Al-Mustaqbal University College
Department of Pharmacy
4th stage
Pharmacology II
Lecture: 8

OPIOIDS

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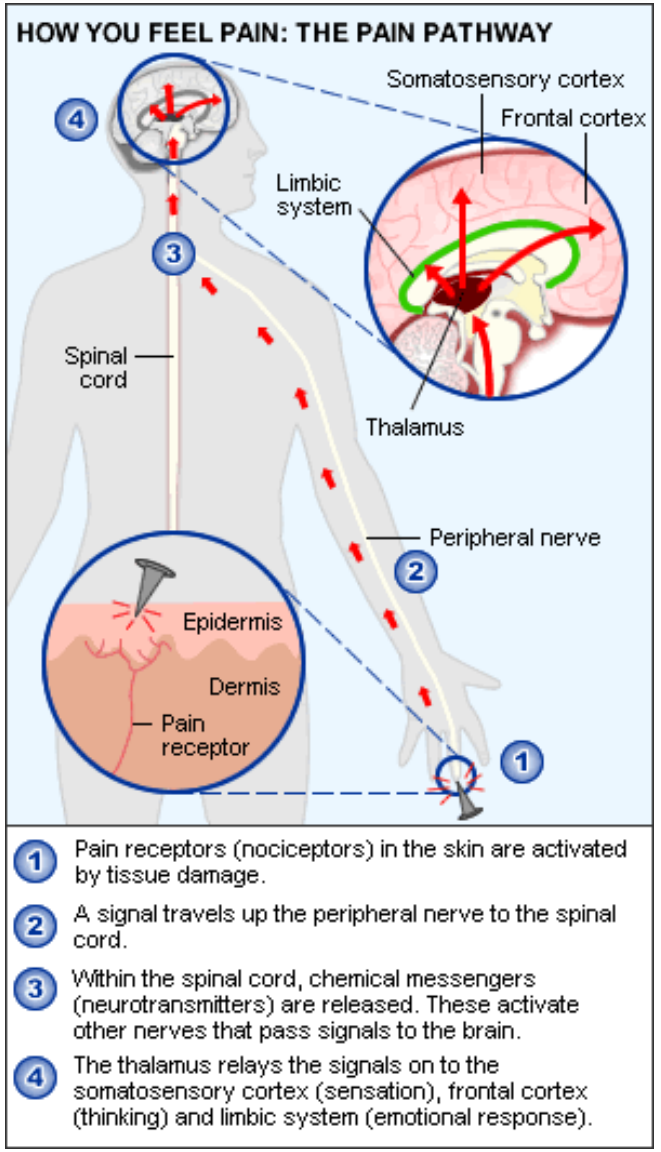
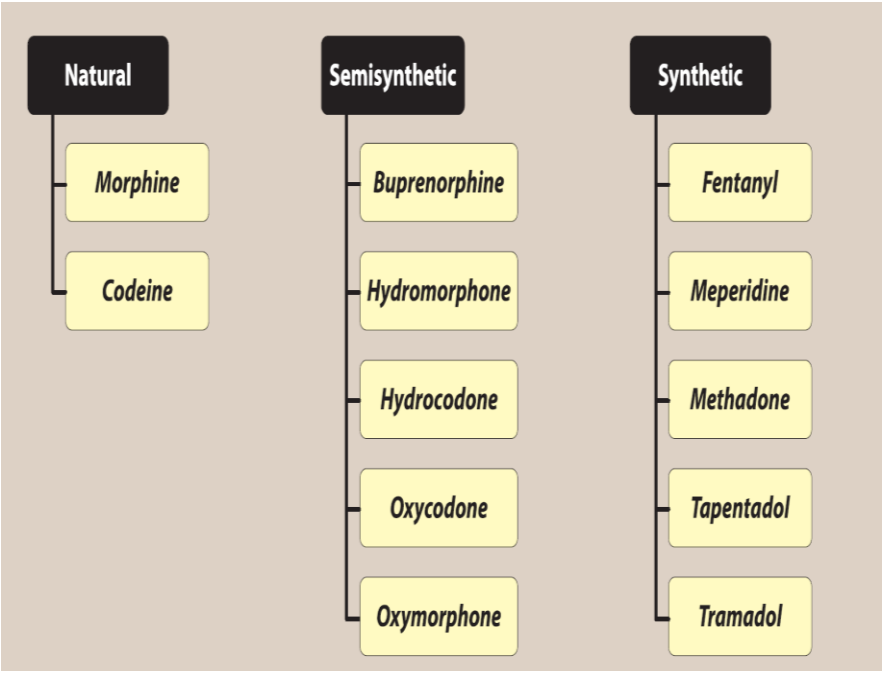
PAIN SENSATION

