Pain Modulation

Pain modulation means pain perception variability which is influenced by:
•Endogenous mechanism
•Exogenous mechanism

Pain modulation can be discussed under following headings:

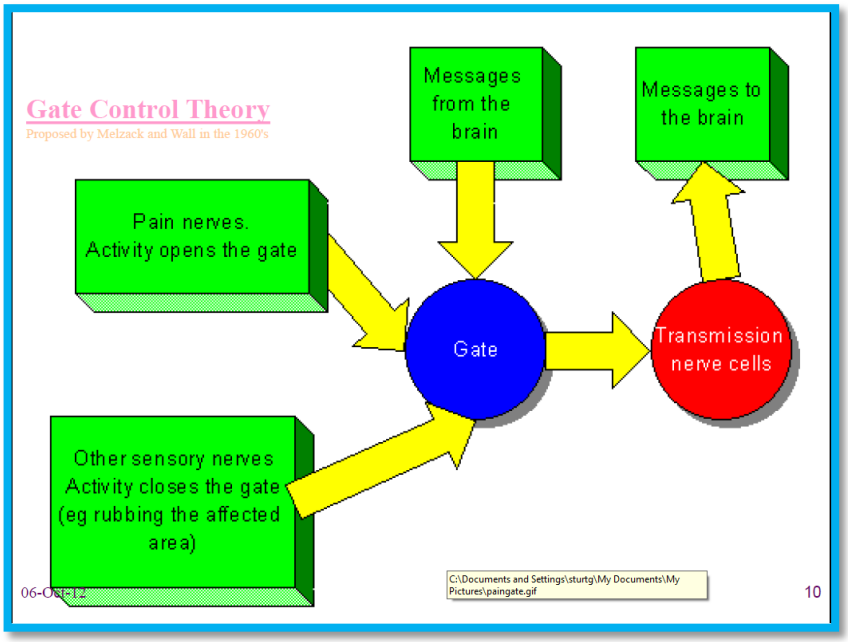
- **Spinal modulation** of pain input
  - Gate theory of pain
- **Supra spinal** modulation
  - Role of periaqueductal grey (PAG) matter
  - Role of Nucleus Raphe Magnus (NRM)
- Pain modulation by use of **Opioid neurotransmitters** eg: endorphin, enkaphalin Dynorphin.

The gate theory of pain control:

- Special neurons located in the grey matter of the spinal cord (**the dorsal horn of spinal cord SGR**) form the gate through which pain impulses must pass to reach brain.
- Three variables control this gate:
  A-Delta fibres (fast pain). (**Strongest**)
  C- fibres (slow pain).
  A-Beta fibres (light touch).

