جامعة الملك سعود
King Saud University

MED437

16th Lecture | The Physiology Team

Physiology of the pain

Objectives:

- ***To know about the receptor of pain.***
- ***The types of neuron responsible for conduction of impulses e.g A-delta and C- types.***
- Mechanism of the pain
- ***Two types of pain e.g fast and slow.***
- ***Know the tracts involved and its functions.***
- ***Know the role of thalamus and cortex in the perception of pain.***

Bold & Italic objectives are included in the medical education guide
This lecture you have to check the questions !!

Done by:

- Team leaders: Fatima Balsharaf , Rahaf Alshammari, Abdulelah Aldossari, Ali Alammari.
- Team members: Renad alsuelmi,Abdullah Alzaid, Esra'a alnazzawi,Haifa Alessa,Ahad alGrain
- Special thanks for drawings : Sara AL Towireb

Colour index:
important
Numbers
Extra

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❖ Terminology

Terminology	Definition
Nociceptor (pain receptor)	primary afferent receptors that respond selectively to noxious stimuli.(subtype of sensory receptor)
spinothalamic tract	also known as anterolateral system or the ventrolateral system) is a sensory pathway from the skin to the thalamus
VP nucleus The ventral posterior nucleus.	is the somato-sensory relay nucleus in thalamus of the brain
topognosis	recognition of the location of a stimulus on the skin. Synonyms : topognosia
Sensory receptors	are specialized peripheral endings of primary afferent neurons.
Noxious stimulus	any stimulus (mechanical like exssive pressure , chemical exssive acidity or thermal exssive heat) that produces tissue damage or threatens to do so the oppisate (≠ innocuous).
Polymodal nociceptors:	respond to a combination of mechanical , chemical , thermal noxious stimuli.
Reception	Response of nerve receptors in the skin and tissues to stimuli resulting from actual or potential tissue damage. - when you only receive the pain
Perception	The process by which pain is recognized and interpreted by the brain.- when you are aware about the pain
Nociceptive pain	Is caused by the presence of a painful stimulus on nociceptors-
Neuropathic pain	Occurs as a result of damage to the nerve fibers with the pain impuls emanating from the nerve itself

❖ To know about the receptor of pain

Pain & Nociception

- What is nociception?
  Refers to the transmission of signals evoked by activation of nociceptors (pain receptors) from periphery to the CNS.
- What is pain?
  - Is perception of unpleasant sensation that originates from a specific body region.
  - Is an unpleasant sensory and emotional experience associated with actual or potential tissue damage.

Significance of pain: why do we feel pain?

If you don't feel pain, you won't protect yourself and try to escape from danger.

- It is a **protective mechanism** meant to make us aware that **tissue damage** is occurring or is about to occur:-
  1. Avoid noxious stimuli
  2. Remove body parts from danger like withdrwal reflex
  3. Promote healing by preventing further damage
  4. Storage of painful experiences in memory helps us to avoid potentially harmful event in the future

- The sensation of pain may be accompanied by behavioural"motor" responses (withdrawal, defense) as well as emotional responses (crying, anxiety or fear).

- Pain is perceived at both the **cortical** & **thalamic** levels "two levels" but grading, scaling and location are features of cerebral cortex.If someone does not have cerebral cortex , he won't describe the pain, he will just say that he feels pain.

To know about the receptor of pain

Pain receptors (nociceptors)

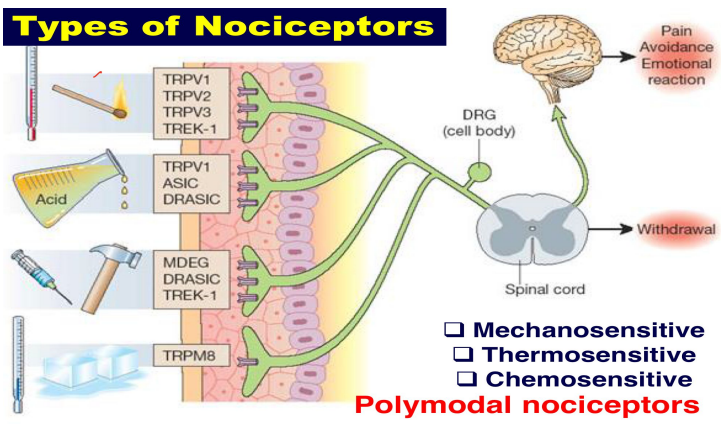
- Definition:

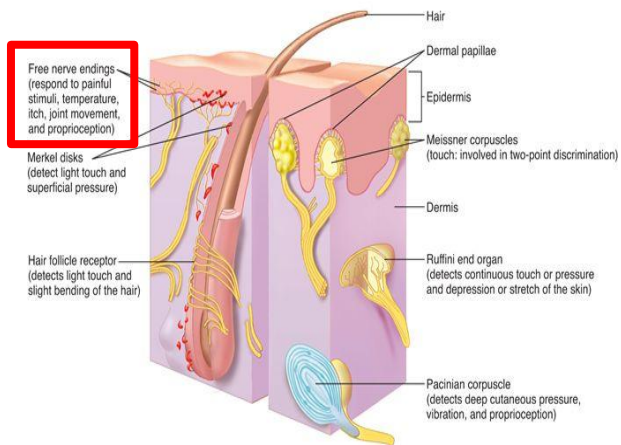
  '' Are special receptors that respond only **to noxious stimuli** and generate nerve impulses which the brain interprets as "pain".

