Opioid analgesics

Opioid

- Endogenous or synthetic
- Produces morphine-like effects
- Blocked by antagonists such as naloxone

Opium

- An extract of the juice of the poppy *Papaver somniferum*
- Produce euphoria, analgesia and sleep
- Prevent diarrhea
- Addiction (dependence)

Morphine analogues

- Compounds closely related in structure to morphine
- Often synthesized from it
- They may be agonists (e.g. **morphine, diamorphine** (heroin) and **codeine**)
- Partial agonists (e.g. **nalorphine** and **levallorphan**)
- Or antagonists (e.g. **naloxone**)

Synthetic derivatives

- Structures unrelated to morphine
- Phenylpiperidine series, e.g. **pethidine** and **fentanyl**
- Methadone series, e.g. **methadone** and **dextropropoxyphene**
- Benzomorphan series, e.g. **pentazocine** and **cyclazocine**
- Semisynthetic thebaine derivatives, e.g. **etorphine** and **buprenorphine**.

Opioid receptors

- Three types of opioid receptors (μ, δ and κ)
- G-protein-coupled receptors
- Inhibit adenylate cyclase (AC)

μ receptors

- Mediate the major pharmacological effects of morphine, including analgesia
- Most of the analgesic opioids are μ-receptor agonists
- Responsible for some major unwanted effects (e.g. respiratory depression, euphoria, sedation and dependence)

κ receptors

- Contribute to analgesia at the spinal level
- May elicit sedation and dysphoria
- Produce relatively few unwanted effects
- Do not contribute to dependence
- Some analgesics are relatively κ-selective.

δ receptors

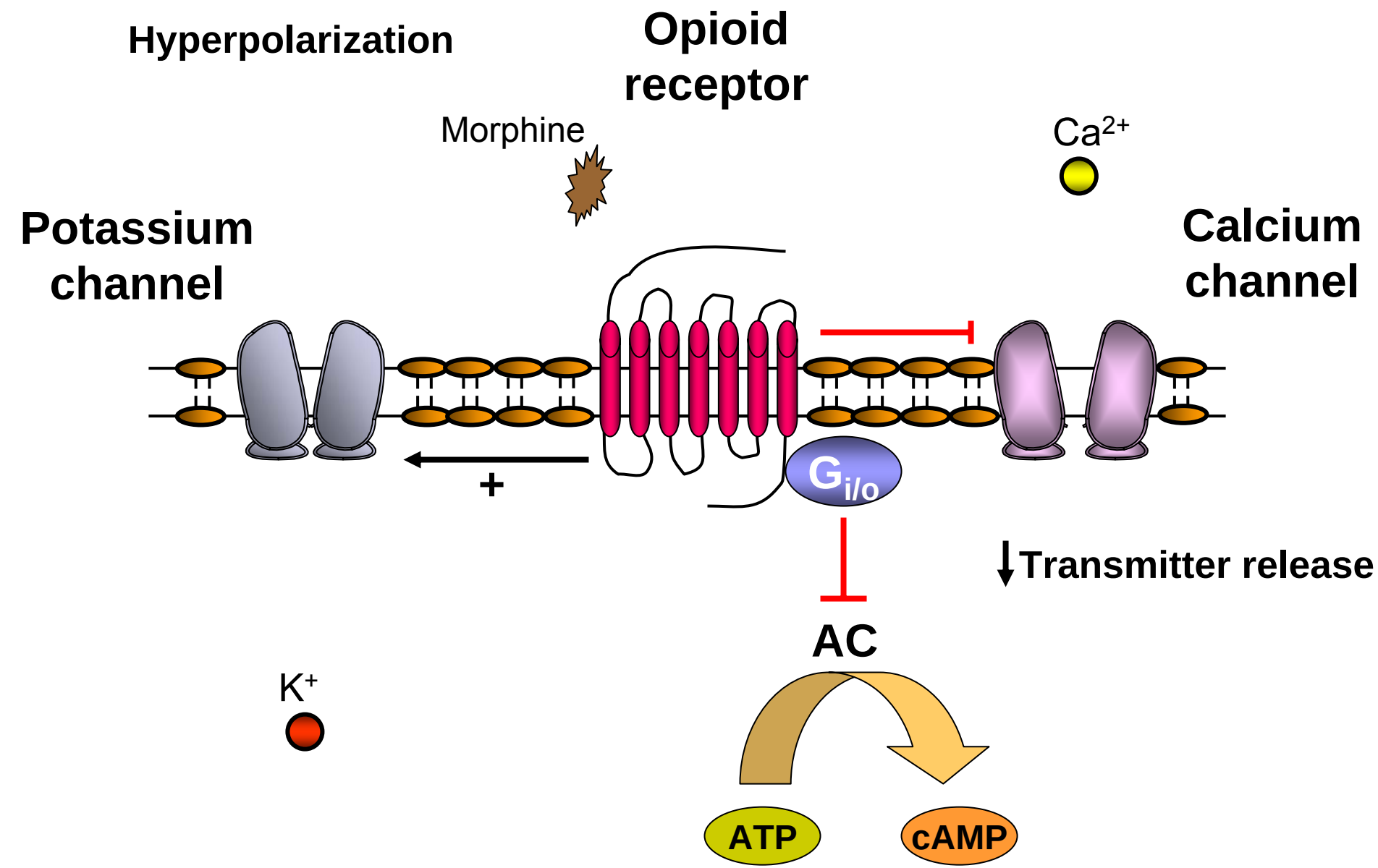
- In the periphery
- May also contribute to analgesia

