PHARMCOLOGY

SHEET NO. 2

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Opioid Analgesics & Antagonists

Source

- Morphine, the prototypical opioid, has long been recognized to be an effective analgesic (relieves severe pain with remarkable efficacy).
- Morphine is obtained from the opium poppy, ***Papaver somniferum*** and ***P album***. After incision, the poppy seed pod exudes a white substance that turns into a brown gum that contains <u>10% morphine</u>.

Classification & Chemistry

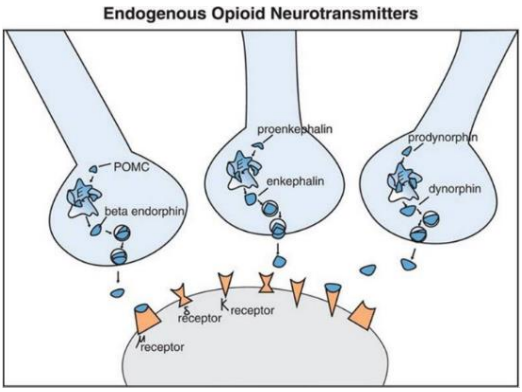
- Opioid drugs include full agonists, partial agonists, and antagonists.
- Opioid antagonists are used as antidotes in cases of opioid overdose and to reduce the drug-patient monitoring-time required post-surgery.

Endogenous Opioid Peptides

- Three families of endogenous opioid peptides have been described in detail :

1) The **endorphins.**
2) The pentapeptide **enkephalins :**
   - methionine-enkephalin **(met-enkephalin).**
   - leucine-enkephalin **(leu-enkephalin).**
3) The **dynorphins.**

- The endogenous opioid peptides are derived from three different precursor proteins and thus different genes.
- These peptides – normally present in small amounts - can be released during **stressful conditions** such as pain or the anticipation of pain to diminish the sensation of noxious stimuli.
- Surprisingly , it seems that these peptides are also released upon thinking about and recalling painful events.
- Endogenous Opioid Peptides act through three types of opioid receptors :
  1) **Mu (μ)**
  2) **Delta (δ)**
  3) **Kappa (κ)**
- <u>All three families of endogenous peptides act on all three receptor types.</u>



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

Notes on the table above : (memorize the whole table)

- All three receptor subtypes (mu ,delta ,kappa) function in supraspinal and spinal analgesia indicating the importance of all three receptor subtypes in the modulation of pain.
- At early stages , minimal sedation helps one relax while still being awake. In later (deep) stages , one sleeps.
- Inhibition of respiration is a lethal adverse reaction of opioids acting on **μ receptor** , however , not all opioid abusers exhibit this adverse reaction due to drug tolerance in which addicts can sustain higher doses over time.
- Both mu and kappa receptors result in slowed emptying of the GIT.
- Psychotomimetic effects are peculiar to kappa receptors.

Common Opioid Analgesics

Table 31–2. Common opioid analgesics.

Generic Name	Trade Name	Approximately Equivalent Dose (mg)	Oral:Parenteral Potency Ratio	Duration of Analgesia (hours)	Maximum Efficacy
Morphine[1]		10	Low	4–5	High
Hydromorphone		1.5	Low	4–5	High
Oxymorphone		1.5	Low	3–4	High
Methadone		10	High	4–6	High
Meperidine		60–100	Medium	2–4	High
Fentanyl		0.1	Low	1–1.5	High
Sufentanyl		0.02	Parenteral only	1–1.5	High
Alfentanil		Titrated	Parenteral only	0.25–0.75	High
Remifentanyl		Titrated[2]	Parenteral only	0.05[3]	High
Levorphanol		2–3	High	4–5	High
Codeine		30–60[4]	High	3–4	Low
Hydrocodone[4]		5–10	Medium	4–6	Moderate
Oxycodone[1,5]		4.5[6]	Medium	3–4	Moderate
Propoxyphene		60–120[6]	Oral only	4–5	Very low
Pentazocine		30–50[6]	Medium	3–4	Moderate
Nalbuphine		10	Parenteral only	3–6	High
Buprenorphine		0.3	Low	4–8	High
Butorphanol		2	Parenteral only	3–4	High

Memorize the information surrounded by rectangles.

Important Notes on the previous table : (memorize the following)

- The appropriate equivalent dose of Morphine is 6-10mg , higher doses might result in respiratory depression and death.
- Meperidine has a second generic name “pethidine”.
- The appropriate equivalent dose of Meperidine is 60-100mg.
- Fentanyl and Sufentanyl are **very potent** drugs used during anesthesia.
- A highly potent drug is one that shows high effectiveness at low doses. For example , Morphine is much More potent than Meperidine although both have the same analgesic effect at the right dose.
- The appropriate equivalent dose of Codeine is 30-60mg.
- A high Oral:Parenteral ratio indicates that a drug can be given orally , while a low ratio indicates that the drug is better given parenterally.

