PHYSIOLOGY

SHEET NO. 4

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In this lecture we are going to talk about the second part of somatic sensation: Pain and Thermal Sensations.

Objectives:

- Define pain and classify it.
- Identify the types of pain:
  - **Fast** (Acute)- Runs through **Ad fibers**, or **slow** (chronic)- Runs **through C fibers.** ○ **Somatic or visceral** (from our internal organs)
- Describe the mechanism of pain and its receptors.
- Follow its pathway to the cerebral cortex and characterize this pathway.
  - There are two pathways, one for fast (acute) pain, and one for slow pain.
- Explain the pain suppression mechanism (**endogenous opiate system and gate control theory**) that acts to suppress the feeling of pain.
  - By opiate, we mean substances derived from opium. Endogenous- Formed in our body. They bind to the receptors for morphine.
- Describe the pathway for **Referred pain.**
  - For visceral pain
  - Remember that our Viscera or internal organs aren't represented in our cerebral cortex.
- Create a complete picture of thermal sensation

What Is Pain?

- Pain is a feeling of **discomfort**.
- It occurs when there is **tissue damage**- what excites pain is damaged tissue that releases certain **chemicals**.
- Pain is a **Protective mechanism** for the body, as it makes us remove or bring ourselves away from the painful stimuli or conditions.
  - That's why pain is a non-adapting sensation.
  - If it were an adapting sensation, we wouldn't remove/move away from the painful stimulus as expected, allowing the damage to aggravate and worsen.
  - Individuals who have diabetes have peripheral neuropathy, where neurons that transmit pain are destroyed. Pain is no longer felt, the tissue damage continues, and worsens, forming a gangrene.

Types of Pain

There are two types of pain, fast pain and slow pain.

Fast pain:

- Is felt within **0.1 sec** of the stimulus/injury.
- Described as **Sharp, pricking, acute pain**. Since this type of pain is acute, that is why it is also referred to as **"electric" pain**.

Slow pain:

- Begins after **a second or more**.
- Described as **throbbing, aching, nauseous and chronic in nature**. This type of pain is often **indescribable** and is **dull**.
- **Example**: Dental pain.
- Aggravates and summates, unlike fast pain.

Pain Receptors and Their Stimulation

- All pain receptors are free nerve endings
- Two categories of receptors:
  1. Mechanical (stretch) and Thermal: Usually for **fast pain**
  2. Polymodal (Sensitive to all three types of stimuli- Mechanical, thermal and chemical). These receptors are usually the receptors for **slow pain.**

- Chemicals that are released from damaged tissue, that excite pain receptors:
  1. **Bradykinin**: Very important substance.
     It is produced by the activation of kallikrein system that acts on Kinins. Bradykinin sensitizes pain receptors.
  2. **Serotonin**
  3. **Histamine**
  4. **Potassium ions, acids**
  5. **Acetylcholine**
  6. **Proteolytic enzymes**

- **Prostaglandins and substance P:**
  - **Enhance** pain by increasing the sensitivity of pain endings but they **do not directly excite them**, they do not cause pain.
  - They only **lower the threshold for pain** and increase the receptor's sensitivity to pain. This makes it easier for you to feel pain.

- The threshold for pain differs from one person to another.

- **NSAIDs** (e.g., Aspirin) inhibit COX1, which targets/works on arachidonic acid. Arachidonic acid is normally converted into Prostaglandins. Aspirin inhibits COX1, decreasing the amount of prostaglandin, increasing the threshold for pain. This is how aspirin acts as an analgesic.

- Pain receptors **do not adapt** to stimuli, and are almost **non adapting**
  - If tissue damage occurs, the individual would not be able to remove or the pain stimuli, had the pain receptors been adapting. Eventually, the damage would continue and worsen, and the receptors would adapt to this damage, and you would not feel any pain.
  - All in all, pain receptors aren't adapting; as long as there is tissue damage, there is pain, and this pain is what drives you to step away or avoid the source of pain.

- Extracts from damaged tissue cause pain when injected under the skin. The pain that is felt is due to the released chemicals from the damaged tissue. These chemicals excite free nerve endings, causing pain.

The rate of tissue damage is the cause of pain (most individuals feel pain at around 45°C).

The figure on the right shows the **relationship between tissue damage and pain.** In this experiment, people were exposed to different temperatures, to find the temperature at which they felt pain. **Most of the people here feel pain at a temperature of about 45°C**. This is because, at this temperature, most of the people will have tissue damage at this temperature.

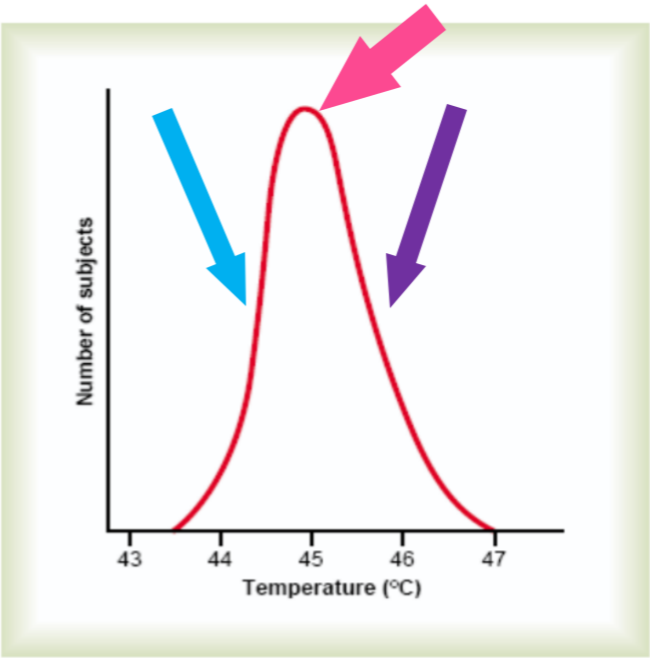


Figure 48–1

Distribution curve obtained from a large number of persons showing the minimal skin temperature that will cause pain. (Modified from Hardy DJ: Nature of pain. J Clin Epidemiol 4:22, 1956.)

Some people have higher threshold for pain, and do not feel it unless exposed to higher temperatures.
Some people have a low threshold for pain, feeling pain at lower temperatures.

- **Bradykinin** causes the most pain and may be the single most important agent that causes the tissue damage type of pain.

- Other substances like histamine, serotonin, acids, proteolytic enzymes do cause pain, but Bradykinin is the most important pain-causing substance.
- The local increase in potassium ion concentration and action of enzymes can contribute to pain as well.