Responses Mediated by Opioid Receptors

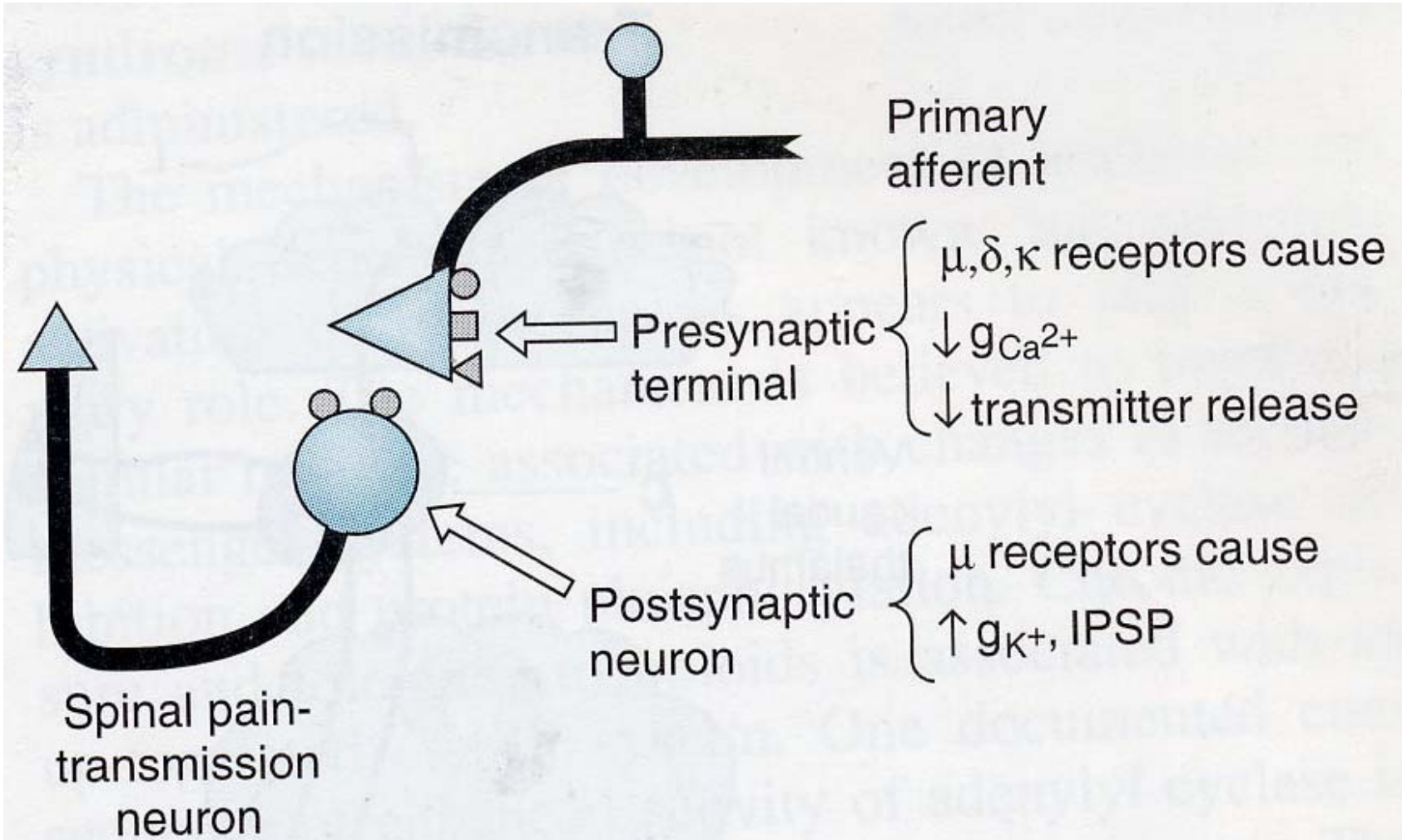
Receptor	Response on Activation
mu	Analgesia, respiratory depression, miosis, euphoria, reduced gastrointestinal motility
kappa	Analgesia, dysphoria, psychotomimetic effects, miosis, respiratory depression
delta	Analgesia