- Pain receptors characteristics:
  - Pain receptors **are the most widely** distributed.
  - 1- Widespread in superficial layers of skin, 2- Fewer in deep tissue 3- absent in brain tissue
  - They are found in largest no. & density in skin, periosteum joint surface, arterial wall,skeletal muscle , parietal layer of serous membrane & duramatar.
  - It has a **protective** function
  - They are specific (have adequate stimulus) in that **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.
  - **Pain sensation can by various type of stimuli** mechanical , thermal , chemical will stimulate the pain receptor the strong stimuli will activate them
  - Localization of pain is less than other type of stimuli - it means we can point out exactly where is the pressure but the pain isn't.
  - **Do not adapt** (or very little) **to repetitive stimulation** (it allows the pain to keep the person apprised of a tissue-damaging stimulus as long as it persists.)
  - All pain receptors are **free nerve endings (is not enclosed in a capsule, Remember pacinian corpuscle is capsulated)**of unmyelinated **C** fibers & small 1 diameter and myelinated **Aδ** fibers.

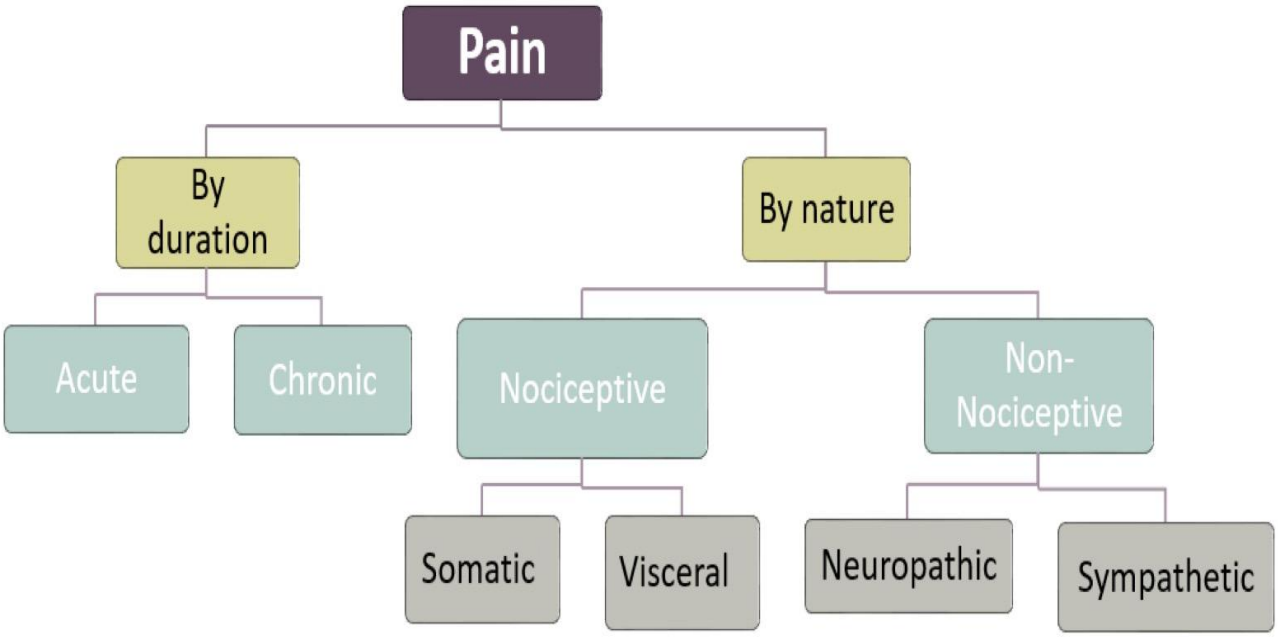
Pain receptors are activated by 3 types of stimuli:

1. **Mechanical** - they elicit fast pain. "Pen prick", cutting , crushing , firm pressure
2. **Thermal** - they elicit also fast pain. "Heat or cold"
3. **Chemical** - they produce slow pain. "Acids or chemical substances"

