PHYSIOLOGY OF 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**.
- 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.

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*Please check out this link before viewing the file to know if there are any additions or changes.

Introduction (Guyton 12th edition Page 583)

❖ 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.
- For a scientific and clinical purposes, pain is defined by the international association for the study of pain (IASP) as:

" An unpleasant sensory and emotional experience associated with actual or potential tissue damage"

❖ 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 helps us to avoid potentially harmful event in the future

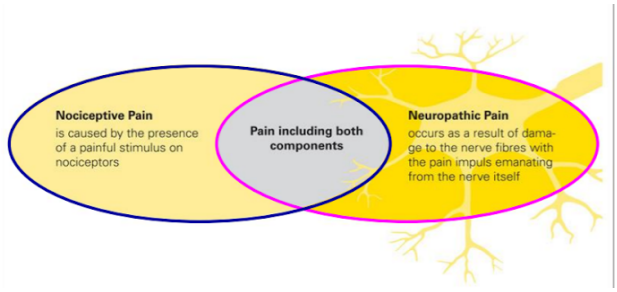
- The sensation of pain may be accompanied by **behavioural responses** (withdrawal, defense) as well as emotional responses (crying, anxiety or fear).
- Pain is perceived at both the **cortical & thalamic** levels.

❖ Definitions:

Sensory receptors	are specialized peripheral endings of primary afferent neurons.

Nociceptors (pain receptors)	primary afferent receptors that respond selectively to noxious stimuli. Nociceptors are subtype of sensory receptor.
Noxious stimulus	any stimulus (mechanical, chemical or thermal) that produces tissue damage or threatens to do so (≠ innocuous). mechanical:e.g. excessive pressure chemical:e.g. excessive acidity thermal : excessive heat
Polymodal nociceptors	respond to various noxious stimuli.

❖ Nociceptive and neuropathic pain:



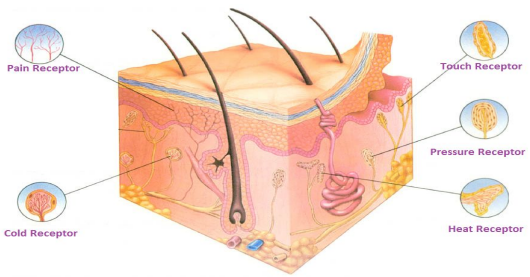
Pain receptors (Guyton 12th edition Page 583)

❖ Definition :

Are special receptors that respond **only to noxious stimuli** and generate nerve impulses which the brain interprets as "pain". (*sherringoton* 1906).

they are specific receptors only for pain sensation different from touch and temperature receptors

❖ Distribution of pain receptor :

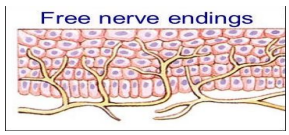


1) **Widespread** in **superficial** layers of **skin**
2) **Fewer** in **deep tissue**
3) **absent** in **brain** tissue

❖ Pain receptors characteristics:

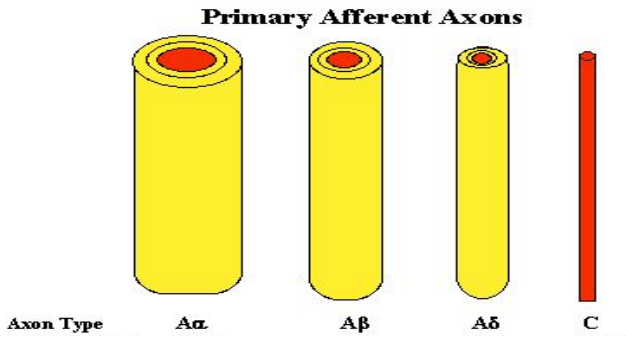
- It has a **protective** function.
- Pain receptors are the most **widely** distributed.

- Pain receptors are **specific** (have adequate stimulus) pain is not produced by overstimulation of the other receptors.
- Pain sensation can be produced by **various types** of stimuli i.e. mechanical, thermal & chemical. Not the normal mechanical, thermal or chemical stimuli will stimulate the pain receptors, the strong stimuli will activate them.
- Pain receptors **don't 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.
- Localization of pain stimuli is **less** exact than that of other modalities.
- Pain receptors are **high threshold** receptors i.e. painful stimuli must be strong & noxious to produce tissue damage.



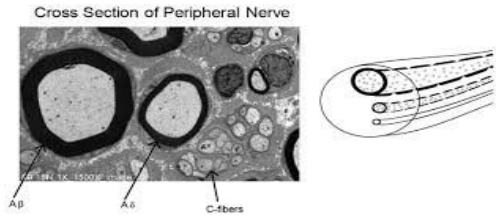
- All pain receptors are free nerve endings[1] of unmyelinated C fibers & small diameter myelinated A δ fibers.

