A pain control(Analgesia) system in the brain and spinal cord

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Objectives of the lecture

After the lectures student should be able to:

To know about the receptor of pain.

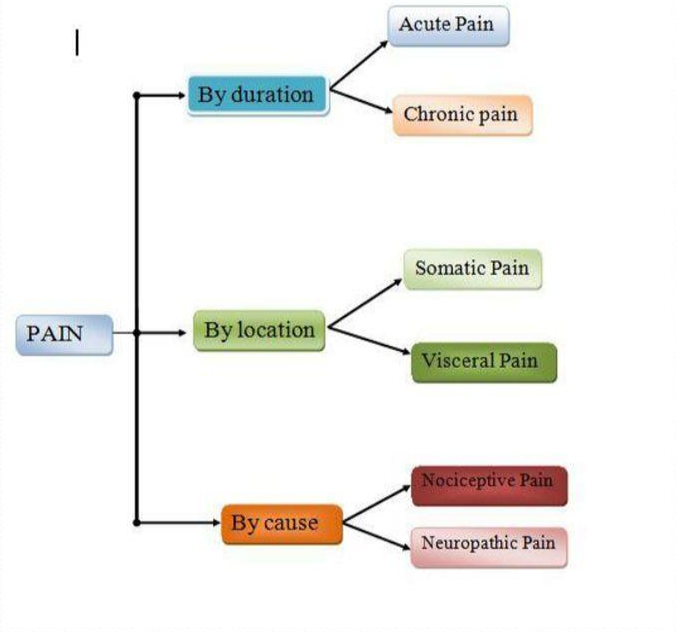
The types of neuron responsible for conduction of impulses e.g A-delta and C- types.

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

Classification of Pain Cont'd

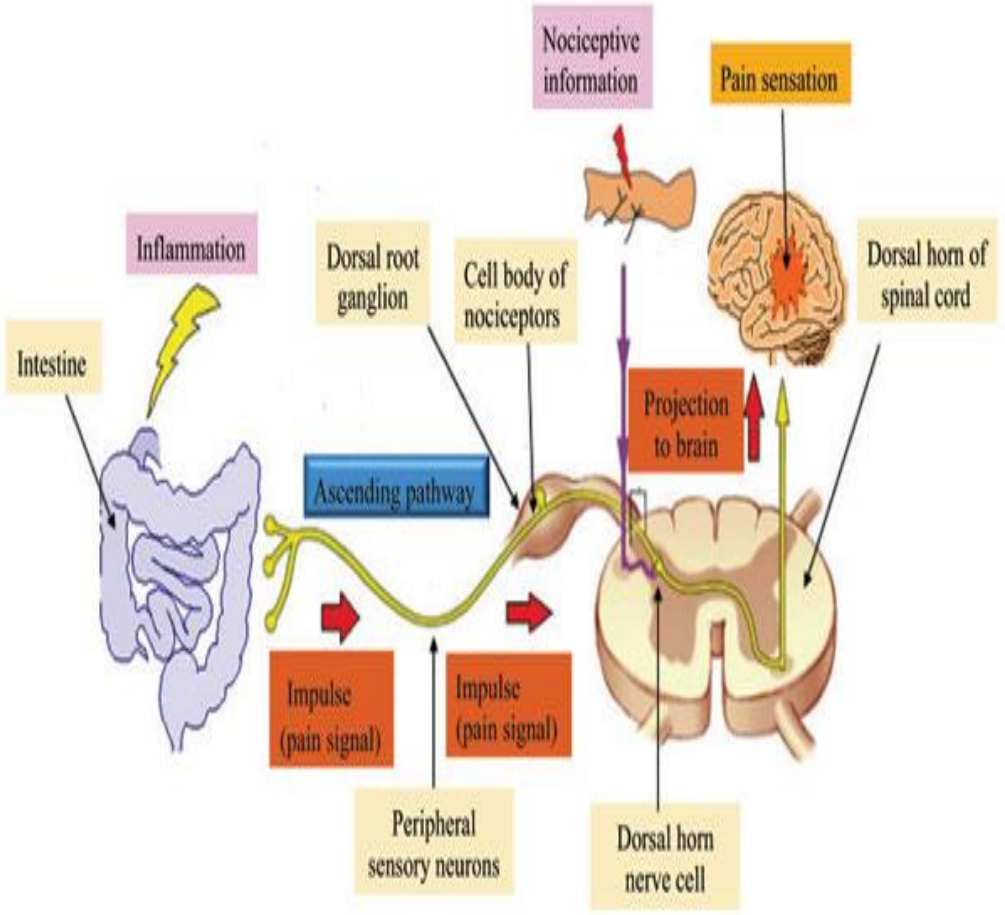


Pain

- Definitions: **An unpleasant sensory and emotional experience associated with actual or potential tissue damage.**
- Pain occurs whenever tissues are being damaged, and it causes the individual to react to remove the pain stimulus
- It is a protective sensation as it prompts an individual to withdraw from damaging situation or stimulus.

