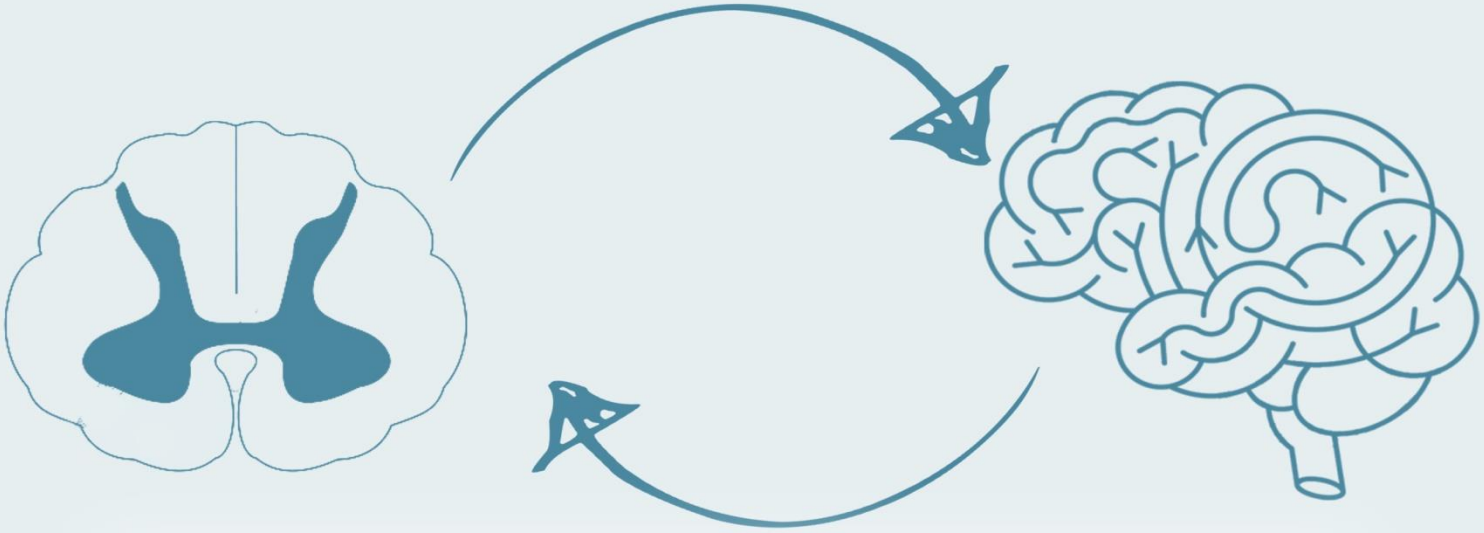

CNS

pharmacology

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number	7
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Opioid Analgesics

Pain is an important symptom as it is usually the symptom that brings the patient to the hospital, and an Analgesic is a drug used to relieve pain. In this sheet we will talk about the Opioid Analgesics.

- They are obtained from Opium which refers to the dried latex obtained from the opium poppy (tears). The scientific name of the plant is *Papaver somniferum.* This plant was discovered thousands of years ago. The active ingredients which were isolated included Morphine, codeine, as well non narcotic ingredients like thebaine and papaverine.

Morpheus is the Greek god of dreams and the son of the god of the sleep

- Sometimes they are called the opioid narcotics because they lead to a state called narcosis (Drowsiness, decreased mental alertness and sedation)

- Endorphins and Enkephalins were discovered in the 1970s and are known as the endogenous morphine (they work on the same receptors)

* Endorphins exist in all the nervous system
* Enkephalins only exist in the brain

- Heroin is a modified morphine by adding an acyl group (6-acylmorphine) and it is administered IV and produces a very rapid action!

➢ The following table compares the opioid analgesics with NSAIDs (non-opioids)

	Opioids	**Non-opioids**
Efficacy	Strong (any severity)	Weak
Prototype	Morphine	Aspirin
Pain Relieved	Any type	Musculoskeletal (inflammation)
Site of Action	Central	Peripheral (mostly) and central
Mechanism	Specific receptor	Interferes with Prostaglandin

		synthesis
Danger	Tolerance & Dependence(addiction)	G.I irritation
Anti-inflammatory	No	Yes
Antipyretic	No	Yes
Antiplatelet	No	Yes

Opioids Receptors:

There are many receptors for the opioids and they differ in their function, location and the affinity to certain endogenous opioid.