❖ Classification of nerve fibers:



Type	I	II	III	IV
	A α	**A β**	**A δ**	**C**
Diameter (µm)	10-20	5-10	2-5	0.5-2
Conduction Velocity (m/s)	70-120	30-70	5-30	0.5-2

❖ Type A and type C fibers :



[1] A receptor nerve endings that is not enclosed in a capsule , atypical free nerve ending consists of a bare axon that may be myelinated or unmyelinated, they are widespread in the superficial layers of the skin, as well as in certain internal tissue.

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

Reception and perception

Reception:	Perception[2]
Response of nerve receptors in the skin and tissues to stimuli resulting from actual or potential tissue damage.	The process by which pain is recognized and interpreted by the brain. The point at which a person experiences pain.

Reception: when you only receive the pain

perception : when you are conscious about this pain

Mechanism of stimulation of pain receptors (nociceptors)

- Pain receptors are **depolarized** either **directly** or through the production of pain producing substances, produced from damaged tissues as a result of inflammation (also called **inflammatory mediators**) e.g. **bradykinin**, **serotonin**, **histamine**, **interleukins**, **substance [3]P**, **K+** , **Ach**, **proteolytic enzymes, calcitonin gene related peptide (CGRP), prostaglandins**.
- Prostaglandins and interleukins lower threshold of pain receptors.

Substance	Potassium	Prostaglandins	Leukotrienes	Serotonin	Bradykinin	Histamine	Substance P

[2] The ability to see, hear, or become aware of something through the senses (الإدراك).
[3] Substance P (SP) is secreted by nerves and inflammatory cells such as macrophages, eosinophils, lymphocytes, and dendritic cells.

Source:	Damaged cells	Platelets	Plasma	Mast cells	Primary nerve afferents

❖ Pain mechanism

Damage and inflammation → release chemical mediators activate or sensitize the receptor endings → cytokines, bradykinin, prostaglandins, and substance P are released → result in transduction → conduction of nerve impulses.

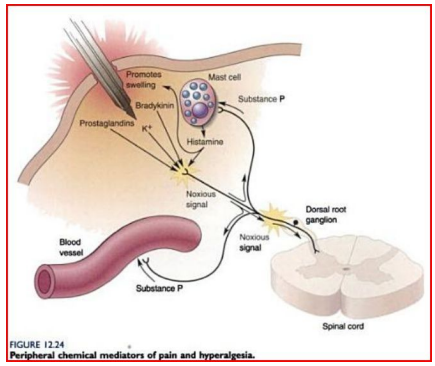
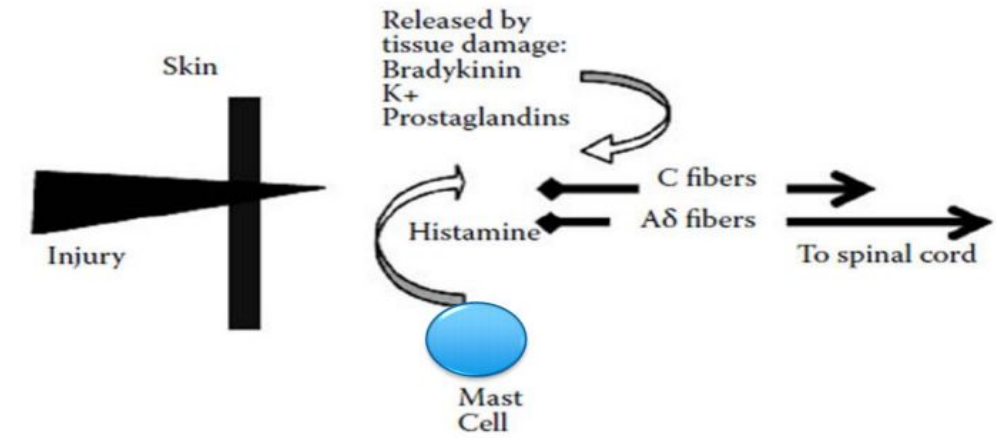


FIGURE 12.24
Peripheral chemical mediators of pain and hyperalgesia.

★ Explanation

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 releasing 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.



