Opioids and Opiates

- Opioid: A substance with a pharmacological action that is like that of opium or its derivatives.
- Opiate: A preparation of opium (morphine, codeine).
- Opium: A dark brown, resinous material obtained from poppy (*Papaver somniferum*) capsule. It contains alkaloids like morphine, codeine, papaverine, noscapine. Of these morphine and codeine are analgesics.
- Narcotic: An analgesic, a CNS depressant and any drug capable of causing physical dependence.

Introduction

Algesia (pain) is an ill-defined, unpleasant sensation, usually evoked by an external or internal noxious stimulus.

Analgesic A drug that selectively relieves pain by acting in the CNS or on peripheral pain mechanisms, without significantly altering consciousness.

Analgesics are divided into two groups,

a) Opioid/narcotic/morphine-like analgesics.
b) Nonopioid / non-narcotic / aspirin-like / antipyretic or antiinflammatory analgesics

CLASSIFICATION OF OPIOIDS (Based on source)

1. Natural opium alkaloids: Morphine, Codeine

2. Semisynthetic opiates: Diacetylmorphine (Heroin), Pholcodeine.

3. Synthetic opioids: Pethidine (Meperidine), Fentanyl, Methadone, Dextropropoxyphene, Tramadol.

Opioid receptors

- μ, κ, δ receptors are present on neurons in the CNS and peripheral tissues.
- Opioid analgesics act primarily through activation of μ receptors.
- Weak interaction with κ receptors.
- Do not interact with δ receptors.
- Endogenous opioid peptides act through all three receptors.

❑ Activation of μ receptors cause analgesia, respiratory depression, euphoria, sedation and physical dependence.

❑ Activation of κ receptors can produce analgesia and sedation.

Morphine

- Morphine is the principal alkaloid in opium and still widely used.
- Act on μ opioid receptor

Pharmacological action

1. CNS- depressant as well as stimulant action

Depressant action	Stimulant action
Analgesic	CTZ: Nausea and vomiting
Sedation (drowsiness)	
Mood and subjective effects: euphoric effect	
Respiratory depression	
Centre centre- depressed	

Morphine

2. CVS

Morphine causes vasodilatation due to:
(a) histamine release.
(b) depression of vasomotor centre.
(c) direct action decreasing tone of blood vessels.

3. GIT- Constipation

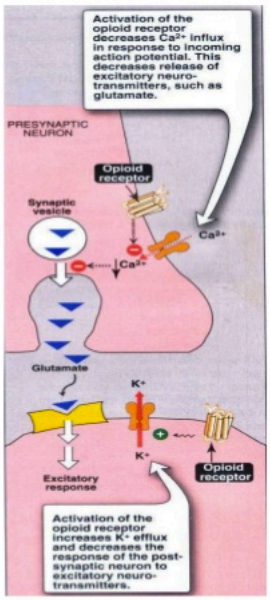
Mechanism of Action

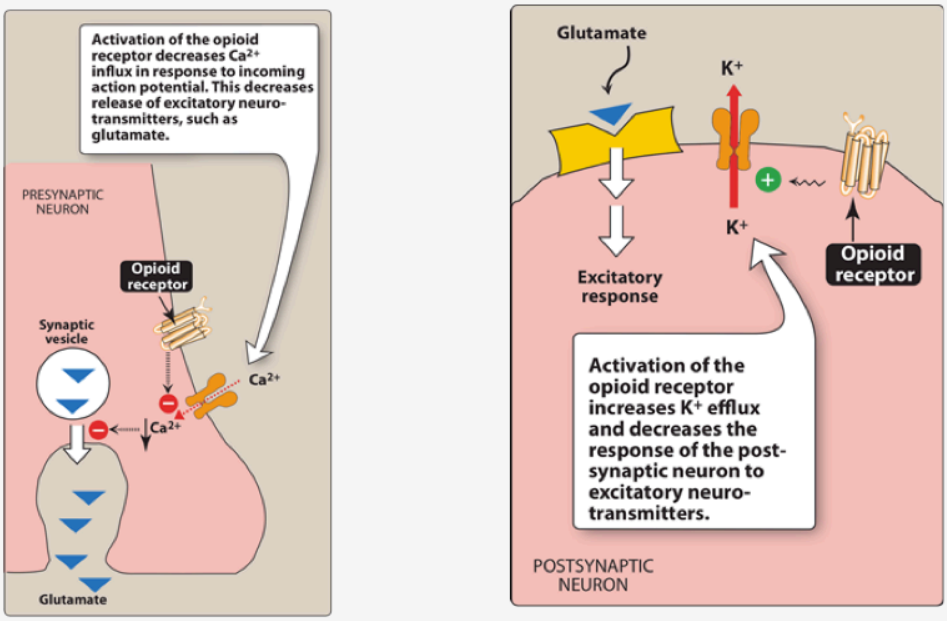
All opioid receptors are G-protein coupled receptors and inhibit adenylate cyclase.

They are also involved in

- Postsynaptic hyperpolarization (increasing K+ efflux)
- Reducing presynaptic Ca^{++} influx

thus inhibits neuronal activity.





Adverse effect

Side effects: Sedation, drowsiness, lethargy vomiting; constipation, Respiratory depression, blurring of vision, urinary retention.

Allergy is uncommon and anaphylactoid reaction is rare. Urticaria, itch, swelling of lips are the manifestations. A local reaction at injection site may occur due to histamine release.