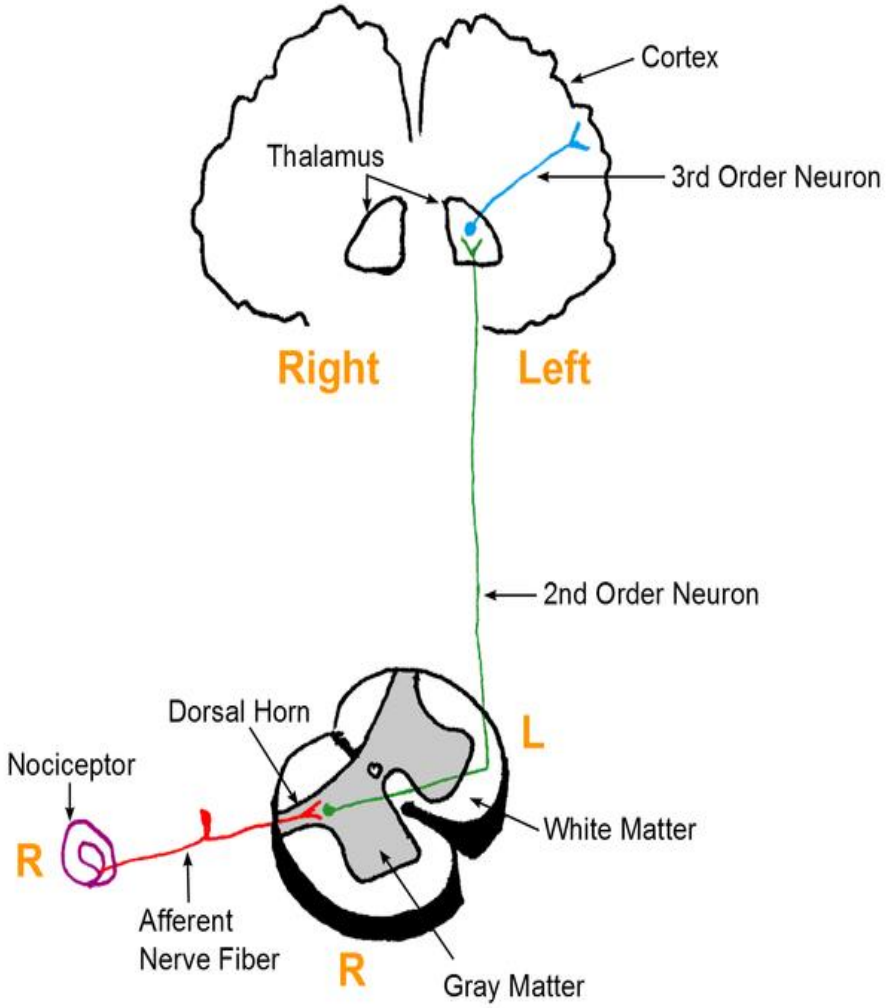
First-order neurons

- Within the pain pathway there are 3 orders of neurons that carry action potentials signalling pain:
- **First-order neurons** – These are **pseudo unipolar** neurons which have cells bodies within the dorsal root ganglion.
- They have one axon which splits into two branches, a peripheral branch (which extends towards the peripheries) and a central branch (which extends centrally into the spinal cord/brainstem).



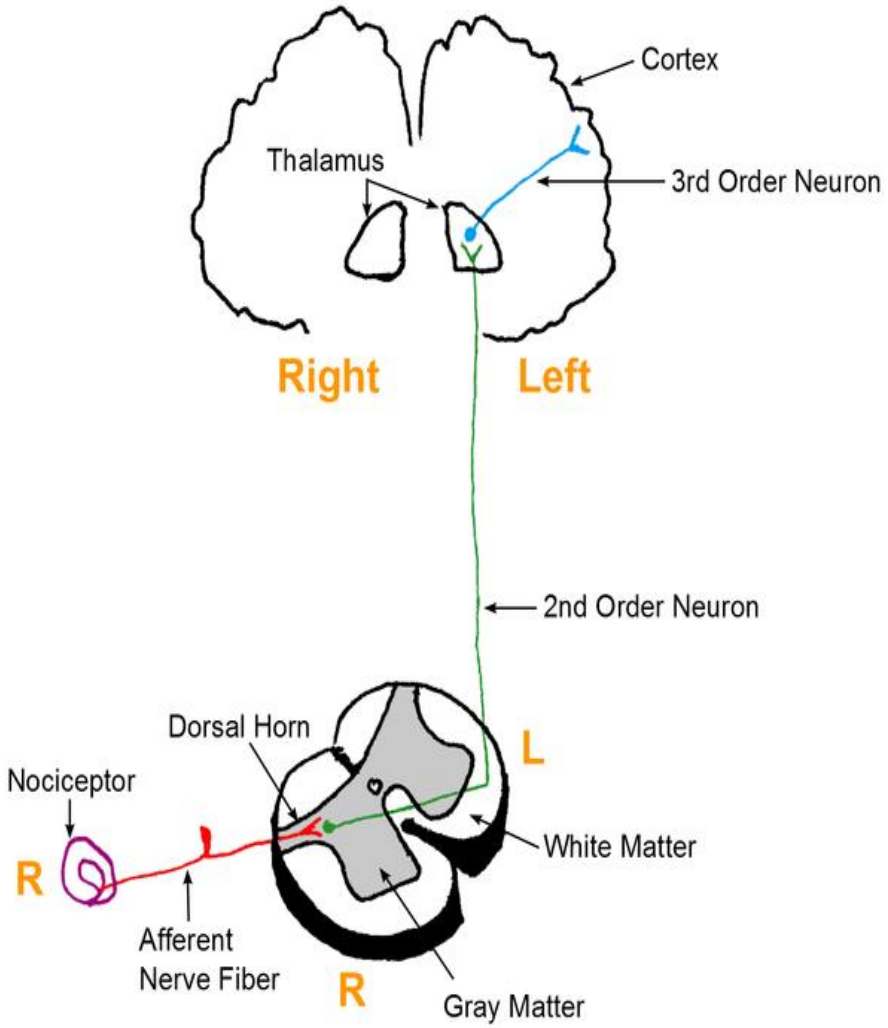
Second-order neurons

- – The cell bodies of these neurons are found in the **Rexed laminae** of the spinal cord, or in the nuclei of the cranial nerves within the brain stem.
- These neurons then decussate in the anterior white commissure of the spinal cord and ascend cranially in the spinothalamic tract to the ventral posterolateral (VPL) nucleus of the thalamus.



Third-order neurons

- The cell bodies of third-order neurons lie within the **VPL** of the thalamus.
- They project via the posterior limb of the internal capsule to terminate in the ipsilateral postcentral gyrus (primary somatosensory cortex).
- The postcentral gyrus is somatotopically organised. Therefore, pain signals initiated in the hand will terminate in the area of the cortex dedicated to represent sensations of the hand.



