Pain Modulation

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Week 7 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 how pain is modulated at the spinal cord level (**Gate control theory**)
- Describe the built-in pain suppression ``**Analgesia**`` system and how this **descending Inhibitory System** is activated from the brain
- 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:

- Spinal (segmental) inhibition: **Gate control theory**
- Supra-spinal (descending) inhibition **or the Built-in analgesic system**

FACILITATION

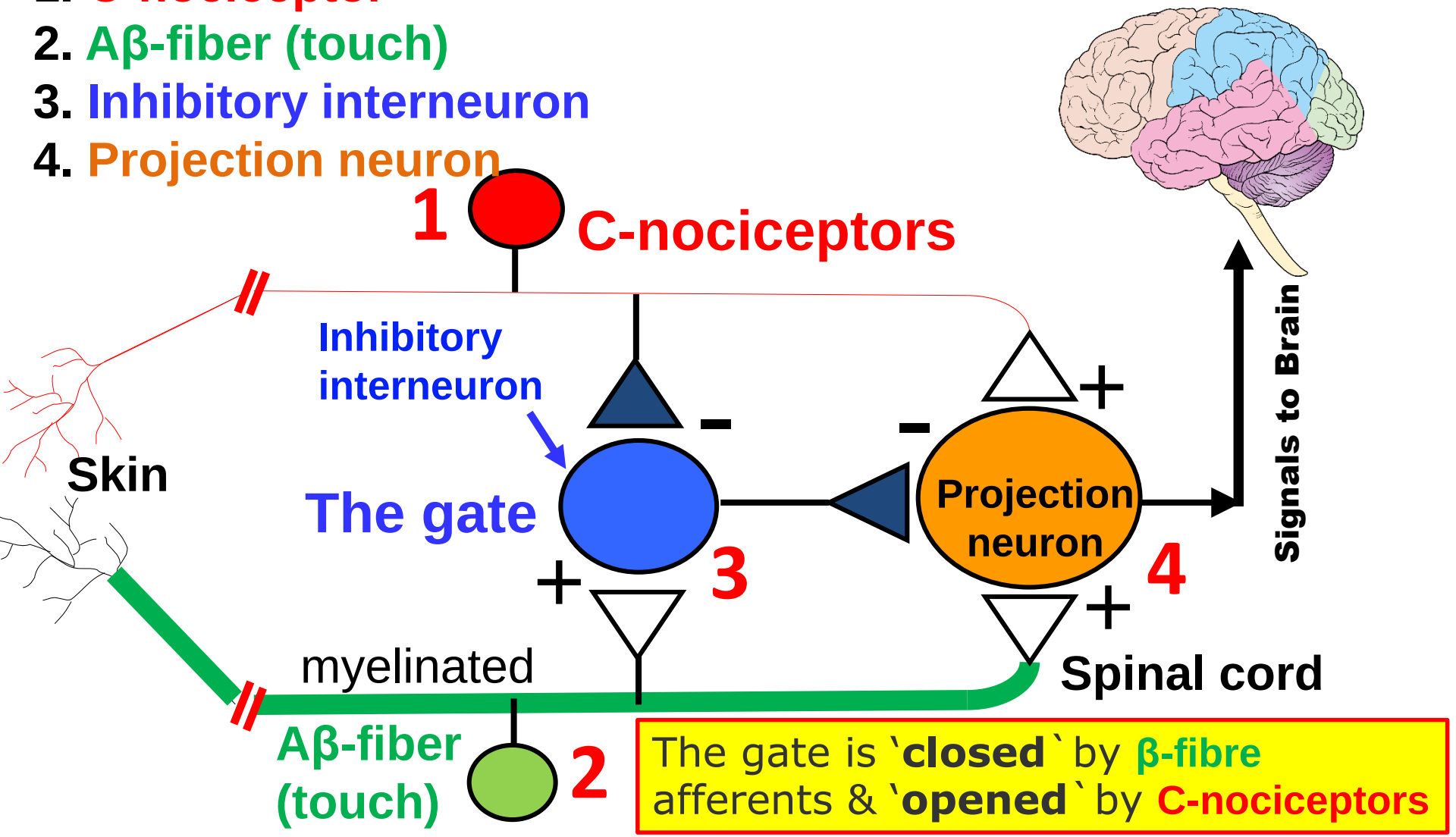
- Peripheral sensitization (release of chemicals after tissue injury)
- Central sensitization (Dis-inhibition)

