Pain Modulation

Khloud Shreif, Rachael Lowe, Eric Robertson, Kim Jackson, Sai Kripa, Kapil Narale

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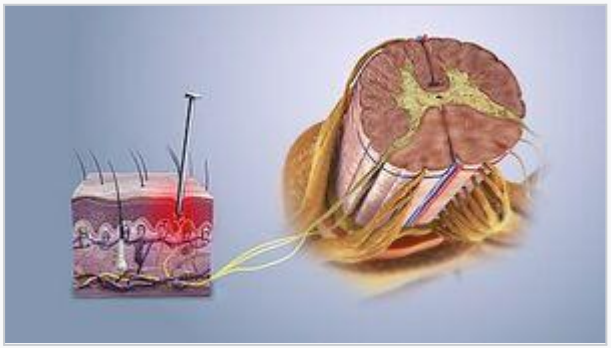
Pain modulation the process of alterations in the pain signals along the transmission pathway of pain, it explains why individuals respond to the same stimulus differently, explains the mechanism of action when using clinical analgesia. Pain control and modulation is a complex chore that is often the primary reason patients seek the services of rehabilitation professionals. Modulation of pain begins with an understanding of the various levels of pain modulation and extends to clinical interventions and protocols designed to reduce pain. For example, opiates are capable of increasing and decreasing pain experience.

Levels of Pain Modulation

Pain modulation is easily classified into 5 discrete levels of interaction. These levels correspond to either important synaptic junctions or significant chemical processes involved in the transmission of pain.

Level 1: Periphery

Level 1 pain modulation refers to events acting in the periphery of the body, at the source of the pain source. The somatosensation defined as the sensation from the skin, mucus, limbs, and joints and classified into: thermoception, nociception, equilibrioception mechanoreception response to (vibration, touch, and pressure), and proprioception.



Nociceptors are peripheral cell nerve endings that initiate pain sensation, respond to a noxious stimulus (thermal, mechanical, or chemical) which in turn trigger action potential to the spinal cord and to higher centers. It is divided into A-delta and C fibers.

- A-delta fibers are large(larger than C- fiber) myelinated, fast conducting fibers, concerned with localized, sharp, and fast sensation of pain.
- C- fibers are small, unmyelinated, slow conducting nerve fibers, concerned with dull, and slow pain sensation.

Under normal conditions, the nociceptors are inactive when there is a noxious stimulus (tissue damage) those pain receptors respond according to the stimulus type and cyclooxygenase-2 is activated to release more PG(prostaglandin) at the site of injury, and the nociceptors will transmit signals to the dorsal horn of spinal cord (first-order neuron) where the firs neuron release chemical substance P to transmit signals..

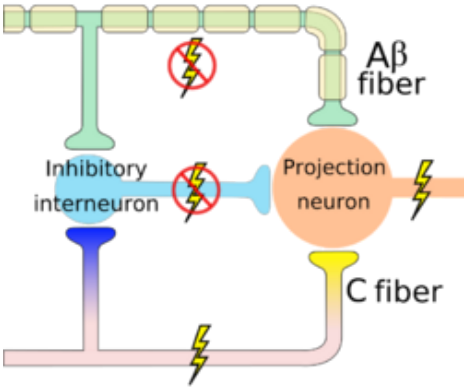
A- beta are myelinated, large diameter, and have the fastest conduction velocity. These fibers respond to non-painful stimuli such as touch sensation, mild pressure, and vibration. A beta stimulated by deep touch that explains why rubbing the painful site relief your pain[1][2].