Adapted from reference 17.

MECHANISM OF ACTION OF OPIOIDS

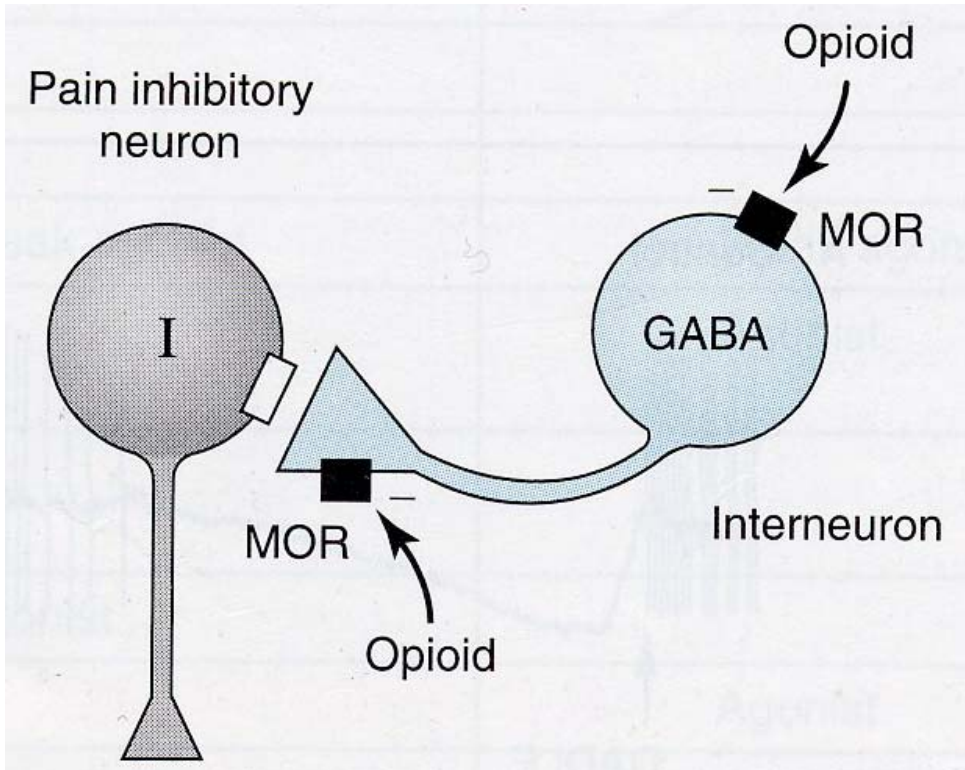


MECHANISM OF ACTION OF OPIOIDS



MECHANISM OF ACTION OF OPIOIDS

- Opioids increase activity in some neuronal pathways by suppressing the firing of inhibitory interneurons



Three main categories

- Pure agonists
- Partial agonists and mixed agonist-antagonists
- Antagonists

Pure agonists

- Includes most of the typical morphine-like drugs
- Have high affinity for μ-receptors and generally lower affinity for δ- and κ-sites
- **Codeine, methadone** and **dextropropoxyphene**, are sometimes referred to as weak agonists

Partial agonists and mixed agonist-antagonists

- **Nalorphine (**mixture of agonist and antagonist actions)
  - An agonist
  - It also inhibits competitively the effect of morphine

- **Pentazocine** and cyclazocine
  - Antagonists at μ-receptors
  - Partial agonists on δ- and κ-receptors

- Cause dysphoria, rather than euphoria (mediated by the κ-receptor)

Antagonists

- Produce very little effect when given on their own
- But block the effects of opioids
- Examples: **naloxone** and **naltrexone**.

PHARMACOLOGICAL ACTIONS

- Morphine is taken as the reference compound
- The most important effects of morphine are on the CNS and the GIT

Effects on the central nervous system

1. *Analgesia*
2. *Euphoria*
3. *Respiratory depression*
4. *Depression of cough reflex*
5. *Nausea and vomiting*
6. *Pupillary constriction*

Analgesia

- Effective in most kinds of acute and chronic pain associated with tissue injury, inflammation or tumour growth
- Less useful in neuropathic pain syndromes (such as phantom limb)

Euphoria

- Powerful sense of contentment and well-being
- Agitation and anxiety associated with a painful illness or injury are reduced
- Depends on the circumstances
- Mediated through μ-receptors
- Balanced by the dysphoria associated with κ-receptor activation

Respiratory depression

- Mediated by μ-receptors
- The most troublesome unwanted effect
- It occurs at therapeutic doses
- It is the commonest cause of death in acute opioid poisoning.