Spinal Inhibition: Gate Control Theory-1

- 4 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

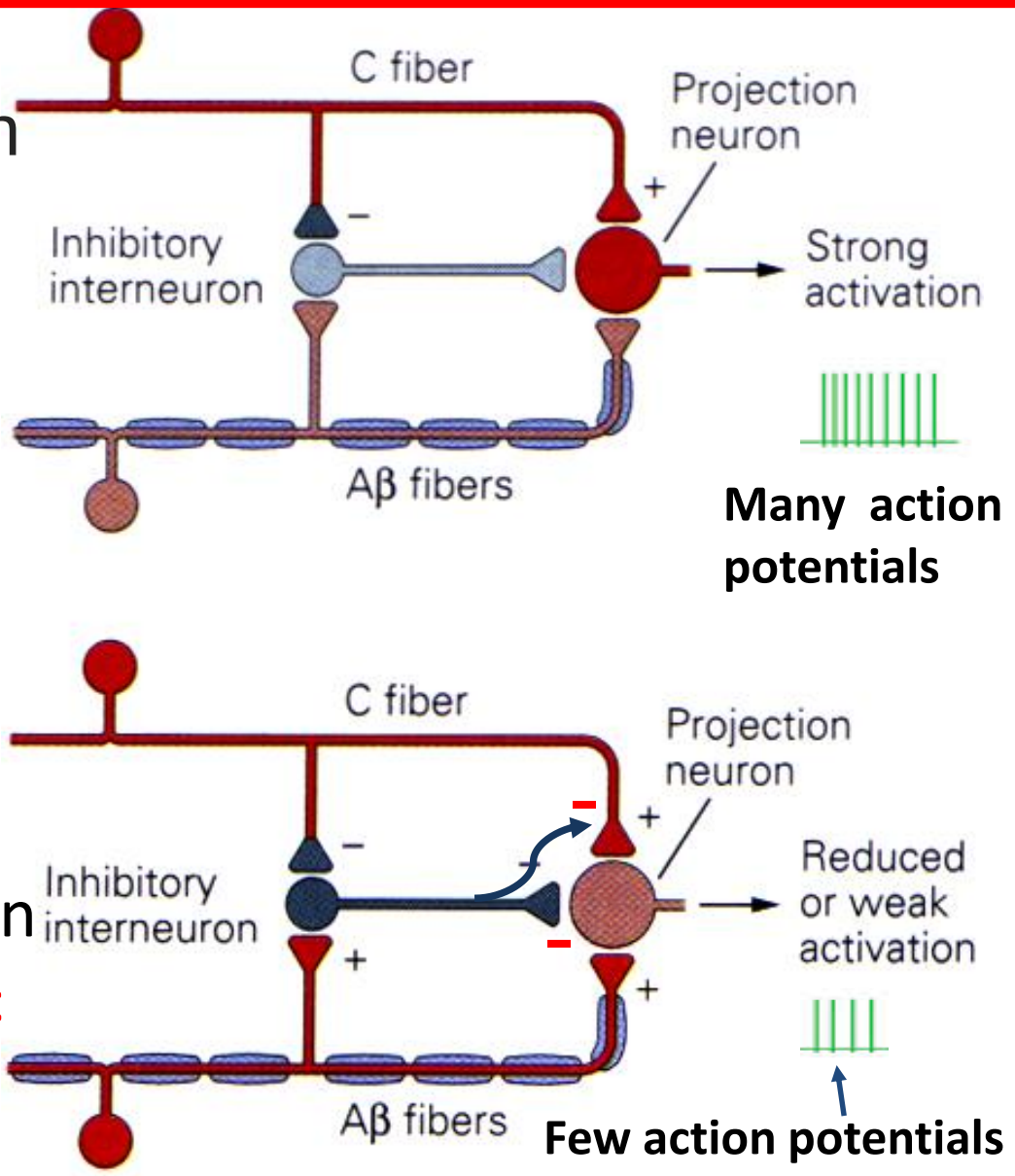
What are the neurotransmitters that are released from neurons involved in the gate control theory?

4 neurons are involved:

- **C-nociceptor: (substance P)**
- **Aβ-fiber (touch): (Glutamate)**
- **Inhibitory interneuron: (GABA, Glycine or encephalin (endogenous opioid))**
- **Projection neuron: (glutamate)**

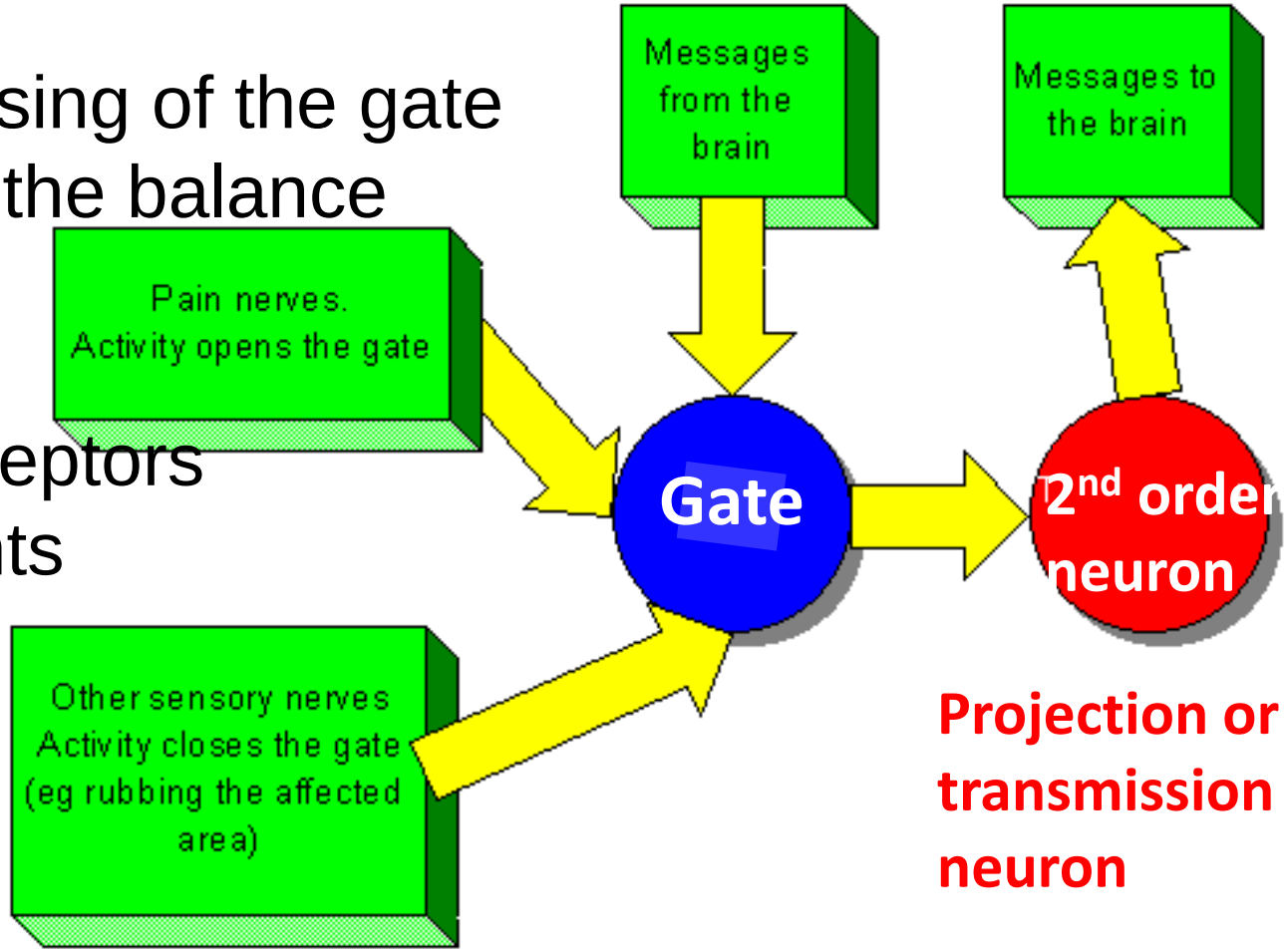
Gate Control of Pain-2

- Projection neuron receives input from both C-fibers and **Aβ-fibers**
- Firing of **C fibers inhibits** the inhibitory interneuron
- Firing of the **Aβ fibers activates** the inhibitory interneuron
- Inhibitory interneuron causes presynaptic inhibition of C-fibers and postsynaptic inhibition of projection n.