- **Pain** is defined as an **unpleasant sensation** that can be either acute or chronic and is a consequence of complex **neurochemical** processes in the PNS & CNS.
- **Alleviation** of pain depends on the specific **type** of pain (<u>nociceptive</u> or <u>neuropathic</u> pain).
- However, for **severe acute** pain or **chronic** malignant or nonmalignant pain, **opioids** can be considered as part of the treatment plan in select patients.



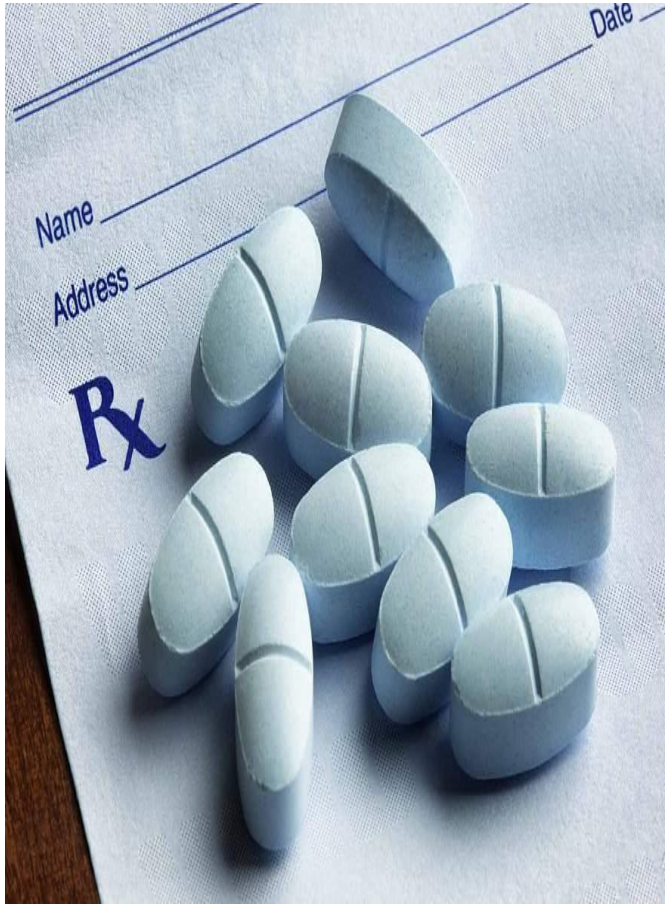
OPIOIDS

- Opioids are **natural**, semisynthetic, or synthetic compounds that produce **morphine-like** effects.
- These agents are divided into chemical classes based on their **chemical structure**.
- **All opioids** act by binding to specific opioid receptors in the CNS to produce effects that mimic the action of **endogenous** peptide neurotransmitters (for example, **endorphins**, **enkephalins**, and **dynorphins**).



OPIOIDS

- Although opioids have a **broad range of effects**, their **primary** use is to **relieve intense pain** that results from surgery, injury, or chronic disease.
- Unfortunately, the widespread availability of opioids has led to the **abuse** of agents with **euphoric** properties.
- **Antagonists** that reverse the actions of opioids are also clinically important for use in cases of **overdose**.