Depression of cough reflex

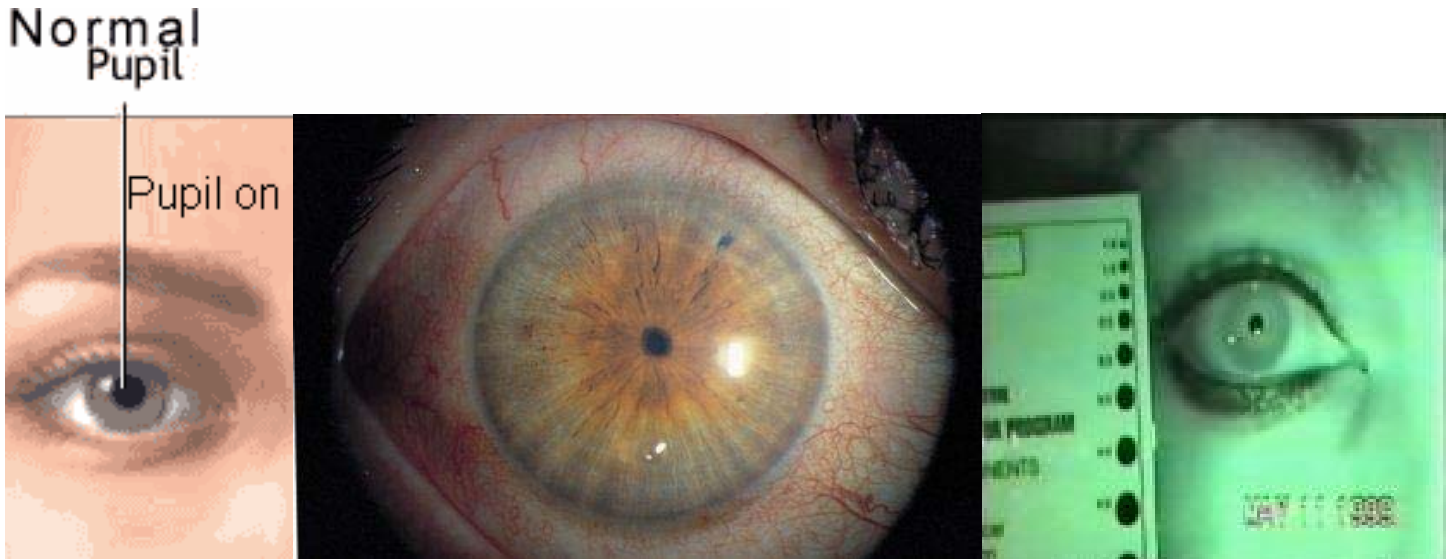
- Cough suppression
- Codeine suppresses cough in subanalgesic doses and is often used in cough medicines
- **Pholcodine** is even more selective
- Constipation (unwanted effect)

Nausea and vomiting

- Occur in up to 40% of patients when they first take morphine
- The site of action is the area postrema (chemoreceptor trigger zone)
- Disappear with repeated administration.

Pupillary constriction

- Caused by μ- and κ-receptor-mediated stimulation of the oculomotor nucleus
- Pinpoint pupils are an important diagnostic feature in overdosage with morphine and related drugs



Effects on the gastrointestinal tract

- Morphine reduces motility of the GIT
- Resulting in constipation
- The receptors involved in these effects are of the μ, κ and δ type

Other actions of opioids

- Morphine releases histamine from mast cells, by an action unrelated to opioid receptors
  - urticaria and itching at the site of the injection
  - or systemic effects, namely bronchoconstriction and hypotension
  - Should not be given to asthmatic patients
- Pethidine does not produce this effect

Other actions of opioids

- Hypotension and bradycardia occur with large doses of most opioids, through an action on the medulla
- Spasm of the ureters, bladder and uterus
- Immunosuppressant effects (increased susceptibility to infections)

TOLERANCE AND DEPENDENCE

Tolerance

- An increase in the dose needed to produce a given pharmacological effect (develops rapidly)
- Detected within 12-24 hours of morphine administration
- Sensitivity returned to normal within about 3 days of removing the drug
- Extends to most of the pharmacological effects of morphine, but with different degree
- The mechanism of tolerance is unclear
- It is not pharmacokinetic in origin and receptor downregulation is not a major factor.

Tolerance

Common Opioid ADEs, Tolerance, and Prevention/Treatment		
ADE	**Development of Tolerance**	**Prevention/Treatment**
Respiratory depression[a]	Yes	Gradual dose titration, naloxone[b]
Constipation	No	Stool softener + stimulant laxative[c]
Sedation and cognitive impairment	Yes	Lower dose, discontinue concomitant CNS depressants, add stimulant, change opioid
Nausea/vomiting	Yes	Antiemetic
Itching	Yes	Antihistamine, change opioid
Urinary retention	Yes	Lower dose

ADEs = adverse drug events; CNS = central nervous system.

[a] Respiratory depression rarely occurs in patients receiving opioid therapy >5 days.[20] Factors predisposing to respiratory depression include overweight, sleep apnea, asthma, or a large, inappropriate increase in opioid dose.

