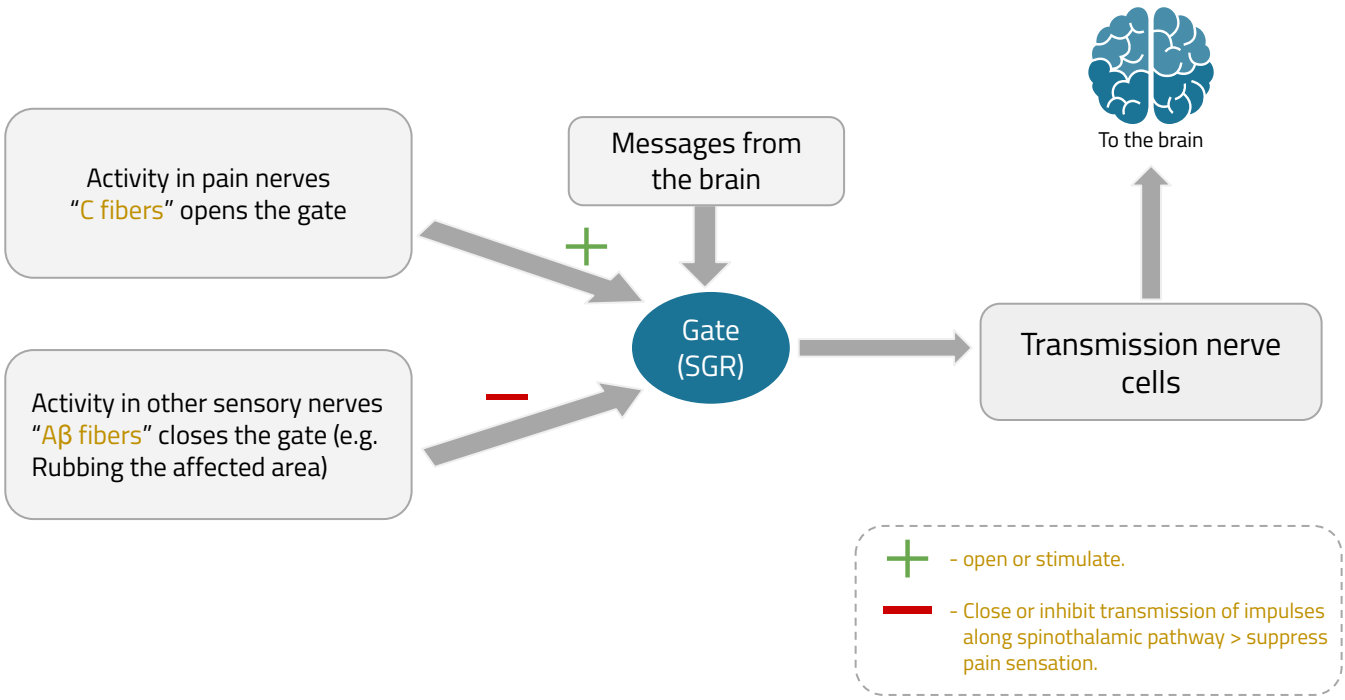
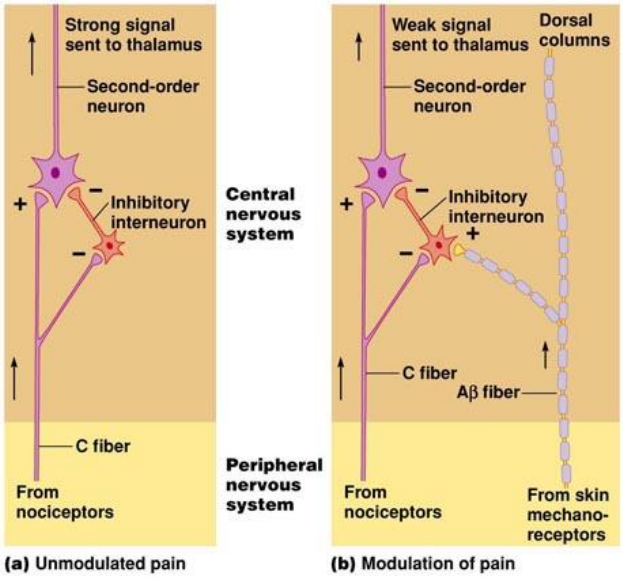
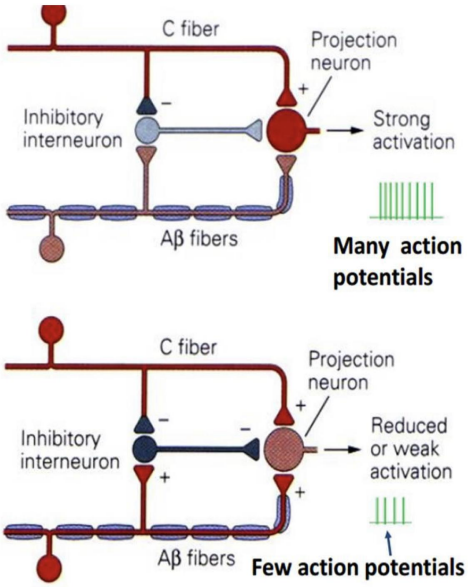