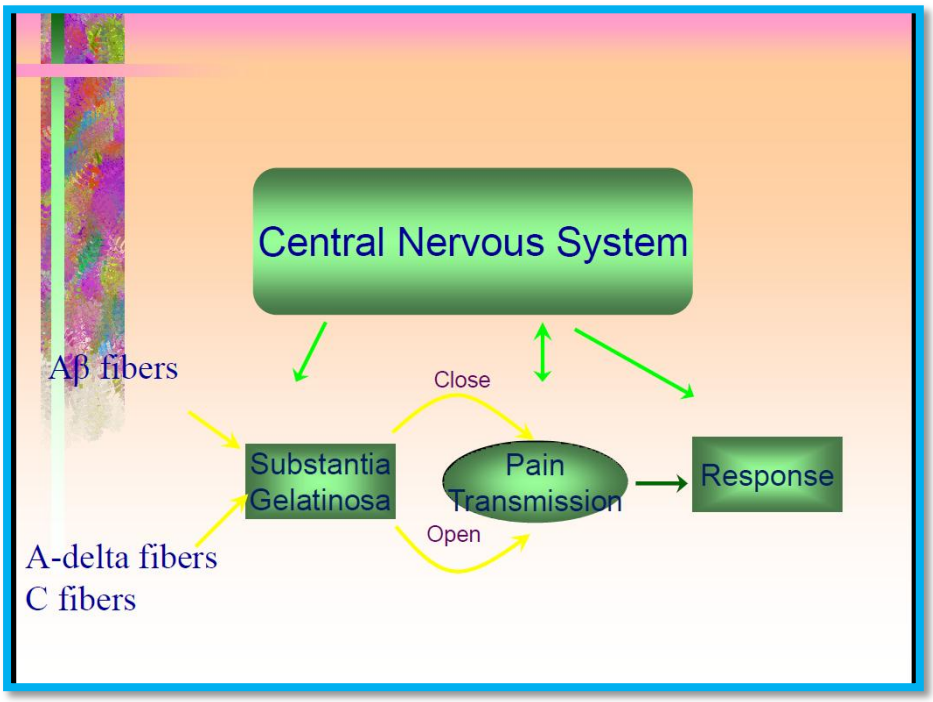
Pain Gate Theory

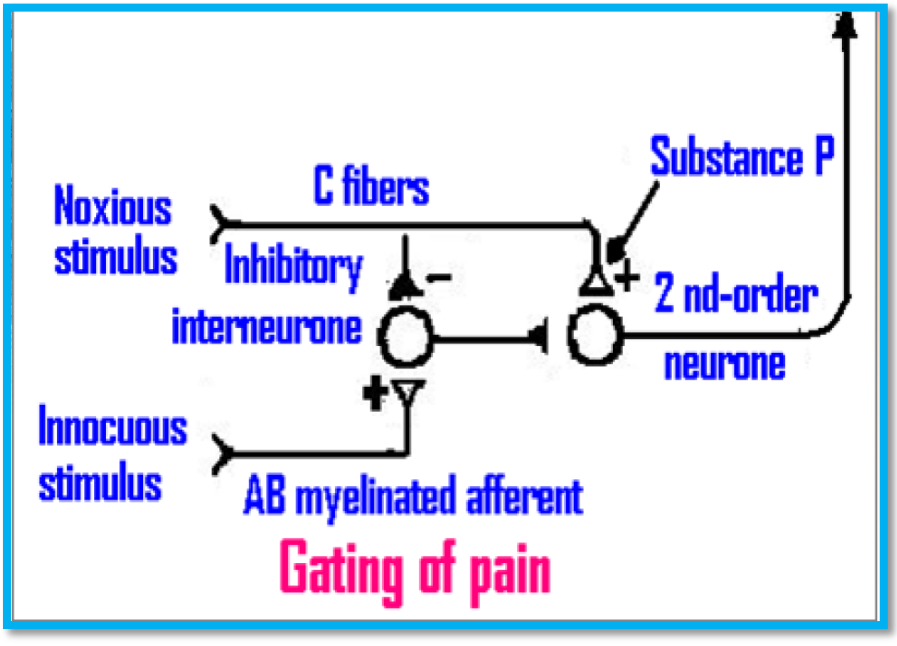
- This gate has the ability to **block** the signals from the **A-delta and C** fibres **preventing** them from reaching the brain.
- Gate opened or closed by 3 factors:
  1.Activity in the **pain** fibres - **opens** the gate.
  2.Activity in other **sensory** nerves - **closes** the gate.
  3.Messages from the brain.



The gate theory of pain control (Cont.)

- **Mechanism**:
  - Impulses coming along type C pain fibers → cause the release of substance P from these fibers →and tend to **open** the gate.
  - While impulses coming along Aβ fibers → tend to keep the gate **closed** by process of **presynaptic inhibition of C fibers and postsynaptic inhibition of secondary neurons in dorsal horn.**
    - **If** impulses in the C and A-Delta Fibres are stronger than the A-beta Fibres the gate opens.
    - **If** impulses in the A-beta Fibres are stronger than the C and A-Delta Fibres the gate closes.
      - A-delta fibres are **always** stronger!





Explanation

Gate Control Theory:

- Having learnt this from practical experience, shaking/rubbing an injured area results in a decreased amount of pain, have you ever wondered **why**?
- The theory behind this is the gate control of pain which states: Pain is a function of the balance between the information travelling into the spinal cord through large (touch, pressure, vibration) nerve fibres [carrying non-nociceptive information] and information travelling into the spinal cord through thin (pain) nerve fibres [carrying nociceptive information]. **If the relative amount of activity is greater in large nerve fibres, there should be little or no pain. However, if there is more activity in small nerve fibres, then there will be pain**.
- Let's go through this theory in **steps**:

1) Both **thin** (pain) and **large** (touch, pressure, vibration) nerve fibres carry information from site of injury to 2 destinations.