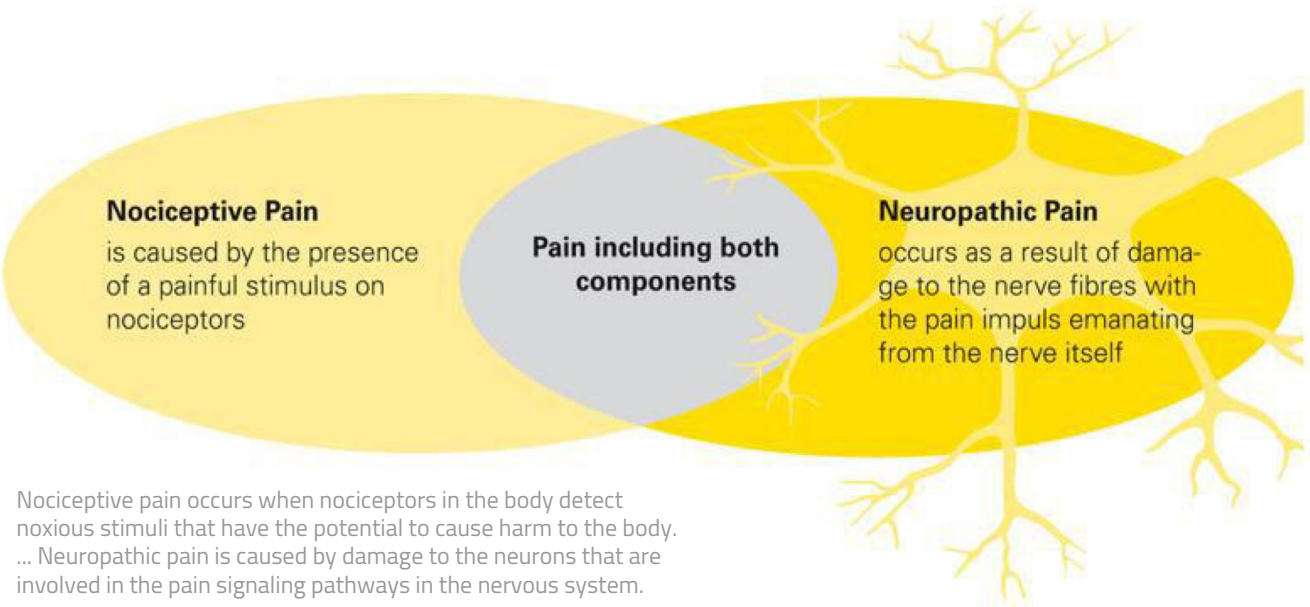




Types of pain



Classification of pain



Nociceptive pain occurs when nociceptors in the body detect noxious stimuli that have the potential to cause harm to the body. ... Neuropathic pain is caused by damage to the neurons that are involved in the pain signaling pathways in the nervous system.

1-Nociceptive Pain

- Sustained primarily by the nociceptive system
- Proportionate to the stimulation of the nociceptor"sharp or dull objects"
- When acute
  - Serves a protective function
  - Normal pain means proportional, localized and occurs at the time of damage
- Pathologic when chronic
- Responds to common analgesics

Examples: **acute burns, bone fracture, and other somatic and visceral pains.** **large fibers**

2-Neuropathic Pain

- Sustained by aberrant processes in PNS or CNS
- Disproportionate to the stimulation of nociceptor
- Serves no protective function
- Pathologic pain
- Resistant to common analgesics

Examples: **painful diabetic & peripheral neuropathies, deafferentation and sympathetically-maintained pains, nerve inflammation, compression**

small-medium fibers

3- **Idiopathic Pain**

No underlying lesion found yet, disproportionate to the degree of clinically discernible tissue injury

4- **Mixed Pain**

Eg; Failed low-back- surgery syndrome Complex regional pain syndrome

❖ Types of pain

Pain can be classified <u>according to the site of stimulation</u> into somatic or visceral

Somatic pain

superficial pain

- It arises from skin or other superficial structures.
- It occurs in 2 phase of **fast pricking** followed by **slow burning** pain.
- It can be **well localized**.
- It may be associated with motor, autonomic, emotional reactions.

Deep pain

- It originates from muscles, joints, periosteum, tendons & ligaments.
- It is **slow prolonged** conducted by type **C fibers**.
- It is **diffuse** (i.e. poorly localized).
- It can initiate reflex contraction of nearby muscles.
- It may be <u>referred</u> to other sites.
- It is caused by: trauma, bone fracture & inflammation, arthritis, muscle spasm & ischemia.

visceral pain

There are few pain receptors in most viscera

Some viscera are pain <u>insensitive</u> e.g. **liver parenchyma, lung alveoli, brain tissue, visceral layer of peritoneum, pleura and pericardium.**

Characters of visceral pain

- It is **slow** pain conducted by **C fibers** (pain arising from parietal peritoneum, pleura and pericardium is sharp, pricking type).
- It is **diffuse**, <u>poorly localized,</u> the patient feels pain arising from inside but he cannot pinpoint it exactly.
- It is often associated with nausea and **autonomic reactions**.
- It can be associated with **rigidity** of nearby muscles.
- It often **referred** to other sites.