The Anterolateral (spinothalamic) Pathway

- The pathway for pain and temperature runs through the **anterolateral spinothalamic pathway**.
- Aside from pain and temperature, this pathway also conveys nerve impulses for **crude touch (poorly localized), crude mechanoreceptive sensation, pressure, itch, and tickle** from the limbs, trunk, neck, and posterior head, to the ***primary somatosensory area in the postcentral gyrus of the cerebral cortex.***
  - The **precentral gyrus**, located in front of the central gyrus, is a **primary motor area**, whereas the **postcentral gyrus** is located in the parietal lobe posterior to the central gyrus, and is a **primary sensory area**.

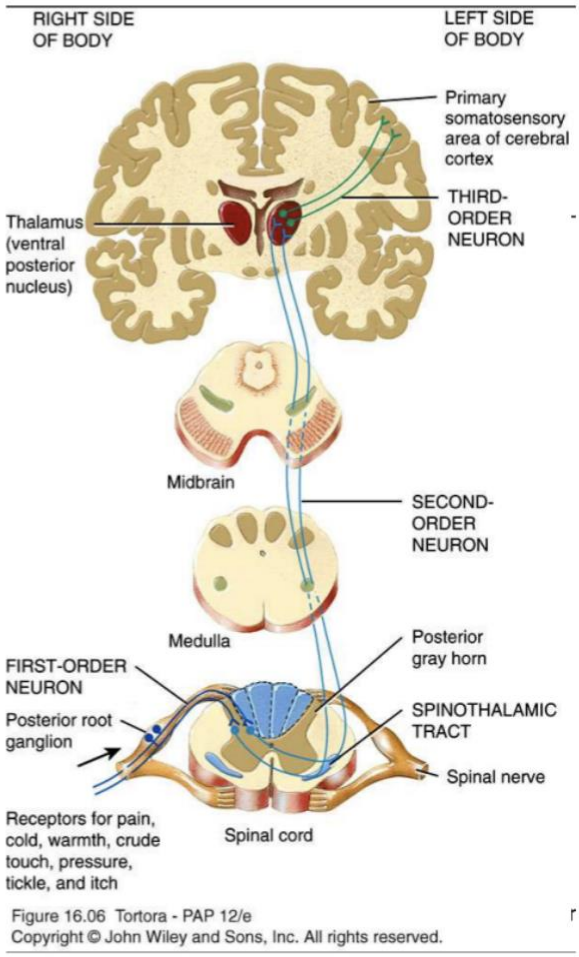


Figure 16.06 Tortora - PAP 12/e

***Note**: By crude, we mean poorly localized. Fine touch, on the other hand, is well-localized.*

- From these receptors:
  1. The ***first order neuron*** of this pathway enters the ***posterior (sensory or dorsal) horn***, and they ***synapse*** at the posterior horn.
  2. After they synapse, they might have ***interneurons*** before they ***cross to the other side***, a***scending in the anterior and lateral column of the spinal cord.***
     - The crossing here is anterior to the central canal; The crossing is at the level of the spinal cord.

- If you remember, in the **dorsal column medial lemniscus**, the crossing is at the level of the **medulla**.
- If you have transection or damage of half of the spinal cord here (shaded) there will be **loss of pain, temperature and crude sensation on the other side.** The neurons coming from here synapse but won't be able to ascend due to the damage.

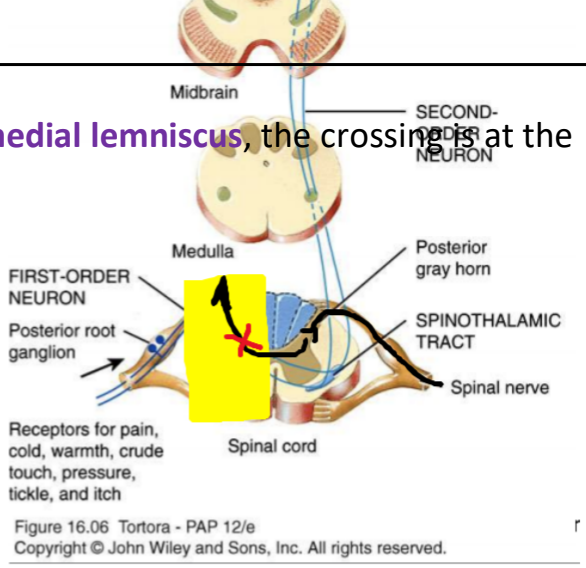


Figure 16.06 Tortora - PAP 12/e

  - The loss of crude touch, pressure, thermal sensation and pain is from the **contralateral side of the spinal cord damage**. On the other hand, in case of the dorsal column, it would be on the ipsilateral side.

3. ***The second order neuron*** then goes to the ***thalamus*** (The ***ventrobasal complex***- *VPL and VPM*).
4. Some pain fibers go to the **intralaminar nuclei**.
   - The fibers that go there are important for the emotional aspect of pain.

Dual Pain Pathways

Since there are two types of pain - fast and slow- each has a different pathway.

- **Fast pain** is transmitted by **type Ad fibers**.
  - These are fast conducting fibers (velocity 6-30 m/sec).
  - They are the **smallest myelinated** fibers.
  - Fast pain fibers are transmitted in the **Neospinothalamic tract.**
- **Slow pain** is transmitted by **type C fibers**
  - These are slow conducting fibers with a speed of (0.5 - 2 m/sec).
  - They are unmyelinated.
  - Slow pain fibers are transmitted in the **Paleospinothalamic tract.**

Characterization of fast and slow pain

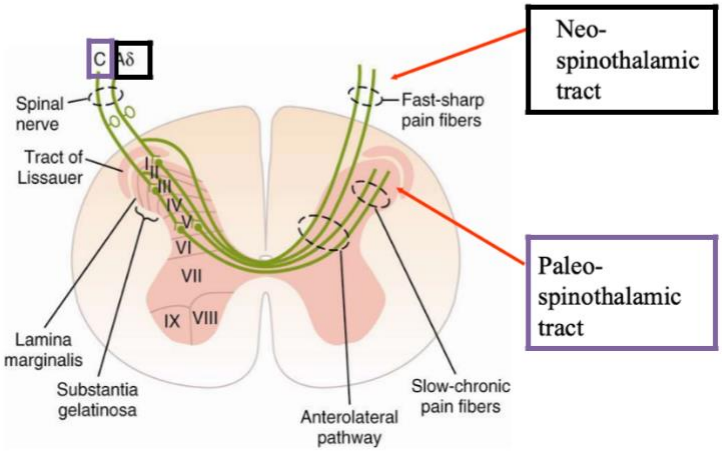
The following table shows the differences between fast and slow pain.

Fast Pain	Slow Pain
Occurs upon stimulation of ***mechanical and thermal nociceptors.***	Occurs upon stimulation ***of Polymodal nociceptors*** that are sensitive to three types of sensation (Mechanical, thermal and chemical)
Carried by small, ***myelinated fibers (Ad)***	Carried by small, ***unmyelinated C fibers***

Produces ***sharp, prickling, electric*** sensation.	Produces ***dull, aching, burning sensation that is hard to describe. Poorly***
Easily localized. (Although localization here isn't as perfect as that in the dorsal column system)	***localized.***
Occurs ***first***	Occurs ***second***.
Acute and ***subsides*** easily. ***Does not aggravate.***	***Chronic*** and ***persists*** for a longer time. Starts as light and bearable pain, then ***aggravates*** and intensifies.

