Pain Modulation

By Laiche Djouhri, PhD

Associate Professor

Dept. of Physiology

Email: ldjouhri@ksu.edu.sa Ext:71044

Week 6 Lecture

Chapter 49

(Guyton & Hall)

Somatic Sensations:II

Pain, headache and Thermal Sensations

Objectives

By the end of this session you are expected to be able to:

- Describe the built-in pain suppression ``**Analgesia**`` system
  - In the Spinal Cord (**Gate theory of pain control**)
  - In the Brain (**Descending Inhibitory System**)
- Describe the brain's opioid system
- Appreciate that pain can also be **facilitated**

Pain Modulation

What is Pain Modulation ?

A decrease or **an increase** in the sensation of pain caused by **inhibition** or **facilitation** of pain signal.

INHIBITION: nociceptive input can be inhibited by:

1. Spinal (segmental) inhibition: **Gate control theory**
2. Supra-spinal (descending) inhibition

FACILITATION

3. Peripheral sensitization (release of chemicals after tissue injury)
4. Central sensitization (Dis-inhibition)

Pain Modulation

Question

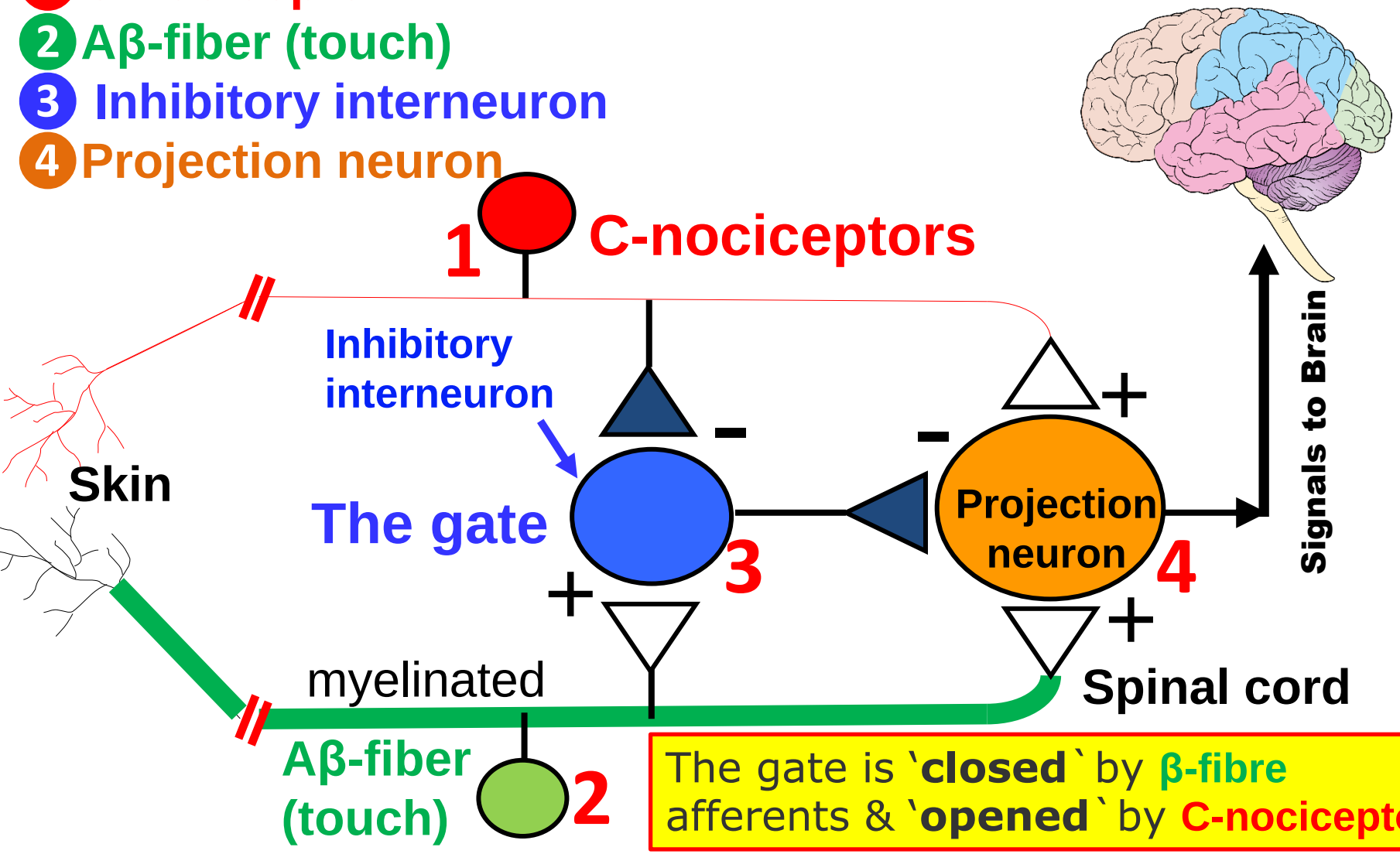
Why does it feel better to rub a bumped skin?

Spinal Inhibition: Gate Control Theory-1

- 4 types of neurons are involved:

Melzack and Wall, 1965

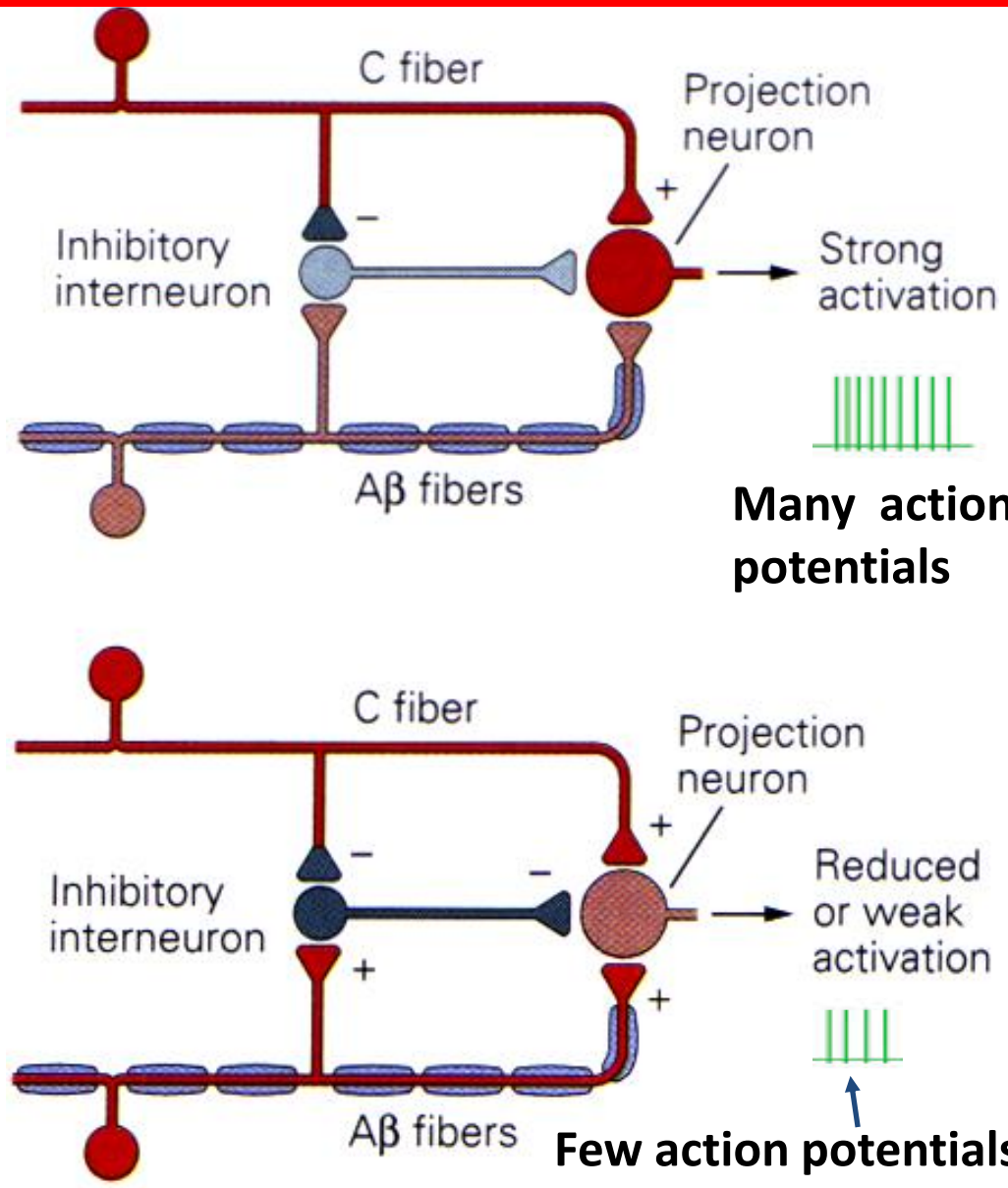
1. C-nociceptor
2. Aβ-fiber (touch)
3. Inhibitory interneuron
4. Projection neuron