Gate Control of Pain-3

- Opening and closing of the gate is dependent on the balance between activity in C-nociceptors and Aβ-touch receptors
- This gate prevents the pain signals from reaching the brain.



- The gate is under control of higher centers.
- The brain sends nerve impulses that travel down the spinal cord to influence the gate.

Gate Control Theory-4

The gate-control theory is the basis for:

- **Rubbing the traumatized area such as a bumped head**
  - The initial trauma activates the A-δ 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 pain singal
- **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
- Post operative pain, osteoarthritis back pain, and other types of pain.

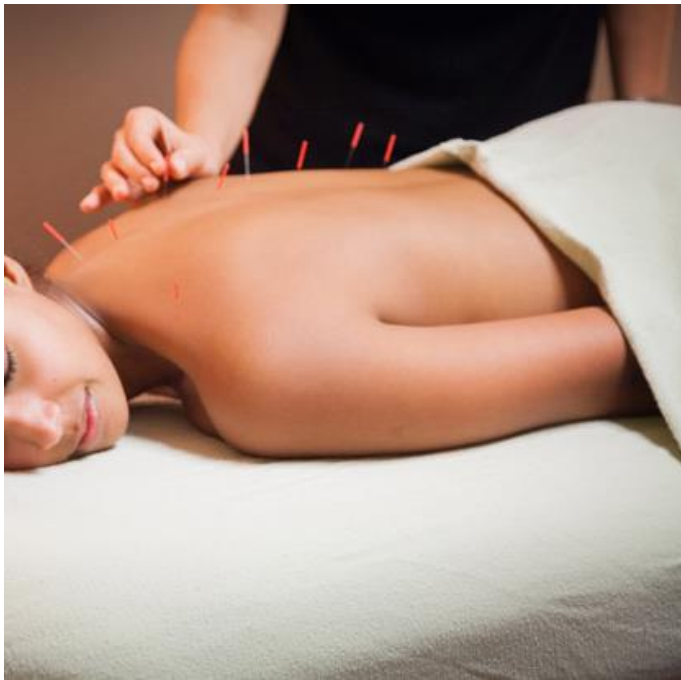
Other Ways of Reducing Pain

- Remove the painful stimulus
  - Withdrawal reflex
  - Treat injury or pathology
  - Analgesics
- Block impulse conduction in peripheral nerve
  - Local anesthetics
- Block synaptic transmission in CNS
  - General anesthesia
  - Narcotic analgesics (e.g. morphine)
- Activate body's own pain control system
- Alternative methods (Acupuncture)

Alternative 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.



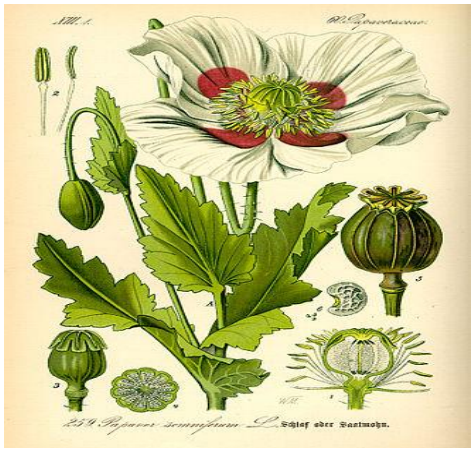
What are Opioids?

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

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

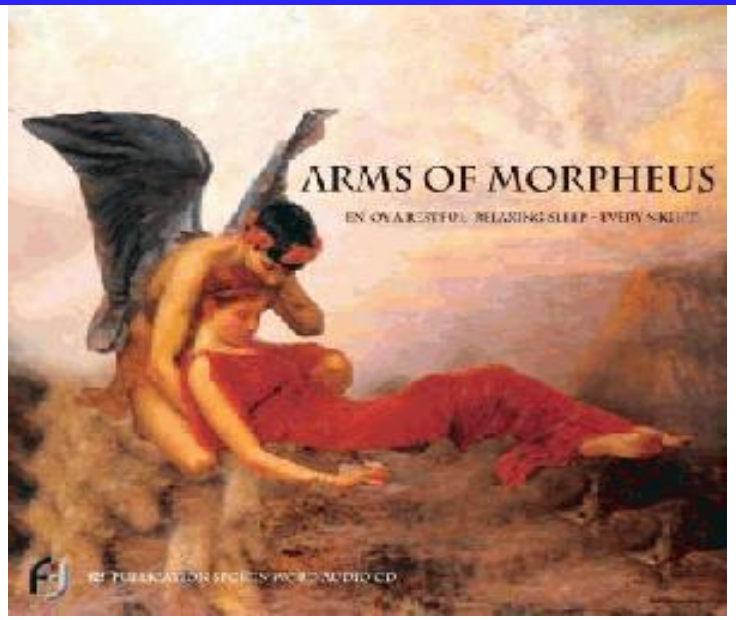
- Used as agent for analgesia, euphoria, sleep and diarrhea.
- Contains **12%** morphine and many alkaloids related to morphine.
- Used with alcohol to treat most diseases