OPIOID RECEPTORS

- The major effects of opioids are mediated by **three** main receptor families, commonly designated as:

1. **μ (mu) receptor**
2. **κ (kappa) receptor**
3. **δ (delta) receptor**

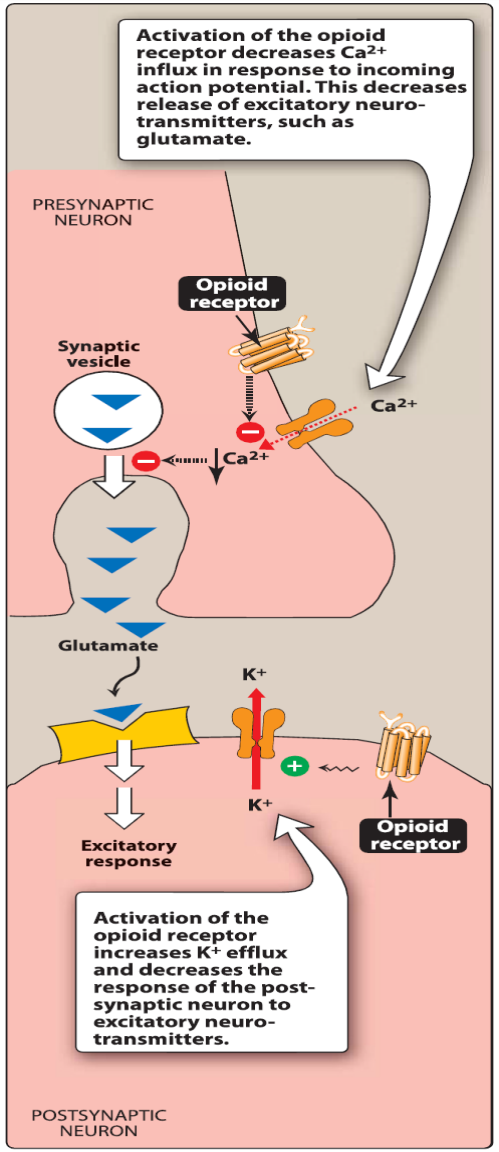
- Each receptor family exhibits a different **specificity** for the drug(s) it binds.
- The **analgesic** properties of opioids are primarily mediated by the **mu receptors** that modulate responses to **thermal, mechanical, and chemical nociception**.
- The **K receptors** also contribute to **analgesia** by modulating the response to **chemical and thermal nociception**.
- The **enkephalins** interact more selectively with **delta** receptors in the periphery.

OPIOID RECEPTORS

- All three opioid receptors are members of the **G protein-coupled** receptor family and they:

1. **inhibit adenylyl cyclase**.
2. **increasing postsynaptic K+ efflux** (hyperpolarization)
3. **reducing presynaptic Ca2+ influx**

- Thus impeding neuronal firing and transmitter release in the spinal dorsal horn



OPIOID AGONISTS

- **Morphine** is the **prototypical strong** mu receptor agonist.
- **Codeine** is less potent and the **prototype** of the **weak** mu opioid agonists.
- Currently available opioids have many differences, such as receptor affinity, pharmacokinetic profiles, available routes of administration, and adverse effect profiles.
- **Comparing** other available opioids to **morphine** is helpful in identifying the unique differences to **guide** the **selection** of a safe and effective pain management regimen.

MORPHINE

1. Mechanism of action:

- It exerts analgesic effects by **interacting with opioid receptors** on the membranes of neuronal cells in the CNS and other anatomic structures, such as the smooth muscles of the gastrointestinal (GI) tract and the urinary bladder.
- Morphine is somewhat **selective to the mu opioid** receptor but has **some** affinity for the **kappa and delta** receptors.
- Morphine also **inhibits the release** of many excitatory **transmitters** from nerve terminals carrying nociceptive (painful) stimuli.