Pharmacokinetics

Absorption

- Most opioid analgesics are well absorbed when given by subcutaneous, intramuscular, and oral routes.
- **Morphine** undergoes extensive **first-pass metabolism**; therefore , the oral dose of the opioid morphine may need to be much higher than the parenteral dose to elicit a therapeutic effect.
- **Codeine** is effective orally because it has reduced first-pass metabolism. Other routes of administration include oral lozenges, and transdermal via transdermal patches.

Distribution

- Opioids rapidly leave the blood compartment and localize in highest concentrations (concentrate) in tissues that are highly perfused such as the brain, lungs, liver, kidneys, and spleen.
- **Drug concentration in skeletal muscle is much lower**, but this tissue serves as the main reservoir for the drug because of its greater bulk (larger size).
- Frequent high-dose administration or continuous infusion of highly lipophilic opioids that are slowly metabolized (e.g. **Fentanyl**) can lead to accumulation in body fat.

Metabolism

- Opioids are converted in large part to **polar** metabolites (mostly glucuronides), which are then readily excreted by the kidneys.
- Morphine is converted into two glucuronide metabolites:

- **Morphine-3-glucuronide (M3G)** --> 90% of the metabolites --> a compound with **neuroexcitatory properties** mediated by GABA/glycinergic system (inhibitory neurotransmitters in the brain) and NOT through μ receptors .
- **Morphine-6-glucuronide (M6G)** --> 10% of the metabolites --> an active metabolite with **analgesic potency four to six times that of its parent compound morphine.**

- These relatively polar metabolites have limited ability to cross the blood-brain barrier. Nevertheless, accumulation of these metabolites may produce unexpected adverse effects in patients with **renal failure** or when exceptionally large doses of morphine are administered.
- This can result in **M3G-induced CNS excitation (seizures)** or enhanced and **prolonged opioid action produced by M6G.**
- Probenecid or other drugs that inhibit the P-glycoprotein drug transporter can enhance CNS uptake of M3G and, to a lesser extent, M6G.
  Note : P-glycoprotein is an efflux protein that prevents the entrance of foreign substances into the body , it is found in the intestinal brush border , kidney , liver, and the choroid plexus in the brain.
- Like morphine, **hydromorphone** is metabolized by conjugation, yielding hydromorphone-3-glucuronide (H3G), which has CNS excitatory properties.
- Esters (e.g. heroin, remifentanil) are rapidly hydrolyzed by tissue esterases. Heroin (diacetylmorphine) is hydrolyzed to morphine, which is then conjugated with glucuronic acid.
- Hepatic oxidative metabolism (CYP450) is the primary route of metabolism of **meperidine (pethidine) , fentanyl**, alfentanil, sufentanyl.
- Accumulation of the demethylated metabolite of **meperidine, normeperidine** (de-methyl meperidine), may occur in patients with renal dysfunction and in those receiving multiple high doses of the drug. In high concentrations, normeperidine may cause **seizures.**
- The P450 isozyme **CYP3A4** metabolizes fentanyl by *N*-dealkylation in the liver.

- **CYP3A4** isozyme is responsible for the metabolism of 50% of the drugs made available for metabolism in the body after their administration , this results in a tremendous amount of drug-drug interactions.
- Codeine is metabolized in the liver by P450 isozyme CYP2D6 to morphine. Patients may experience either no significant analgesic effect or an exaggerated response based on differences in metabolic conversion (PMs Vs EMs).

Codeine CYP2D6 Metabolism		
	Poor metabolizers	**Extensive metabolizers**
Speed of metabolism	Slow	Fast
Effect	Poor analgesic effect , analgesia confined mainly to codeine (little amount of morphine is formed)	Strong analgesic effect , might exhibit adverse effects including respiratory depression (huge amounts of morphine will be formed)

Excretion

Polar metabolites, including glucuronide conjugates of opioid analgesics, are excreted mainly in the urine.