Activation of First Order Neurons

- **Nociceptors**
- Some first-order neurons have specialist receptors called **nociceptors** which are activated through various noxious stimuli. Nociceptors exist at the free nerve endings of the primary afferent neuron.
- Since nociceptors are free nerve endings this means they are **unencapsulated** cutaneous receptors.
- This is opposed to encapsulated cutaneous receptors (e.g. Merkel's discs) which detect other sensory modalities such as vibration and stretching of the skin.
- Similar to other sensory modalities, each nociceptor has its own receptive field. This means one nociceptor will transduce the signal of pain when a particular region is skin is stimulated.
- The size of **receptive fields** varies throughout the body and there is often overlap with neighbouring fields.

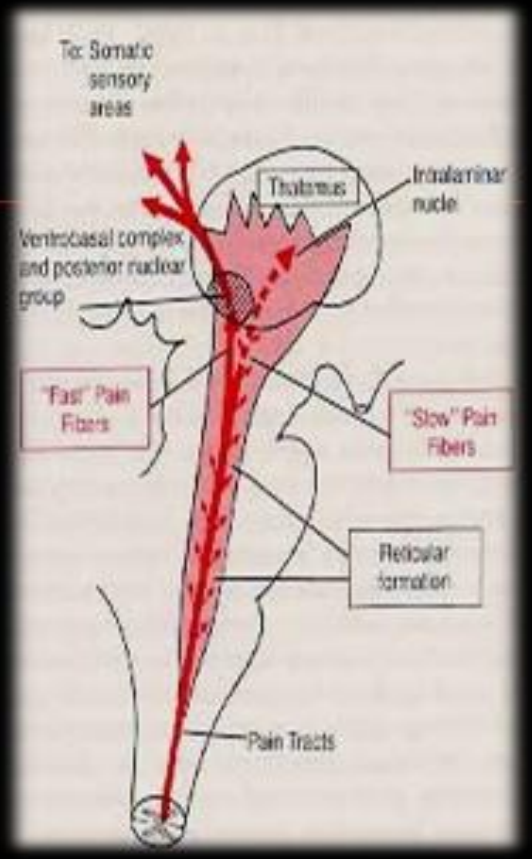
- The size of cortical representation in the **somatosensory cortex** of a particular body part is also related to the size of the receptive fields in that body part. For example, because the fingertips have small receptive fields, and thus a greater degree of sensory acuity, they have a larger cortical representation.
- Nociceptors can be found in the skin, muscle, joints, bone, and organs (**other than the brain**) and can fire in response to a number of different stimuli. Different types of nociceptors exist:
- **Mechanical** nociceptors – detect the distension of skin (stretch) and pressure which elicit sharp, pricking pain.
- Chemical nociceptors – detect exogenous and endogenous chemical agents, such as prostanoids, histamines etc.
- **Thermal** and mechano-thermal nociceptors – detect thermal sensations that elicit slow and burning, or cold and sharp in nature, pain.
- **Polymodal** nociceptors – detect mechanical, thermal, and chemical stimuli.

Transmission to the Spinal Cord

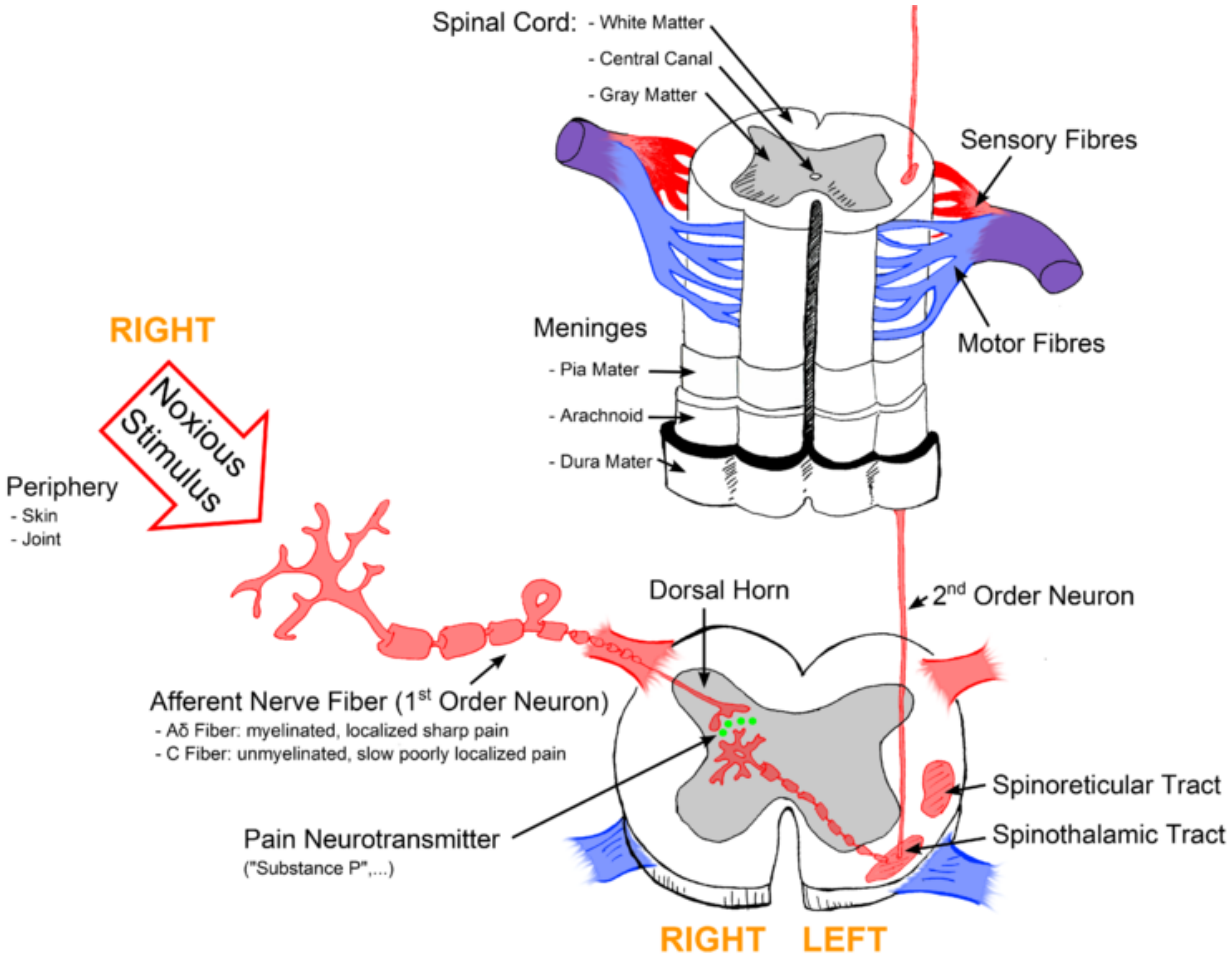
- Signals from mechanical, chemical, thermal, and mechano-thermal nociceptors are transmitted to the dorsal horn of the spinal cord predominantly via **Aδ fibres.** These myelinated fibres have a low threshold for firing and a fast conduction speed. Hence, they are responsible for transmitting the first pain felt.
- In addition, Aδ fibres permit the localisation of pain and form the afferent pathway for the reflexes elicited by pain.
- Aδ fibres predominantly terminate in **Rexed laminae I** where they mainly release the neurotransmitter, glutamate.
- Polymodal nociceptors transmit their signals into the dorsal horn through **C fibres**. C fibres are **unmyelinated** and a slow conduction speed.
- For this reason, C fibres are responsible for the secondary pain we feel which is often dull, deep, and throbbing in nature. These fibres typically have large receptive fields and therefore lead to poor localisation of pain.