2) The 2 destinations are:

(a) dorsal horn of spinal cord; transmission cells that carry pain signals up to the brain and

(b) inhibitory interneurons that impede transmission cells' activity.

3) When both nerve fibres are active → transmission cells are excited

4) Activity in thin fibres → inhibitory cells are impeded; allowing transmission cells to fire

5) Activity in large fibres → inhibitory cells excited; inhibiting transmission cell activity

6) Hence, the more large nerve fibres activated in comparison to thin ones, the less pain is felt.

7) So, WITHOUT any stimulation: both large and thin nerve fibres are quite and the inhibitory interneurons BLOCKS the signal in the projection neuron (that connects to the brain); gate is CLOSED; NO PAIN

8) With NON-PAINFUL stimulation: large nerve fibres are activated; activating the projecting neuron AND activating the inhibitory interneurons (which now blocks the signal in the projection neuron that connects to the brain); gate is CLOSED; NO PAIN

9) With PAINFUL stimulation: thin nerve fibres become more active, activating the projection neuron AND BLOCKING the inhibitory interneurons; pain signal is NOT BLOCKED; gate is OPEN; PAIN!

10) So this is the explanation behind skin rubbing, shaking the painful part, transcutaneous electrical stimulation & acupuncture; to STIMULATE **mechanoreceptors** that ACTIVATE neurons of dorsal column large fibres, allowing them to TAKE OVER the thin fibres' activity.

The gate theory of pain control (Cont.)

- So is that what controls the gate only?

No, there is also control by HIGHER CENTRES called **control triggers**

- How do these centres control the gate?

Via specialised nerve impulses that arise in the brain, inhibitory and excitatory nerve signals travel down and influence the gate sensitising it to either C or A-β fibres.

Supra spinal modulation (Special pain control analgesic system)

•This is a specific system that **blocks** pain transmission in CNS. Its major constituents are, so **what areas of the brain are responsible for pain REDUCTION?**

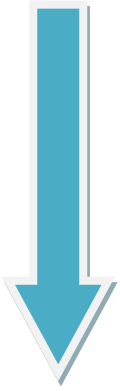
- ✓ Periaqueductal Gray (PAG) – in midbrain
- ✓ Nucleus raphe magnus (NRM) – in upper medulla
- ✓ Periventricular nucleus – in hypothalamus, near 3rd ventricle
- ✓ Pain inhibitory complex (PIC) – in dorsal horn of spinal cord:
  - It consists of multiple short encephalinergic neurons that terminate on central endings of pain conducting afferent fibers
  - When stimulated the released encephalin cause pre & postsynaptic inhibition of pain transmission i.e it prevents the release of substance P from pain nerve endings.