The gate theory of pain control (Cont.):

- Projection neuron receives input from both C-fibers and Aβ fibers.
- Impulses coming along type C pain fibers cause the release of "substance P" from these fibers and inhibits the inhibitory interneuron (open the gate).
- While impulses coming along Aβ fibers tend to keep the gate closed by activating the inhibitory interneuron.
- When pain and touch fibers are stimulated together, gate will be closed & pain is not felt.
- Implies a non-painful stimulus can block the transmission of a noxious stimulus.





(a): Stimulation of nociceptors > impulses carried along type c fibers > inhibition of the inhibitory interneuron > stimulation of the second order neuron > projection of pain up to cerebral cortex > pain perception.

(b): Type Aβ fibers (touch receptor) stimulated at the same time this will cause > stimulation of the inhibitory interneuron > so inhibit activation of second order neuron > inhibit pain transmission.

Gate Control Theory of Pain cont...:

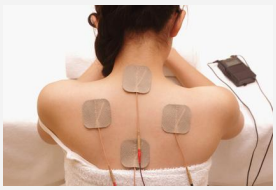
L28

The Gate Theory Explains The Pain Relief By:

1. Skin rubbing*

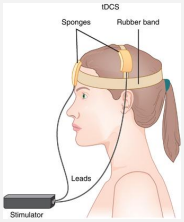
2. Shaking the painful part*

3. Transcutaneous Electrical Nerve Stimulation (TENS):



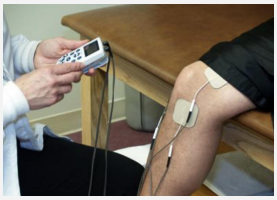
- The gate-control mechanism of pain modulation and serves as the rationale behind the use of transcutaneous electrical nerve stimulation (TENS) for pain relief.
- TENS uses electrodes to activate Aα and Aβ fibers in the vicinity of the injury.
- TENS stimulates sensory nerves to block pain signals, stimulate endorphin production to help normalize sympathetic function.

4. TRANSCRANIAL DIRECT CURRENT STIMULATION (TDCS):*



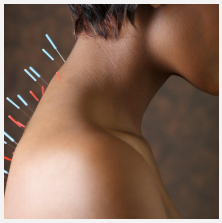
- It is a non-invasive procedure in which a device sends a small Direct Current (DC) across electrodes in the areas of interest on the scalp to modulate brain function.
- This current flow can increases or decreases the neuronal excitability in the specific area being stimulated, based on which type of stimulation.
- When the current passes from the anode to the cathode, it may increase the activity of the brain at the anode site and decrease the activity of the brain near the cathode site.

5. Interferential Stimulation:*



- Interferential Stimulation differs from TENS because it allows a deeper penetration by using two frequencies of the tissue with more comfort (compliance) and increased circulation.
- Stimulate parasympathetic nerve fibers for increased blood flow.

6. Acupuncture الإبر الصينية / Inhibition of Pain Transmission by Tactile Sensory Signals.*



- Stimulation of large type Aβ sensory fibers from peripheral tactile receptors depress transmission of pain signals from the same body area by lateral inhibition in the spinal cord.
- The simultaneous physical and psychogenic excitation of the central analgesia system is the basis of pain relief by acupuncture.
- The analgesic effect of electroacupuncture may involve the release of endogenous opioids and activation of descending pain modulatory pathway.