[b] Naloxone should be reserved for select patients and administered cautiously and by a slow intravenous infusion.[20-25]

[c] The first-line regimen for prevention of opioid-induced constipation is docusate sodium 50-300 mg orally daily and senna 1-2 tablets (8.6 mg sennosides per tablet) orally 2-4 times a day. A soft bowel movement every 1-2 days is the goal of therapy.[18,25-28]

Adapted from references 16-28.

DEPENDENCE

- Involves two separate components
  - Physical dependence
  - Psychological dependence

Physical dependence

- Associated with physical withdrawal syndrome:

Depressed mood and anxiety. Dysphoria
Piloerection, lacrimation or rhinorrhea
Frequently, "high" attention
Hyperalgesia, joint and muscle pain
Diarrhea and gastrointestinal cramping, nausea, or vomiting
Pupillary dilatation and photophobia
Insomnia
Autonomic hyperactivity (e. g., hyperreflexia, tachycardia, hypertension, tachypnea, sweating, hyperthermia)
Yawning

Physical dependence

- Lasting for a few days
- Precipitated by μ-receptor antagonists
- Rapidly abolished by re-administration of morphine
- Weak, long-acting μ-receptor agonists, such as methadone, may be used to relieve withdrawal symptoms.

Psychological dependence

- Associated with craving
- Lasting for months or years
- Rarely occurs in patients being given opioids as analgesics
- Codeine, pentazocine and buprenorphine, are much less likely to cause physical or psychological dependence.

PHARMACOKINETIC ASPECTS

- Morphine is slowly and erratically absorbed
- Commonly given by IV or IM injection to treat acute severe pain
- Oral morphine is used in treating chronic pain
- Slow-release preparations are available to increase its duration of action
- Codeine is well absorbed and normally given by mouth

PHARMACOKINETIC ASPECTS

- The plasma half-life of most morphine analogues is 3-6 hours
- Most morphine-like drugs undergo considerable first-pass metabolism
- Therefore, markedly less potent when taken orally than when injected
- Hepatic metabolism is the main mode of inactivation, usually by conjugation with glucuronide

PHARMACOKINETIC ASPECTS

- Morphine 6-glucuronide
  - More active as an analgesic than morphine itself
  - May contributes to the pharmacological effect
- Morphine 3-glucuronide
  - May antagonise the analgesic effect of morphine
- Morphine glucuronides are excreted in the urine

PHARMACOKINETIC ASPECTS

- Low conjugating capacity in neonates
  - Morphine-like drugs have a much longer duration of action
  - Morphine-like drugs should not be used in the neonatal period, nor used as analgesics during childbirth
- Pethidine is a safer alternative for this purpose