MORPHINE

2. Actions

a. Analgesia:

- Morphine and other opioids **relieve pain** by raising the pain threshold at the spinal cord level and by altering the brain's perception of pain.

b. Euphoria:

- Morphine produces a **powerful** sense of contentment and **well-being**.
- Euphoria may be caused by **disinhibition** of the dopamine-containing neurons of the **ventral tegmental area**.

c. Respiration:

- Morphine causes **respiratory depression** by reduction of the **responsiveness** of medullary respiratory center neurons to **carbon dioxide**.
- Respiratory depression is the most common cause of **death** in acute opioid overdoses.

MORPHINE

2. Actions

d. Depression of cough reflex:

- Both morphine and codeine have **antitussive** properties.
- The **receptors** involved in the antitussive action appear to be **different** from those involved in analgesia.

e. Miosis:

- The **pinpoint pupil** characteristic of morphine use results from stimulation of **mu** and **K** receptors.
- This is important **diagnostically** because many **other** causes of coma and respiratory depression produce **dilation** of the pupil.

f. Emesis:

- Morphine directly **stimulates** the CTZ in the area postrema that causes vomiting.

MORPHINE

2. Actions

g. Gl tract:

- Morphine relieves **diarrhea** by **decreasing** the motility and increasing the tone of the intestinal circular smooth muscle and **increasing** the tone of the anal sphincter.
- Morphine can also **increase** biliary tract pressure due to **contraction** of the gallbladder and **constriction** of the biliary sphincter.

h. Cardiovascular:

- Morphine has **no major effects** on blood pressure or heart rate at **lower** dosages, but **hypotension** and **bradycardia** may occur at **higher** doses.
- Because of respiratory depression and carbon dioxide retention, **cerebral vessels dilate** and increase **cerebrospinal** fluid pressure.
- Morphine is usually **contraindicated** in individuals with **head trauma** or **severe brain injury**.

MORPHINE

2. Actions

i. Histamine release:

- Morphine **releases** histamine from mast cells causing urticaria, sweating, and vasodilation.
- Because it can cause **bronchoconstriction**, morphine should be used with **caution** in patients with **asthma**.

j. Hormonal actions:

- Prolonged use of morphine may lead to **opioid-induced androgen deficiency** due to **suppression** of the hypothalamic-pituitary-gonadal axis (**HPA**).
- This results in **decreased** production of sex hormones, especially **testosterone**.

k. Labor:

- Morphine may **prolong** the **second stage** of labor by transiently **decreasing** the strength, duration, and frequency of **uterine contractions**.

MORPHINE

3. Pharmacokinetics

a. Administration:

- Morphine has a **linear** pharmacokinetic profile; however, **absorption** of morphine after oral administration is **slow**.
- **Extended-release** oral preparations provide more consistent plasma levels.
- Because **significant first-pass** metabolism of morphine occurs in the liver, subcutaneous and intravenous (IV) injections produce the most reliable response.

b. Distribution:

- Morphine **rapidly enters** all body tissues, including the **fetuses** of pregnant women.
- It should **not** be used for analgesia during **labor**.
- Only a **small percentage** of morphine crosses the **BBB**, because morphine is the **least lipophilic** of the common opioids.
- By contrast, the **more lipid-soluble** opioids, such as **fentanyl** and **methadone**, readily penetrate the CNS.

3. Pharmacokinetics

c. Fate:

- Morphine is conjugated with **glucuronic** acid in the liver to **2 active** metabolites (morphine-6-glucuronide [**M6G**] and morphine-3-glucuronide [**M3G**]), which are renally excreted.
- **M6G** is a **very potent** analgesic.
- **M3G** does **not** have analgesic activity but is believed to cause **neuroexcitatory** effects.
- The duration of action of morphine is **4-5 hrs** when administered **systemically** to opioid-na"ive individuals.
- But considerably **longer** when injected **epidurally** because the **low lipophilicity** prevents redistribution from the epidural space.