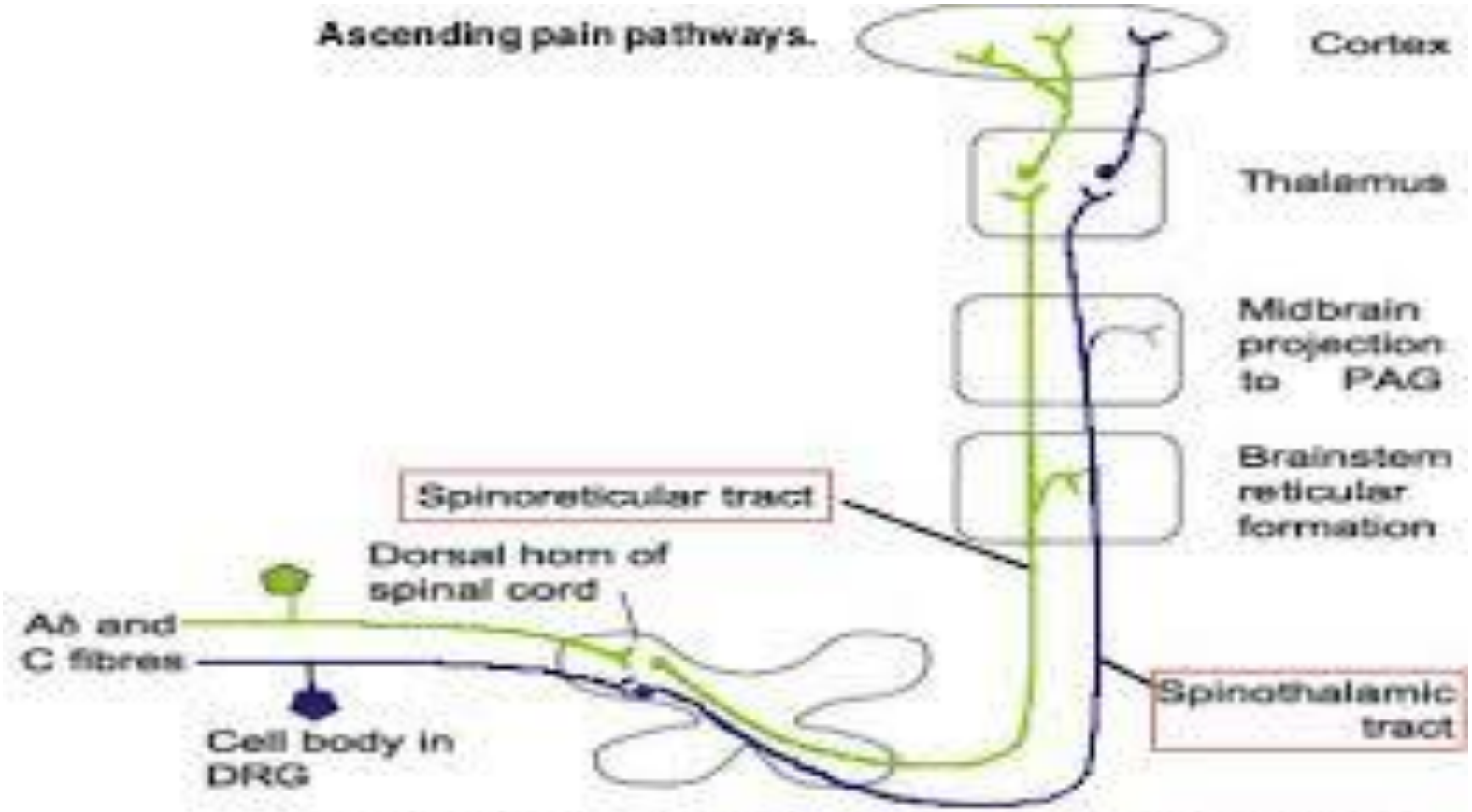
Fast pain & Slow pain

- ***Fast pain:*** **is also described as sharp pain, pricking pain, Acute pain, electric pain. it is elicited by mechanical and thermal type of stimuli.**
- ***Slow pain*** **is also called as, slow burning pain, aching pain, throbbing pain, nauseous pain, chronic pain. slow pain can be elicited by mechanical, thermal and chemical stimuli.**



- Compared to Aδ fibres, C fibres have a high threshold for firing.
- However, noxious stimuli can cause sensitisation of C fibres and reduce their threshold for firing.
- C fibres predominately terminate in **Rexed laminae II** (known as **substantia gelatinosa**) and release the neurotransmitter **substance P**. Other neurotransmitters are released by primary afferent neurons terminating within the spinal cord such as aspartate and vasoactive peptide.
- A variety of factors are released upon tissue damage which leads to the activation of nociceptors. These include:
- Arachidonic acid
- Potassium
- Histamine
- Bradykinin
- Lactic acid
- ATP
- Many of these factors are also pro-inflammatory and lead to acute inflammation in the area of damage.