The gate is `**closed**` by β-fibre afferents & `**opened**` by **C-nociceptors**

Gate Control of Pain-2

- Projection neuron receives input from both C-fibers and **Aβ-fibers**
- Firing of **C fibers inhibits** the inhibitory interneuron(open gate)
- Firing of the **Aβ fibers activates** the inhibitory interneuron (close gate)
- The theory implies that a **non-painful stimulus** can reduce transmission of a noxious stimulus.



Gate Control Theory-3

The gate-control theory is the basis for:

- **Rubbing the traumatized area such as a bumped head**
  - The initial trauma activates the A-delta and, eventually, C-fibers
  - Rubbing stimulates the A-beta (**touch**) fibers, which activate inhibitory interneuron to **close** the spinal gate
  - This inhibits transmission of the painful stimulus
- **The use of non-noxious cold & heat to relief pain**
- **The use of transcutaneous electrical nerve stimulation (TENS) for pain relief (see next slide).**

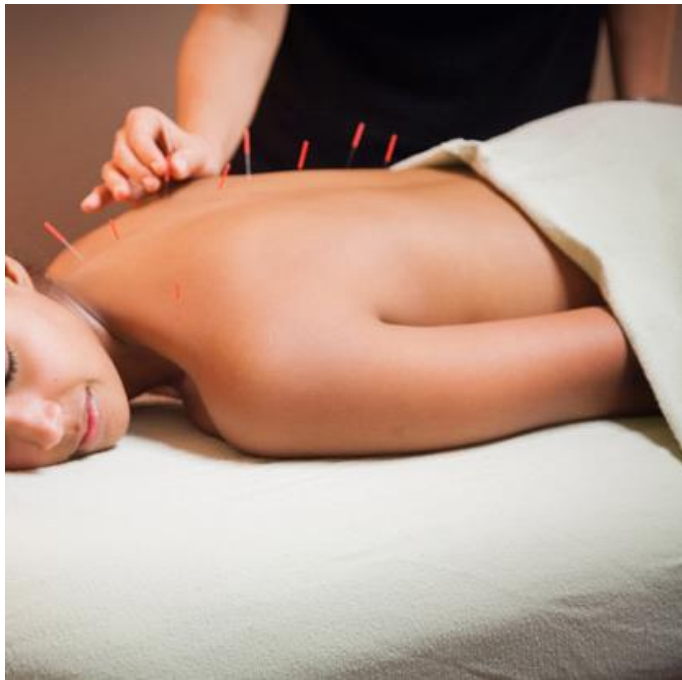
Transcutaneous Electrical Nerve Stimulation (TENS)

- The gate-control theory is also the basis for the use of TENS for pain relief.
- Uses a battery-operated unit with electrodes applied to the skin to produce a tingling, vibrating, or buzzing sensation in the area of pain (**self-operated**)
- Decreases pain for up to **several hours,** by stimulating the **non-pain receptors** in the same area as the fibers that transmit pain
- Used for **post operative pain**, **osteoarthritis,** back pain, and other types of pain.

Inhibition of Pain Transmission: Acupuncture

- Extremely fine needles are inserted at certain sites in the body for treating pain
- Is a treatment derived from **ancient Chinese medicine**
- Technique for **balancing the flow of energy** (Traditional Chinese medicine)

- Western GPs see it as points to **stimulate nerves**, muscles and connective tissue.
- It is thought to boost the body's **natural painkillers** (**opioids**) and increases blood flow.



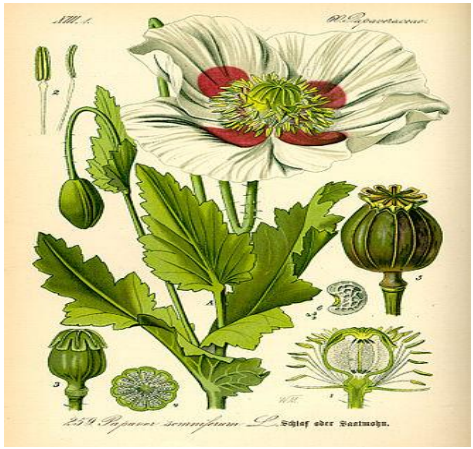
What are Opioids?