MORPHINE

4. Adverse effects:

- With most mu agonists, **severe respiratory depression** can occur and may result in death from an acute opioid overdose.
- **Respiratory drive** may be **suppressed** in patients with respiratory disorders such as obstructive sleep apnea, and emphysema.
- O**pioid-induced constipation** (OIC) is a common adverse effect.
- Initial management includes a nonprescription stimulant laxative such as **senna**.
- Peripherally acting mu-opioid receptor antagonist such as **methylnaltrexone** is also available for the treatment of OIC.
- **Lubiprostone** is a chloride channel activator that is indicated for **OIC** and **IBS**.

MORPHINE

5. Tolerance and physical dependence:

- **Repeated use** produces **tolerance** to the respiratory depressant, analgesic, euphoric, emetic, and sedative effects of morphine.
- **Tolerance** usually does **not** develop to **miosis** (constriction of the pupils) or **constipation**.
- Physical and psychological **dependence** can occur with morphine and other agonists.
- **Withdrawal** produces a series of autonomic, motor, and psychological responses that can be severe, although it is rare that withdrawal effects cause death.

MORPHINE

6. Drug interactions:

- The **depressant** actions of morphine are **enhanced** by coadministration with **CNS depressant** medications such as phenothiazines, monoamine oxidase inhibitors (MAOIs), and benzodiazepines.
- **Guidelines** for opioid prescribing urge clinicians to **avoid simultaneous** prescribing of opioids and benzodiazepines.
- A **black box warning** also has been included on the labeling of both opioids and benzodiazepines to alert prescribers of this dangerous combination.

CODEINE

- **Codeine** is a **naturally** occurring opioid and a **weak** analgesic compared to morphine and is used for **mild to moderate** pain.
- The **analgesic** actions of codeine are derived from its **conversion to morphine** by the **CYP2D6** enzyme.
- **CYP2D6** activity varies among patients, and **ultrarapid** metabolizers may experience **higher levels** of morphine, leading to possible overdose and toxicity.
- **Life-threatening** respiratory depression and **death** have been reported in **children** who received codeine.
- Codeine is commonly used in **combination** with acetaminophen for the management of **pain**.
- The drug exhibits good **antitussive** activity at doses that do not cause analgesia.

DEXTROMETHORPHAN

- **Dextromethorphan** is a synthetic cough depressant.
- It has relatively **no analgesic** action and a much **lower** potential for **abuse** in usual **antitussive doses**.
- It is preferred over codeine in most situations where cough suppression is needed.

OXYMORPHONE

- Oxymorphone is **orally active**, a **semisynthetic** analog of morphine.
- Oxymorphone given **parenterally** is approximately **ten times** more **potent** than morphine.
- But when administered **orally**, the potency drops to about **three times** that of morphine.
- Oxymorphone is available in both **immediate-release** and **extended-release** oral formulations.

OXYCODONE

- Oxycodone is an **orally active**, **semisynthetic** analog of codeine.
- Oxycodone is approximately **two times** more potent than morphine.
- It is available in an **immediate-release** formulation, alone or in combination with acetaminophen, aspirin, or ibuprofen.
- An **extended-release** formulation is also available.
- Oxycodone is mainly **metabolized** via the CYP2D6 and CYP3A4 enzymes.

HYDROMORPHONE

- Hydromorphone is **orally active**, a **semisynthetic** analog of morphine.
- **Oral** hydromorphone is approximately **4-7 times** more potent than oral morphine.
- It is **preferred** over morphine in patients with **renal dysfunction** due to less accumulation of active metabolites.

HYDROCODONE

- Hydrocodone is the **methyl ether** derivative of **hydromorphone**, but is a **weaker** analgesic than hydromorphone, with oral analgesic efficacy **comparable** to that of **morphine**.
- This agent is often **combined** with acetaminophen or ibuprofen to treat moderate to severe pain.
- It is also used as an **antitussive**.
- Hydrocodone is **metabolized** in the liver to several metabolites, one of which is **hydromorphone** via the actions of CYP2D6.