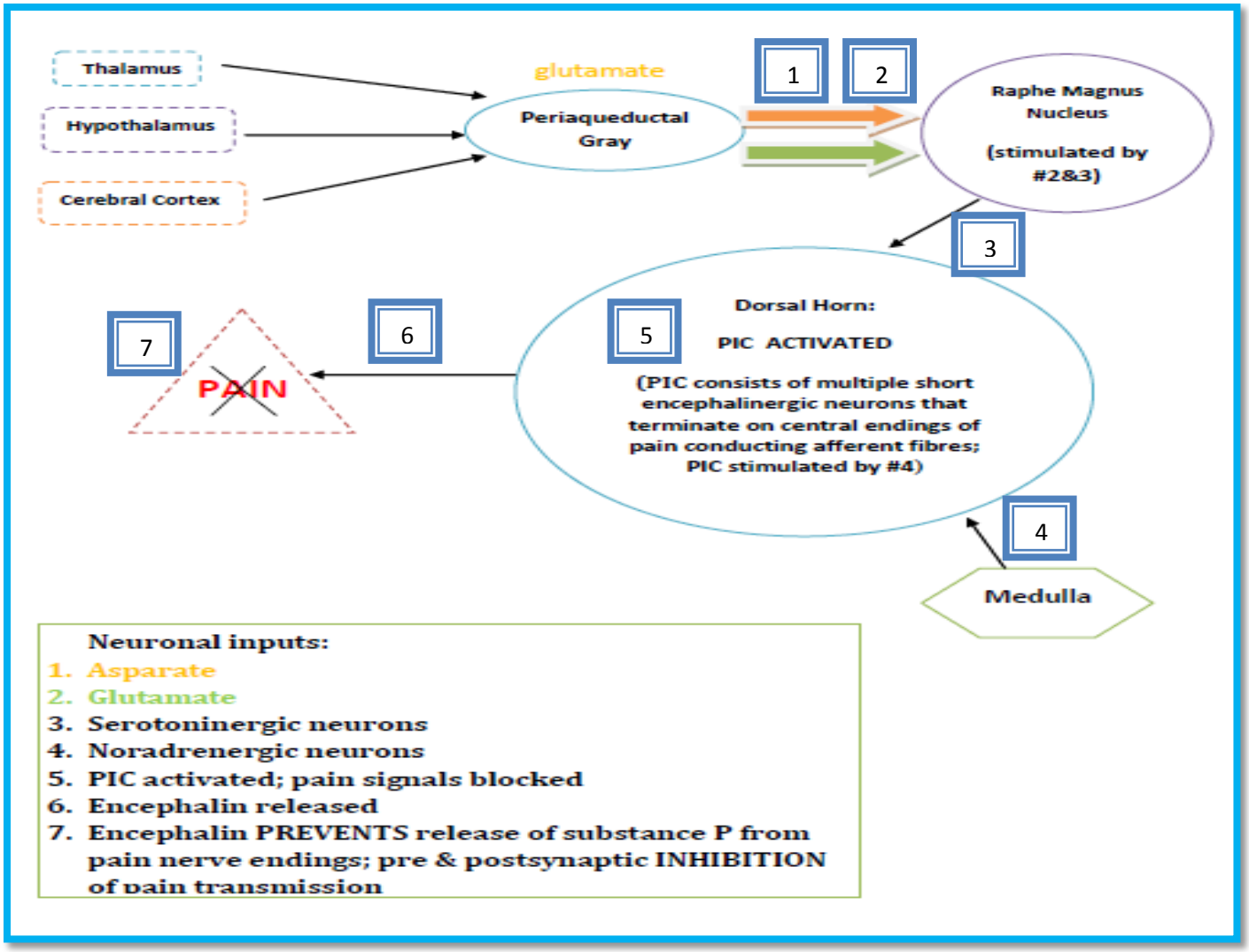
Analgesia occurs as follows:

•Periaqueductal grey area receives neuronal inputs from thalamus, hypothalamus, cerebral cortex.

•PAG projects neurons containing aspartate & glutamate that stimulate raph magnus nucleus (RMN)

•RMN projects serotoninergic neurons, this in addition to noradrenergic neurons project from adjacent medulla to dorsal horn. They block pain signals by activating PIC.





Opiod receptor modulation:

What are opioid peptides?

- Opioid peptides are morphine-like substances present in body.
- They are natural analgesic substances that act by binding to opiate receptors in **analgesic system** and **dorsal horn of SC on central ending of pain conducting pain fibers.**

Mechanism of opiod neurotransmitter action:

- **Endorphin**: Neurons using endorphin or enkaphalin are found in PAG where they inhibit GABAnergic interneurons that normally suppress the anti-nociceptor neurons
- **Enkephalin**: It is used by interneurons in lamina II responsible for inhibiting the lamina – I nocioceptor-specific spinothalamic neurons
- **Dynorphin**: In hypothalamus, PAG, reticular formation, and dorsal horn.
- Endogenous morphin: In terminals forming synapses with neuron having μ-opioid receptors in pain modulating pathways.