The following figure shows **types of pain and their associated fibers:**

- The **Ad fibers**: Transmit **fast pain**
- **C fiber**: Transmits **slow pain**



- **Fast pain:**
  1. Is transmitted through A delta fibers and once it enters the posterior horn**, it does not form many synapses, it only forms one or two.**
  2. It then crosses to the other side anterior to the central canal, ascending through the anterior and lateral aspect of the spinal cord.
     - Given that it **has very few synapses**, there will be a **less synaptic delay**. This is why this type of pain is **fast**.

Each synapse has what is called **Synaptic Delay**. *A **greater number of synapses** will give rise to **greater/longer synaptic delay**, making the sensation **Slow**.* On the other hand, with ***fewer synapses**, there will be **less synaptic delay**, making the sensation **Fast**.*

- **Slow Pain**:
  1. Is transmitted through slow C fibers, which are slower than Ad fibers. **In the posterior horn they have many synapses**, and diversions.
  2. They then cross to the other side, and the second order neuron ascends to the ventrobasal complex of the thalamus.
     - Given that there are **a greater number of synapses in the posterior horn for slow pain**, there will be **greater synaptic delay**. This is why, along with the use of C fibers, this sensation of pain is going to be **slow**.

Remember, fast pain is transmitted through a tract called **Neo-spinothalamic tract**. Slow pain is transmitted through the **Paleo-spinothalamic tract** | **Paleo: Older** **Neo: New**

Neospinothalamic Tract

1. On entering the spinal cord, pain fibers may travel up or down 1-3 segments and terminate on neurons in the dorsal horn.
2. **2nd order neuron** crosses immediately to the opposite side anterior to the central canal, and passes to the brain in the anterolateral columns of the spinal cord.
3. A) Some neurons terminate in the **reticular substance (Less than 25%)**
   B) **Most** go all the way to the **ventrobasal complex of the thalamus** (VPL and VPM).

   - **Note: Fast pain does not travel to the intralaminar nuclei, unlike slow pain.**

4. **3rd order neurons** go to the cerebral cortex- **to the primary somatosensory cortex**.
5. Some fibers reach the thalamus. When they do**, some terminate** or end in the thalamus. Other fibers **complete their journey to the cerebral cortex**. The ones that complete their journey are important for the localization of pain.
   - **Why is this important?** Even if the cerebral cortex or the postcentral gyrus is destroyed, pain can still be felt at the level of the thalamus. However, the localization of pain is poor **(Remember that reaching the cerebral cortex is important for pain localization).**

- Fast-sharp pain can be localized well. However, fast pain fibers must be **stimulated with other tactile receptors for the pain to be highly localized.**

Paleospinothalamic Tract

- Type C pain fibers terminate in the substantia gelatinosa laminae II and III of the spinal cord and make one or two local connections before giving rise to 2nd order neurons which cross immediately and pass to the brain in the anterolateral columns of the spinal cord.
- Here they have too many synapses in the posterior horn of the spinal cord, and great synaptic delay, which is is why they are slow.

Termination:

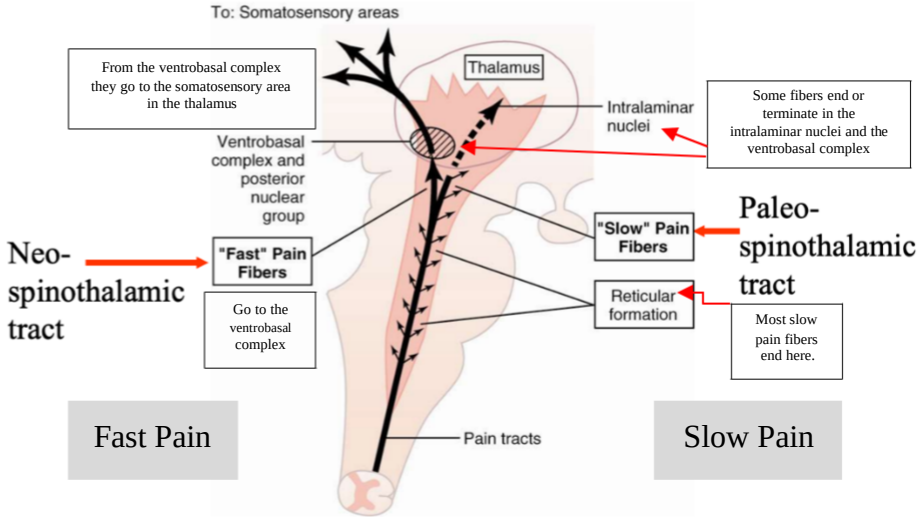
- Only **10 to 25 % of the fibers terminate in the thalamus**, specifically in the VBC or the intralaminal nuclei of the thalamus.
- Most terminate diffusely in the:
  1. **Reticular nuclei of the brainstem** (medulla, pons and mesencephalon/midbrain)
     - The fibers that terminate here are important for activation of the **reticular activating system (RAS) in the brain stem, awakening someone.**
     - We said that dental pain is slightly painful at first. However, this slow pain aggravates and becomes too painful. Because it is too strong, it ascends and terminates at the reticular formation of the brain stem → Activating the reticular activating system → Awakens the cellular cortex. This is why the person experiencing the pain wakes up in the middle of the night with severe tooth pain.
  2. **Tectal area of the mesencephalon (midbrain)**
  3. **Periaqueductal gray region/matter**, around the aqueduct of the fourth ventricle
     - 2 and 3 are important for activating the descending analgesia system.

- From the lower reticular areas of the brain stem, some neurons stay there, while others project to the **intralaminar nuclei of the thalamus, hypothalamus and other basal brain regions.**
  - These regions are important for the **emotional aspect of pain.**

- The paleospinothalamic tract is **Poorly localized**, because they are transmitted through **slow conducting fibers (C fibers)** and have **too many synapses** in the posterior horn of the spinal cord. This means **slow pain is poorly localized**, often only the affected limb or part of the body is recognized.

The figure shows both tracts.

- Fast pain fibers go to the **ventrobasal complex.** From there they go to the **somatosensory area of the cerebral cortex** in the thalamus.