Spinal Cord:
- White Matter
- Central Canal
- Gray Matter
Sensory Fibres
Motor Fibres
Meninges
- Pia Mater
- Arachnoid
- Dura Mater
RIGHT
Noxious Stimulus
Periphery
- Skin
- Joint
Dorsal Horn
2nd Order Neuron
Afferent Nerve Fiber (1st Order Neuron)
- Aδ Fiber: myelinated, localized sharp pain
- C Fiber: unmyelinated, slow poorly localized pain
Spinoreticular Tract
Spinothalamic Tract
Pain Neurotransmitter
("Substance P",...)
RIGHT
LEFT



DRG dorsal root ganglion, PAG periaqueductal grey matter

Descending Modulation of Pain

- Within the central nervous system, there are three types of **opioid receptors** which regulate the neurotransmission of pain signals. These receptors are called mu, delta, and kappa opioid receptors.
- They are all **G protein-coupled receptors** and their activation leads to **a reduction in neurotransmitter release** and cell **hyperpolarisation,** reducing cell excitability.
- Exogenous opioids, such as morphine, provide excellent analgesia by acting on these receptors. Likewise, our body contains endogenous opioids which can modulate pain physiologically. There are three types of endogenous opioids:

- **B-endorphins** – which predominately binds to mu opioid receptors
- **Dynorphins** – which predominately bind to kappa opioid receptors
- **Enkephalins** – which predominately bind to delta opioid receptors
- Opioids can regulate pain on a number of levels, both within the spinal cord, brain stem, and cortex. Within the spinal cord, both dynorphins and enkephalins can act to reduce the transmission of pain signals in the dorsal horn. This is because the **post-synaptic** ends of second-order neurons have opioid receptors within the membrane. In addition, the **pre-synaptic** ends of first-order neurons contain opioid receptors.

- When endogenous opioids act on these receptors it reduces neurotransmitter release from the first-order neuron, and causes hyperpolarisation of the second-order neuron. Together, this reduces the firing of action potentials in the second-order neuron, **blocking** the transmission of pain signals.

- A pain control or analgesic system exists within the brain and spinal cord
- Morphine is a powerful pain killer(analgesic) found in opium.it acts by combining with receptors in the CNS.There are two major types of compounds with morphine like properties have been isolated from the brain they include the endorphins and encephalins.
- The word endorphin comes from putting together the words “endogenous,” meaning from within the body, and “morphine,” which is an opiate pain reliever. In other words, endorphins got their name because they are natural pain relievers.

Endorphins

- consist of a large group of peptides.
- They are produced by the central nervous system which are plenty in the hypothalamus and pituitary.
- Since endorphins act on the opiate receptors in our brain.
- They reduce pain and boost pleasure, resulting in a feeling of well-being.
- Endorphins are released in response to pain or stress, but they're also released during other activities, like eating, exercise, or sex.

- They are present in high concentration in woman during parturation.
- This suggest that these naturally occurring peptides form the body own analgesia system.
- Endorphins are secreted together with ACTH from the anterior pituitary in stressful conditions. This explains why injuries are painless during games.
-

Enkephalins

- are small peptides that can serve as neurotransmitters in the brain.
- Enkephalins are found in high concentration in the brain as well as in the cells of adrenal medulla. In response to pain, norepinephrine, a hormone that is activated in fight-or-flight response is released along with endorphins.
- these are naturally occurring peptides found in high concentration in the periaquiductal gray matter. They interact with opiate receptors found in the dorsal horn periaquiactal grey matter hypothalamus and limbic system.

Enkephalin

- Enkephalin influence pain by producing two sets of effects.
- one is directly inhibiting transmission of painful stimuli through **dorsal horn** by closing the pain gate
- and the other is by modifying the emotional state of the individual via **limbic system** and causing a sense of well being in an individual.

- The enkephalins and endorphins function as excitatory transmitter substances that activate portion of brain analgesic system .The concentration of enkephalines and endorphines increase following electrical stimulation of the brain stem.

- The analgesis system consists of three major components which are
- 1.The periaqueductal grey area of the midbrain surrounding the aqueduct of sylvius.
- The Raphe Magnus Nucleus.
- Pain inhibitory complex located in the dorsal horn of the spinal cord.

- The descending analgesic pathways originate from the periaqueductal gray area,which send signals to the medullary raphe magnus nucleus.
- From here the signals are transmitted down the spinal cord to terminate in the substansia gelatinosa where they release enkephalins.
- These enkephalins act to prevent pain impulse conduction in the substantia gelatinosa,which tend to close the spinal cord pain gate.

- Encephalin cause presynaptic inhibition of both type C and type A pain fibers where they synapse in the dorsal horn.
- The mechanism of this inhibition appears to be that enkephalin blocks Ca influx into the sensory terminals, thereby blocking the release of substance P.
- The analgesia system thus blocks pain signals at the initial entry point at the spinal cord.