Tolerance and dependence

- High degree of tolerance can be developed to morphine and related opioids if the drug is used repeatedly.
- Morphine produces pronounced psychological and physical dependence, its abuse liability is rated high.
- **Withdrawal** of morphine is associated with marked drug-seeking behaviour.
- Physical manifestations are - lacrimation, sweating, anxiety, fear, restlessness, gooseflesh, mydriasis, tremor, insomnia, diarrhoea, dehydration, rise in BP, palpitation and rapid weight loss.
- Treatment: consists of withdrawal of morphine and substitution with oral methadone (long-acting, orally effective) followed by gradual withdrawal of methadone.

Precaution and contraindication

- It is dangerous in patients with respiratory insufficiency (emphysema, pulmonary fibrosis, cor pulmonale), sudden deaths have occurred.
- Bronchial asthma: Morphine can precipitate an attack by its histamine releasing action.
- Elderly male: chances of urinary retention are high.

Codiene

- methyl-morphine, occurs naturally in opium, and is partly converted in the body to morphine.
- It is less potent than morphine (1/10th as analgesic), also less efficacious; is a partial agonist at μ opioid receptor.
- The degree of analgesia is comparable to aspirin (60 mg codeine ≈ 600 mg aspirin); can relieve mild to moderate pain only.
- it is more selective cough suppressant (only 1/3rd as potent as morphine); subanalgesic doses (10-30 mg) suppress cough.

Pethidine

- synthesized as an atropine substitute in 1939, and has some actions like it.
- chemically unrelated to morphine, it interacts with opioid receptors and its actions are blocked by naloxone.
- Important differences in comparison to morphine are:

1. analgesic efficacy approaches near to morphine and is greater than codeine.
2. After i.m. injection, the onset of action is more rapid but duration is shorter (2-3 hours).
3. It does not effectively suppress cough.
4. constipation and urinary retention are less prominent.
5. It is equally sedative and euphoriant, has similar abuse potential.
6. It causes less histamine release and is safer in asthmatics.

Uses

- as an analgesic (substitute of morphine) and in preanaesthetic medication, but not for cough or diarrhoea.
- It is the preferred opioid analgesic during labour-at equianalgesic doses, neonatal respiratory depression is less marked, but still significant.

A/E: similar to morphine except those mentioned above. Some atropinic effects (dry mouth, blurred vision, tachycardia)

Dose: 50-100 mg i.m., S.c.

Fentanyl

A pethidine congener, 80-100 times more potent than morphine, both in analgesia and respiratory depression.

Transdermal fentanyl has become available for use in cancer or other types of chronic pain for patients requiring opioid analgesia.

Transdermal patch delivering 25 µg/hr, 50 µg/hr or 75 µg/hr; the patch is changed every 2-3 days.

Methadone

- A synthetic opioid, chemically dissimilar but pharmacologically very similar to morphine-has analgesic, respiratory depressant, emetic, antitussive, constipating and biliary actions similar to morphine.
- The abuse potential is rated lower than morphine.
- Tolerance develops more slowly.
- Methadone has been used primarily as substitution therapy of opioid dependence: 1 mg of oral methadone can be substituted for 4 mg of morphine and 20 mg of pethidine.
- used as an analgesic for the same conditions as morphine; dose 2.5-10 mg oral or i.m. but not s.c.

Tramadol

- This centrally acting analgesic relieves pain by opioid as well as additional mechanisms.
- Its analgesic action is only partially reversed by the opioid antagonist naloxone. [affinity for opiods receptor are low]
- Tramadol causes less respiratory depression, sedation, constipation, urinary retention
- Side effects are dizziness, nausea, sleepiness, dry mouth, sweating
- indicated for mild-to-moderate short-lasting pain due to diagnostic procedures, injury, surgery, etc, as well as for chronic pain including cancer pain, but is not effective in severe pain.
- Dose: 50-100 mg oral/i.m./slow i.v. infusion (children 1-2 mg/kg) 4-6 hourly.

Uses of Morphine and its congeners

1. As analgesic: MI, cancer pain, burn, postoperative
2. Preanaesthetic medication
3. Balanced anaesthesia and surgical analgesia
4. Relief of anxiety and apprehension
5. Acute left ventricular failure
6. Cough- codiene
7. Diarrhoea- codiene

Opioids antagonist

1. Agonist-antagonists (κ analgesics)

Nalorphine, Pentazocine, Butorphanol

2. Partial/weak μ agonist + κ antagonist

Buprenorphine

3. Pure antagonists

Naloxone, Naltrexone, Nalmefene

Buprenorphine

- highly lipid-soluble k analgesic that is 25 times more potent than morphine.
- A/E: Sedation, vomiting, miosis and cardiovascular effects are similar to morphine, but constipation is less marked. Postural hypotension is prominent.
- Use: long lasting painful conditions requiring an opioid analgesic, e.g. cancer pain. Also recommended for premedication, postoperative pain, in myocardial infarction and in the treatment of morphine dependence.
- Dose: 0.3-0.6 mg i.m., s.c. or slow i.v., also sublingual 0.2-0.4 mg 6-8 hourly.

Naloxone

- blocks μ receptors at much lower doses than those needed to block K or δ receptors.
- is the drug of choice for morphine poisoning **(0.4-0.8** mg i.v. every 2-3 min: max 10 mg) and for reversing neonatal asphyxia due to opioid use during labour

Naltrexone: It is chemically related to naloxone and is another pure opioid antagonist.

CLASSIFICATION OF OPIOIDS ANALGESICS AND ANTAGONISTS

1. Strong agonist: Morphine, pethidine, fentanyl

2. Moderate agonist: codiene, tramadol

3. Mixed agonist and antagonist: pentazocine, buprenorphine

4. Antagonist: Naloxane, Naltrexone