Slow pain fibers:

- Like we said, **most fibers** end at the **reticular formation of the brain stem** and are important for activation of the Reticular Activation System, which activates the cerebral cortex, to awaken the person.
- **Other fibers** go to the **Ventrobasal complex and the intralaminar nuclei**. The intralaminar nuclei is important for the emotional aspect of pain.
- **Very few fibers complete their pathway to the cerebral cortex**. That is why this type of pain is **poorly localized; most of the fibers do not go all the way to the cerebral cortex.**

Appreciation of Pain

- Removal of the somatosensory areas of the cortex **does not destroy the ability to perceive pain.** That is because our ability to perceive pain also comes from the **thalamus**, but with poor localization.
- Pain impulses to **lower areas (thalamus)** can cause **conscious perception of pain**. ○ Therefore, the cerebral cortex is important for determining the quality of pain, and the location (Localization of pain).

- Stimulation of the **reticular areas (RAS activation)** of the brain stem and **intralaminar nuclei of thalamus** (where pain fibers terminate) causes widespread arousal of the nervous system.
  - ○ That is why people wake up in the middle of the night because of aggravating pain.

Analgesia System of the Brain and Spinal Cord

This system of the brain is known as the **Endogenous Analgesia System**, or **Endogenous Opiate System**, because it uses substances that are similar to opium (opiates).

- The brain has the capability to suppress pain fibers through this endogenous analgesia (analgesics secreted in the brain).
  1. **Periaqueductal gray area neurons** send axons to:
     - ○ Nucleus **raphe magnus** in the medulla oblangata
     - ○ Nucleus **paragigantocellularis**.
  2. **Raphe magnus and paragigantocellularis neurons** send axons to the **dorsal horn** of the spinal cord.
  3. These synapse with **interneurons** that secrete endogenous opiates.

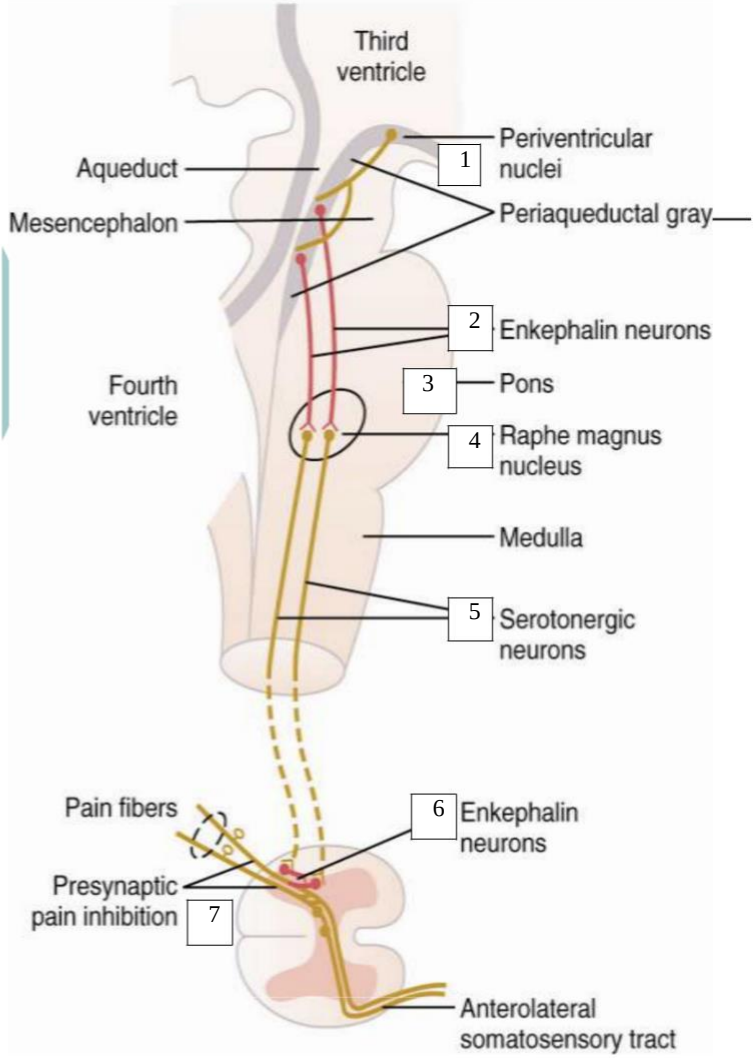
4. These neurons activate a pain inhibitory complex in the spinal cord.

- We have three types of endogenous opiates:
  1. **Enkephalins**:
     - Are pentapeptides.
     - Very small but can suppress pain.
     - They bind to receptors for opiates.
     - **Two** types: Met-enkephalin and Leu-enkephalin.
  2. **Dynorphin**:
     - **200 times** more active than morphine.
  3. **Endorphin/ Beta endorphin**: → anterior pituitary
     - Is split from the **proopiomelanochorticoprotein**, the patent or the large protein from which **ACTH adinocorticotriopic hormone** is derived.
       - Opio: gives Opiate, melano: MCH, chorticoprotein: ACTH