Opium الأفيون

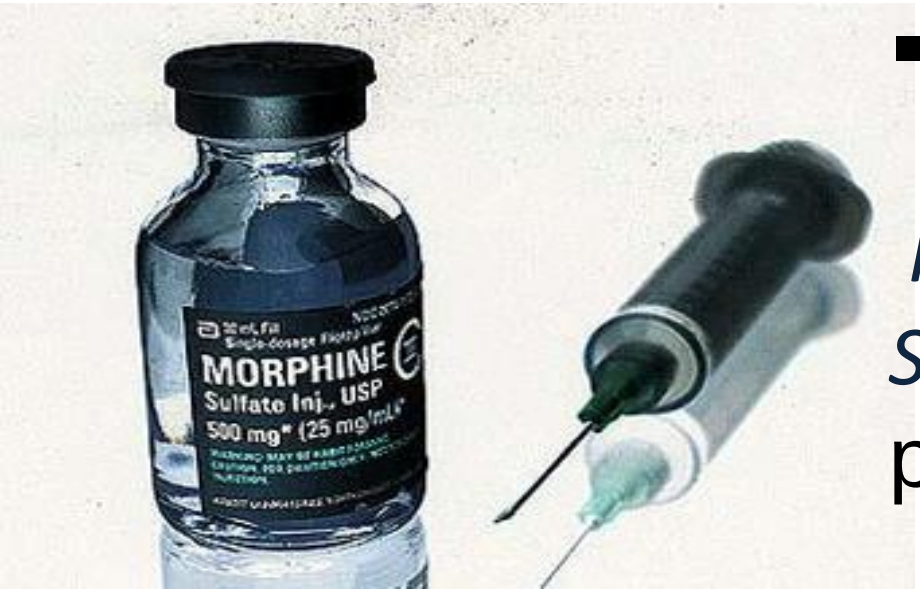


Papaver Somniferum
الخشخاش المنوم

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

INHIBITION: nociceptive input can be inhibited by:

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FACILITATION

- Peripheral sensitization (release of chemicals after tissue injury)
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Descending Pain Control System (The Built-in Analgesic System)

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

The system uses endogenous opioids (**natural pain killers**)

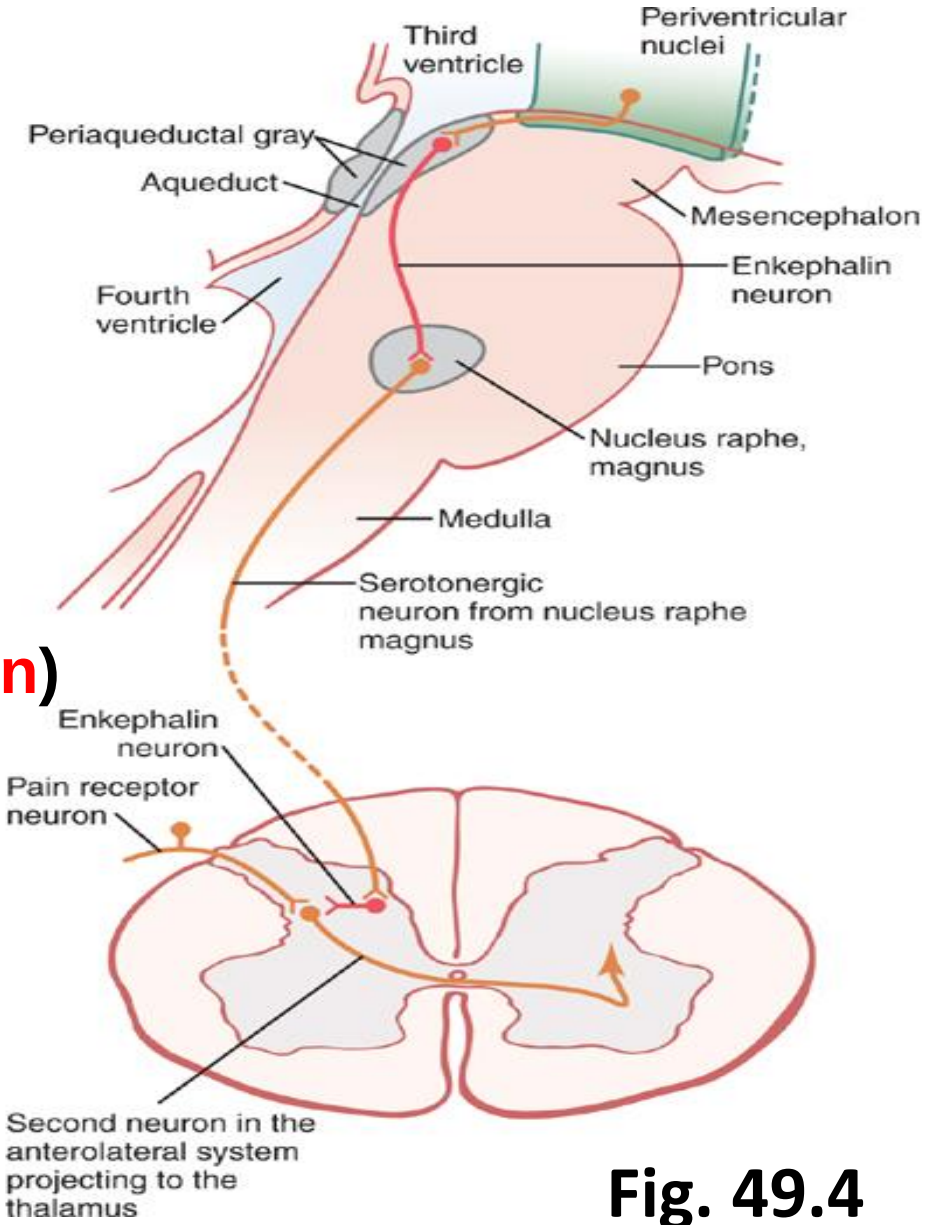
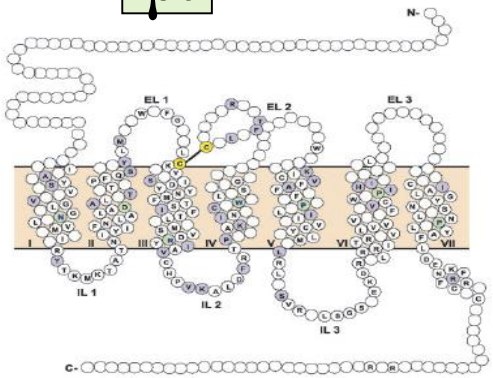