Receptor Subtype	Functions	Endogenous Opioid Peptide Affinity
μ (mu)	Supraspinal and spinal analgesia; sedation; inhibition of respiration; slowed gastrointestinal transit; modulation of hormone and neurotransmitter release	Endorphins > enkephalins > dynorphins
δ (delta)	Supraspinal and spinal analgesia; modulation of hormone and neurotransmitter release	Enkephalins > endorphins and dynorphins
κ (kappa)	Supraspinal and spinal analgesia; psychotomimetic effects; slowed gastrointestinal transit	Dynorphins > > endorphins and enkephalins

- The **μ** receptors are the main receptors

➢ The following table shows the effects of the opioids receptors in details

Notes:

- Sigma and delta are not involved in the analgesia

	Mu1	Mu2	Kappa	Sigma	Delta
The classical agonist	Morphine		Bemazocine	N-allylcyclazocine	Morphine Leu-enkephalin
Analgesia?	Analgesia	No analgesia	Analgesia;	No analgesia	No analgesia

			excessive heat		
Respiratory rate	Apnea	Apnea	Apnea	Tachypnea	Apnea
CNS	Indifference	Sedation	Sedation	Delirium	
Side effects	Miosis		Miosis	Mydriasis	
	Nausea &Vomiting				Nausea &Vomiting
	Constipation				
	Urine retention		Diuresis		
	Pruritus				Pruritus
	Temperature increase				
Tolerance	Tolerance		Little tolerance		Tolerance
Cross tolerance			No mu cross tolerance		mu cross tolerance

- Indifference means he feels the pain, but he just doesn't care about it
- The doctor said that Mu is the one we care about, the others are for comparison

Opioids can be chemically classified into:
- Peptides (the endogenous opioids are peptides)
- Alkaloids, could be: - Natural (from plants), like morphine
  - Semisynthetic (structural modification)
  - Synthetic

The study of opioid peptides did not only reveal the mechanism of action for them, but also helped in understanding:
• Placebo effect; it is thought that it is related to the release of endorphins
• Acupuncture (الوخز بالابر او الابر الصينية); due to stimulation of nerve endings to release endorphins
• Stimulation Induced Analgesia; use electrodes in certain areas of brain to release endogenous morphines
• Regulation of the release of pituitary hormones

Sites of action for opioids:

- Substantia gelatinosa - Periventricular area - Periaqueductal grey

- Hypothalamus - Thalamus
- Striatum - Limbic System
- Nucleus accumbens

Receptor mechanisms of analgesic drugs

The primary afferent neuron originates in the periphery and carries pain signals to the dorsal horn of the spinal cord, where it synapses via glutamate and neuropeptide transmitters with the secondary neuron.

Pain stimuli can be attenuated in the periphery (under inflammatory conditions) by opioids acting at mu -opioid receptors (MOR) or blocked in the afferent axon by local anesthetics.

Action potentials reaching the dorsal horn can be attenuated at the presynaptic ending by opioids and by calcium blockers, alpha 2 agonists.

Opioids also inhibit the postsynaptic neuron, as do certain neuropeptide antagonists acting at tachykinin (NK1) and other neuropeptide receptors.

Cellular Mechanisms of Action

- Inhibit adenylate cyclase, so decrease cAMP
- Inhibit Ca++ entry by decreasing phosphorylation of voltage operating Ca++channels
- Enhance K+ efflux
- The net result is an increase in release of DA, 5HT, nociceptive peptides like substance P, resulting in blockage of nociceptive transmission

Actions of <u>Morphine</u>

Morphine has two sets of effects; depressant and stimulant effects

Depressant Effects of Morphine:

- Suppression of pain, analgesia (specifically the response to pain (Indifference))
- Drowsiness and decreased mental alertness, sedation (narcosis)
- Decreased respiration (apnea) → the cause of death
- Increased intracranial pressure
- Decreased myocardial oxygen demand (used in MI emergency)
- Suppression of cough, antitussive (remember codeine antitussive)
- Decreased peristalsis → constipation
- Inhibition of fluid and electrolyte accumulation in the intestinal lumen
- Decreased gastric acid secretion
- Inhibition of emetic center
- Slight decrease in body temperature
- Decreased release of LH and FSH

The doctor said it is like if the body is turned off

Stimulant Effects of Morphine:

- Euphoria → addictive
- Constriction of pupils, miosis *this proves he is turned off by having eyes closed
- Stimulation of chemoreceptor trigger zone (induce vomiting, but 1st dose only)
- Increased tone of intestinal smooth muscle
- Increased tone of sphincter of Oddi, increased biliary pressure
- Increased tone of detrusor muscle
- Increased tone of vesical sphincter → no urination
- Increased release of prolactin and antidiuretic hormone
- Proconvulsant in overdose.

Pharmacokinetics

As all CNS drug, they are very lipid soluble.
Can be given by any route but are subjected to first pass effect so we prefer IV administration.

Therapeutic Uses:

- Acute severe pain (not mild pain as for NSAIDs)
- Chronic Pain: but we should first try: nonopiates → weaker opiates → opioids but on a regular fixed schedule, because haphazard administration leads to addiction
- Myocardial Infarction
- Obstetric Anesthesia
- Pulmonary Edema: relieve anxiety and cause peripheral pooling
- Severe watery diarrhea not responsive to other drugs

Adverse Effects of Opioids:

• Behavioral restlessness, tremulousness, and hyperactivity
• Respiratory depression
• Nausea and vomiting
• Increased intracranial pressure
• Postural hypotension accentuated by hypovolemia
• Constipation
• Urinary retention
• Itching and urticarial

☠**Contraindications:**

• Head Injury; because the drug will mask the neurological symptoms of the injury
• Shock and decreased blood volume
• Chronic Hypoxic Conditions (Asthma for example)

Good Luck