Analgesia system of the brainstem and spinal cord Ipsilateral system

As you can see here,

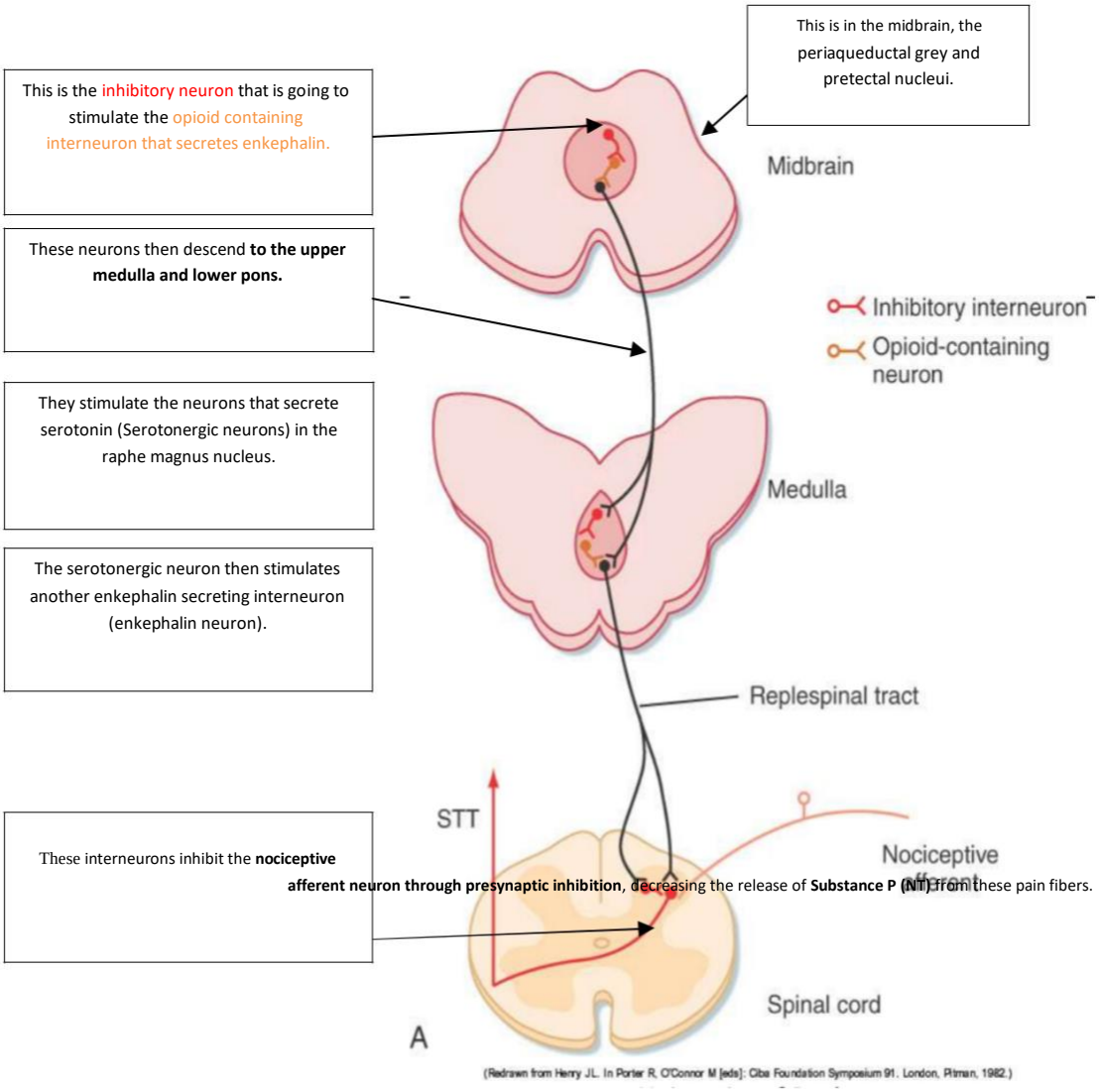
1. Pain fibers end at the **periventricular nuclei and periaqueductal gray matter**.
2. They then stimulate neurons that secrete enkephalins (Enkephalin Neurons).
3. These neurons descend down to the **medulla and pons area**.
4. They synapse with the neurons from the **Raphe magnus nucleus** or **paragigantocellularis nucleus**.
5. The second order neurons descend to the spinal cord and secrete **serotonin** (Serotonergic neurons), which will stimulate enkephalin interneurons in the spinal cord.



6. The enkephalin neurons synapse pre-synaptically to pain-transmitting fibers.
7. Through **presynaptic inhibition**, they **decrease the release of neuropeptides** that are used as neurotransmitters for pain (Substance P).
8. So, the stimulation of these interneurons (enkephalin neurons) presynaptically inhibit pain fibers, lowering the secretion of neuropeptide Substance P.
9. If it suppresses pain transmission through the anterolateral somatosensory pathway, pain fiber stimulation is decreased.
    - This descending tract is an ipsilateral tract. If it starts from the right side it will affect the right side of the spinal cord, and vise versa.

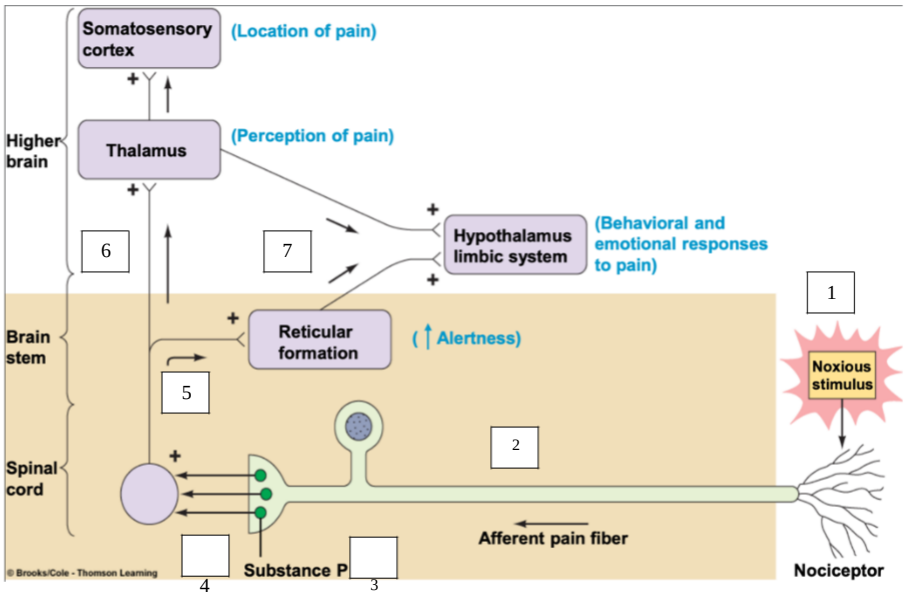
This figure further illustrates how this ipsilateral system works.

Again, remember that this is an **ipsilateral tract,** where the pain is suppressed before the signal crosses to the other side of the spinal cord.



How it works:

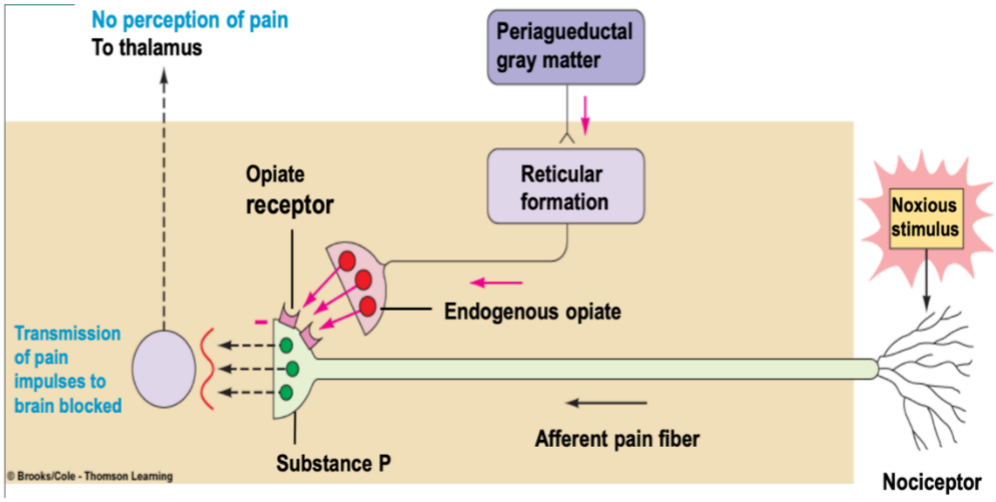
1. The **noxious stimulus** is the painful stimulus, and it stimulates the free nerve endings.
2. This runs through an **afferent pain fiber**.
3. In the spinal cord, the afferent pain fiber releases the **neuropeptide Substance P**, which causes prolongation of the stimulation.