All are supposed to stimulate mechanoreceptors (Aβ fibers) that activate neurons of dorsal column, the collaterals (inhibitory interneurons) relieve pain*

Gate Control Theory of Pain cont...:

Central Control Trigger:*

- Specialised nerve impulses arise in the brain itself and travel down the spinal cord to influence the gate.
- It can send both inhibitory and excitatory (open or close the gate) messages to the gate sensitising it to either C or A-β fibres.
- The inhibitory neurons make a pain blocking agent called encephalin.
- Encephalin is an opiate substance which can block substance P, the neurotransmitter from the C fibers, and this keeps the gate closed.

Conditions That Open Or Close The Gate

	Conditions that open the gate	Conditions that close the gate
Physical Conditions	• Extent of the injury. • Inappropriate activity level.	• Medication. • Counterstimulation, e.g. massage.
Emotional Conditions	• Anxiety or worry. • Tension. • Depression.	• Positive emotions. • Relaxation. • Rest.
Mental Conditions	• Focusing on the pain. • Boredom.	• Intense concentration or distraction. • Involvement and interest in life activities.

Supra spinal modulation (Pain Suppression) (Special pain control analgesic system)

This is a specific system that blocks pain transmission in CNS. Its major constituents are:

The Periventricular & Periaqueductal Gray Areas:	- Enkephalin Neurons In the mesencephalon and upper pons. - It send signals to Raphe magnus nucleus. - These neurons surround portions of the third and fourth ventricles and the aqueduct of Sylvius.
Raphe Magnus Nucleus (RMN):	- A thin midline nucleus located in the lower pons and upper medulla. - From these nuclei, second-order neurons go down the dorsolateral columns in the spinal cord & secrete Serotonin which act on local neurons to secrete Enkephalin.
Pain inhibitory complex:	- In dorsal horn of spinal cord. - It consists of: multiple short enkephalinergic neurons that terminate on central endings of pain conducting afferent fibers. - When stimulated the release enkephalin cause pre & postsynaptic inhibition of pain transmission. presynaptic: inhibit release of NT by substance p. postsynaptic: by hyperpolarization.

Analgesia system of the brain and spinal cord, showing:*

(1) inhibition of incoming pain signals at the cord level.

(2) presence of enkephalin-secreting neurons that suppress pain signals in both the cord and the brain stem.

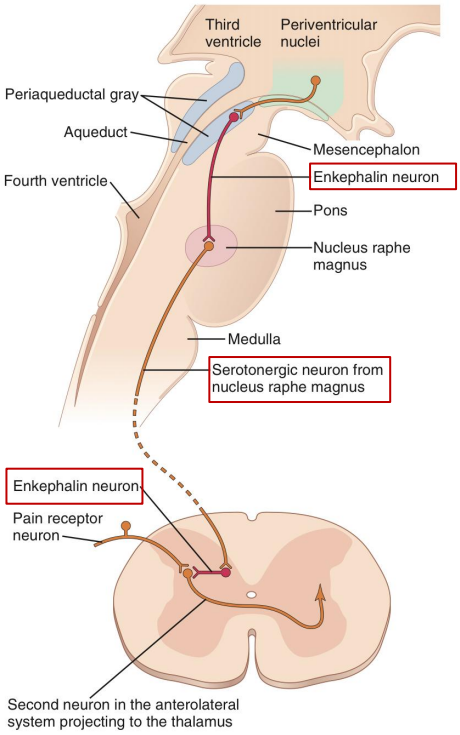


Figure 49-4. Analgesia system of the brain and spinal cord, showing (1) inhibition of incoming pain signals at the cord level and (2) presence of *enkephalin-secreting neurons* that suppress pain signals in both the cord and the brain stem.

Analgesia Occurs As Follows:*

1. Enkephalin neurons from PAG (periaqueductal gray) and periventricular areas send signals to RMN.
2. RMN projects serotonin- ergic neurons to dorsal horn.
3. Serotonin- ergic neurons act on local neurons (PIC) at dorsal horn to release encephalin.

At this point, the analgesia signals can block the pain before it is relayed to the brain.

Opioid Peptides and Pain Modulation*

- They are natural analgesic substances (morphine-like substances) present in body.
- They act by binding to opiate receptors in analgesic system and dorsal horn of SC on central ending of pain conducting pain fibers.
- E.g. endorphin, encephalin, dynorphin, endogenous morphine.
- Beta Endorphin is 50 times more potent than morphine and Dynorphin is 200 times more potent than pure morphine.