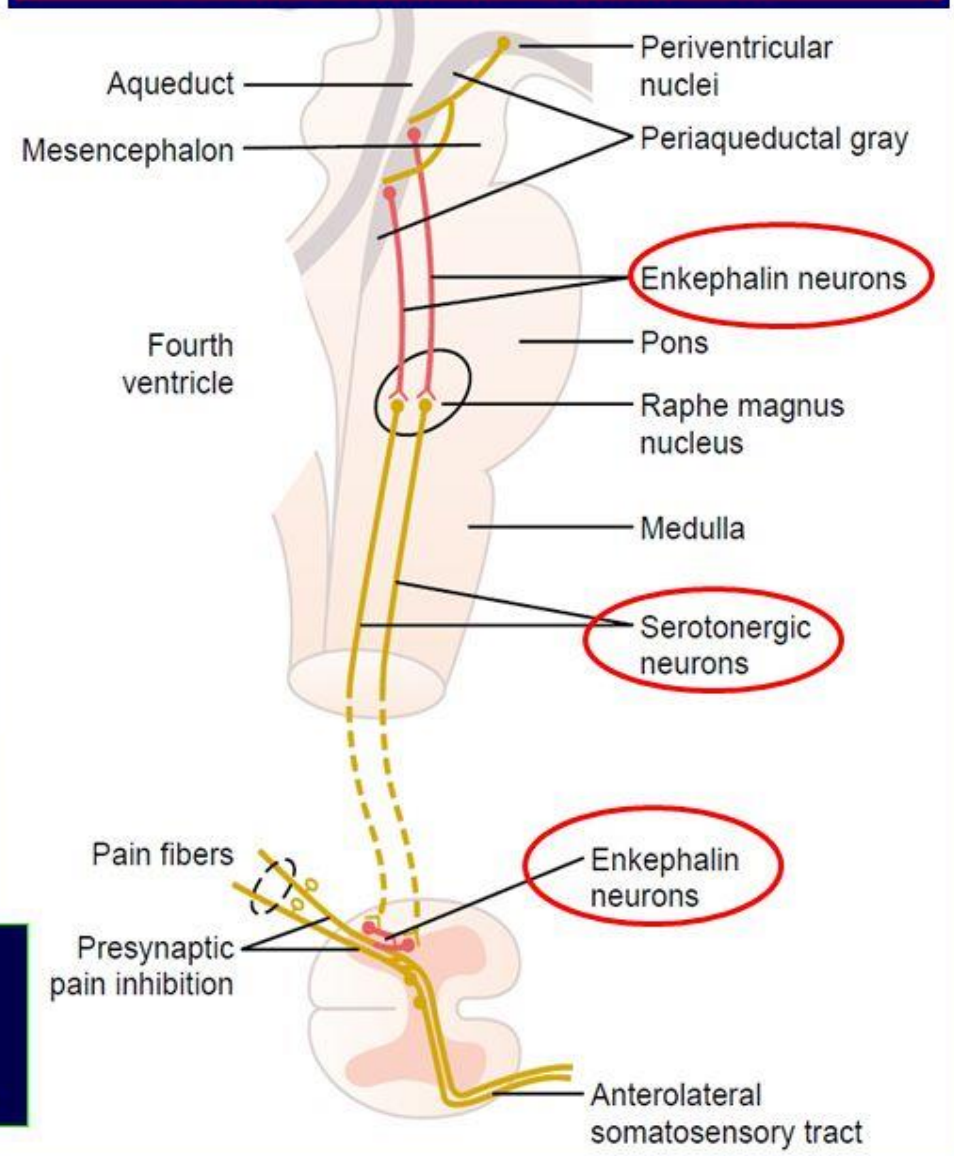
(1) Enkephalin Neurons from periaqueductal gray and periventricular areas of the mesencephalon and upper pons send signals to

(2) Raphe magnus nucleus, in the lower pons and upper medulla From these nuclei, second-order N go down the dorsolateral columns in the spinal cord & secrete Serotonin which act on local neurons to secrete Enkephalin

(3) a pain inhibitory complex in the dorsal

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

Pain Suppression ("Analgesia") System in the Brain and Spinal Cord



Opiates in the human body

- Opiates drugs such as morphine, heroin, codeine,and opium are potent pain killers derived from poppy plant.
- These drugs after pain perception making it easy to tolerate.The human produces its own opiates called endorphins.
- Like the poppy derived opiates they structurally resemble endorphins which influence mood and perception of pain.

- Researchers identified several types of endorphins in the human brain which is associated with pain relief such as accupuncture and analgesia to mother and child during child birth.

definitions

Hyperalgesia.

- Hyperalgesia is an increased painful sensation in response to additional noxious stimuli

Allodynia

- Allodynia is pain resulting from a stimulus that does not normally produce pain. For example, light touch to sunburned skin produces pain because nociceptors in the skin have been sensitized as a result of reducing the threshold of the silent nociceptors

Referred pain

- Pain perceived at a location other than the site of the painful stimuli. Referred pain is when the pain you feel in one part of your body is actually caused by pain or injury in another part of body.
- irritation of a visceral organ frequently produces pain that is felt not at that site but in some somatic structure that may be a considerable distance away.
- Such pain is said to be referred to the somatic structure.

- Two mechanisms
- Dermatomal rule
- Convergence projection theory.