Causes of visceral pain

1-Distension of a hollow organs 2-Inflammation of an organ.3-Ischemia e.g. pain due to myocardial ischemia.

N.B: Cutting, crushing are not painful when applied to viscera because the pain fibers are scanty, so whenever you cut , you will involve just few fibers. In contrasts, inflammation of viscera will cause distention of its wall that will involves broad pain fibers.

❖ Mechanism of stimulation of pain receptors (nociceptors)

- Pain receptors are depolarized either **directly** or through the **production** of pain producing substances from damaged tissues as a result of inflammation (also called inflammatory mediators) e.g. bradykinin, histamine, substance P, calcitonin generelated peptide (CGRP), interleukins, prostaglandins, K+ , Ach, proteolytic enzymes.

Chemical substances released during tissue damage

Substance	Potassium	Prostaglandins	Leukotrienes	Serotonin	Bradykinin	Histamine	Substance P*
Source	Damaged cells			Platelets	plasma	Mast cells	Primary nerve afferents

* is secreted by nerves and inflammatory cells such as macrophages, eosinophils, lymphocytes, and dendritic cells.

Pain Producers

Bradykinin, serotonin, Histamine, K+ ion, Acids, proteolytic enzymes. calcitonin gene-related peptide (CGRP), interleukins, Ach.

Pain Sensitizers

PGs & substance – P enhance the sensitivity of pain receptors. For instance, when a patch of your skin is burned , this area will be very sensitive.

Pain mechanism

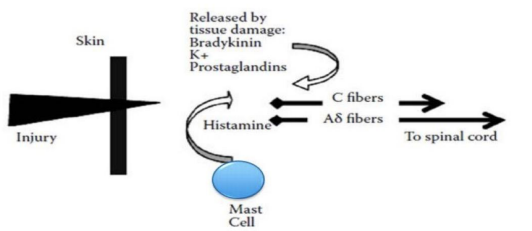
Injured tissue releases bradykinin and PG that activate nociceptors, which in turn release substance P. Substance P acts on mast cells to cause degranulation and release of histamine which also activates nociceptors. Substance P causes extravasation and CGRP dilates blood vessels which result in edema. Then, edema causes additional release of bradykinin. Serotonin (5-HT) is released from platelets and activates nociceptors.

Damage and inflammation → Release chemical mediators activate or sensitize the receptor endings

Cytokines, bradykinin, prostaglandin, Substance p → Results in transduction

Conduction of nerve impulse

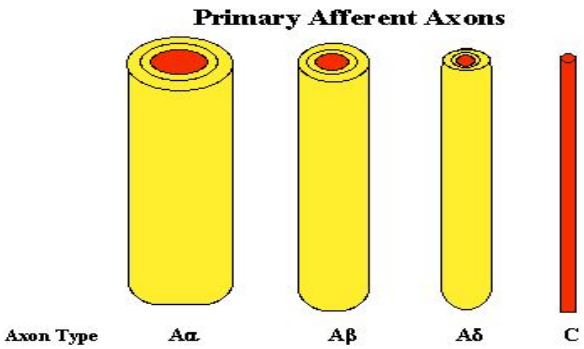
Histamine and substance P are also responsible of **edema and swelling.**



Some chemicals released by tissue damage that stimulates nociceptors. In addition release of substance-P, along with histamine, produce vasodilation and swelling.

The types of neuron responsible for conduction of impulses

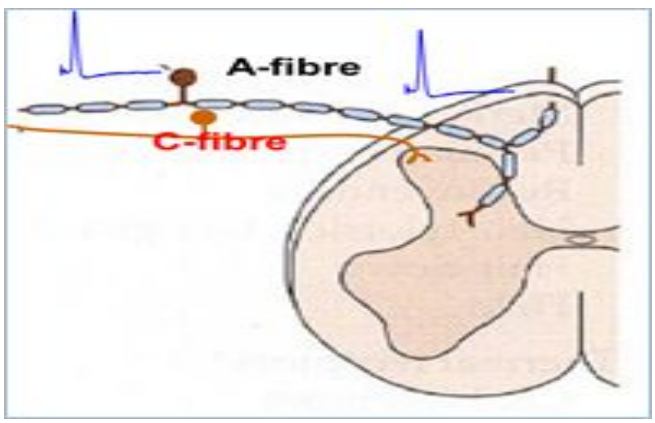
Classification of Nerve fibres



Type	I	II	III	IV
	Aα	Aβ	Aδ	C
Diameter (μm)	10-20	5-10	2-5	0.5-2
Conduction Velocity (m/s)	70-120 In dorsal column	30-70	5-30	0.5-2