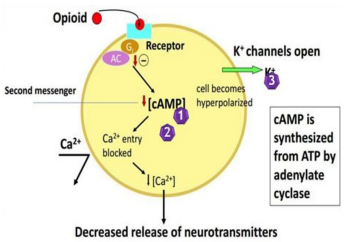
Mechanism of actions of Opioid peptides on pain transmission:*

They exerts their analgesic effects by acting at various sites in peripheral & CNS.

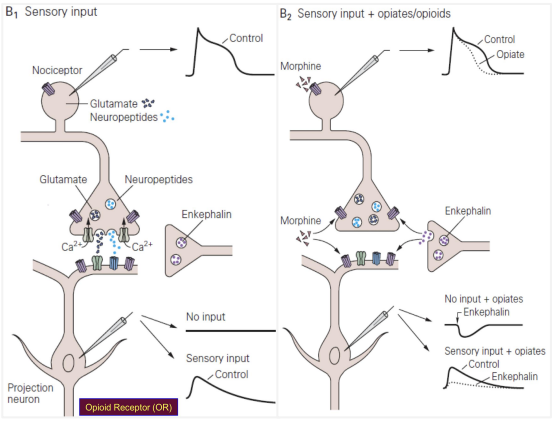
	Direct	Indirect
mechanism	- Inhibiting discharge of nociceptor neurons. - Inhibiting release of substance P from central terminal of nociceptor neurons. - Cause inhibition of dorsal horn spinothalamic neuron.	- Activating the descending inhibitory pathway be exciting periaqueductal grey neurons. - Activating neurons in the brain stem which release NE and serotonin which suppress pain transmission directly or indirectly via activation of enkephalinergic containing inhibitory interneurons.

Cellular Actions Of Opioid Peptides:

- Reduction of cAMP synthesis by inhibiting Adenyl cyclase. 1
- Inhibition of transmitter release by inhibiting opening of Ca++ channels. 2
- Hyperpolarization by facilitating opening of voltage gated K+ channels. 3



- Activation of the presynaptic opioid receptor leads to a decrease in Ca++ influx, resulting in a decrease in release of glutamate and substance P.
- Activation of the postsynaptic opioid receptor hyperpolarizes the dorsal horn interneuron by causing an increase in K+ conductance.
- Decrease duration of the EPSP in the dorsal horn neuron.
- Activation of opioid receptor on dorsal root ganglia cell bodies also contributes to reduced transmission from nociceptive afferents.

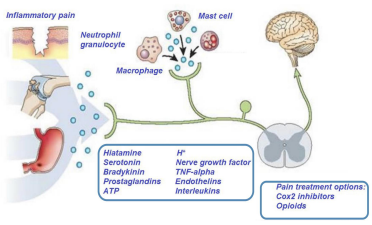


Pain Facilitation

Pain Facilitation

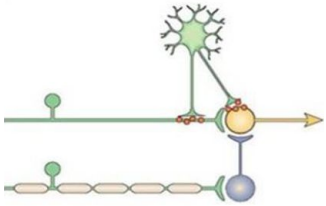
Peripheral Sensitization

Inflammatory mediators can directly activate nociceptors or cause their sensitization (decrease threshold as prostaglandins).

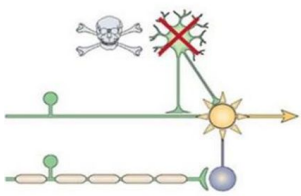


Dis-inhibition (Central)

Pain transmission is controlled by inhibitory interneurons



Loss of these inhibitory interneurons after excessive release of glutamate results in increased excitability of projection neurons (second order neurons of spinothalamic tracts) and thus enhanced pain sensation



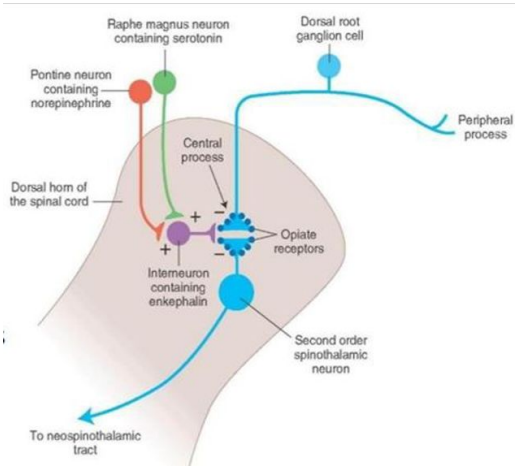
The whole page is on girls slide only.