4. Substance P stimulates the pain conducting fibers in the spinal cord.
5. These conducting fibers ascend upwards, activating the reticular activating system (which is important for wakefulness).
6. At the same time, some fibers go to the **thalamus**.
7. From the **thalamus** and the **RAS**, some fibers go to the **hypothalamus limbic system**. ○ The fibers that reach this system are important for behavioral and emotional responses to pain.
   ○ In the thalamus, you may have perception of pain, but the pain is only localized if the fibers reach the somatosensory cortex.

This figure shows the Endogenous Opiate System/Endogenous Analgesia System.

1. Fibers go to the periaqueductal gray matter.
2. From there, they reach the reticular formation (which includes the Raphe Magnus nucleus in the upper medulla lower pons area).

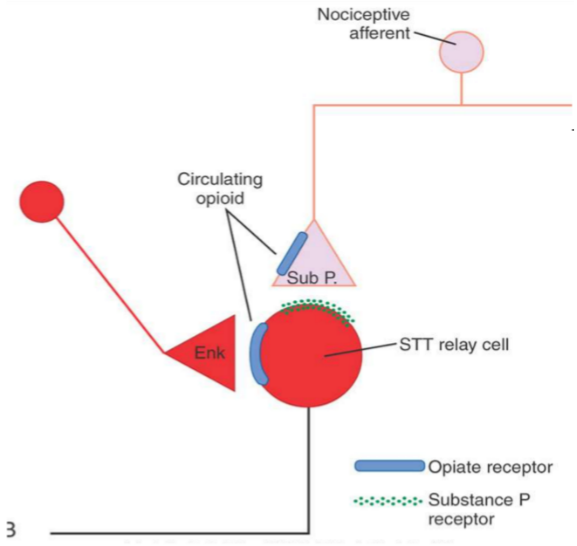


3. From the Raphe Magnus Nucleus, descending fibers secrete serotonin (Serotonergic Neurons).
4. Serotonergic fibers synapse with fibers that secrete opiates.
5. Once endogenous opiates are secreted from the interneurons, they cause presynaptic inhibition of the afferent fibers that transmit pain and secrete the neuropeptide substance P.
6. This inhibition decreases the release of substance P.
7. This blocks the transmission of pain impulses to the brain.

Again there are three main types of Opiates involved/used as neurotransmitters in this system:

1. Enkephalin
    a. Met-enkephalin
    b. Leu-enkephalin
2. Dynorphin (which is 200 times more active than morphine)
3. Beta Endorphin

Nociceptive stimulus stimulates afferent fibers → Substance P is secreted → Descending fiber from the endogenous opiate system stimulates enkephalin → Postsynaptic and Presynaptic inhibition → Substance P release is decreased → Transmission of pain is blocked/decreased.



- Higher brain levels, the periventricular nuclei of the hypothalamus and the medial forebrain bundle, can activate the periaqueductal gray region (leading to activation of the descending pathway of the endogenous analgesia system) and suppress pain.

Pain Suppression Mechanism

- Nerve fibers in the **periventricular nucleus and the periaqueductal gray** secrete enkephalin at their nerve endings.
- Nerve fibers from the **Raphe Magnus**, which receive information from the enkephalin releasing neurons, secrete serotonin at their nerve endings. These neurons are called seratonergic neurons.
- The serotonin causes the local neurons to secrete enkephalin.

- Enkephalin is believed to cause both pre- and post-synaptic inhibition of type C and type Ad pain fibers where they synapse in the dorsal horns.

How was the Endogenous Opiate System discovered?

- As you know, opiates morphine and its derivatives or substances derived from opium suppress pain, which explains why theyre given **during anasthesia**.
- It is uncommon that something external or exogenous could have associated receptors in our bodies, because such substances are supposedly not found in our bodies.
- They thought that since opiates have receptors in our bodies, in the brain, there must be substances that work like opiates or have similar receptors to morphine receptors.
- In the early 1970's it was discovered that an injection of minute quantities of morphine into the area around the third ventricle produced a profound and prolonged analgesia. This started the search for "morphine receptors" in the brain.
- They then identified several "opiate-like" substances. All are breakdown products of three large molecules: **proopiomelanocortin which forms b -endorphin, MSH and ACTH, proenkephalin- which forms enkephalin, and prodynorphin- which forms dynorphin; these are endogenous opiates.**

Endogenous Opiate Systems

- The major opiate substances: b endorphin, met-enkephalin, leu-enkephalin, dynorphin.
  - The enkephalins and dynorphin are found in the brain stem and spinal cord.
  - The b endorphin is found in the hypothalamus and the pituitary.

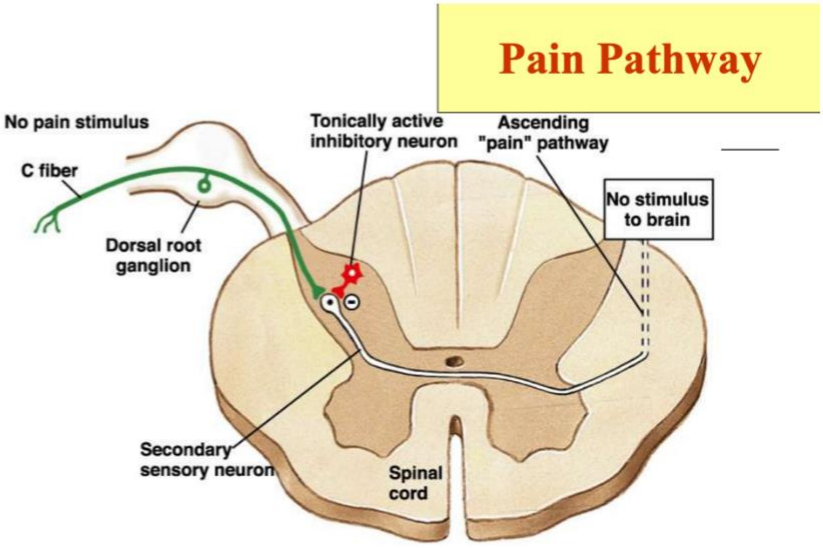
Function of the Opiate System

1. Pain suppression during times of stress.
2. An important part of an organism's response to an emergency is a reduction in the responsiveness to pain.
   - This is effective in defense, predation, dominance and adaptation to environmental challenges.
3. It is theorized that acupunctures (Chinese Needles) work through the stimulation of the Opiate system, releasing these endogenous opiates. If you stimulate certain areas of our body, these areas then stimulate the release of endogenous opiates in the brain.