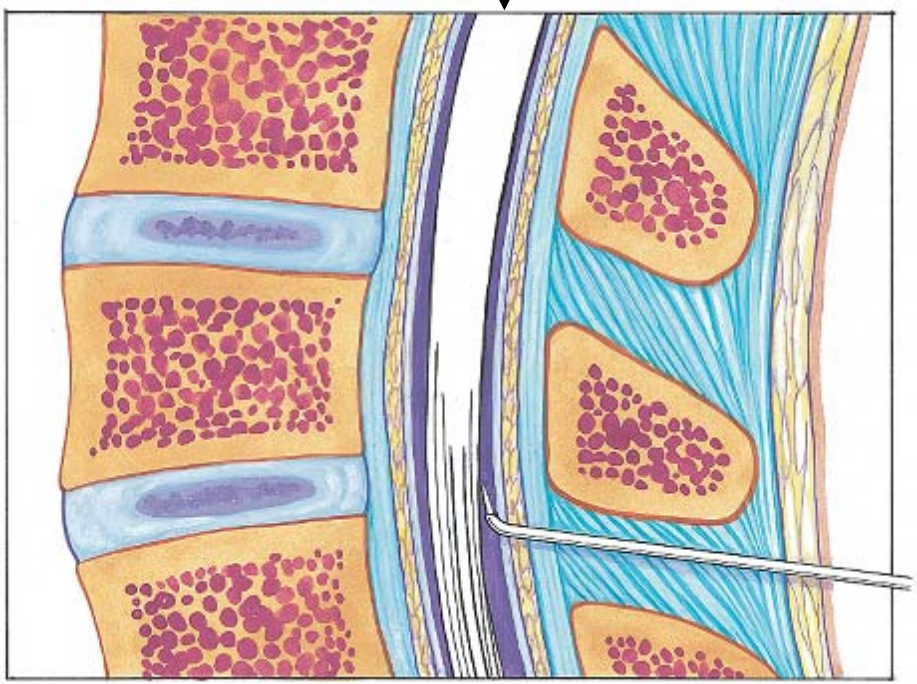
PHARMACOKINETIC ASPECTS

- Diamorphine and codeine are metabolized to morphine, which accounts for all or part of their pharmacological activity

- Morphine produces very effective analgesia when administered intrathecally
  - The sedative and respiratory depressant effects are reduced