Type-A & Type-C Fibers

Small	Medium	Large
< 30 μm	31-40 μm	> 40 μm
Nociceptors		Non-Nociceptors "Polymodal"



Qualities of the pain Important (phenomenon of double pain)

type	Fast pain	Slow pain
Also called	Fast/Sharp/immediate (1st) pain. Intense , pricking	slow/diffuse/delayed (2nd) pain Burning , aching , throbbing "unbearable " , dull , chronic pain
location	Usually Somatic not visceral	Can occur in skin or any internal organ\tissue.
onset	Very rapid felt within 0.1 sec	Slow felt after 1 second or more
Associated with:	Reflex withdrawal.	Destruction of tissue.
Localization:	Well localized	Diffuse (poorly localized) Responsible for"Emotional aspect pain" → misery
Fiber (mediated by:)	Type Aδ fibers nociceptors	Type C fibers nociceptors.
Terminate at:	I and V laminas	II and III laminas.
NT:	Glutamate	Substance P

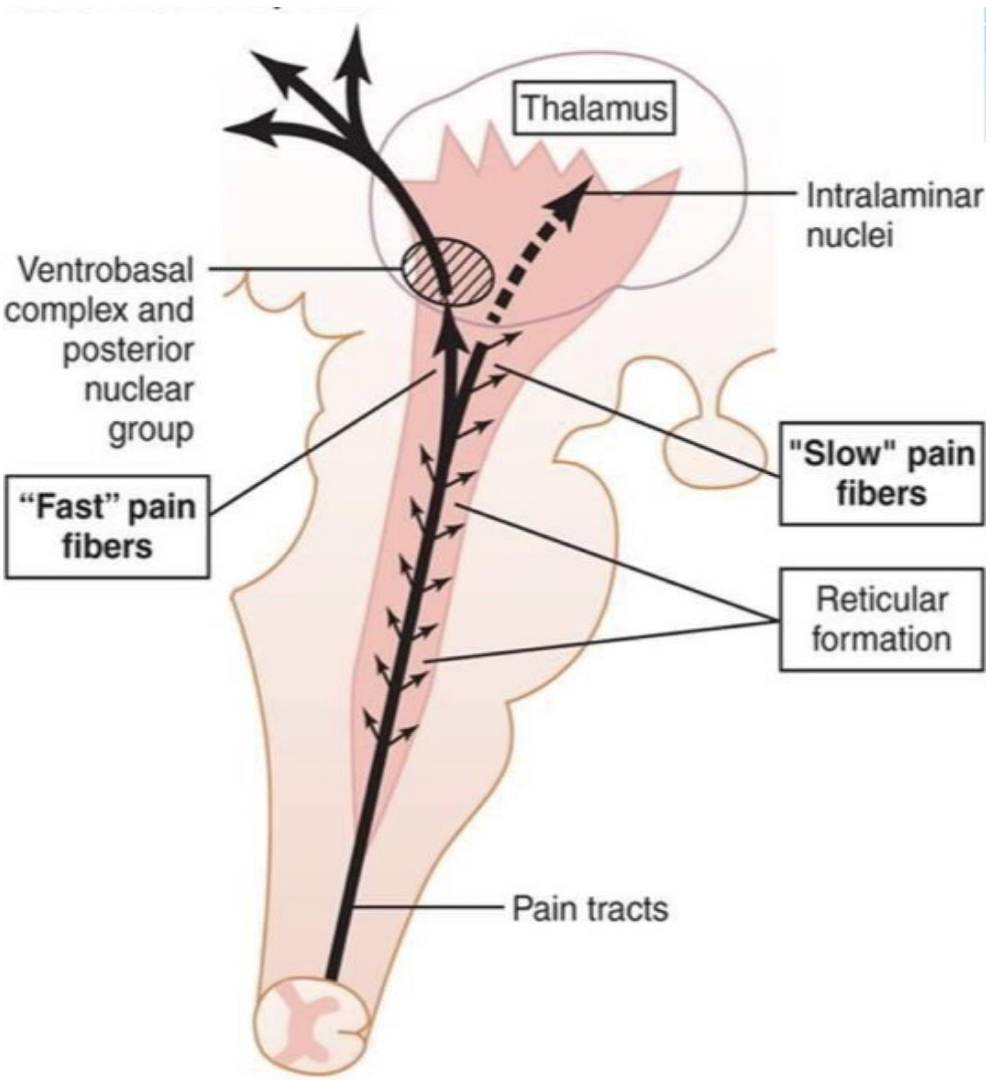
Pathway of pain

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

	The neospinothalamic pathway	**The paleospinothalamic pathway:**
Transmits	This transmits **fast** pain.	this transmit **slow** pain sensation.
1st neurone	Are mainly **A** afferent nerves. They terminate at lamina **I & V** of dorsal horn.	They are mainly type **C** fibers. They enter spinal cord via dorsal roots, terminate at **substantia gelatinosa in laminae II & III** of dorsal horn(substantia gelatinosa).
2nd neurone	These constitute the tract. They start at dorsal horn, cross to opposite side and ascend in lateral column of spinal cord. The fibers ascend in brain stem to terminate in **ventrobasal complex** of thalamus.	• They start at SGR(Substantia gelatinosa of rolando), cross to opposite side in front of central canal, ascend in lateral column of SC & **terminate at:** **- Reticular formation of brain stem.** **- Intralaminar nuclei of thalamus.** **- Hypothalamus & adjacent region of basal brain.** Impulses arriving these regions have strong arousal effects and can be perceived.
3rd neurone	These start at thalamus & **most** fibers project to **somatosensory cortex.**	- These start at thalamus, - **Few** fibers project to **cerebral cortex.(somatosensory)**