- **Opioids:** refer to drugs in a generic sense, natural or synthetic, with morphine-like actions
- **Opiates:** restricted to synthetic morphine-like drugs

Opium الأفيون

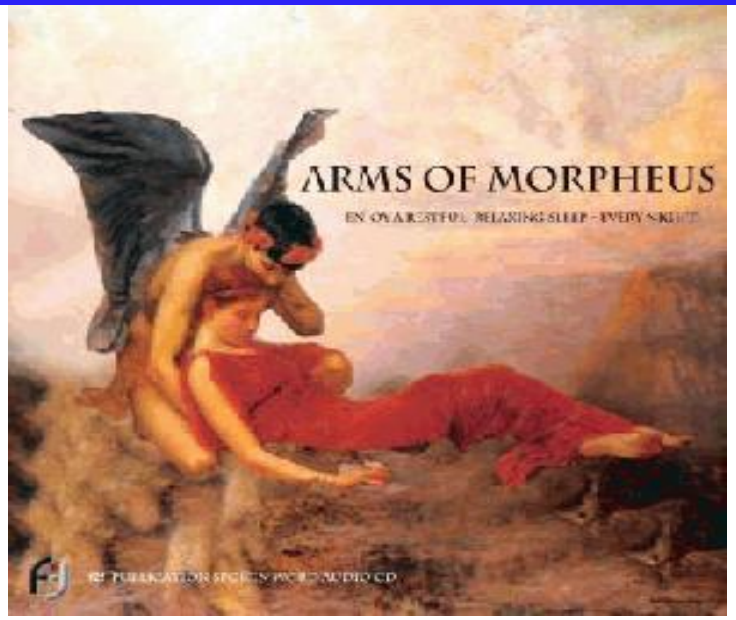
Opium (أفيون): extract of juice of the poppy (**Papaver Somniferum**)

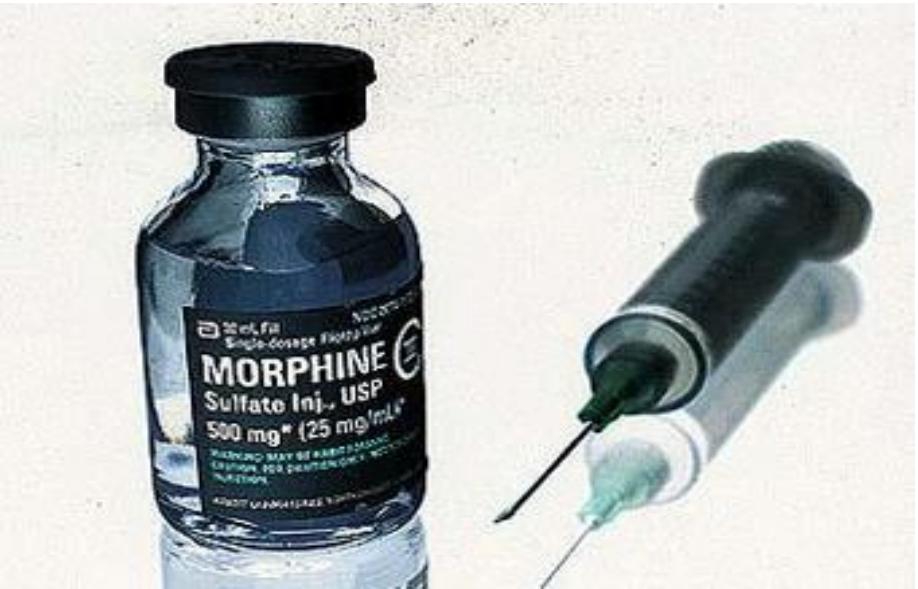
- Used as agent for analgesia, euphoria, sleep and diarrhea.
- Contains **12%** morphine and many alkaloids related to morphine.
- Used with alcohol to treat most diseases



Papaver Somniferum
الخشخاش المنوم

What is Morphine?





- *Morphine is named after **Morpheus***, the Greek god of **dreams**. Morpheus is the son of **Hypnos**, the god of **sleep.**
- **God`s own gift!!**
- Was isolated from opium, in 1805 by *Friedrich Wilhelm Adam Sertürner*, a German pharmacist

Pain Modulation

What is Pain Modulation ?

A decrease or **an increase** in the sensation of pain caused by **inhibition** or **facilitation** of pain signal.

INHIBITION: nociceptive input can be inhibited by:

1. Spinal (segmental) inhibition: **Gate control theory**
2. Supra-spinal (descending) inhibition

FACILITATION

3. Peripheral sensitization (release of chemicals after tissue injury)
4. Central sensitization (Dis-inhibition)

Descending Pain Control System (The Built-in Analgesic System)

1. **Periventricular nucleus** project to **PAG (4th ventricle)**
2. **Periaqueductal Gray (PAG)**
   - Opioid Receptors
   - Projects to **Raphe Nuclei**
3. **Raphe nucleus**
   - Projects to dorsal horn
   - Release **serotonin**
4. **Locus coeruleus (not shown)**
   - Projects to dorsal horn
   - Release **noradrenaline**
5. **Enkephalin-containing interneurons** in spinal cord

The system uses endogenous opioids (natural pain killers)

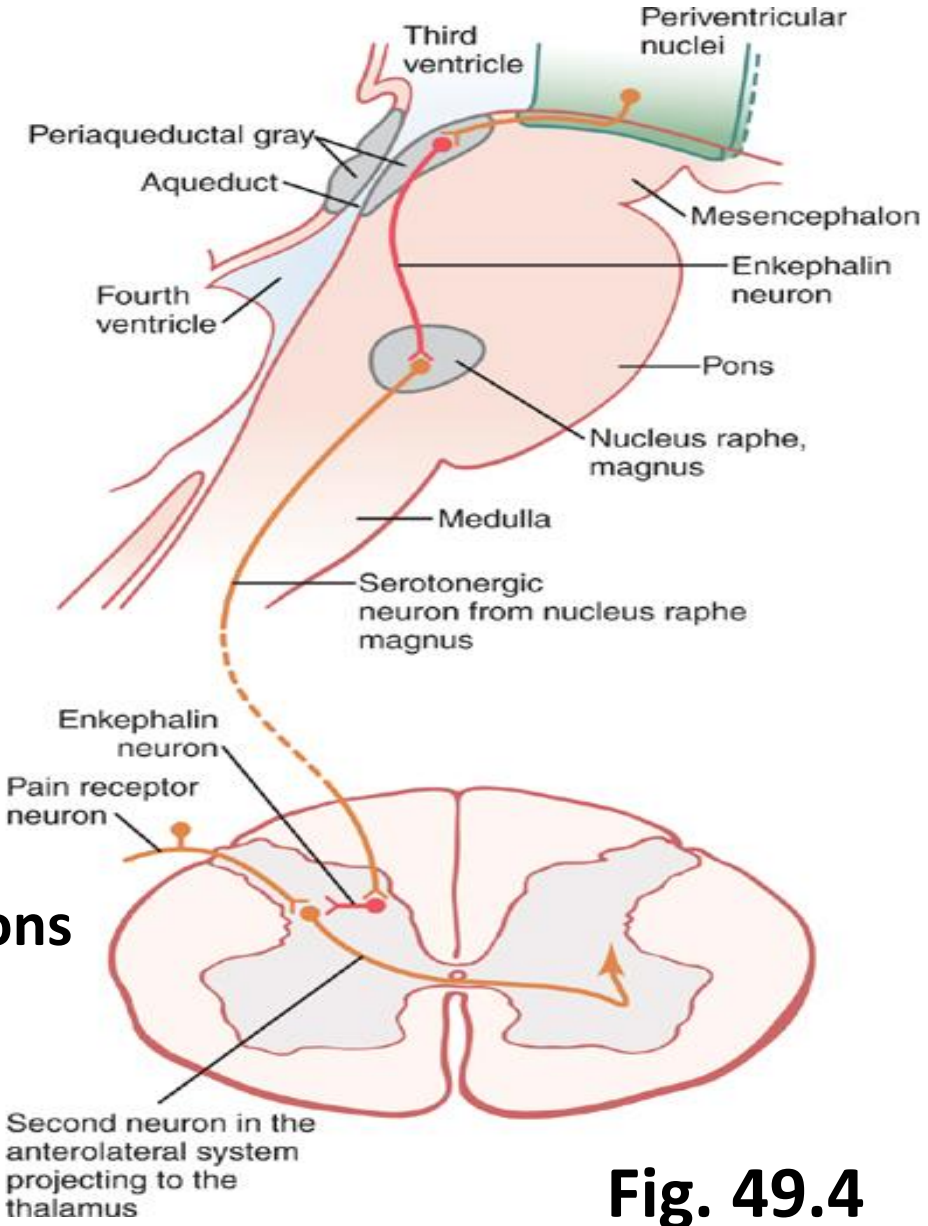
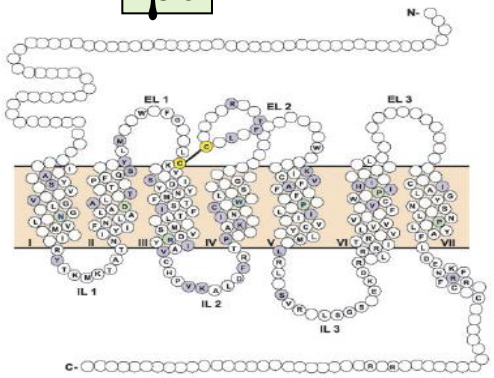