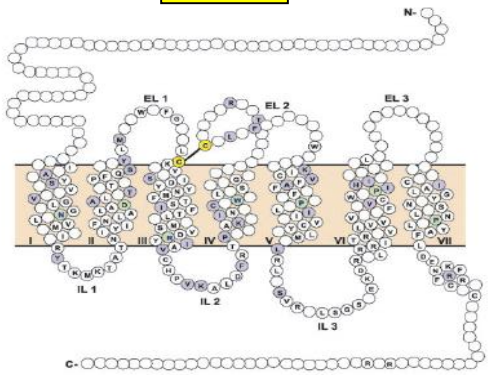
Fig. 49.4

Endogenous Opioid Peptides & Opioid Receptors

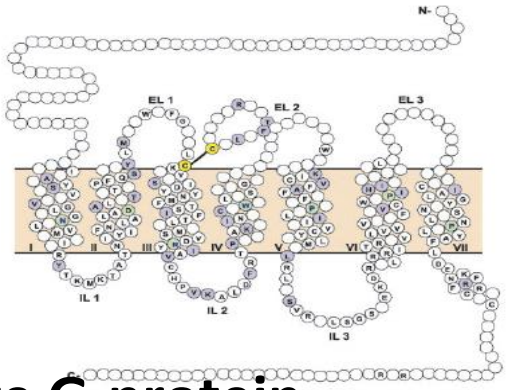
μ mu



δ delta



K kappa



Endogenous Opioids

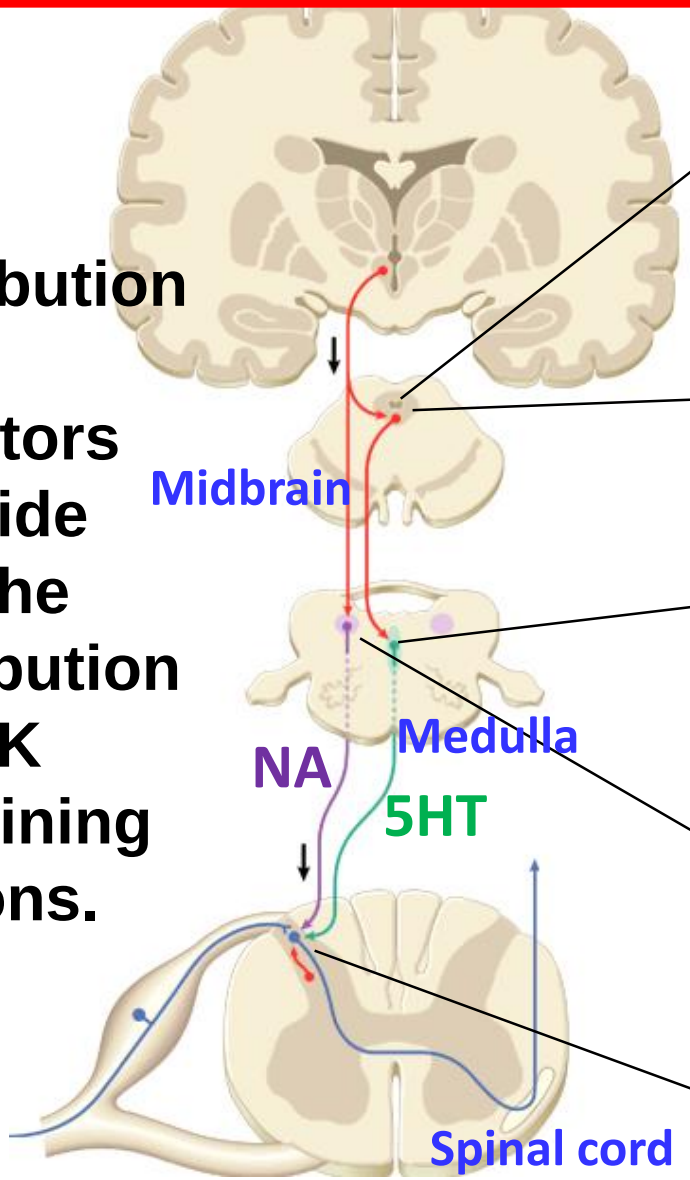
- Enkephalins
- Endorphins
- Dynorphins

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

σ sigma

How Does the Analgesic System cause Analgesia?

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



PAG receives inputs from thalamus, hypothalamus, cerebral cortex.

PAG projects neurons that stimulate raphe nucleus & locus ceoruleus

Raphe nucleus release 5-HT causing inhibition of projection neurons

locus ceoruleus release Noradrenaline (NA) that also inhibits projection neurons

5-HT and NA activate Enkephalin-containing inhibitory Interneuron (not shown)

Sites of Actions of Opiates on Pain Transmission

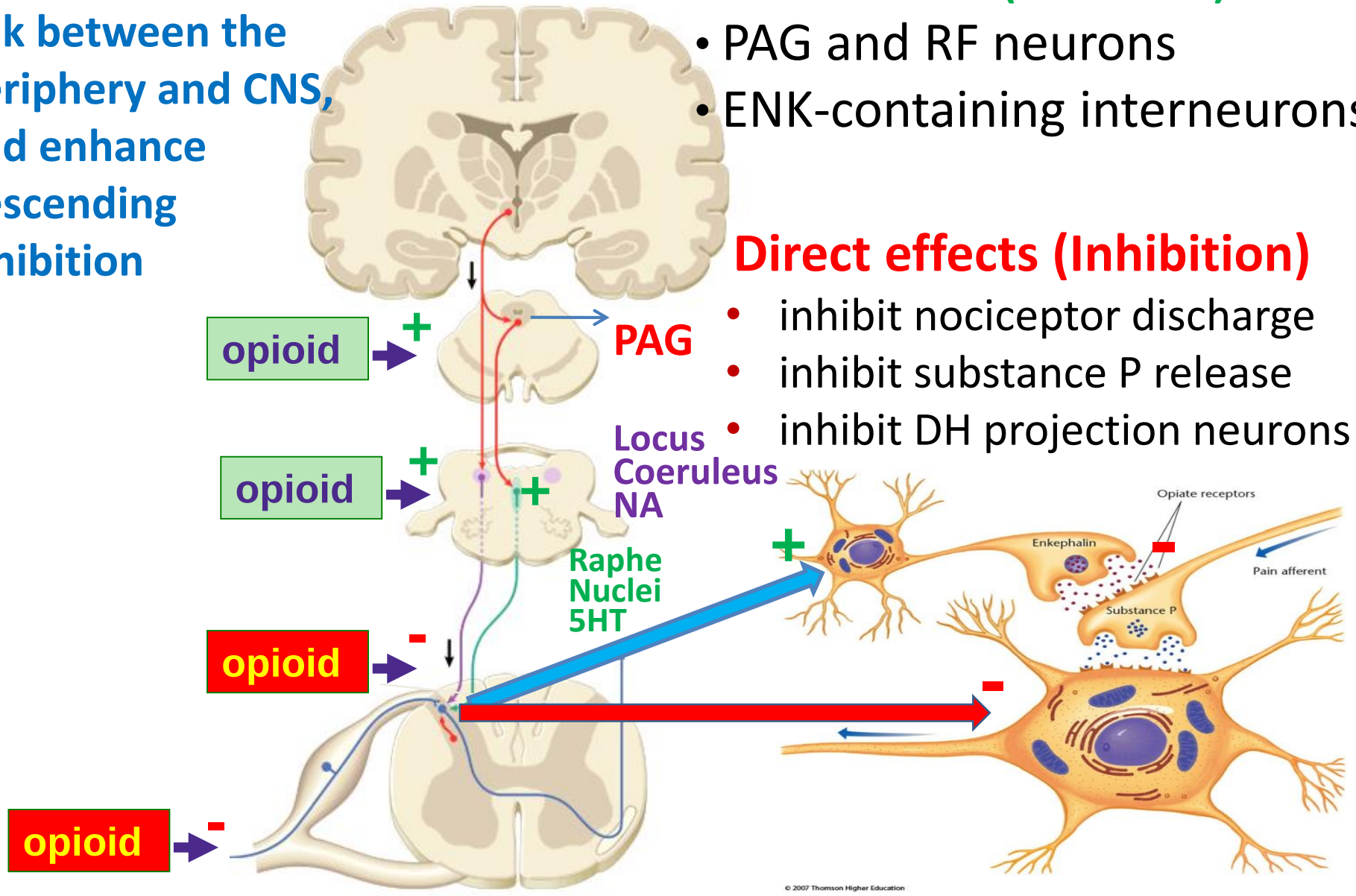
Opiates inhibit the link between the periphery and CNS, and enhance descending inhibition