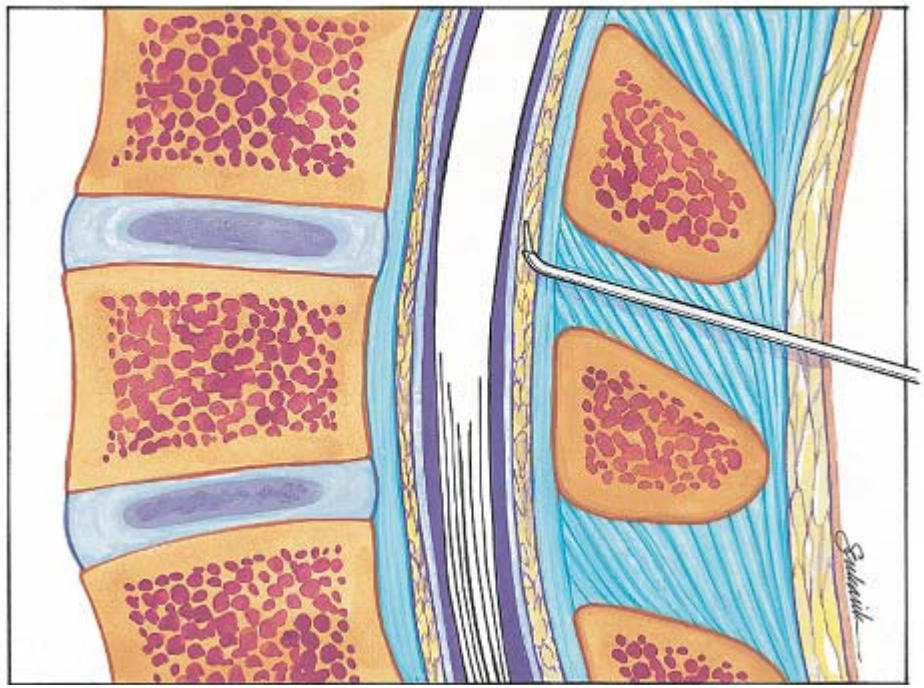
Intrathecal route

Subarachnoid space



Epidural route

Epidural space

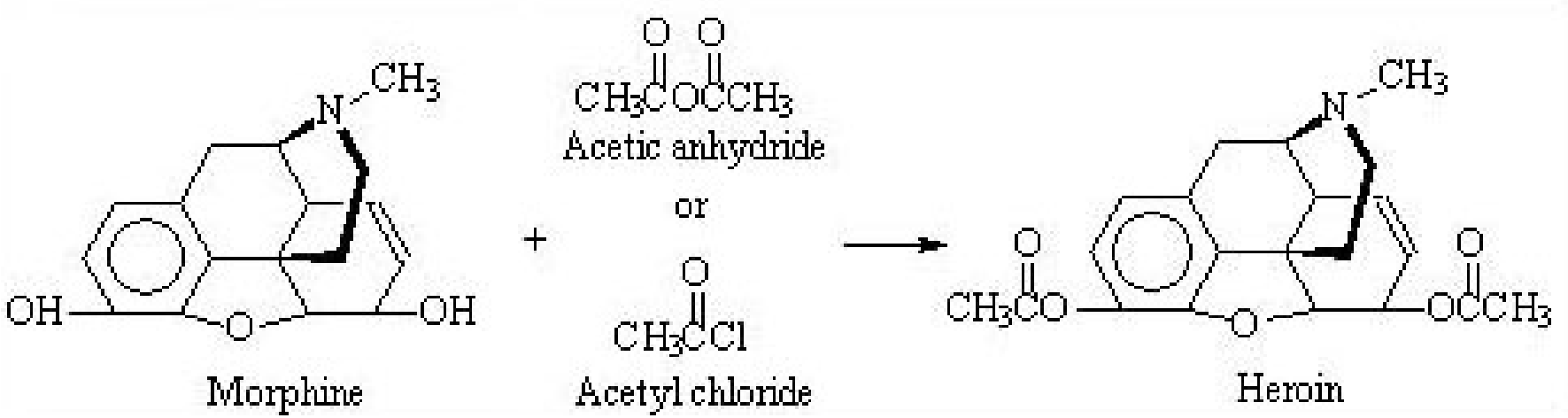


UNWANTED EFFECTS

- Acute overdosage with morphine results in:
  - Coma
  - Respiratory depression
  - Constricted pupils
- Treated by giving naloxone intravenously

Heroin (Diamorphine)

- Diacetyl derivative of morphine



- In the body, it is rapidly deacetylated to morphine

Heroin (Diamorphine)

- It has a greater lipid solubility
- It crosses the blood-brain barrier more rapidly than morphine and gives a greater effect
- Less emetic than morphine
- As morphine, it causes respiratory depressant and dependence
- Its duration of action (about 2 hours) is shorter than that of morphine.

Codeine (3-methoxymorphine)

- Is more reliably absorbed by mouth than morphine
- Has marked antitussive activity
- Used mainly as an oral analgesic for mild types of pain (headache, backache, etc.)
- It is often combined with paracetamol

Codeine

- Has only 20% or less of the analgesic potency
- Unlike morphine, it causes little or no euphoria and is rarely addictive
- It produces the same degree of respiratory depression as morphine
- It causes constipation

Codeine

- **Dihydrocodeinone** (hydrocodone) very similar to codeine
- **Dextropropoxyphene** is similar to codeine but has a longer duration of action