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

Classification of pain:

❖ Qualities of the pain (phenomenon of double pain):

type	**Fast** (1st) **pain** (immediate - fast)	**Slow** (2nd) **pain** (delayed or second)
Also called	Acute, **sharp, intense, pricking** or	**Burning**, aching, **diffuse**, dull,

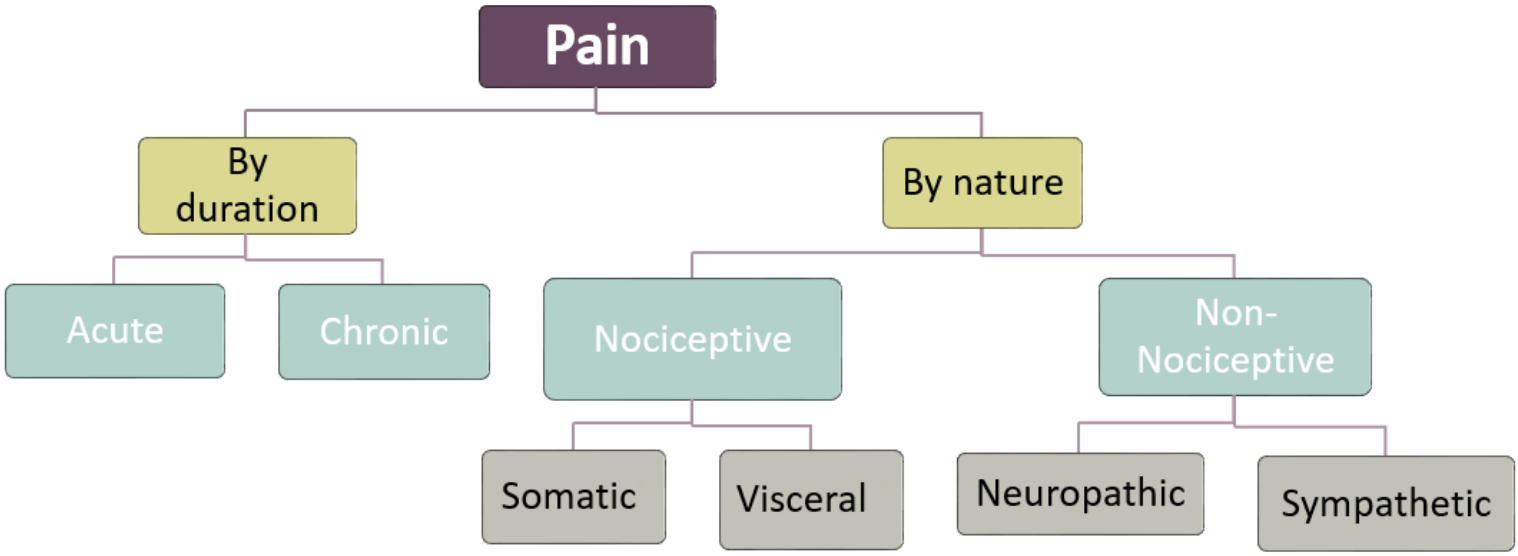
	electric pain.	throbbing "unbearable" or chronic.
Location:	Usually Somatic not visceral.	Can occur in skin or any internal organ\tissue.
Onset:	Very rapid felt within 0.1 sec, and lasts for short time	Slow felt after 1 second or more, and lasts for longer duration
Associated with:	Reflex withdrawal.	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.

❖ According to the site of stimulation:

1- Somatic pain.		2-Visceral Pain.
A. Superficial pain	**B. Deep pain**	
It arises from the skin or any other superficial structures.	It originates from: - muscles - joints - periosteum - Tendons - ligaments.	There are few pain receptors in most viscera. - some viscera are pain **in**sensitive, **for example:** Liver parenchyma, lung alveoli, brain tissue, **visceral** layer of peritoneum, pleura and pericardium.

It occurs in 2 phase of **fast pricking followed** by **slow burning pain**.	It is **slow prolonged** conducted by **type C fibers**.	Slow pain conducted by **C fibers.** **(**Pain arising from **parietal peritoneum**, pleura and pericardium are **sharp-pricking type)** **Pain in theses areas is conducted via Aδ fibres.**
Well **localized**	**Diffuse** (poorly localized[4]) and it may be referred to other sites.	**- Diffuse** (poorly localized). The patient feels the pain arising from inside but he cannot pinpoint it exactly - It often referred.
It may be associated with: **motor**, **autonomic** and **emotional reactions**.	**It can initiate:** Reflex contraction of nearby muscles.	**It's often associated with** **nausea** and **autonomic reaction**, and can be associated with **rigidity** of nearby muscles.
	It is caused by: - trauma, - bone fracture and inflammation. - Arthritis. - muscle spasm. - Ischemia.	**Casues:** - Destination[5] of a hollow organs[6]. - Inflammation of an organ. - Ischemia e.g. pain due to myocardial ischemia. - Cutting, crushing are not painful when applied to viscera.