Indirect effects (activation)

- PAG and RF neurons
- ENK-containing interneurons

Direct effects (Inhibition)

- inhibit nociceptor discharge
- inhibit substance P release
- inhibit DH projection neurons

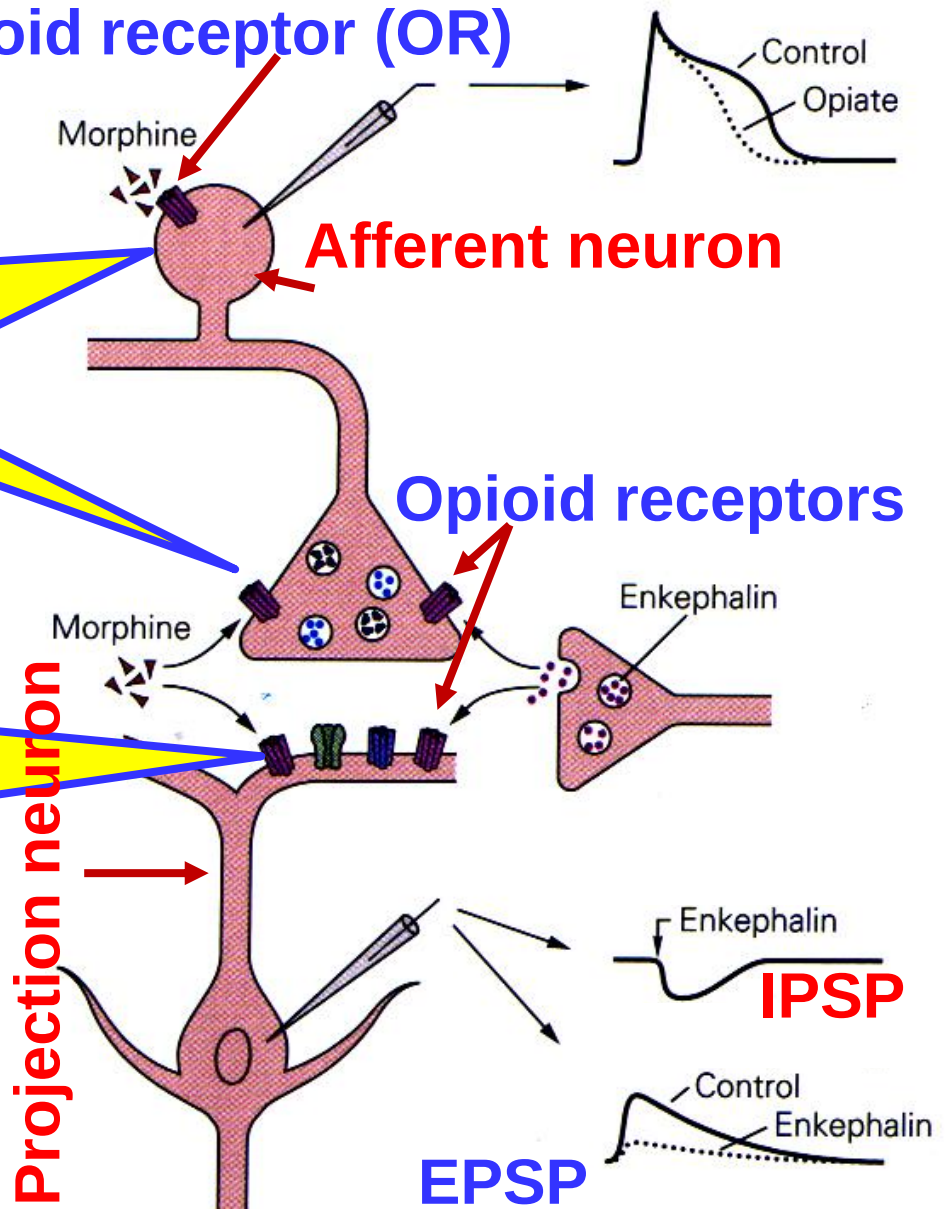


Pain Modulation: Effects of opioids

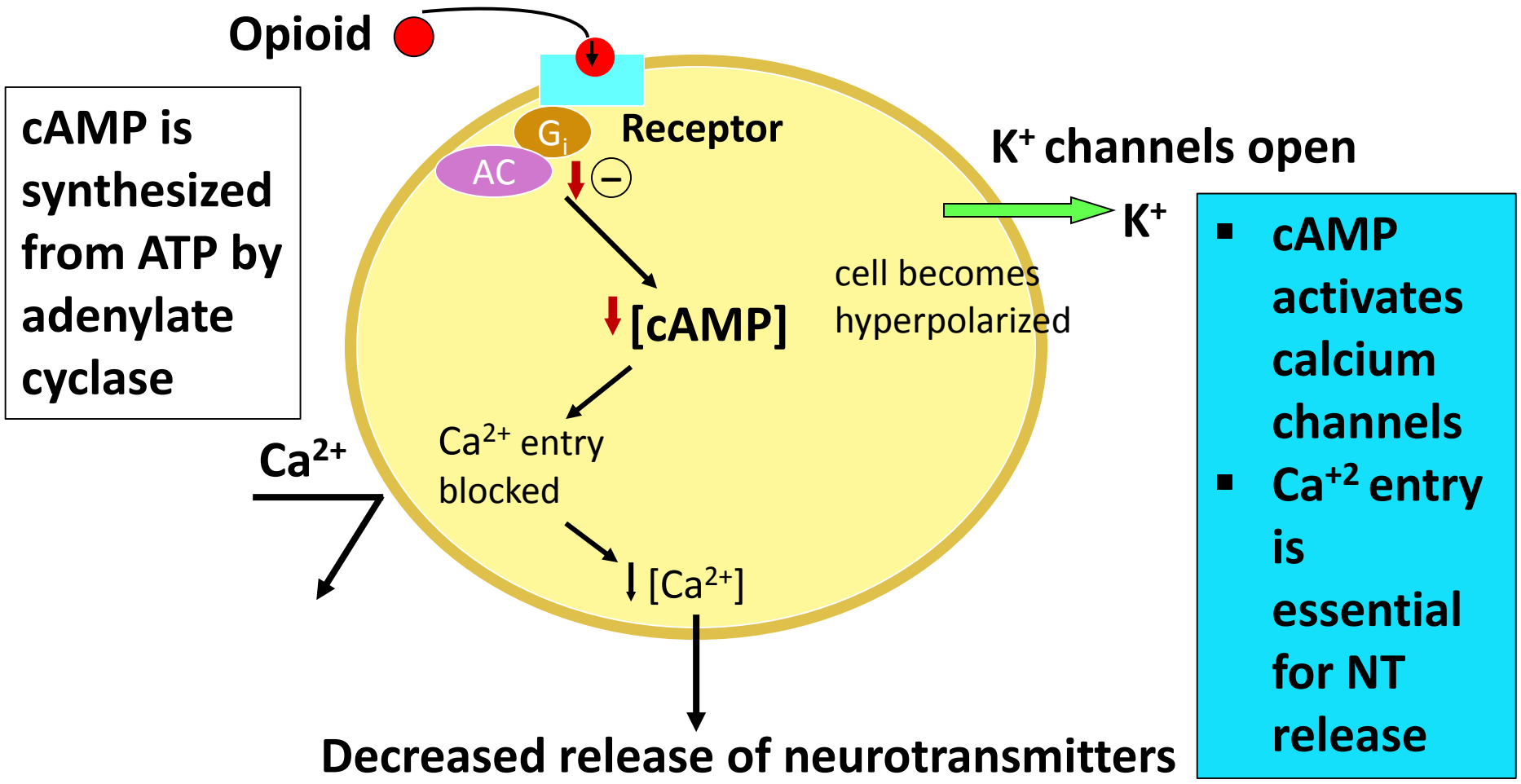
Activation of opioid receptors on cell bodies of DRG neurons and on pre-synaptic