Level 2: Dorsal Horn

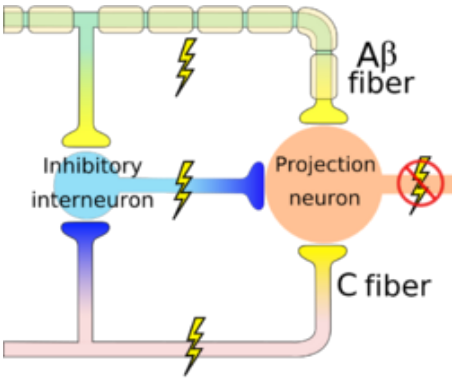
Level 2 pain modulation refers to events in the dorsal horn of the spinal cord. The modulation at the level of the spinal cord takes place at Substantial Gelatenosa of Ronaldo SG under the theory of gate control theory GCT, it was proposed for the first time in 1965 by Ronald Melzack and Patrick Wall, this theory explains pain transmission and modulation depending on large(**A-Beta**) and small (**C-fibers**) sensory fibers. At homeostasis conditions, the gait is closed and no pain signals are transmitted (the inhibitory interneuron I block the projection neuron which transmits pain signals and connects them to the brain).

When small nociceptors fibers are stimulated by noxious stimulus action potential signals are transmitted which in turn inhibit the inhibitory interneuron (I) and the projection neuron is activated the gate is opened and pain signals are transmitted to the brain. When action potential transmits through the first-order neuron that in turn activates the vesicles to release the *substance P* which propagates the transmission of pain signals.

If large sensory fibers(**A-Beta**) are activated by deep touch for example the transmitted signals activate the inhibitory interneuron and which blocks the projection neuron, the gate is close and no pain[3]. Interruption of pain signals at dorsal horn effect on spinothalamic tract to the cortex.

- 

gate opened

- 

gate closed

The modulation at the level of the spinal cord produces a localized analgesic effect and it receives another control from the descending pathway to cause diffuse inhibition of pain.

Level 3: Fast Neuronal Descending Pathways and Endogenous

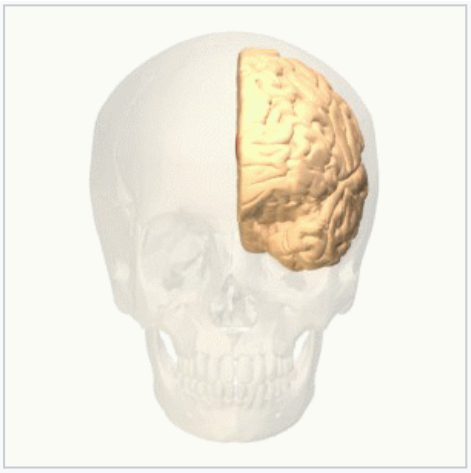
The descending inhibitory pathway/ pain modulation mechanism depend on the release of opioids at the SG it controls/ inhibits signals transmission between the the 1st and 2nd order

neuron. The descending pathway starts from periaqueductal gray matter PAG in the midbrain, then to raphe nucleus in the medulla to the dorsal horn of the spinal cord where:

These pathways release serotonin and noradrenergic neuron to inhibit the release of substance P from the presynaptic cleft of the first order neuron.

Stimulate the inhibitory interneuron to release opioids (endorphin, enkephalin) which in turn inhibit the presynaptic form releasing substance P and inhibit the post synapse of the second-order neuron from transmitting signals.

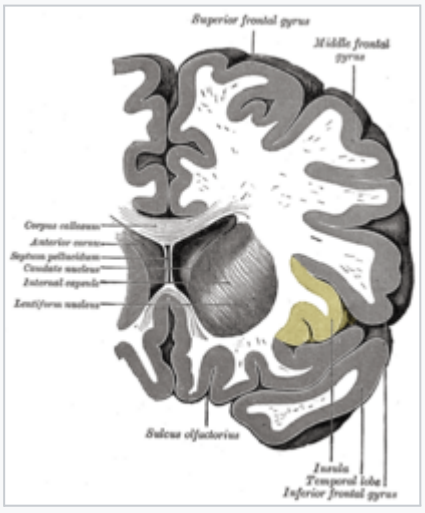
[4] **Level 4: Cortical**



Anterior cingulate cortex.