Pain and Tactile Fibers

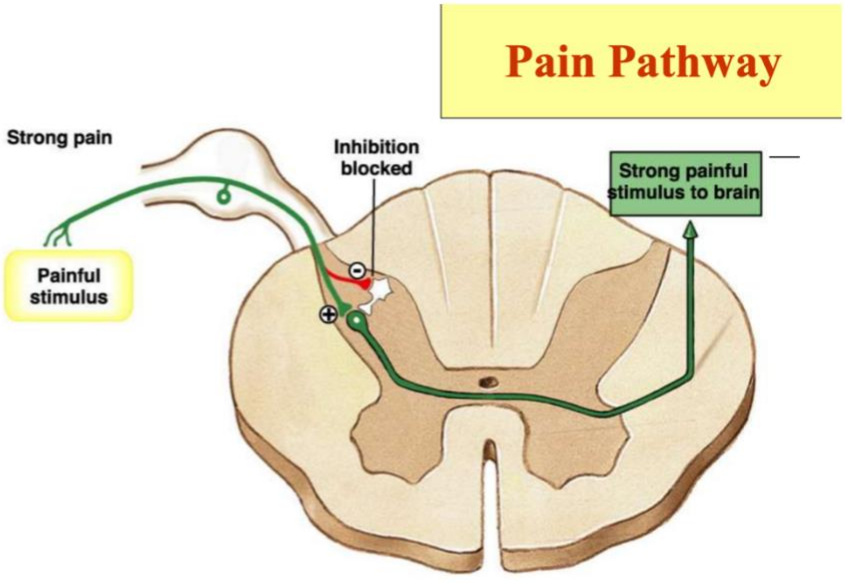
- Another theory for pain suppression: Stimulation of large type A b sensory fibers from peripheral tactile receptors can depress or suppress the transmission of pain signals, **"the gate control hypothesis".**
  - This is a **mechanical theory** not a chemical theory.
- **Mechanism**: **Lateral inhibition of the pain fiber** by the sensory fiber.
- Mechanism of action of massage, liniments, electrical stimulation of the skin.
- If you feel pain, you tend to scratch the area to suppress the feeling of pain. If you scratch the area, you stimulate the large tactile receptors. This stimulation was found to suppress the feeling of pain.

This figure shows the slow pain fibers (C fibers). Their nuclei are found in the **dorsal root ganglia.** They synapse at the **dorsal horn** with the second order neuron that **transmits pain along the ascending pathway**. A tonically active inhibitory neuron suppresses pain if activated.



How is it activated and inhibited?

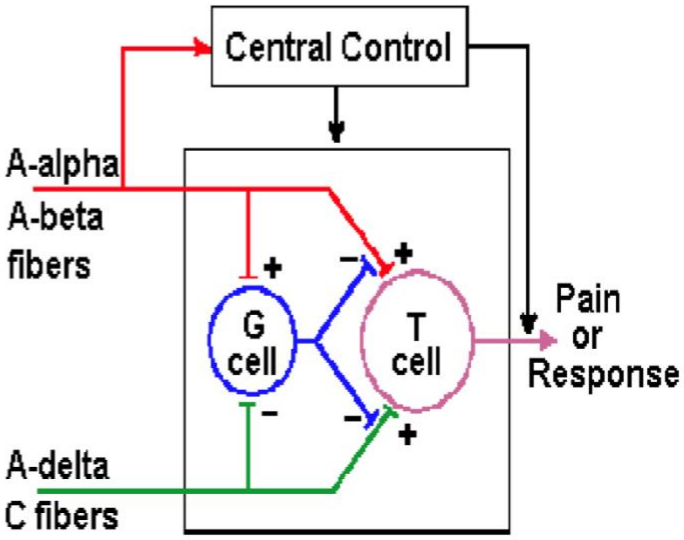
- If the pain **is very strong**, the diverging fiber from the afferent neuron (1st order neuron) inhibits the tonically active inhibiting neuron.
  - Inhibition of the tonically active neuron prevents it from blocking pain transmission – **The person feels pain.**

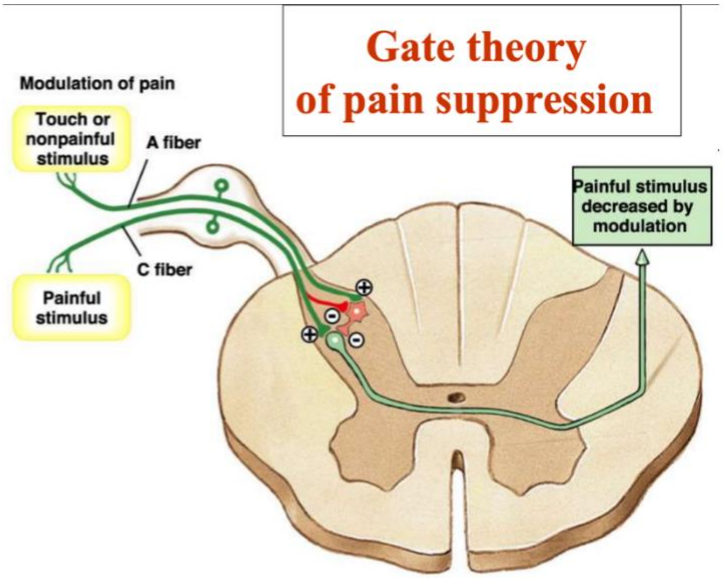


- Sometimes the feeling of pain is inhibited by the tonically active inhibitory neuron if you have weak pain.
- The activity of these tonically active inhibitory neurons **differs from one person to another.**
  - This explains why people have **different thresholds for pain**:
    - The higher the activity of the tonically active neuron, the higher the threshold for pain.
    - The lower the activity of these neurons, the lower the threshold.

Gate control theory of pain suppression

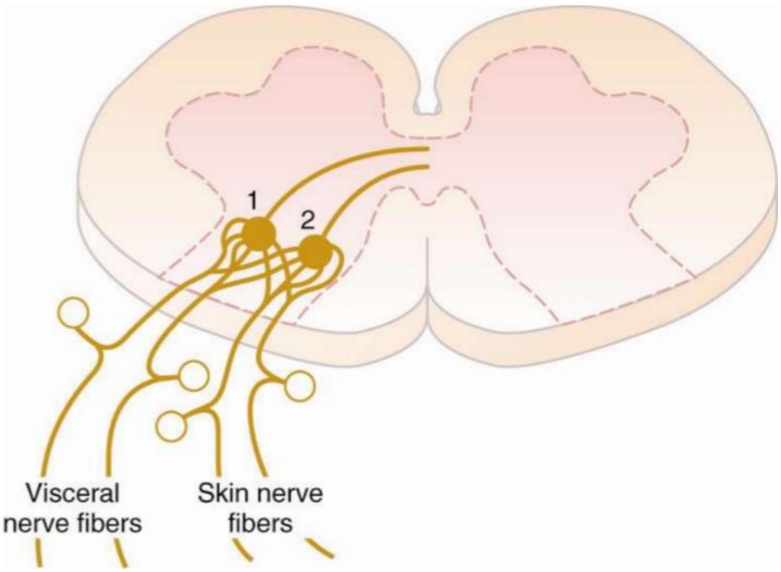
- Stimulation of A delta and C fibers transmits pain. How?
  - Their stimulation **inhibits the gate cell (G cell).**
  - They stimulate the **transmitting cell (T cell)**
    → **Pain is felt.**
- Stimulation of **A alpha and beta fibers** (Mechanoreceptors- tactile receptors) through mechanical touch:
  1. This stimulates the G cells (the tonically active inhibitory neurons).
  2. Activated G cells cause presynaptic inhibition of the pain fibers and transmitting cells (T cell).
  3. This leads to decreased release of the neurotransmitter substance P.
  4. This inhibits or decreases the T cell stimulation → pain transmission is inhibited → No pain is felt.