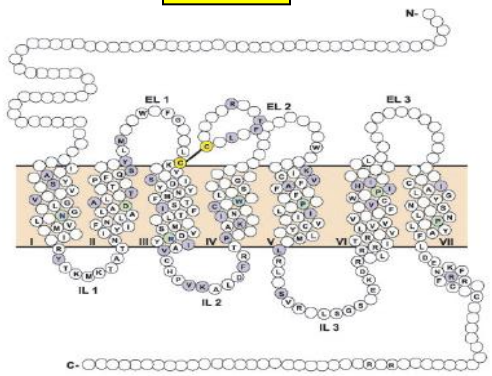
Fig. 49.4

Endogenous Opioid Peptides & Opioid Receptors

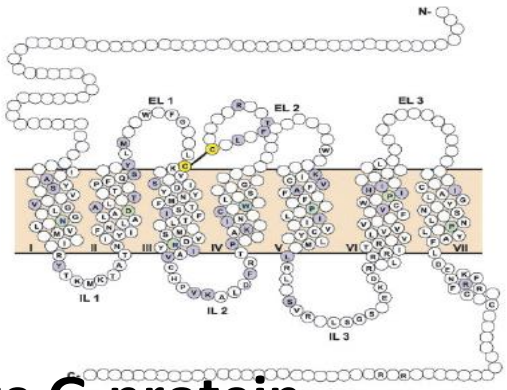
μ mu



δ delta



K kappa



Endogenous Opioids

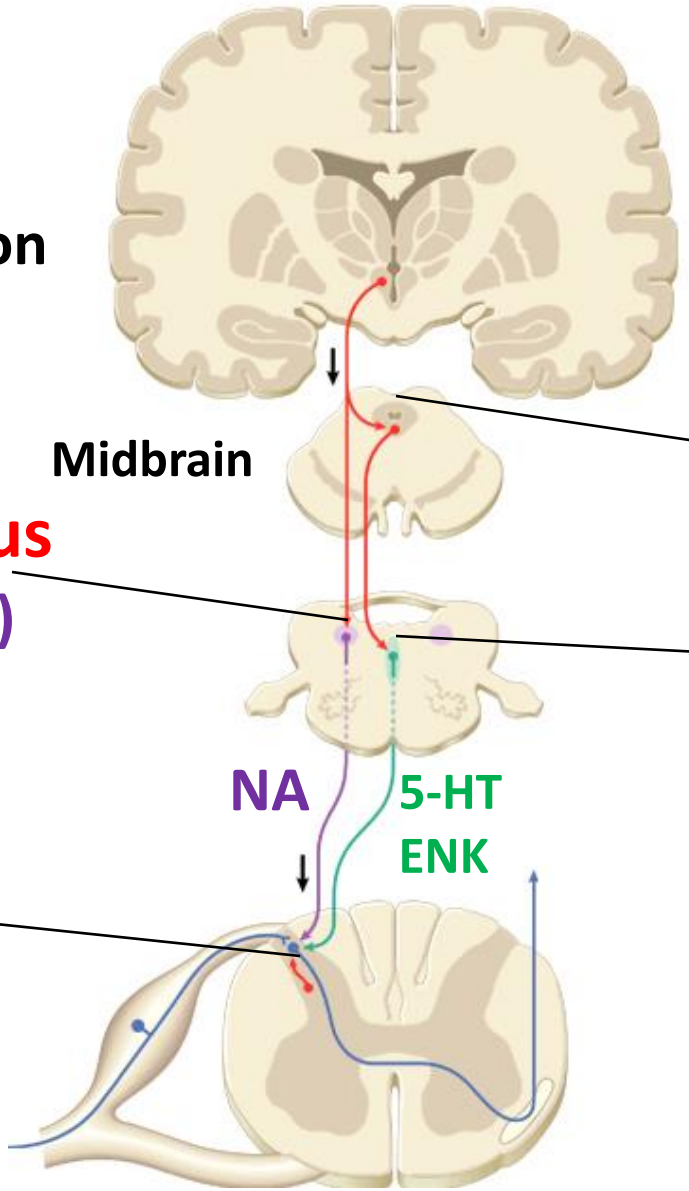
- **Endorphins**
- Enkephalins
- Dynorphins

- **Opioid receptors are G-protein coupled receptors**
- **CNS distribution:**
  - Cerebral cortex
  - Amygdala
  - Thalamus
  - Hypothalamus
  - **Midbrain (PAG)**
  - **Spinal cord**
- **Periphery**

σ sigma

Distribution of Endogenous Opioids and their Receptors

Distribution of mu receptors coincide with the distribution of ENK containing neurons.



Sites of actions of Opiates on pain transmission

Opiates inhibit the link between the periphery and CNS, and enhance descending inhibition