terminals causes a decrease in Ca^{++} influx resulting in a decrease in release of glutamate & Substance P

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



Cellular Actions of Opioids



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

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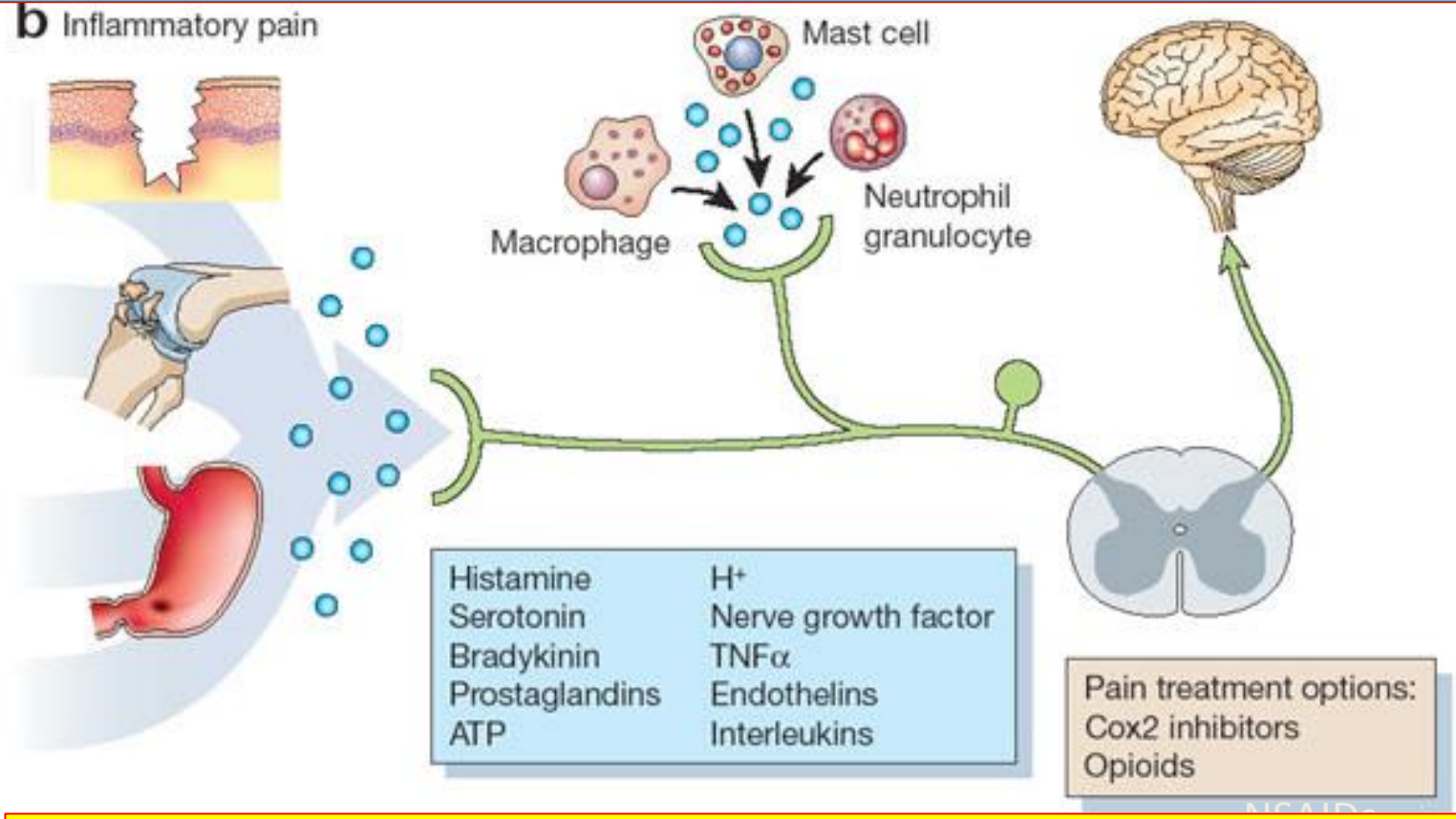
Pain Facilitation: Peripheral Sensitisation (PS)