Pharmacodynamics

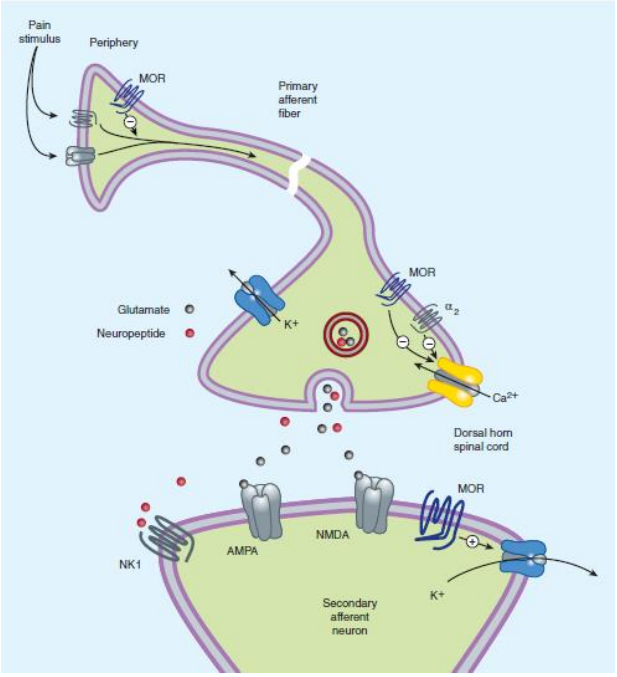
Mechanism of Action

Cellular actions

- Opioid agonists produce analgesia by binding to specific G protein-coupled receptors that are located in brain and spinal cord.
- The opioids have two well-established direct G protein-coupled actions on neurons:

- They close voltage-gated Ca 2+ channels on **presynaptic** nerve terminals and thereby reduce transmitter release (large number of neurotransmitters including Glutamate ,Substance P ,Acetylcholine ,Norepinephrine ,serotonin).
- They hyperpolarize and thus inhibit **postsynaptic** neurons by opening K + channels.

Receptor Types



- The figure on the right show potential receptor mechanisms of analgesic drugs.
- The primary afferent neuron (cell body not shown) 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 μ-opioid receptors (MOR) or blocked in the afferent axon by local anesthetics (not shown).
- Action potentials reaching the dorsal horn can be attenuated at the presynaptic ending by opioids and by calcium blockers (ziconotide), α 2 agonists, and possibly, by drugs that increase synaptic concentrations of norepinephrine by blocking reuptake (tapentadol).
- Opioids also inhibit the postsynaptic neuron, as do certain neuropeptide antagonists acting at tachykinin (NK1) and other neuropeptide receptors.

Relation of physiologic effects to receptor type

- The majority of currently available opioid analgesics act primarily at the μ-opioid receptor. Analgesia and the euphoriant, respiratory depressant, and physical dependence properties of morphine result principally from actions at μ receptors.

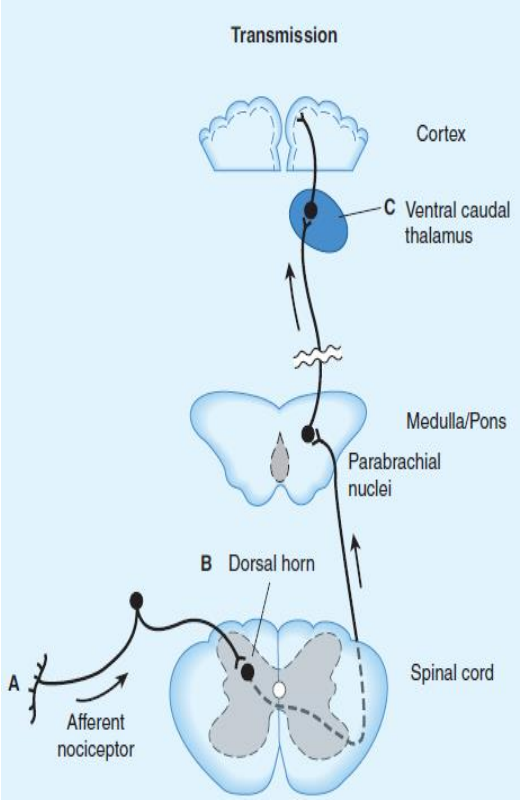
- **Euphoria :** intravenous drug users who receive intravenous morphine experience a pleasant floating sensation with lessened anxiety and distress.

- Compounds that show preference for κ opioid receptors (**butorphanol and nalbuphine**) can cause analgesia with a reduced incidence of respiratory depression or propensity for addiction and dependence, however, they can cause dysphoria (**Remember : Psychotomimetic effect**).

- **Dysphoria** : an unpleasant state characterized by restlessness and malaise.