Opioid Antagonist: Naloxone

- Used to reverse opioid overdose
- Displaces receptor-bound opioids
- Good for overcoming respiratory and CV depression

Different Pain sensations:

Hyperalgesia	Excessive Pain
Allodynia	Pain caused by any other sensation e.g. touch will cause pain.
Muscular Pain	Less blood flow in the muscles (ischemia).
Causalgia	Burning pain
Stress induced analgesia	Mild degree of pain is not felt if the other part of the body has excessive pain. It's a well known phenomenon seen when the soldier is wounded in battle field but feels no pain until the battle is over. The cause is not known may be it is similar to Gate control hypothesis.
Phantom pain	Pain felt in an amputated part long after amputation was done.
Thalamic Syndrome	Obstruction of the thalmogeniculate branch of the posterior cerebral artery Affects posterior thalamic nuclei. Prolonged severe pain**.**
Trigeminal neuralgia	It is excruciating intermittent pain by stimulation of trigger area in the face e.g. Washing of face, combing hair, blast of air on face. It results from compression of trigeminal nerve root by blood vessels
Chronic pain	•Chronic pain can be considered as bad pain because it persist long after injury and is often refractory to pain killers. •Chronic pain caused by nerve injury is called neuropathic pain.
Neuropathic pain	•Caused by the damage to peripheral nerve. •The distal cut end develops a scar tissue forming rounded ball (neuroma) which is sensitive to pressure. •Repeated activation causes continuous pain. •Examples post herpetic neuralgia and diabetic neuropathy.

Sites and mechanisms of pain relief:

- Block production of inflammatory mediators.e.g. Aspirin & nonsteroidal antiinflammatories.
- Sympathectomy can be useful.
- Exogenously administration of opoid like drugs.
- Electrical stimulation of the dorsal column can alleviate pain originating below site of stimulation.
- Selective activation of large diameter afferent fibers by transcutaneous electrical nerve stimulation.
- Stimulation of brainstem sites or administration of drugs which can modify serotoninergic or adrenergic neurons e.g. antidepressants.

Test your knowledge – for both pain lectures 6+29:

1- Pain is:

a) Unconscious activity caused by a harmful stimulus

b) Any unpleasant sensation with/without tissue damage

c) Neural process of processing noxious stimuli

d) Any unpleasant sensation associated with tissue damage whether or not individual is aware of

2- Natural mechanisms of pain relief are:

a) Gate control and electrical stimulation

b) Gate control

c) Gate control and pain analgesic system

d) No natural mechanism

3- Radiating pain is usually in origin:

a) Visceral

b) Muscular

c) Facial

d) Neuropathic

4- 46 y/o female presenting with severe facial pain upon strange stimuli such as applying her everyday make-up, what is the most probable diagnosis and what's its explanation?

a) Thalamic syndrome; damage of thalamus

b) Trigeminal neuralgia; congenital defect in cranial nerve 5

c) Trigeminal neuralgia; compression of cranial nerve 5

d) Herpes zoster

5- All are true except:

a) Activity in thin fibres lead to impedance of inhibitory cells

b) Activity in large fibres lead to impedance of inhibitory cells

c) Thin fibres carry pain impulses

d) Activity in both fibres cause excitement in transmission cells

6- All are responsible for pain reduction except:

a) Post thalamic nuclei

b) Periaqueductal gray

c) Nucleus raphe magnus

d) Periventricular nucleus

7- All are true regarding encephalin except:

a) Prevents release of substance P

b) Pre and postsynaptic inhibition of pain transmission

c) Stimulated by noradrenergic neurons

d) Released from ventral horn

8- NSAIDs ' analgesic effect is conducted by:

a) Blocking nerve endings

b) Inhibit release of inflammatory mediators

c) A placebo effect only

d) Block transfer of signals at spinal level

9- Regarding referred pain:

a) Appendicitis pain is referred to umbilical area

b) Kidney stone pain is referred to suprapubic area

c) Fractured radius pain is referred to finger tips

d) Angina pain is referred to umbilical area

10- Neuralgia is:

a) Pain following nerve damage

b) Shrinkage of acute nerve endings

c) Cannot be treated surgically

d) Only seen in amputees

11- Phantom limb phenomenon is:

a) Only seen in amputees

b) May be encountered in post cancer breast surgery

c) Done due to inability of brain to reorganise the surgical event

d) Cannot be treated

Answers:

1) B
2) C
3) A
4) C
5) B
6) A
7) D
8) B
9) A
10) A
11) B