The various released chemicals can sensitize nociceptors leading to enhanced pain sensitivity



PS also occurs during neuropathic pain states

What is Neuropathic Pain (NP) ?

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

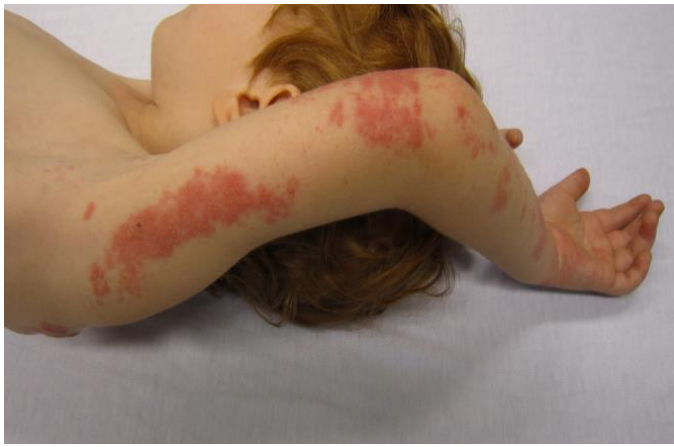
- **Features of NP**
  - About 5% of the world population
  - Resistant to the current analgesic therapy
  - Can persist for years
- **Classification of NP:**
  - Central NP: Damage of CNS (e.g. after stroke)
  - Peripheral NP: damage of PNS (e.g. diabetes)
- **Clinical Symptoms of Peripheral NP**

  Hyperalgesia, Allodynia & Spontaneous Pain

Diseases that may cause Neuropathic Pain

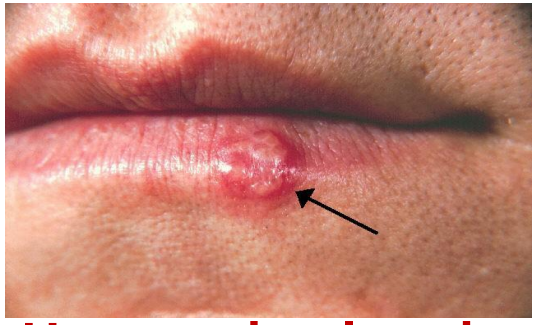
- Infection (e.g. postherptic neuroalgia caused by shingles)
- HIV
- Autoimmune diseases (e.g. multiple sclerosis)
- Vascular disease (e.g. stroke)
- Cancer.
- **Metabolic disease (diabetes)**
- **Trauma/lesion (axotomy or nerve entrapment).**
- **Chemotherapy**

Herpes zoster



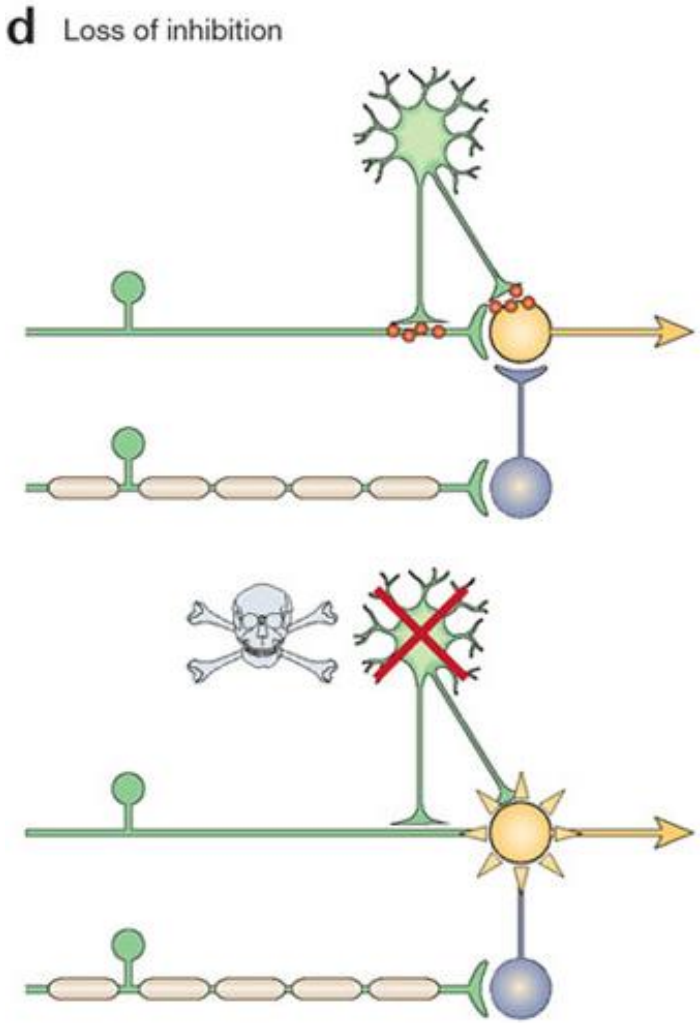
Varicella zoster virus

Herpes simplex
(does not cause NP)



Herpes simplex virus

Pain Modulation: Disinhibition



- 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**

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 (e.g during chronic pain states)


Thank You
Any Questions
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