College of Dentist medicine Pharmacology 3rd year

Opioid Agonists and Antagonists

- Pain is an unpleasant sensation and emotional experience associated with actual or potential tissue damage.
- Alleviation of pain depends on its type for e.g.: with headache or mild to moderate arthritic pain, NSAIDs are enough and effective.
- Neuropathic pain is the pain originated in the CNS, best responds to anticonvulsants, (tricyclic antidepressantsTCAs or serotonin-norepinephrine reuptake inhibitors SNRIs rather than to NSAIDs or opioids.
- **However, for sever or chronic malignant pain, opioids are the drugs of choice.**
- **Opioids** are natural or synthetic compounds that produce morphine-like effects. All drugs in this category act by binding to specific opioid receptors in the CNS to produce effects that mimic the action of endogenous peptide neurotransmitter e.g.: endorphine, enkephaline and dynorphine.

Nociception

- Pain alerts us to ongoing potential tissue damage and the ability to sense pain is vital to our living.
- Nociception is the physiological process by which the pain is perceived.
- Our nervous system is altered to injury by the activation of the peripheral terminal of highly specialized primary sensory neurons called "nociceptor".
- Their cell bodies lie in the dorsal root ganglia of the spinal cord. Glutamate, an amino acid, is the main excitatory neurotransmitter released in these synapses.
- Glutamate release can be inhibited by opioids, cannabinoids,

- Other neurotransmitter involved on the nociception process is the substance P.

Clinical pain is generally divided into three broad categories:

1- **Acute pain** such as that experienced after trauma or surgery, typically resolved with healing of the injured tissue.

2- **Chronic pain** is the pain that persists beyond the period expected for healing or the pain that is associated progressive or persistent non-malignant disease. Chronic pain may be due to continuous stimulation of nociceptor in the damaged tissue e.g.: rheumatoid arthritis.

3-Cancer-related pain which results from primary tumor, metastatic disease or the effects of chemotherapy or radiation.

Opioid Receptors

Opioids interact with opioid receptors present in the CNS, peripheral nerves, GIT cells and other regions. They include**: μ-receptors**, **k-receptors** and **delta-receptor**. These receptors correspond to their endaogenous ligands: dynorphine, enkephaline and β-endorphine. The analgesic properties are mainly due to μ-receptors.

Distribution of receptors

1) Brainstem: opioid receptor influence respiration, cough, nausea &vomiting., pupil &gastric secretion.
2) Spinal cord
3) Hypothalamus
4) Limbic system
5) Periphery

6) Immune cells: opioid-binding sites have also been found on immune cells.

All three opioid receptors are members of G-protein family and inhibit adenylyl cyclase.

Classification of Opioid Agonists

They classified as **1- strong** and **2- intermediate** according to their analgesic properties and addiction:

A) STRONG AGONISTS

1. **Morphine**: morphine remains the most widely used opioid for the treatment of severe pain.

Mode of action:

- Opioids exert their major effect by interacting with opioid receptors in the CNS and other tissues such as GIT and urinary bladder.
- Opioids cause1- hyperpolarization of nerve cells,2- inhibition of neuronal firing and3- presynaptic inhibition of transmitter release.
- Morphine act at k-receptors in the spinal cord and it decreases the release of substance P which modulates pain reception in the spinal cord.

a) Analgesic actions: morphine relieves pain by raising pain threshold at spinal cord.

b) Euphoria: morphine causes powerful sense of contentment & well-being.

c) Respiration: it depresses respiration by reduction of the sensitivity of respiratory center to CO_2. Respiratory depression is the most common cause of death in acute opioid overdose.

d) Depression of cough reflex: both morphine and codeine have antitussive properties.

e) Miosis

f) Emesis: morphine directly stimulates the central trigger zone that causes vomiting.

g) On GIT: morphine relieves diarrhea by decreasing the motility of intestine.

h) Cardiovascular: at usual doses, morphine has no effect on BP or HR except at large doses when it causes hypotension and bradycardia.

i) Histamine release: morphine releases histamine from mast cells so it can cause bronchoconstriction and it is contraindicated in asthmatics.

