Opioid Analgesics & Opioid Antagonists

Prof. Saed .M.dalaen

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Opioid Analgesics

- Narcotic analgesics: relieve **pain** & induce **sedation**
- Opioids:
  - **Natural**: **morphine**, **codeine** (from opium poppy)
  - **Synthetic: pethidine, methadone**
  - **Semisynthetic: heroin**
- Cultivation of opium poppy (الأفيون, الخشخاش) is restricted & under strict governmental control



Opioid Receptors

- Opioid receptors: in the **brain** & spinal **cord**
- Involved in **transmission** & **modulation** of pain
- **Major** opioid receptors:

  1. **mu (μ_1 & μ_2)**
  2. **Delta (δ_1 & δ_2)**
  3. **Kappa (κ_1, κ_2 & κ_3)**

Opioid receptor activation

- **Spinal & supraspinal sites**
- **G protein–coupled** receptors
  - **Open potassium** channels
  - **Prevent** opening of **calcium** channels

  Therefore:
- **Reduce** neuronal **excitability**
- **Inhibit release** of pain neurotransmitters

Opioid receptor activation

- **Activation** of opioid receptors leads to:
  - **Reduction** of neurotransmitter **release (Ach, noradrenaline, serotonin & substance P)**
  - **Inhibition** of postsynaptic neurons concerned with pain-transmission in the spinal cord

Opioid Receptors

- **mu-receptors** are most important:
  - **μ_1: analgesia, euphoria,physical dependence**
  - **μ_2: Respiratory depression, inhibition of gut** motility
- **κ**: **Analgesia** at **spinal** cord level & dysphoria
- **Delta** receptors role is not clear

Opioid receptor distribution

- **Spinal** (dorsal horn neurons)
- **Supraspinal** regions (medulla, midbrain & Cerebral C)
- Opioid pain-relief:
  - **Activation** of opioid receptors
  - **Inhibit** release of excitatory neurotransmitters
  - **Inhibit** dorsal horn pain **transmission** neurons
  - **Release** of **endogenous** opioid **peptides**

Endogenous Opioid peptides

- Opioids act at sites in the brain concerned with pain modulation
- **Sites** contain **peptides** with opioid-like actions
  - **Endorphins, dynorphins, enkephalin**
- **Precursors** present at these sites
- Also in adrenal medulla & ENS in gut
- Released during stress (pain or anticipation of pain)

Opioid agonists classification

- **According to analgesic efficacy:**
  - Agonist (morphine)
  - Partial agonist (pentazocine)
- **High** efficacy:
  - **Morphine, Pethidine, Diamorphine**, Methadone
- **Low** efficacy:
  - **Codeine**, **Pentazocine,** Dextropropoxyphene

Pharmacokinetics

- Well absorbed from sites of administration & from MM
- Given **parenterally, orally**
- Some have high **1st pass metabolism** & so low bioavailability (morphine)
- New routes (nasal insufflation, trans-dermal)

Pharmacodynamics

- **Morphine** is the prototype:
- Acts on **μ1** receptors: **analgesia, euphoria & dependence**
- On **μ2** receptors: **respiratory depression, constipation**

Pharmacodynamics of morphine

1. **CNS actions:**

- **CNS depression:**
  - **Analgesia**
  - **Sedation**
  - **Respiratory depression**
  - **Cough suppression**

Pharmacodynamics of morphine

- **CNS excitation:**
  - **N & V** (stimulation of brainstem CTZ)
  - **Miosis** (stimulation of the 3rd nerve)
  - **Increase reflexes & convulsion: pethedine**
- **Loss of appetite**
- **Mood changes**
- **Dependence**

Pharmacodynamics of morphine

2. Peripheral NS:

- **Analgesia**
- **Anti-inflammatory** actions
- **Inhibition** of **immune** system

Pharmacodynamics of morphine

3. Smooth muscle stimulation

- **GIT**:
  - **Constipation:**
    - increase segmentation & decreased peristalsis
  - **Gastric** emptying delayed
  - **Increased intracolonic** pressure
  - **Biliary spasm;** increase intrabiliary P. (spasm of sphincter of Oddi)