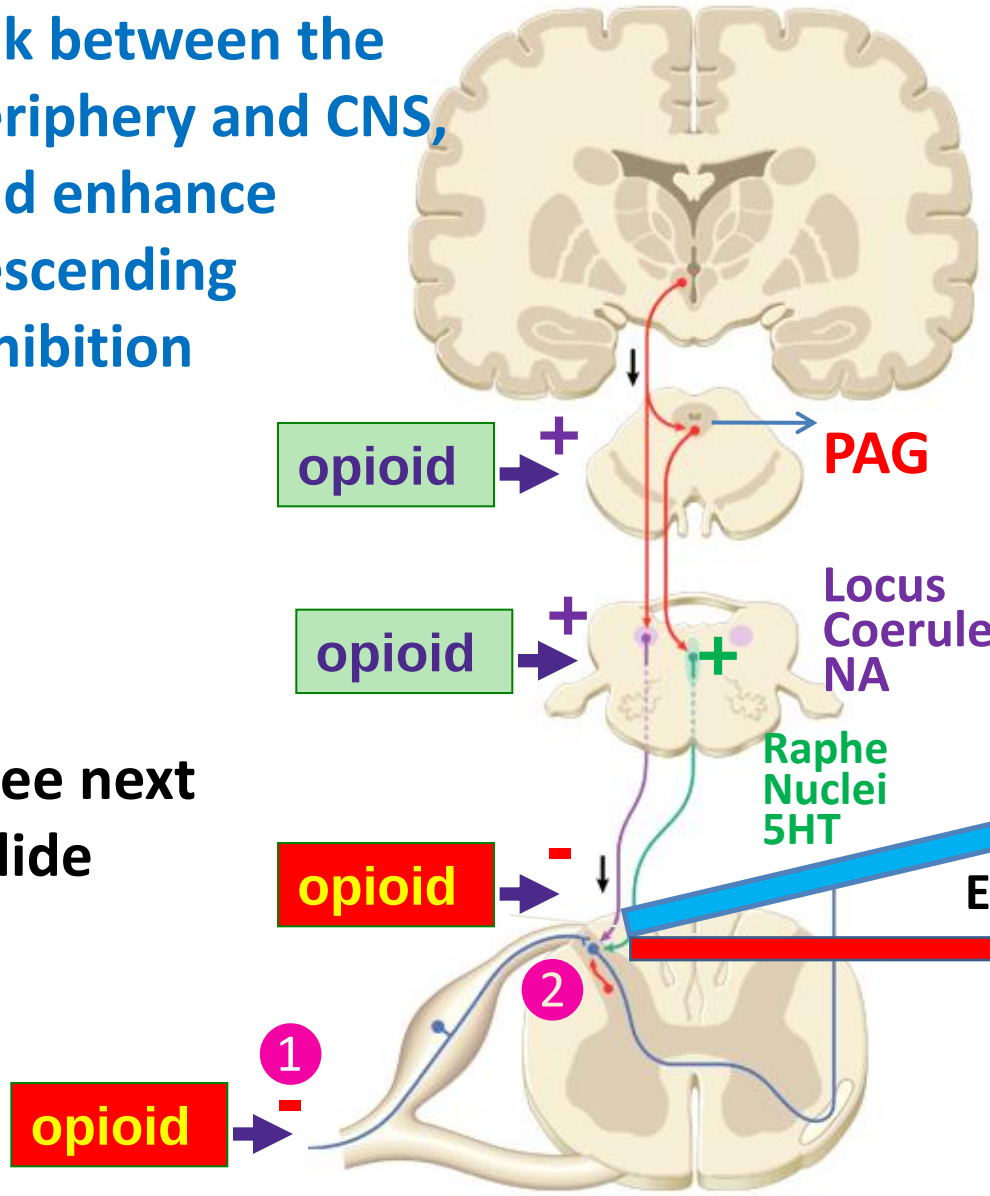
Indirect effects (activation)

- PAG and RF neurons
- ENK-containing interneurons

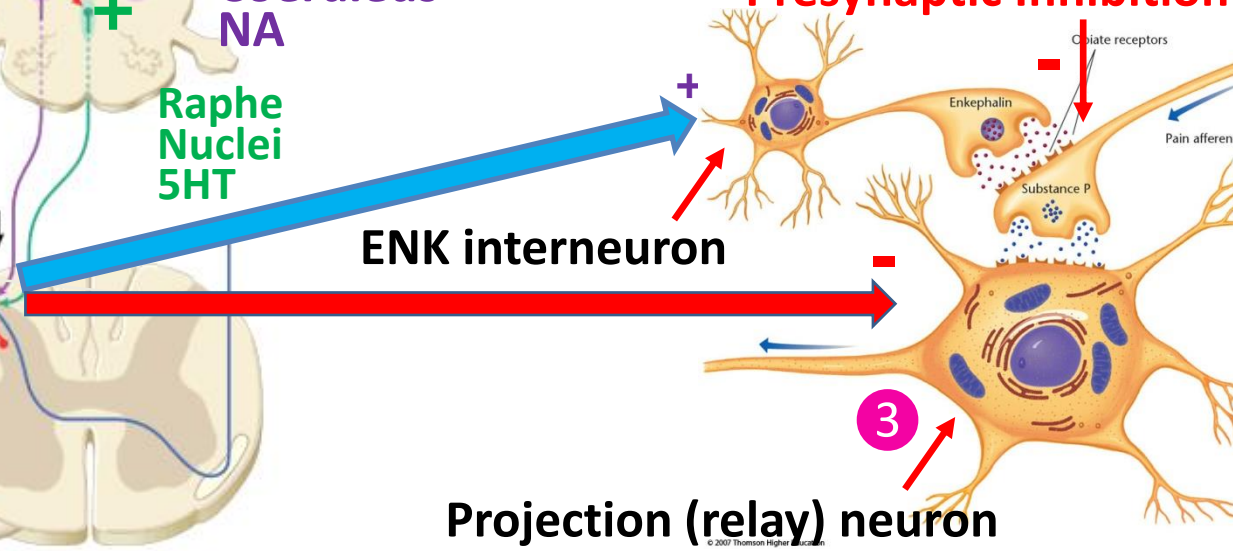
(**presynaptic inhibition**)

Direct effects

1. Inhibit nociceptor discharge
2. Inhibit substance P release
3. Inhibit dorsal horn projection neurons



See next slide



Sites of actions of Opiates on pain transmission

- They exert their analgesic effects by acting at various sites in the peripheral & CNS
- Inhibit pain transmission both directly and indirectly:

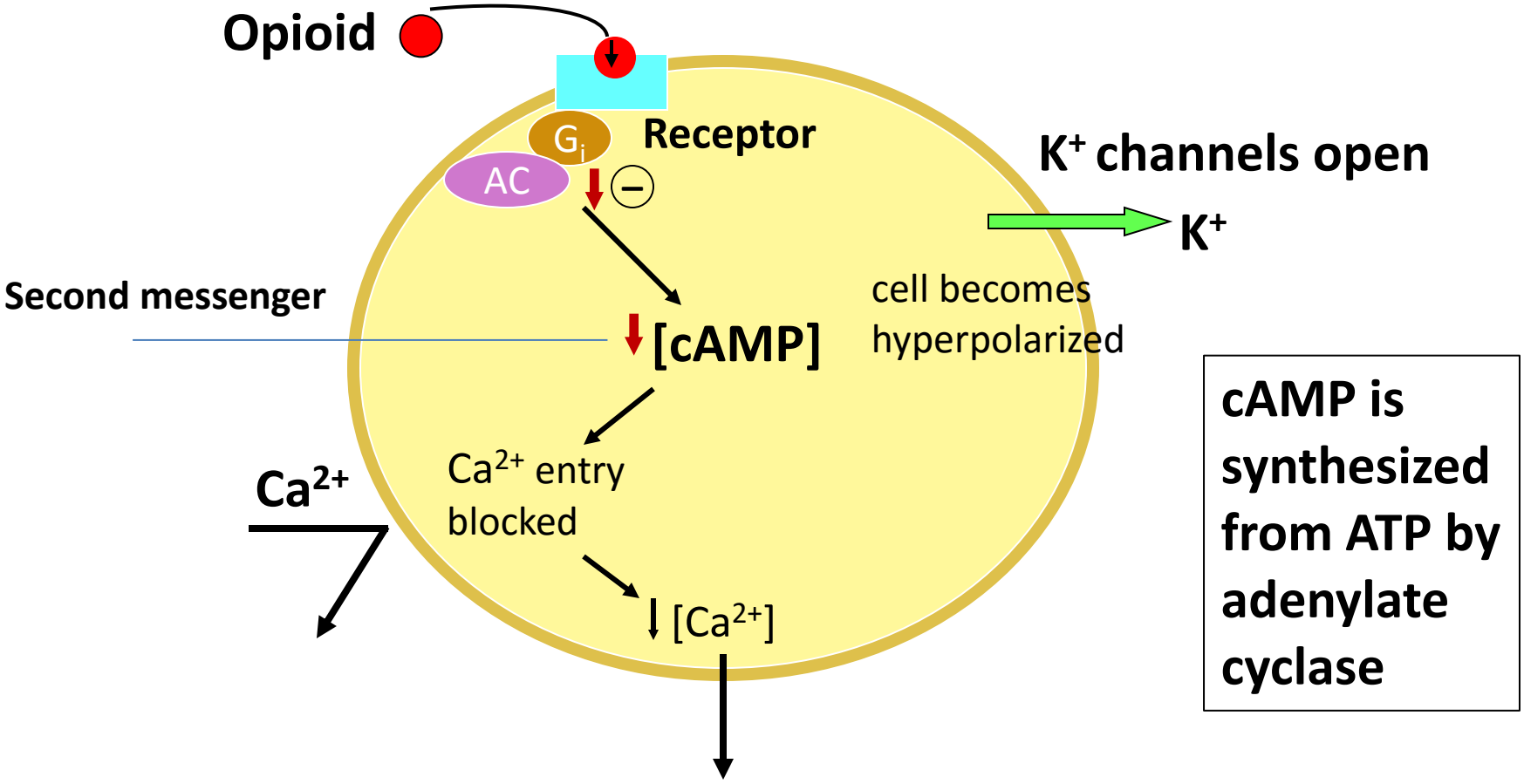
A. Direct Effects

1. Inhibit discharge of nociceptive neurons (both their spontaneous activity & evoked activity to noxious stimuli)
2. Inhibit release of SP from the central terminals of nociceptors .
3. Cause inhibition of dorsal horn projection neurons or spinothalamic neurons that convey the pain signal into the thalamus

B. Indirect Effects

1. Activate the descending inhibitory pathway by exciting PAG neurons
2. Activate neurons in brain stem which release NE and serotonin which can suppress pain transmission directly or indirectly via activation of the ENK containing inhibitory interneurons.

Cellular Actions of Opioids



cAMP is synthesized from ATP by adenylate cyclase

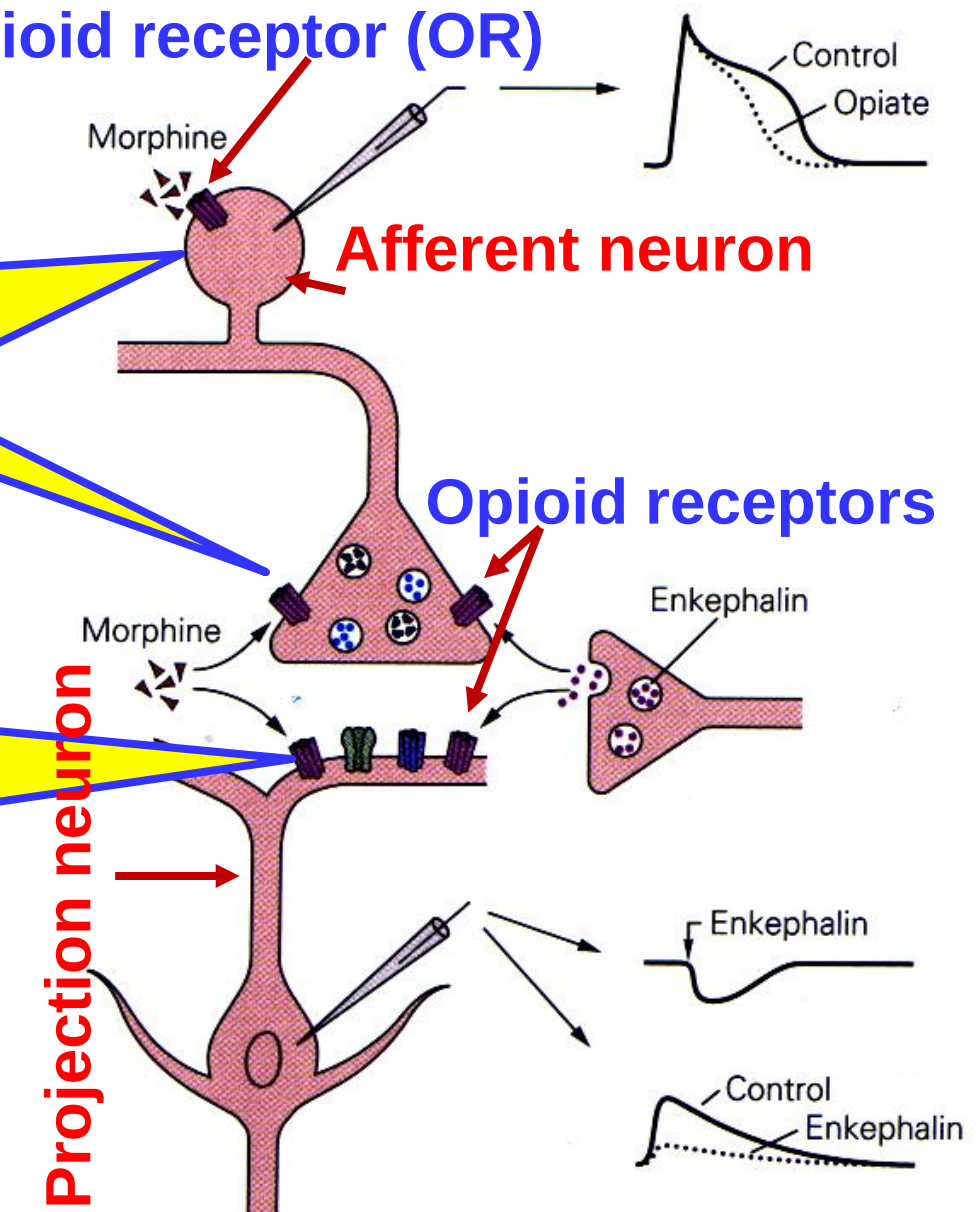
- Reduce cAMP synthesis by inhibiting **adenylate cyclase** (AC).
- Facilitate opening of K channels causing hyperpolarization
- Inhibit opening of Ca^{+2} channels ⟹ inhibition of transmitter release.