Therapeutic Uses

1) Analgesia: morphine is very potent analgesic, patients taking opioid for analgesia often report less distress, even when they can still perceive pain.
2) Treatment of diarrhea

Pharmacokinetics

- Morphine is commonly given IM, IV or orally. It can also be given per rectum.
- It is available as sustained-release for oral route which is used for terminal patients with malignant diseases.

Adverse Effects of Morphine

- Severe respiratory depression occurs and can result in death from acute opioid poisoning.
- Vomiting and constipation may occur.
- Urinary retention, **dry mouth which may lead to dental ulcers.**
- *Tolerance and physical dependence*: repeated use produces tolerance to the respiratory depression, analgesic, euphoric &sedative effects of morphine.

2. Pethidine (Meperidine)

- Pethidine act at μ-receptors.

- It also causes respiratory depression as morphine but it does not cause pin-point pupil, but rather it causes pupils to dilate.
- Pethidine also has atropine-like effects.
- Pethidine causes less urine retention than morphine.
- Its duration of action is 2-4 hours.

Uses: Pethidine is used for any type of severe pain, but it has no effects on cough or diarrhea.

3. **Methadone:**
    - It is a synthetic orally effective opioid that is approximately equal in potency to morphine and act at μ-receptor.
    - It is commonly used as a maintenance drug in opioid addiction.
    - It is used also in cancer and non-malignant pain.
    - The addict patients then slowly weaned from methadone.
    - It is well absorbed orally.
    - The main feature of methadone is its long-duration of action due to its high protein binding and slow hepatic metabolism.
    - It accumulates in the tissue where it is slowly released.
4. **Fentanyl:**
    - This drug is chemically related to morphine and it is the first short-acting opioid developed for use in anesthesia.
    - It is approximately 100-fold more potent than morphine.
    - It is highly lipid-soluble and has rapid onset & short duration of action (15-30 min).
    - It is given IV, epidural, intrathecal, oral and as transdermal patch.

- It is used in cardiac surgery because it has no effect on myocardial contractility.

5. **Heroin (diamorphine):**
   - Diamorphine is a synthetic drug was first made from morphine.
   - It is generally lipid-soluble so it diffuses into the brain more rapidly than morphine causing marked euphoria when taken by injection.
   - It's half-live about 3 minutes.

B) **MODERATE AGONISTS**:

1) **Codeine**:
   - It is obtained naturally or by methylation of morphine.
   - It has a low affinity for opioid receptors & most of its analgesic effect result from its metabolism to morphine (10%).
   - Its antitussive effect is due to codeine itself.

Uses:

1. Mild to moderate pain 2- Persistent cough 3- Symptomatic control of diarrhea

2) **Propoxyphene**:
   - This is a derivative of methadone is used to relieve mild to moderate pain.
   - It is often used in combination with aspirin or acetaminophen.

3) **Tramadol:**

- A centrally-acting analgesic that binds to μ-receptor.
- It also inhibits re-uptake of noradrenaline & serotonin.
- Used to manage moderate-sever pain.

OPIOID ANTAGONIST

The opioid antagonists bind with high affinity to opioid receptors but do not activate these receptors. Antagonists rapidly reverse the effects of agonists such as heroin and precipitate acute withdrawal symptoms. They're also used to diagnose opioid addiction.

1) ***Naloxone:*** it is a competitive antagonist at μ-, k-, delta and receptor, within minutes it reverse the effects of most opioids if given IV. It reverses coma & respiratory depression of opioid overdose. Because its short duration of action, the patient may return back & respiratory depression, so repeated doses are sometimes necessary.
2) ***Naltrexone:*** this drug is similar to naloxone but it has a longer duration of action and a single dose of it blocks the effect of injected heroin for up to 48 hours.