FENTANYL

- Fentanyl is a **synthetic** opioid chemically related to **meperidine**.
- It has **100-fold** the analgesic potency of morphine and is used for **anesthesia** and **acute pain** management.
- The drug is **highly lipophilic** and has a **rapid onset** and **short duration** of action (15-30 minutes).
- It is usually administered **IV**, **epidurally**, or **intrathecally**.
- **Fentanyl** is combined with **local anesthetics** to provide **epidural analgesia** for labor and postoperative pain.
- It is **metabolized** to inactive metabolites by CYP3A4, and drugs that **inhibit** this isoenzyme can **potentiate** the effect of fentanyl.

PARTIAL AGONISTS AND MIXED AGONIST -ANTAGONISTS

- **Partial agonists** bind to the opioid receptor, but they have less intrinsic activity than full agonists.
- There is a **ceiling** to the pharmacologic effects of these **partial agonists**.
- Drugs that **stimulate** one receptor but **block** another are termed **mixed** agonist-antagonists.
- The effects of these drugs depend on previous exposure to opioids.

PARTIAL AGONISTS AND MIXED AGONIST -ANTAGONISTS

A. Buprenorphine

- It acts as a potent **partial agonist** at the **mu receptor** and an **antagonist** at the **K** receptors.
- It is **very lipophilic** and has a **longer** duration of action due to its high affinity for opioid receptors when compared to morphine.
- Due to the **high affinity** for the mu receptor, buprenorphine can **displace** full mu agonists, leading to **withdrawal symptoms** in an opioid-dependent patient.
- Because of the partial mu agonist activity, buprenorphine provides a **"ceiling effect**; causing **less euphoric** effects and **lower abuse** potential than that of full agonists.
- Buprenorphine is available in sublingual, transmucosal, buccal, parenteral, subdermal, and transdermal formulations.
- The drug is approved for **moderate to severe** pain.

B. Pentazocine

- Pentazocine acts as an **agonist on K** receptors and is a **weak antagonist** or partial agonist at **mu receptors**.
- It can be administered either **orally** or **parenterally**.
- Pentazocine produces **less euphoria** compared to morphine, but in higher doses, respiratory depression, increased blood pressure, tachycardia, and hallucinations can occur.
- Pentazocine should be used with **caution** in patients with **angina** or **coronary artery disease** since it can increase blood pressure.

OTHER ANALGESICS

B. Tramadol

- Tramadol is a **centrally-acting** analgesic that binds to the **mu** opioid receptor.
- It undergoes extensive **metabolism** via CYP2D6, leading to an **active metabolite**, which has a much **higher affinity** for the mu receptor than the parent compound.
- In addition, it weakly **inhibits the reuptake** of norepinephrine and serotonin.
- It is used to manage **moderate to severe** pain.
- Tramadol should be used with **caution** in patients with a history of **seizures**.
- As with other agents that bind the mu opioid receptor, tramadol has been associated with **misuse and abuse**.

OPIOIDS ANTAGONISTS

A. Naloxone

- Naloxone is a **competitive antagonist** at mu, K, and delta receptors, with a **10-fold** higher **affinity** for mu than for kappa receptors.
- It rapidly **displaces** all receptor-bound opioid molecules and, therefore, can reverse the effects of a morphine overdose, such as respiratory depression and coma within **1-2** minutes of **IV** administration.
- Naloxone can also be administered **intramuscularly**, **subcutaneously**, and **intranasally**, with a slightly **longer** onset of **2-5** minutes.
- Naloxone is available in an **autoinjector** and a nasal inhaler for community distribution for treatment of opioid overdose involving heroin or prescription opioids.

B. Naltrexone

- **Naltrexone** has actions similar to those of naloxone, but it has a **longer duration** of action and can be given **orally**.
- For example, a **single oral dose** of naltrexone blocks the effect of injected heroin for up to **24 hours**, and the **intramuscular** formulation blocks the effect for **30 days**.
- Naltrexone has been reported to cause **hepatotoxicity** and monitoring of hepatic function is recommended.

THANK YOU FOR YOUR ATTENTION