Pain Modulation: Effects of opioids

Activation of opioid receptors on cell bodies of DRG neurons and on pre-synaptic terminals causes a decrease in Ca^{++} influx resulting in a decrease in release of glutamate & Substance P

Activation of post-synaptic ORs hyperpolarizes the projection neuron by causing an increase in K^{+} conductance

↓ duration and size of the EPSP in the projection neuron



Pain Modulation

What is Pain Modulation ?

A decrease or **an increase** in the sensation of pain caused by **inhibition** or **facilitation** of pain signal.

INHIBITION: nociceptive input can be inhibited by:

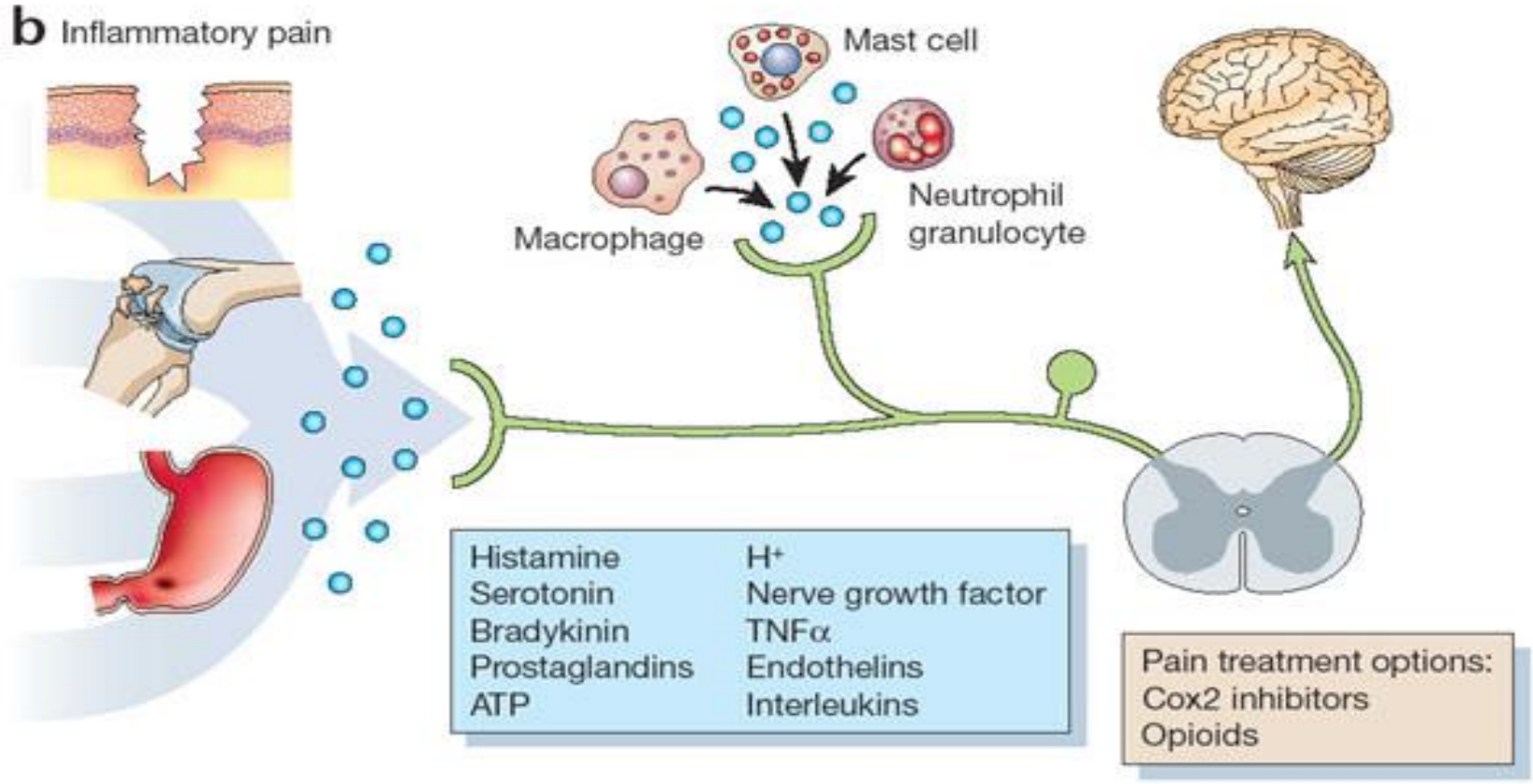
1. Spinal (segmental) inhibition: **Gate control theory**
2. Supra-spinal (descending) inhibition

FACILITATION

3. Peripheral sensitization (release of chemicals after tissue injury)
4. Central sensitization (Dis-inhibition)

Pain Facilitation: Peripheral Sensitisation

Inflammatory mediators can directly activate nociceptors or cause their sensitization (decreased threshold)



Peripheral sensitization also occurs during neuropathic pain states

What is Neuropathic Pain ?

``Pain initiated or caused by a primary lesion or dysfunction in the nervous system`` ***(IASP), 1994***

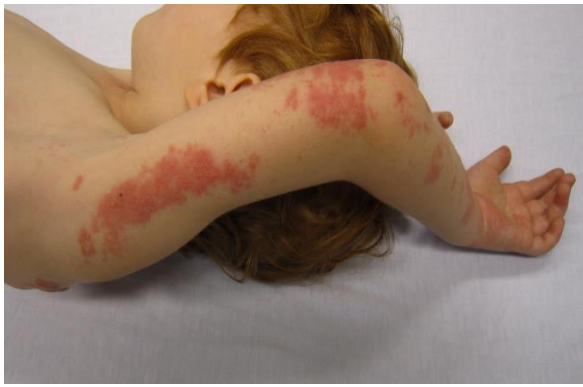
- **Features of NP**
  - More than 5% of the world population
  - Resistant to the current analgesic therapy
  - Can persist for years
- **Classification of NP:**
  - Central NP: Damage of CNS
  - Peripheral NP: damage of PNS
- **Clinical Symptoms of Peripheral NP**

  Hyperalgesia, Allodynia & Spontaneous Pain

Diseases that may cause Neuropathic Pain

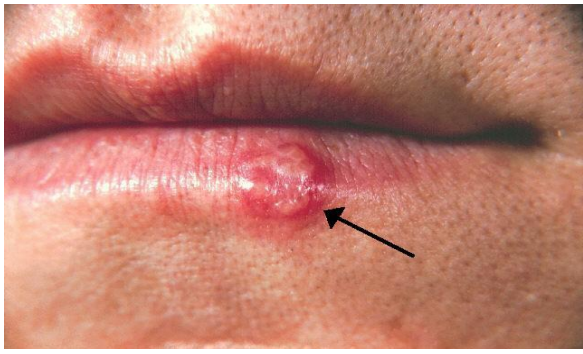
- Infection (e.g. postherptic neuroalgia caused by shingles)
- HIV
- Autoimmune diseases (e.g. multiple sclerosis)
- Vascular disease (e.g. stroke)
- Cancer.
- Metabolic disease (diabetes)
- Trauma/lesion (axotomy or nerve entrapment).
- Chemotherapy