The noxious stimulus transmit to the cortex via spinothalamic tract that relay as a 3rd interneuron in the somatosensory area. Pain signals at the cortex induce pain modulation by two mechanisms:

- The cortex activate the PAG in the midbrain to activate the descending pathway (top-down control of pain) that interrupt and inhibit pain signals at the dorsal horn as mentioned before, so by extension the spinothalamic tract is inhibited[5].
    - The interaction between different areas; cerebral cortex, limbic forebrain structures, basal ganglia, the importance of this interaction is to perceive the noxious but as a non-painful. For example activation of the Anterior cingulate cortex (ACC) and the Rostral agranular insular cortex (RAIC) by noxious stimulus showed activation of these areas and an increase in the regional cerebral blood flow (rCBF) to these areas. **ACC** plays a role in pain transmission and is believed to be related to placebo analgesia and has a role with conditioned learning[6][7].



- Insular cortex.

Rostral agranular insular cortex also affect on the descending inhibitory pathway and is responsible for pain learning and memory. There is a study suggest that paraventricular hypothalamic nucleus send projections of oxytocinergic that support GABA neurotransmission and activate descending spinal noradrenergic mechanisms[8].

Physical Therapy Interventions for Pain Modulation.

A systematic review delivered by Arribas-Romano A, et al 2020, demonstrated that the physiotherapy modalities can alert pain perception with chronic musculoskeletal pain CMP through a decrease in temporal summation, increase conditioned pain modulation, and a slight improvement in central sensitization, and manual therapy and strengthening exercises were the most effective to produce these changes[9]. A combination of more than techniques demonstrated a significant increase in conditioned pain modulation.

Manual Therapy

Manual therapy showed an increase in the activity of cortical pain modulatory regions such as the insular cortex RAIC and periaqueductal gray substance PAG[9].

- Myofascial release and Message.
- Joint mobilization, low-velocity mobilizations[9].

- Spinal manipulative therapy: reduces the pain expectancy and strain occurs with exercise[10]

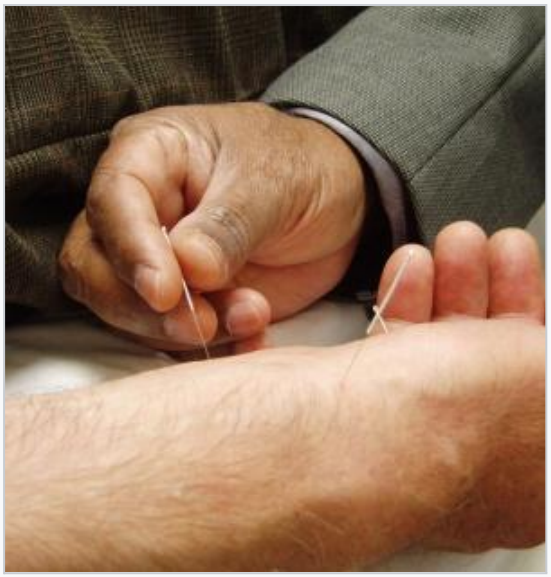
Modalities

- **Transcranial magnetic stimulation/ direct current stimulation.**

An important modality to reduce perception in chronic pain conditions and proved to have a significant difference when compared to a sham technique[11]. The precentral cortical area of the motor cortex is the most target area for pain modulation.

Transcutaneous Electrical Nerve Stimulation (TENS). TENS mechanism depend on gate control theory and release of endorphins and encephalin.

- **Low Level Laser Therapy.**
- **Acupuncture**



Acupuncture is used as a complementary modality for pain management, and it is mechanism depends on releasing of endogenous opioids, serotonin, and norepinephrine[12]. The variability in its effect may refer to the method of application, the number of needles, and the duration of application. There are studies with low to moderate quality that demonstrated a decrease in pain intensity with modest benefits especially with chronic pain(chronic low back pain, tension headache, chronic headache, migraine headache, and myofascial pain)[13]and slight improvement with acute conditions and this improvement is not clinically significant and may refer it to the placebo effect and other RCT there was no difference between sham and verum acupuncture and it may be used with patients who are not tolerable to other standard therapies[12].

- Dry needling.
- Interferential Therapy

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