Neurotransmitters for Pain Modulation

- **Serotonin**
- **Noradrenaline**
- **Encephalin**

- The serotonergic and noradrenergic neurons are crucial in the supraspinal modulation.

- Destroying these neurons with neurotoxins blocks their analgesic actions.



Terms frequently used :

Some Clinical Abnormalities of Pain and Other Somatic Sensations

Hyperalgesia

- Excessive Pain (e.g due to sunburn).
- Increased sensitivity to Pain.

Allodynia

- Pain caused by any other sensation (e.g. touch).
- A person feels pain from stimuli that don't normally cause pain due to central sensitization. For example, lightly touching your skin or brushing your hair might feel painful.
- clinical feature of many painful conditions, such as neuropathies,complex regional pain syndrome, postherpetic neuralgia, fibromyalgia, and migraine.

Causalgia

- Burning pain.
- It is chronic burning pain condition seen after the section (damage, cutting) of a nerve Triggered by a simple stimulus e.g. breeze or vibration.

Muscular Pain

Girls only

- Less blood flow in the muscles (ischemia). Lactic acid accumulation

Fibromyalgia: Pain Without Injury

Boys only

- The occurrence of body-wide pain in the absence of tissue damage, as in fibromyalgia, interferes with all aspects of a person's life and undermines their credibility.
- The problem is that normal activities can be exhausting, sleep is disturbed, the ability to concentrate is impaired, gastrointestinal function is often abnormal, persistent headaches are common, and the unrelenting pain that no one can see is often detrimental to their personal and professional lives--as it creates a "credibility gap."

Headache

Boys only

The brain tissues themselves are almost totally insensitive to pain.

Tugging on the venous sinuses around the brain, damaging the tentorium, or stretching the dura at the base of the brain can cause intense pain that is recognized as headache. Also, almost any type of traumatizing, crushing, or stretching stimulus to the blood vessels of the meninges can cause headache.

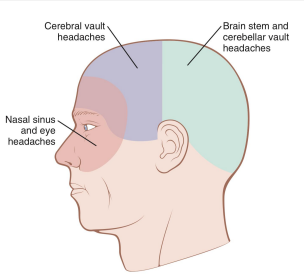


Figure 49-9. Areas of headache resulting from different causes.

Some Clinical Abnormalities of Pain and Other Somatic Sensations

Thalamic syndrome

It is a neurological condition that results from a brain stroke affecting the thalamus.*

- Obstruction of the thalamogeniculate branch of the posterior cerebral artery.
- Affects posterior thalamic nuclei.
- Prolonged severe pain with variable quality (Dejerine Roussy Syndrome).

Trigeminal neuralgia

Neuralgia: sharp pain along a nerve pathway (eg; Trigeminal N).*
Trigeminal neuralgia: It is excruciating intermittent pain by stimulation of trigger area in the face.*

- e.g. Washing of face, combing hair, blast of air on face.*
- It results from compression of trigeminal nerve root by blood vessels.*

Stress induced analgesia

Pain suppression response that occurs during or following exposure to a stressful or fearful stimulus.*

- It's a well known phenomenon seen when the soldier is wounded in battle field but feels no pain until the battle is over.
- Mild degree of pain is not felt if the other part of the body has excessive pain.
- The cause is not known, may be it is similar to gate control hypothesis.

Phantom pain sensations or Phantom limb pain

Impression of pressure and pain that an individual experiences relating to a limb or an organ that is not physically part of the body.

- Even if phantom limb is experienced as spatially detached from the body, it is still felt to belong to the patient.
- Our brain can reorganize at the ventral posterior thalamic nucleus if sensory input is cut off even after that part is amputated.
- Paraplegic people experience phantom limbs. They can even experience continually cycling legs.
- It is the emotional and motivational systems that cause the phantom limb experience.