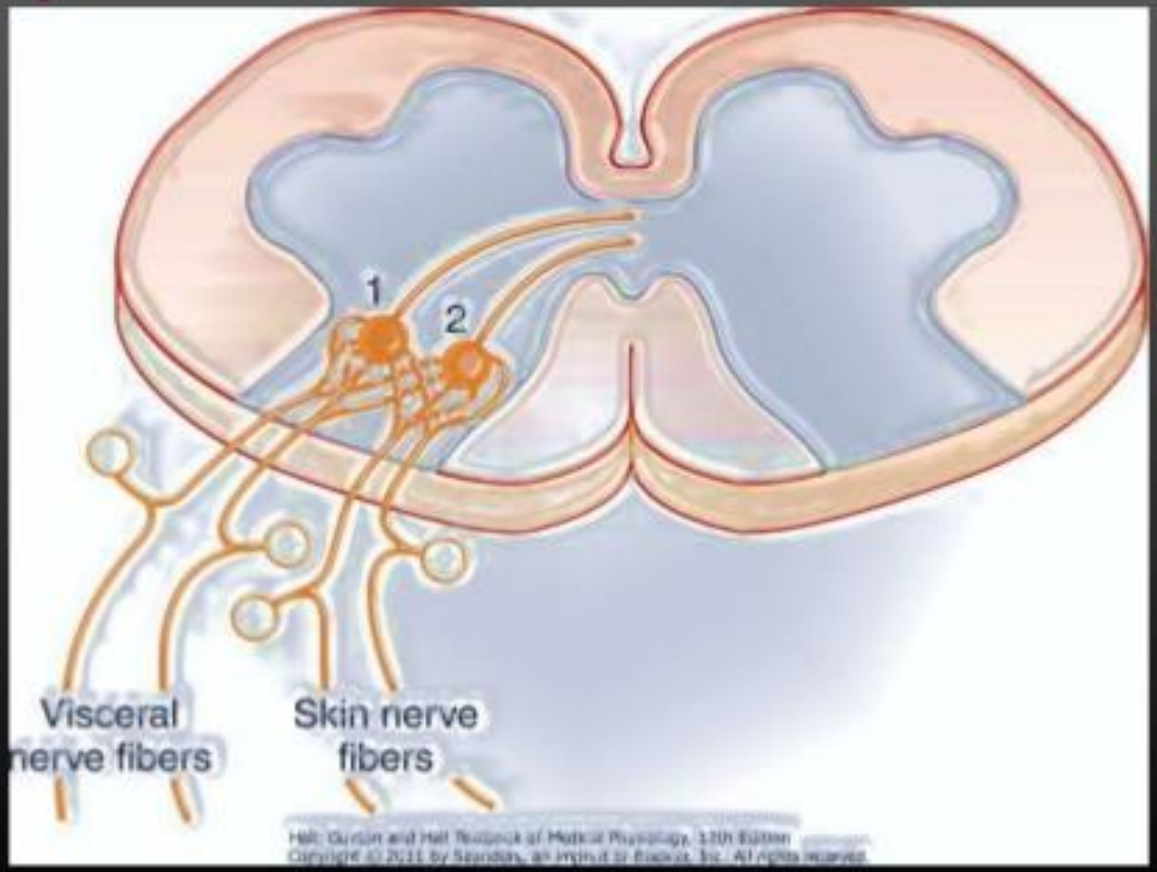
Dermatomal rule

- 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.This principal is called Dermatomal Rule.
- For instance the heart and inner aspect of the left arm.
- Testicles and ureter kidney(from urogenital ridge).

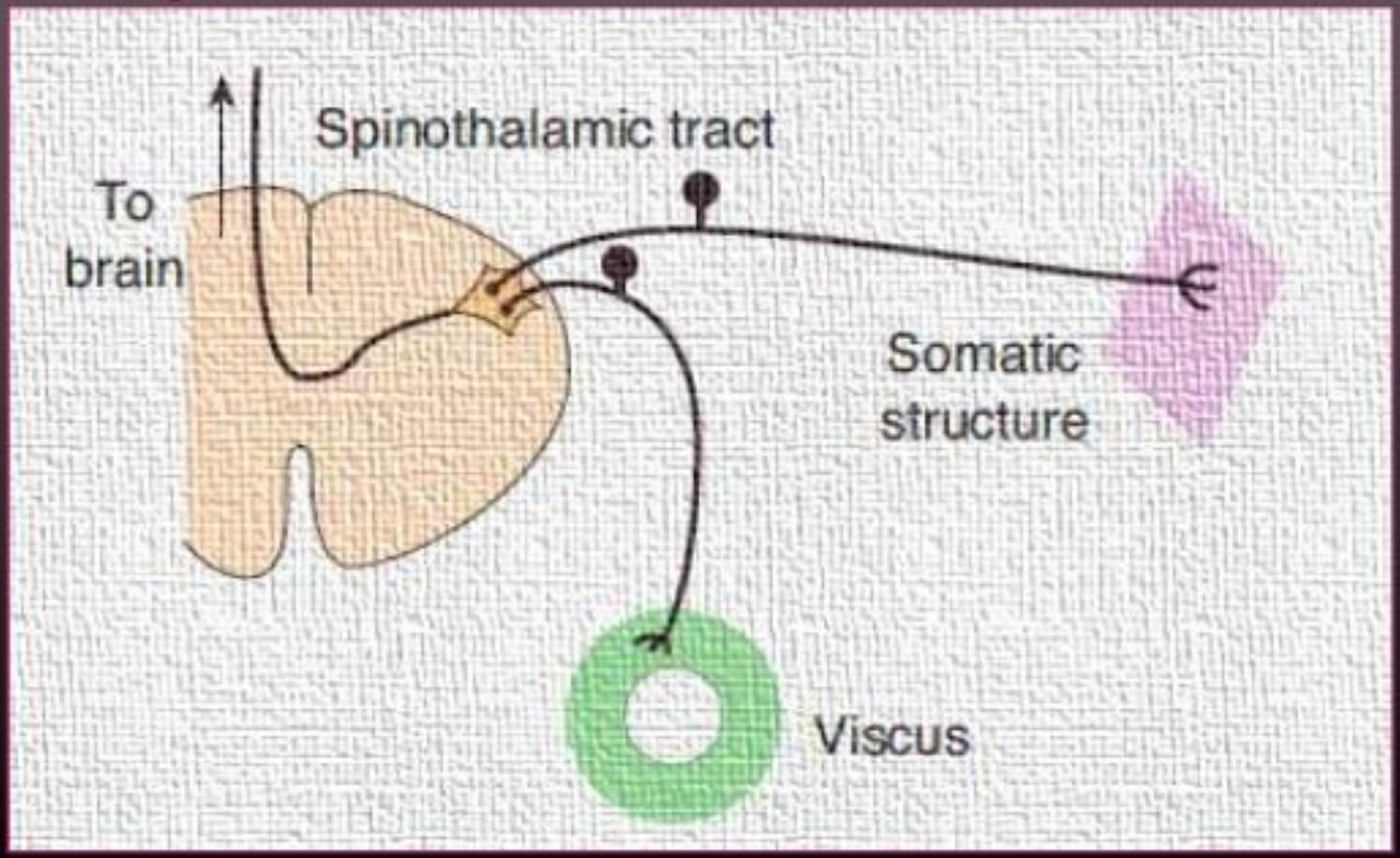
Convergence projection theory.