❖ Know the role of thalamus and cortex in the perception of pain.

- Full perception of pain occurs when signals enter Reticular formation of brain stem, thalamus & basal regions.
- Somatosensory cortex plays important role in **topognosis** i.e. localization & interpretation of pain quality.
- **Fast pain is localized** better than **slow pain** because signals carried in **neospinothalamic tract** reach **somatosensory cortex**, while a small proportion of paleospinothalamic pathway reach there"usually terminates at thalamus".
- Most of the slow pain fibers project to reticular formation & then proceed to thalamus (posterior nuclei) .
- Reticular system project to all parts of brain "especially slow pain" but specially to cerebral cortex therefore they cause arousal from sleep.



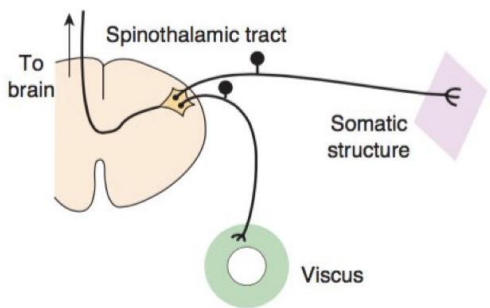
Referred Pain

- This is pain that is felt away from its original site.
- It is most frequent with visceral pain & deep somatic pain but **cutaneous pain is not referred.**
- Pain is referred according to dermatomal rule.
- When pain is both localized and referred it is called **radiating pain**

Convergence theory

- Afferent pain fibers from skin area & diseased viscera that develop from **same embryonic segment** converge on 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 nociceptive stimuli originate more frequently

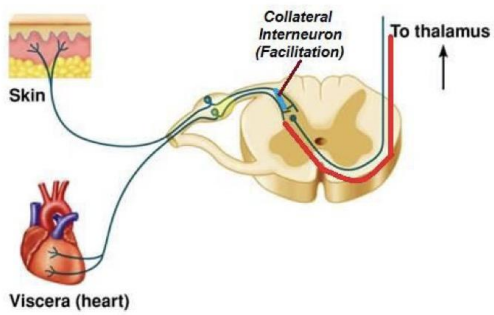
Afferent fiber that come from the skin and the afferent fiber that come from the diseased viscus (both developed from the same embryonic segment) have distinct first order neuron, both of the fibers will synapse on the same second order neuron "converge" and finally stimulate the same neuron in the cortex.- The brain misinterprets the information (thinking that the inputs come from the skin rather than the diseased viscus because normally the nociceptive stimuli originating more frequently in the skin) resulting in feeling the pain in the original site of the stimulus (viscera) and the skin (referred pain)