Congenital Analgesia

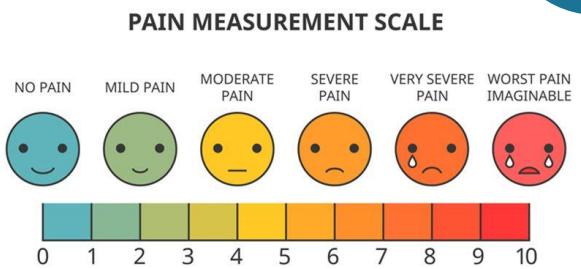
Congenital insensitivity to pain (CIP), also known as congenital analgesia, is one or more rare conditions in which a person can not feel (and has never felt) physical pain due to gene mutations.

- A well-known case of congenital insensitivity to pain is a girl referred to as 'Miss C' who was a student at McGill university in Montreal in the 1950s.
- She was normal in every way, except that she could not feel pain. When she was a child she had bitten off the tip of her tongue and had suffered third-degree burns by kneeling on a radiator.
- She did not feel any pain when she was given strong electric shocks or when exposed to very hot and very cold water. When these stimuli were presented to her she showed no change in heart rate, blood pressure or respiration.
- She died at the age of 29 as a result of her condition, because she damaged her knees, hips and spine

Boys only

PAIN SCALES*

- Visual Analog Scale.
- Locate area of pain on a picture.
- McGill pain questionnaire.
- Evaluate sensory, evaluative, & affective components of pain.
- 20 subcategories, 78 words.



Applied*

1. What will happen if sensory area SI is removed?

Ans. persons ability to interpret the quality of pain & precise location of pain will be affected.

2. Why patient with chronic pain syndrome have difficulty in sleeping?

Ans. Paleospinothalamic pathway sends information to reticular formation and thalamic nuclei which are part of brain activating / alerting system, therefore chronic pain syndrome causes difficulty in sleep.

Mechanism Of Pain Relief*

- Block production of inflammatory mediators .e.g. Aspirin & nonsteroidal anti-inflammatories.
- Exogenously administration of opioid like drugs. morphine
- Electrical stimulation of the dorsal column. Aβ fibers
- Selective activation of large diameter afferent fibers by transcutaneous electrical nerve stimulation.
- Stimulation of brainstem sites or administration of drugs which can modify serotoninergic or adrenergic neurons e.g. antidepressants.

Placebo Effect*

- Sometimes a person can have a response to a placebo (العلاج الوهمي). The response can be positive or negative. For instance, the person's symptoms may improve. Or the person may have what appears to be side effects from the treatment. These responses are known as the "placebo effect."

- Placebo stems from the Latin word for “I shall please”.
  - Used to describe pain reduction obtained from a mechanism other than those related to the physiological effects of the treatment.
  - Linked to **psychological mechanisms**.

- All Treatments TM have some degree of placebo effect.
  - Most studies involving the use of a sham treatment (ultrasound set at the intensity of 0) and an actual treatment have shown decreased levels of pain in each group.

MCQ & SAQ:

Q1: which of the following doesn't cause visceral pain:

A. inflammation.
B. ischemia.
C. cut.
D. distension.

Q2: The pathway that has C fibers as its 1st order neurons is responsible for:

A. 20% pain conduction, Slow pain.
B. 20% pain conduction, fast pain.
C. 80% pain conduction, Slow pain.
D. 80% pain conduction, fast pain.

Q3: Which of the following is responsible for the closure in gate control theory during its activity:

A. Aβ fibers.
B. C fibers.
C. Aδ fibers.
D. projection neuron.

Q4: Which of the following nerve fibers usually mediate nociception that is interpreted as sharp, easily localized pain?

A. A. A-alpha.
B. A-beta.
C. A-delta.
D. C.

Q5: Transformation of noxious stimuli into electrical signal called action potentials by peripheral A delta & C nerve fibers.

A. Transmission.
B. Modulation.
C. Perception.
D. Transduction.

Q6: A referred pain refers to:

A. Pain which experienced in part of the body other than where it originated.
B. Pain from a part of the body which has been amputated or otherwise removed.
C. Pain which psychological origin.
D. Pain which promotes immobilization.

answer key:
1: C
2: C
3: A
4: C
5: D
6: A

1-what is the role of the cerebral cortex in pain perception?

2- what are the variables that control the gate control theory?

A1: Slide 17

A2: 1- Type C fibers (slow pain) 2- Type A-β fibers (light touch) 3- inhibitory interneurons 4- projection neuron.

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