- Second mechanism for referred pain may be convergence of somatic and visceral pain fibers on the same second order neurons in dorsal horn that project to the thalamus and then to the somato sensory cortex. This is called the convergence projection theory.
- Somatic and visceral neurons converge in lamina 1-V1 of the ipsilateral dorsal horn.Neurons in lamina V11 receive afferents from both sides of the body. Explains referral of pain to the side opposite that of the source of pain i,e affected organ.

Convergence– projection theory



Convergence– projection theory



Convergence– projection theory

The somatic nociceptive fibers normally do not activate the second-order neurons. But……..

- If prolongation of visceral stimulus
- facilitation of the somatic fiber endings
- stimulate the second order neurons
- brain interprets activity in a pathway as arising from somatic sources
- Referred pain in somatic area

Headache

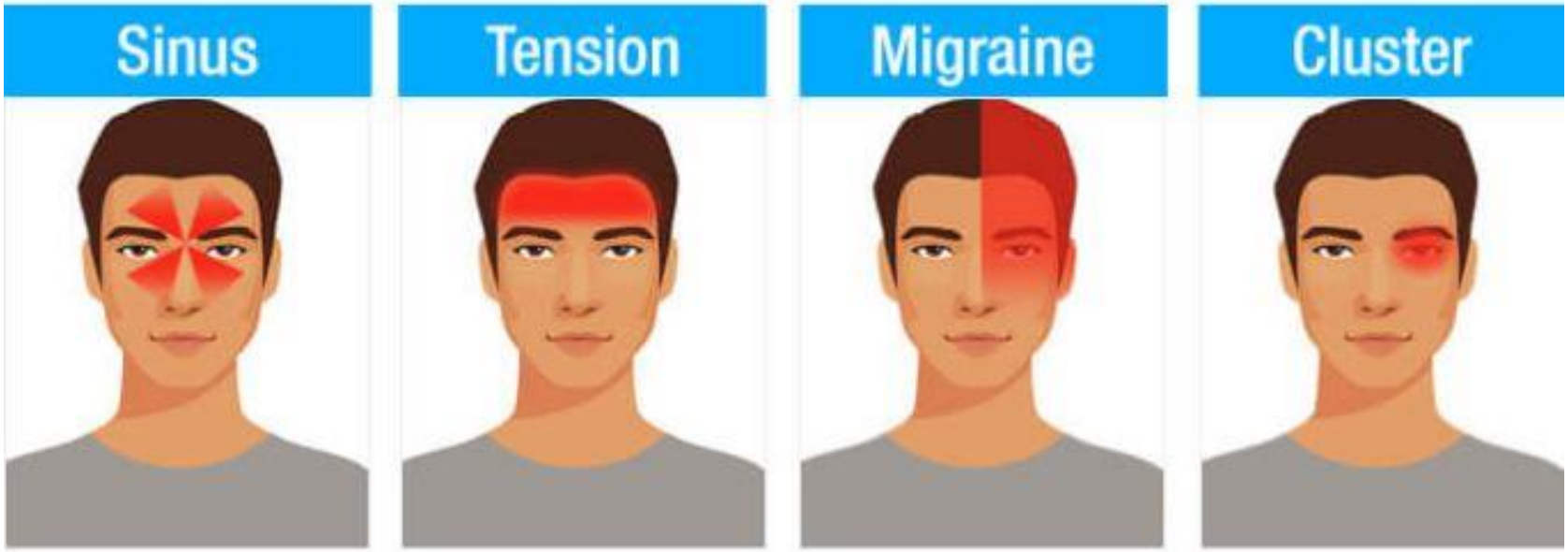
- Headache, is one of the most common of all human physical complaints. Headache is actually a symptom rather than a disease a stress response, vasodilation (migraine), skeletal muscle tension (tension headache), or a combination of factors.

- **Definition :**
- A headache is a pain or discomfort in the head , scalp , or neck .

Types of headache :

- 1) tension type headache
- 2) migraine headache
- 3) cluster headache
- 4) other types of headache

Headache Type



- **Tension type headache :**
- Is the most common type of headache , is characterized by bilateral location . It is usually mild or moderate intensity & not aggravated by physical activity
- Tension type headache is sub categorize as
- **1) infrequent episodic**
- **2) frequent episodic**
- **3) chronic**

- **Etiology :**
- It caused due to sustained pain full contraction of the muscles of the scalps & neck
- **Clinical manifestation :**
- Headache does not involve nausea or vomiting
- Photophobia – sensitivity to light
- Phonophobia – sensitivity to sound

- **Migraine headache :**
- Migraine headache is a recurring pain characterized by unilateral or bilateral throbbing Pain
- Migraine type of headache occurs more in females then males
- It is associated with anatomical or nervous system dysfunction .

- **Etiology :**
- Different theories suggest different causes
- 1) vascular theory = vasoconstriction followed by vasodilation with resulting in changes in blood flow causes the throbbing pain .
- 2) second theory suggest that pain is results from muscular tension & is re

- 3) biochemical changes = changes in serotonin level

3) cluster headache:

it involves repeated headaches that can occur for weeks to months at a time followed by a period of remission.

Clinical manifestation :

Pain around the eye , forehead , cheeks , nose or gums

Swelling around the eye

Facial flushing

- **<u>Other type of headache</u>** :
- This type of the headache may be the first symptoms of the other illness
- It should be due to some other illness such as a subarchnoid hemorrhage , brain tumors , trigeminal neuralgia , & any other systemic disease