Herpes zoster



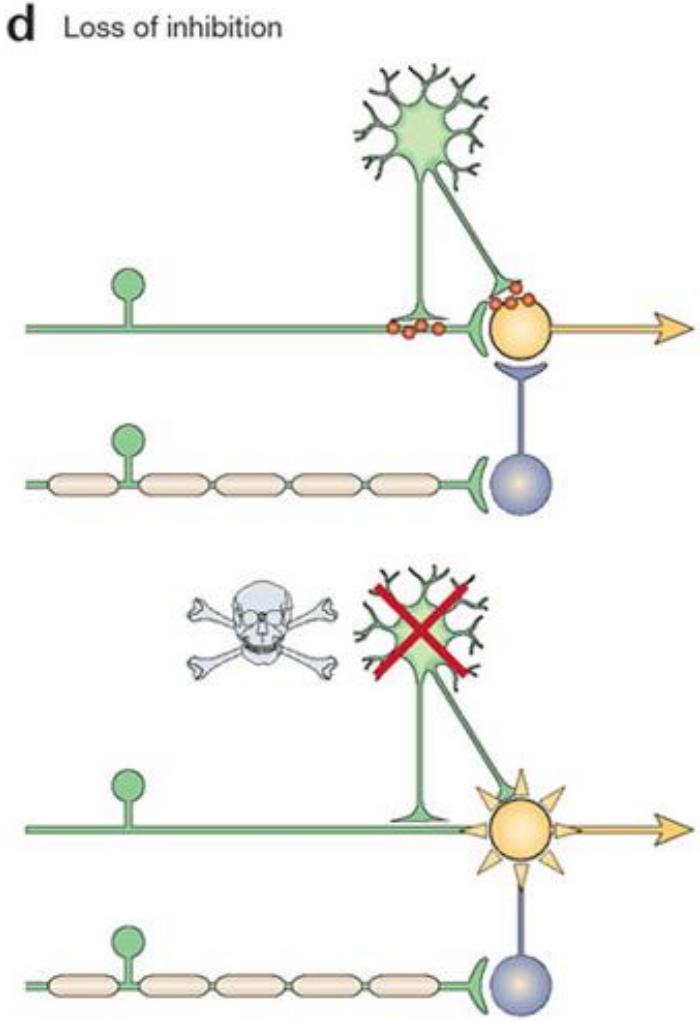
Varicella zoster virus

Herpes simplex (does not cause NP)



Herpes simplex virus

Pain Modulation: Dis-inhibition



- Pain transmission is controlled by **inhibitory interneurons**
- Loss of these inhibitory interneurons after excessive release of **glutamate**.
- Result in increased excitability of projection neurons and thus **enhanced pain**

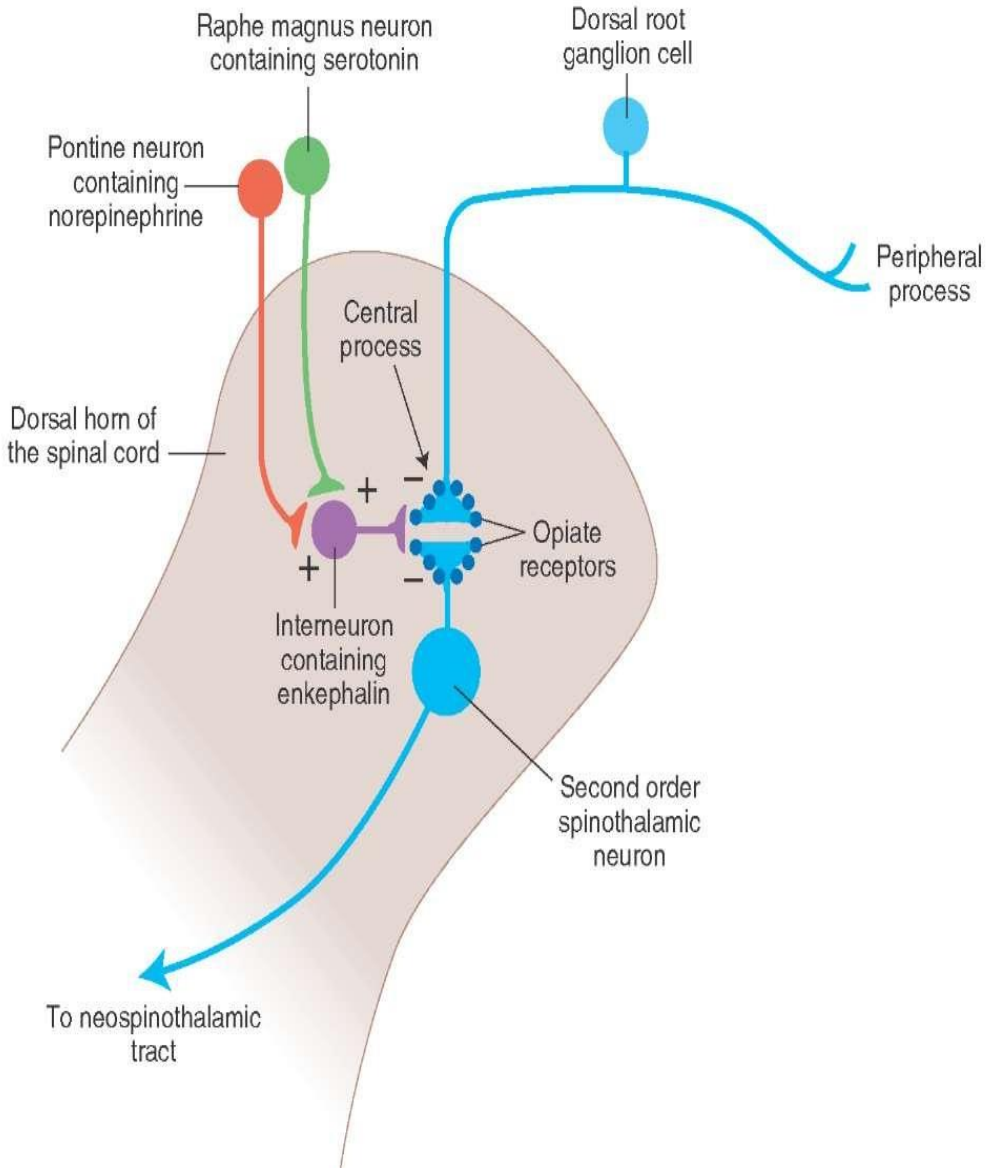
Debbie Maizels

Pain Modulation: Neurotransmitters

- **Serotonin**
- **Noradrenaline**
- **Enkephalin**

- The serotonergic and noradrenergic neurons are crucial in the supra-spinal pain modulation

- Destroying these neurons with neurotoxins blocks the analgesic actions of opioids



Summary

- Pain can be modulated by the balance of activity between nociceptive and non-nociceptive afferent inputs (**the gate control theory**)
- Pain can be controlled by central mechanisms through pain control descending inhibitory pathways
- Endogenous opioids contribute to the pain control system
- Serotonin and noradrenaline are the other non-opioid neurotransmitters that are involved in pain control mechanisms
- Pain modulation is bidirectional: can be inhibited or facilitated during chronic pain states


Thank You
Any Questions
WisdomTimes.com