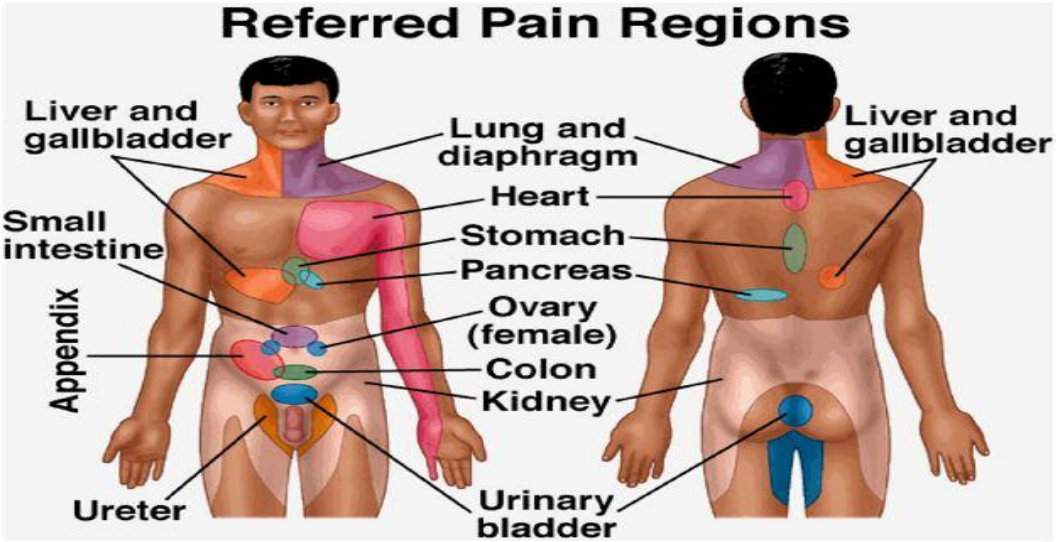
Facilitation theory

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

Normally, pain afferent fibers of the skin are always sending impulses but not enough to produce pain.
- What happens then ?
visceral afferent pain fibers give collaterals to the neuron that receives pain from a certain area of the skin (viscera and the area of skin that developed from the same embryonic segment). - So when there is impulses coming from the diseased viscera through visceral afferent pain fibers, it well raise the excitability of the neuron that receive pain from the skin to reach the threshold
level → signals will reach the brain and projected to the skin causing pain



Types of pain

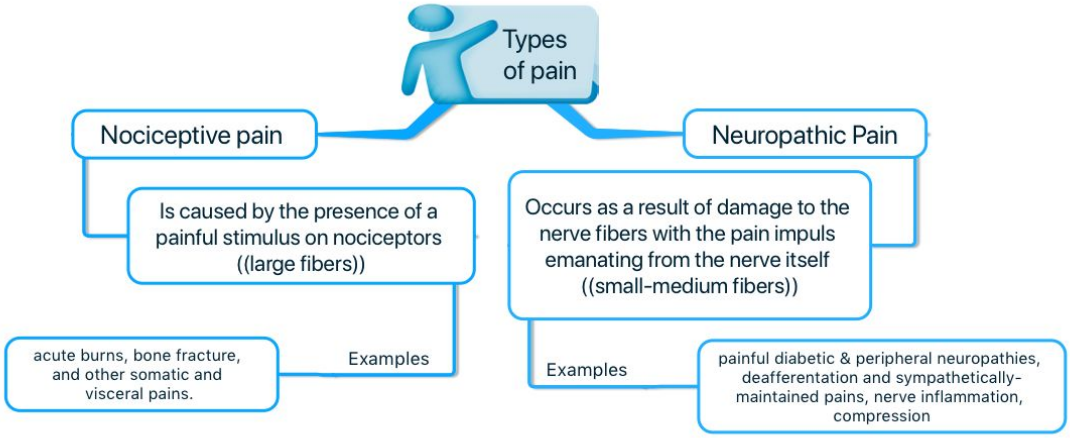


Organ	Site of referred pain
Meninges	Back of head &neck
Heart	Central chest, left inner side arm,Jaw,left shoulder
Diaphragm	Shoulder tip
Esophagus	Behind sternum
Stomach, duodenum	Epigastrium
Small bowel, pancreas	Around umbilicus
Large bowel, bladder	Lower abdomen
Kidney	Loin
Ureter	Testicles
Trigone of bladder	Tip of penis
Hip	Knee
Uterus	Low back
Appendix	Umbilicus