Receptor distribution and neural mechanisms of analgesia

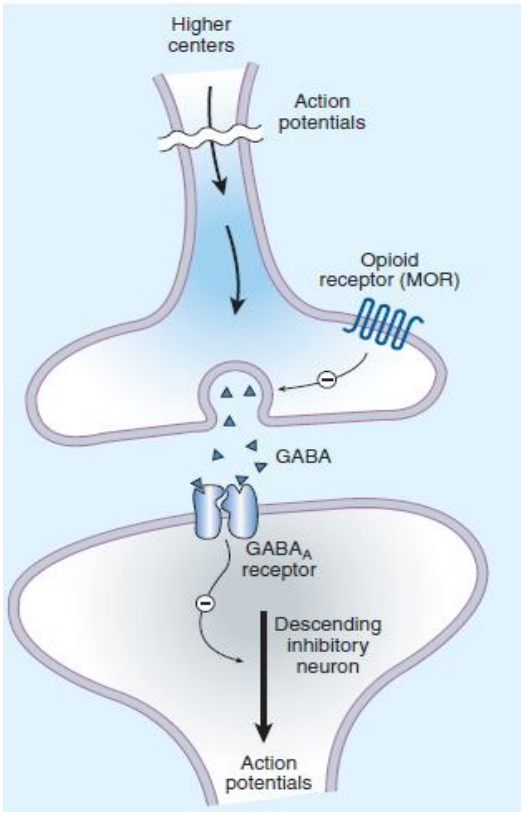
❖ Putative sites of action of opioid analgesics.
Sites of action on the afferent pain transmission pathway from the periphery to the higher centers are shown.
A: Direct action of opioids on inflamed or damaged peripheral tissues
B: Inhibition also occurs in the spinal cord .
C: Possible sites of action in the thalamus.



- Opioids exert a powerful analgesic effect directly on the spinal cord. This ***spinal action*** has been exploited clinically by direct application of opioid agonists to the spinal cord, which provides a regional analgesic effect while reducing the unwanted respiratory depression, nausea and vomiting, and sedation that may occur from the ***supraspinal actions*** of systemically administered opioids.

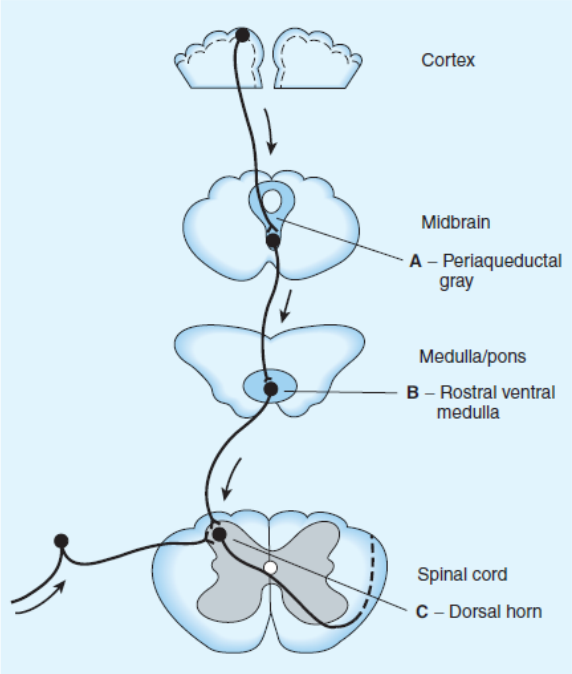
❖ Brainstem local circuitry underlying the modulating effect of μ-opioid receptor (MOR)-mediated analgesia on **descending pathways**.

- The pain-inhibitory neuron is indirectly activated by opioids (exogenous or endogenous), which inhibit an inhibitory (GABAergic) interneuron. This results in *enhanced* inhibition of nociceptive processing in the dorsal horn of the spinal cord.
- **Opioids inhibit GABA-mediated (GABAergic) synaptic transmission by reducing the probability of presynaptic neurotransmitter release , therefore , GABA interneurons will not be stimulated and will not be able to perform their function , aka inhibition of the descending inhibitory neuron.**



❖ Opioid analgesic action on the descending inhibitory pathway.

- Sites of action of opioids on pain-modulating neurons in the midbrain and medulla including :
  (A) The midbrain periaqueductal gray area
  (B) Rostral ventral medulla
  (C) The locus caeruleus indirectly control pain transmission pathways by **enhancing descending inhibition to the dorsal horn.**



☆ **Test yourself :**

Regarding opioid analgesics , which of the following statements is true?

A. Morphine 6 glucuronide is 4-6 times more potent than fentanyl.
B. Pethidine is metabolized by *N*-dealkylation in the liver.
C. δ opioid receptors are peculiar for their psychotomimetic effect.
D. Nalbuphine has a reduced incidence of respiratory depression compared to morphine.
E. The spleen serves as a reservoir for opioid drugs.
F. Direct spinal action of opioids carries higher risk of adverse reactions compared to supraspinal action.