Pharmacodynamics of morphine

- **Bronchospasm:**
  - Opioids are C/I in asthma & COAD
- **Ureteric** contraction**:**
  - Opioids may worsen ureteric colic
- Bladder **sphincter** contraction:
  - Urine retention in patients with BPH

Pharmacodynamics of morphine

- **Uterine muscle:**
  - morphine prolongs labour
- **Cardiovascular actions:**
  - Arteriolar & venular **vasodilatation**
  - **Histamine release:** vasodilatation
  - **Bradycardia**
- **Neuroendocrine** actions:
  - **Stimulate ADH & prolactin & Inhibit LH**

Clinical Uses of Opioid analgesics

- **Analgesia:**
  - Moderate-severe acute pain (PO, labour)
  - Chronic pain in dying patients
- **Left Ventricular failure:**
  - Venodilatation & arteriolar dilatation
  - Sedation
  - Decreased sympathetic effects on the heart
  - Decreased respiratory distress

Clinical Uses of Opioid analgesics

- **Premedication** in painful conditions
- **Anti-diarrhoeal** using codeine, diphenoxylate

Adverse effects

- **Nausea** & vomiting
- **Constipation**
- **Respiratory depression**
- **Bronchospasm**
- **Dependence; physical & psychological**

Opioid dependence

- **Physical** and psychological
- **Withdrawal** syndrome:
  - Within 12 hours
  - craving for the drug, rhinorrhoea,
  - Lacrimation, shivering, hyperventilation
  - Nausea, diarrhoea, colic
  - Increase HR & BP, mydriasis, flushing
  - Methadone & clonidine are useful

Tolerance

- May occur within days
- To **analgesic** & **respiratory** depression
- Not to **miosis** nor to **constipation**
- Cross-tolerance occur

Contraindications

- **Liver** disease
- **Asthma** & **COAD**
- **Head injury** & raised **intracranial** pressure
- **Hypothyroidism & Addison's disease**

Codeine

- t ½ of 3 hours
- About 10% of it is converted into morphine

- Uses include:
  - **Analgesic**: mild to moderate pains
  - **Anti-diarrhoeal**
  - **Antitussive**

Pethidine (Meperidine)

- **Differs** from **morphine** in being:
  - **Lower efficacy**
  - **Shorter duration** analgesia (2-3 hours)
  - Does **not constipate**
  - **Less urinary retention**
  - Does not prolong **labour**
  - **Less hypnotic**
  - Has **atropine-like** effects

Pethidine

- Used orally & parenterally
- **Metabolism:** in the **liver** & **excretion** in **urine**
- Widely used in obstetrics

- **Overdose of pethidine**
  - CNS stimulation, myoclonus & convulsions
  - Pupil may show miosis or mydriasis

Methadone

- t ½ is 8 hours
- **Synthetic; s**imilar to morphine
- **Longer duration** of action (24 hours)
- Used to **cover opioid withdrawal**
- **Dependence:**
  - **less severe** & **slower** to develop & **withdrawal** manifestations are **milder**
- May be used also for **severe cough**

Diamorphine (Heroin)

- **Semisynthetic, most potent addicting** drug
- **Illegal** manufacturing
- **Converted** within minutes into monoacetyl morphine & then to **morphine**
- Used **parenterally;** t ½ is 3 min
- Uses:
  - **acute severe pain**
  - chronic pain in dying **patients**

Mixed Agonist-Antagonist opioids; Pentazocine (Fortral; sossegon)

- **Partial agonist**
- At kappa receptors; some affinity to mu receptors
- May cause **dysphoria & withdrawal precipitation in morphine addicts**
- **Less potent, shorter duration,** less dependence, less respiratory depression
- Useful in **moderate to severe pain** and chronic pains
- **Avoided in AMI;** may increase blood pressure

Opioid receptor antagonists; Naloxone

- **Pure competitive antagonist**
- Acts on mu receptors
- t ½ is 75 min
- **IV** in opioid overdose toxicity
- **Reverses** respiratory depression in 2 min
- Doses may be repeated as necessary
- Can precipitate withdrawal in addicts

Opioid receptor antagonists; Naltrexone

- mu opioid receptor antagonist
- Can be used **orally**
- **Longer duration** of action (t ½ 10 hr)
- Useful in **chronic addicts**
  - as clonidine-naltrexone