Visceral Pain: Proposed Neuronal Circuit for Referred Pain

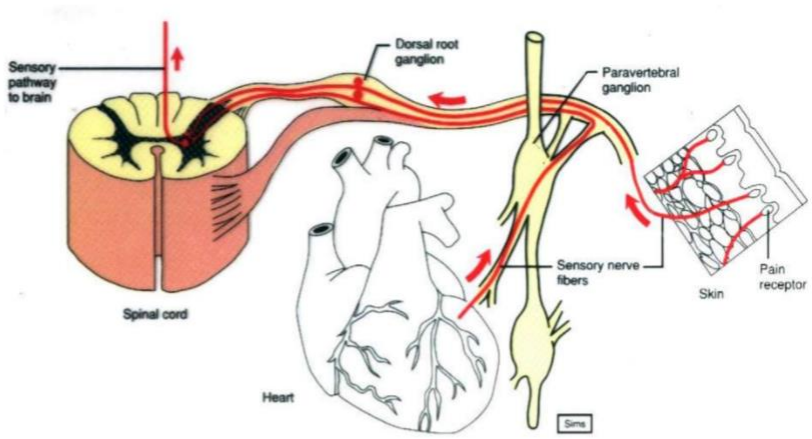
- Visceral pain coming from a particular organ usually is not felt in that particular area, since there is no representation of our viscera in the cerebral cortex.
- So, the cerebral cortex interprets this information or sensation as if it were coming from a somatic area.
- The viscera aren't supplied by somatic nerves; they are supplied by autonomic nerves.



- Autonomic nerves from the viscera enter the same segment which another somatic nerve (supplying part of the skin) enters.

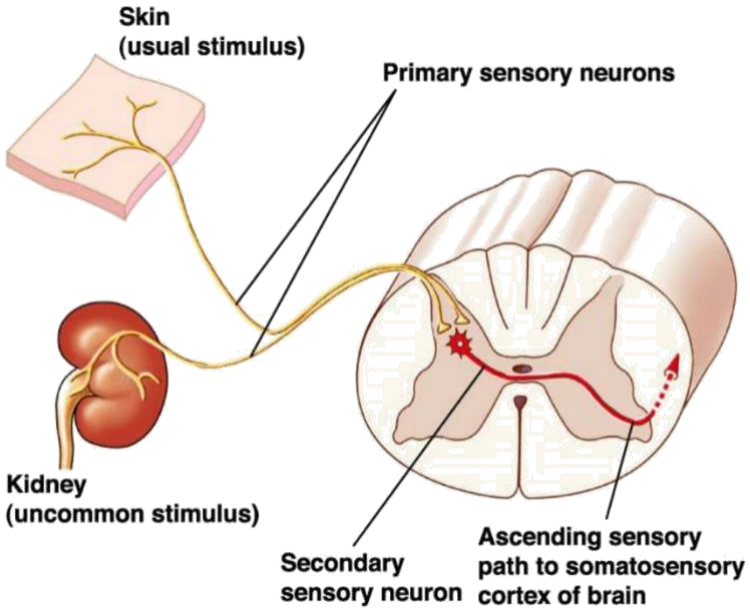
Example: The Heart

- **The heart** is derived from **C8, T1 and T2 segments.** It is supplied by **autonomic nerves.**
- The **skin of the left upper limb**, derived from the **ectoderm** of **C8, T1 and T2** **is supplied by somatic nerves.**



- These somatic nerves enter the same segment that the autonomic nerves entered from the heart.
- The autonomic nerves of the heart synapse with the same interneuron that transmits pain from the skin of the left upper limb. These neurons transmit pain to the representation of the left upper limb in the cerebral cortex.
- The neuron that carries pain from the heart synapses with the second order neuron which has the same connection to the nerves coming from the left upper limb.
- The pain is perceived by the cerebral cortex to have come from the left upper limb, although the pain is coming from the heart. This happens because the heart has no cerebral representation. **This visceral pain is called Referred Pain.**

Figure: Kidney Pain.



- Autonomic nerves carrying sensations from the kidneys enter a segment of the spinal cord which also receives sensations from the **skin of the loin**.
- Once the cerebral cortex receives these signals, the pain is perceived to have originated from our **lower back (loin region)** when it is actually pain from the **kidney**. This kidney pain has been REFERRED to the loin.

- Pain from an internal organ that is perceived to originate from a distant area of the skin, **because the skin has representation in the cerebral cortex.**
- The mechanism is thought to involve intermingling of second order neurons from the skin and the viscera. The second order neuron synapses with both **autonomic fibers coming from the viscera, as well as somatic fibers coming from the skin.**
- Viscera have **few sensory fibers except for pain fibers.** ○ Viscera have very few pain receptors.
- **Visceral pain is considered slow and can summate.**
  - ○ **Highly localized** damage to an organ may result **in little pain, because with the low density of pain receptors not enough fibers are stimulated in a localized area to feel pain.**
  - ○ **Widespread damage** can lead to **severe pain because it will summate.**

Localization of Visceral Pain

- Localization of visceral pain depends on the **dermatome of embryological origin**
- Examples:
  1. **Heart**: Pain in the neck, sternum, left shoulder and arm (left upper limb)
  2. **Stomach**: Region above the umbilicus
  3. **Colon**: Region below the umbilicus
  4. **Appendix**: Pain in the umbilicus, and then the pain descends to the right lower quadrant. (The appendix is derived from T10, and so is the umbilicus.)

- The appendix is derived from the mesoderm of T10.
- The skin of the umbilicus is derived from the ectoderm of T10.
- Pain from the appendix is first felt as pain around the **umbilicus**; slow, chronic pain that is hard to describe.
- **If the appendix is inflamed, this leads to inflammation of the peritoneum, which is supplied by somatic nerves.**
- This explains why, at some point, the pain descends to the right lower quadrant, at the area surrounding the peritoneum.

5. **Kidney**: The loin
6. **Liver and gallbladder**: On various areas of the right side including the right shoulder
7. **Ureter**: Genitalia