[4] You can not tell the site of pain exactly .
[5] The state of being distended, stretched out, or enlarge.
[6] A visceral organ that is a hollow tube or pouch (as the stomach or intestine) or that includes a cavity (as of the heart or bladder) which subserves a vital function.



Referred pain (Guyton 12th edition Page 588)

❖ **What does "referred pain" mean?**

It is the pain that is felt away from its original site.

❖ **Most frequent with:** visceral pain & deep somatic pain but cutaneous pain is not referred.مثلا لما يوجعك كتفك ما يصلح تقولين اكيد هذا اللم ريفيرد بسبب اصبع رجلي المنجرح

-Pain is referred according to **dermatomal rule**.

When pain is referred, it is usually to a structure that developed from the same embryonic segment or dermatome as the structure in which the pain originates.

❖ **Examples:**

Knowledge of the common sites of pain referral from each of the visceral organs is of importance to a clinician, some of the best-known examples are:

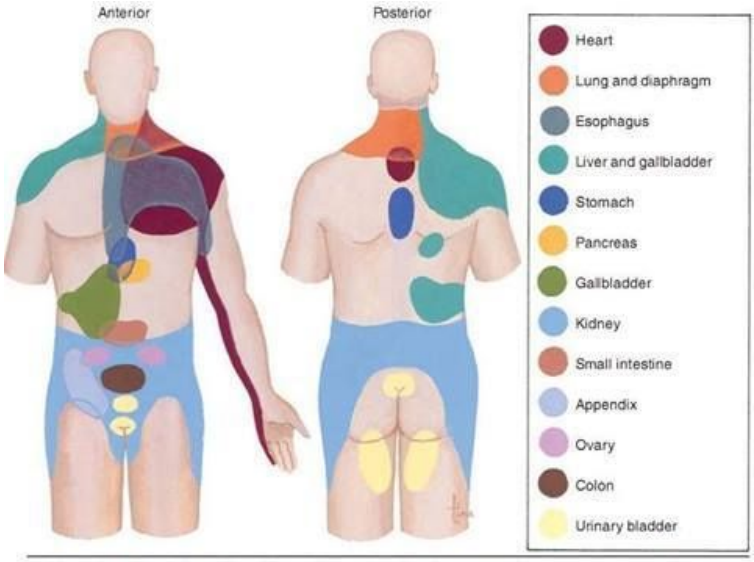
- **Cardiac pain** is referred to the **jaw**, **left shoulder** & **inner side of left arm**.

Because the heart and the arm have the same segmental origin.

neck, Jaw, shoulder or left arm pain :اللي كان منها clinical feature of MI تذكروها من الـ

- **Pain of appendicitis** is referred to **periumbilical** region.
- **Pain from the ureter** is referred to **testicular** region.

Because the testicle has migrated with its nerve supply from the primitive urogenital ridge, from which the kidney and ureter have developed.



Referred pain. The sites for referred pain from various organs are shown.

Another examples:

organ :	Site of referred pain:	organ :	Site of referred pain:
Meninges	Back of head & neck	Ureter	Testicles
Heart	Central chest, left arm	Trigon of bladder	Tip of penis
Diaphragm	Shoulder tip	Hip	Knee
Esophagus	Behind sternum	Appendix	Umbilicus
Stomach, duodenum	Epigastrium	Uterus	Low back عشان كذا لما تجيك الدورة تحسين بألم اسفل ظهرك
Small bowel, pancreas	Around umbilicus	Kidney	Loin
Large bowel, bladder	Lower abdomen		

❖ Mechanism of referred pain :

1. 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 have been arising from cutaneous nociceptors, because this is where nociceptive stimuli originate more frequently.

★ **Explanation:**

- 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)

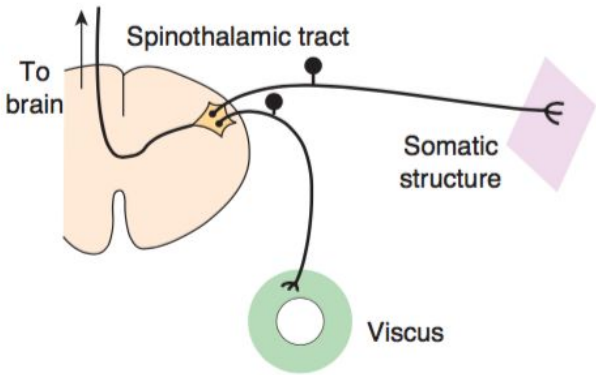


Diagram of the way in which convergence of somatic and visceral nociceptive fibers in lamina VII of the dorsal horn may cause referred pain.