Quick review

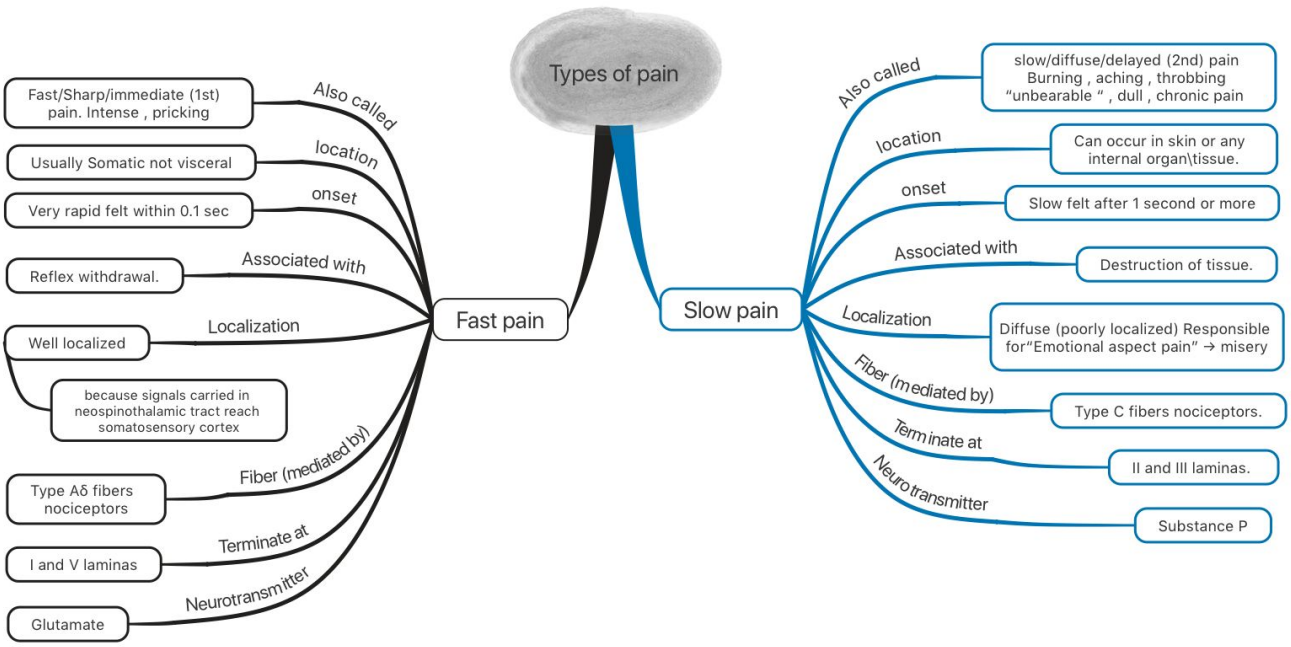
PAIN

- Is perception of unpleasant sensation that originates from a specific body region.
- is perceived at both the **cortical** & **thalamic** levels "two levels" but grading, scaling and location are features of cerebral cortex.



NOCICEPTION

- Refers to the transmission of signals evoked by activation of nociceptors (pain receptors) from periphery to the CNS.
- **Do not adapt** (or very little) **to repetitive stimulation**
- All are **free nerve endings** **(is not enclosed in a capsule, Remember pacinian corpuscle is capsulated)**



- Pain Producers Bradykinin, serotonin, Histamine, K+ ion, Acids, proteolytic enzymes. calcitonin gene-related peptide (CGRP), interleukins, Ach.
- Sensitizers PGs & substance – P enhance the sensitivity of pain receptors.
- When pain is both localized and referred it is called **radiating pain**

1. **Pain receptors in the skin are typically classified as which of the following?**
A)Encapsulated nerve endings. B) A single class of morphologically specialized
C)he same type of receptor that detects position D) Free nerve endings

2.**A 43-year-old man sustained a lower back injury that causes severe chronic pain. His physician prescribes benzodiazepine sedation medications to help him sleep. Which response best describes why this man has difficulty sleeping without medication?**
A)Depression of the amygdala B) Depression of reticular formation
C)Excitation of the amygdala D) Excitation of reticular formation
E) Loss of somatic sensations F) Loss of visceral sensations

3.**Which substance enhances the sensitivity of pain receptors but does not directly excite them?**
A) Bradykinin. B) Serotonin. C) Potassium ions. D) Prostaglandins.

4. **Which of the following is an important functional parameter of pain receptors?**
A) Exhibit little or no adaptation B) Not affected by muscle tension
C) Signal only lexion at joint capsules D) Can voluntarily be inhibited

5.**Which of the following substances is not considered mainly as a pain producer?**A)Substance P B)Leukotrienes C)Potassium ions D) Histamine

6**. Pain from the stomach is referred to which area of the body?**
A) Upper right shoulder area
B) Abdominal area above the umbilicus
C) Proximal area of the anterior and inner thigh
D) Abdominal area below the umbilicus

7. **Which of the following is the basis for referred pain?**
A) Visceral pain signals and pain signals from the skin synapse with separate populations of neurons in the dorsal horn.
B) Visceral pain transmission and pain transmission synapse with separate populations of neurons in the dorsal horn from the skin are received by a common set of neurons in the thalamus.
C)Visceral pain signals are rarely of sufficient magnitude to exceed the threshold of activation of dorsal horn neurons.
D) Some visceral pain signals and pain signals from the skin provide convergent input to a common set of neurons in the dorsal horn.

8.**Which statement concerning visceral pain signals is correct?**
A) They are transmitted along sensory fibers that course mainly with sympathetic nerves in the abdomen and thorax
B) They are not stimulated by ischemia in visceral organs
C) They are transmitted only by the lightly myelinated δ-type A sensory fibers
D) They are typically well localized

1)D
2)D
3)D
4)A
5)A
6)B
7)D
8)A

SAQ: Please fill up the gaps on the table below which is comparison between fast and slow pains?!

type	Fast pain	Slow pain
Also called		
onset		
Localization:		
Fiber (mediated by:)		
Terminate at:		
NT:		

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

person's 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?

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.