2. Facilitation theory:

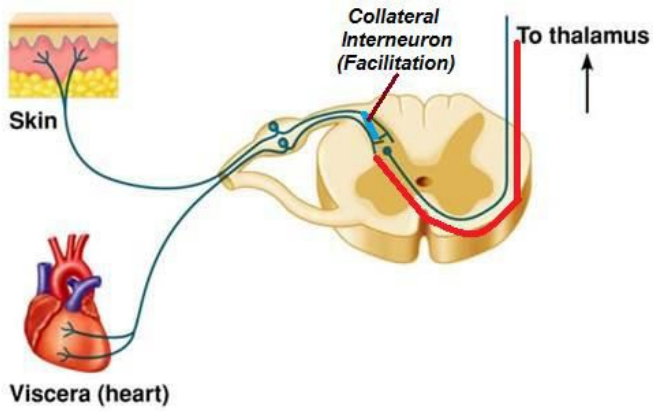
- Afferent pain fibers from skin are always carrying impulses, not enough to produce pain, so impulses from diseased viscus pass through afferents which give collaterals to ST neurons receiving pain fibers from skin.
- As a result, ST[7] neurons' excitability is raised (they are facilitated) to reach a threshold level.
- The signals reaching the brain are projected to skin area and pain is felt in skin dermatome.

★ **Explanation:**

- Normally, pain afferent fibers of the skin are always sending impulses but not enough to produce pain.
- What happens then ?

[7] Somatic tract.

- 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



Pain pathways (Guyton 12th edition Page 584)

Pain sensation is carried by **lateral spinothalamic tracts**[8] which includes 2 separate pathways:-

	Neospinothalamic pathway.	Paleospinothalamic pathway.
Trans mits	Fast pain.	Slow pain.
1st order neuron	- Mainly **A δ** afferent fibers. - Terminate at lamina **I & V** of dorsal horn.	- Mainly type **C** fibers. - Enter the spinal cord via dorsal roots. - Terminate at **substantia gelatinosa** in laminae **II and III** of dorsal horn.
2nd order neuron	-These constitute the tract - Start at the dorsal horn, cross to the opposite side, then ascend in lateral column of spinal cord. - The fibers ascend in the	- Start at SGR[9], cross to opposite side in front of central canal, then ascend in lateral column of spinal cord. **- Terminate at:** * Reticular formation of the brain stem.

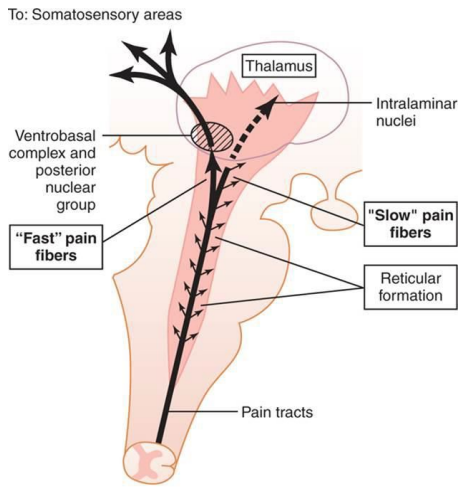
[8] A bundle of nerve fibres that have a common origin, common pathway (in the spinal cord), and common termination in the somatic area of the brain.
[9] Substantia gelatinosa of rolando.

	brainstem and **terminate in ventrobasal complex of thalamus**.	*Intralaminar nuclei of thalamus. * Hypothalamus & adjacent region of basal brain. Impulses arriving these regions have strong arousal effects and can be perceived.
3rd order neuron	- Starts at thalamus. - **Most** fibers Projects to **somatosensory cortex**.	- Starts at thalamus. - Few fibers Project to **all parts of cerebral cortex.** - few fibers to somatosensory cortex

Role of thalamus and cerebral cortex in pain perception (Guyton 12th edition Page 586)

- Full perception of pain occurs when signals enter **reticular formation** of brainstem, **thalamus** and **basal regions**.
- The **somatosensory cortex** is important for topognosis[10] i.e**. localization and interpretation of pain quality**.
- Fast pain is localized <u>better than</u> slow pain.. **Why?**

because signals carried in neospinothalamic tract reach somatosensory cortex, while a small proportion of paleospinothalamic pathway reach there



★ References:

- 435 girls slides and notes.
- Guyton and hall textbook of medical physiology - 12th edition.
- Ganong's review of medical physiology.

[10] Recognition of the location of a stimulus on the skin.