- About 10% of the population is resistant to the analgesic effect of codeine, because they lack the demethylating enzyme which converts it to morphine

Pethidine (meperidine)

- Very similar to morphine (pharmacological and euphoric effects and dependence)
- However, it tends to cause restlessness rather than sedation
- Its duration of action is appreciably shorter than that of morphine
- It has an additional antimuscarinic action, which may cause dry mouth and blurring of vision as side-effects

Pethidine (meperidine)

- The route of metabolic degradation is different
- Pethidine is partly N-demethylated in the liver to norpethidine, which has a hallucinogenic and convulsant effect
- Large oral doses of pethidine produces an overdose syndrome rather different from that of morphine
- Pethidine is preferred to morphine for analgesia during labour, because it is shorter acting

Pethidine (meperidine)

- When pethidine is given to patients receiving monoamine oxidase inhibitors, severe reactions, consisting of:
  - Excitement
  - Hyperthermia
  - And convulsions

- This seems to be caused by inhibition of an alternative metabolic pathway, leading to increased norpethidine formation

Methadone

- It has less
  - sedative action
  - physical and psychological dependence
- Long duration of action (plasma half-life >24 hours)
- Used to treat addiction
- In the presence of methadone, an injection of morphine does not cause the normal euphoria

OPIOID AGONIST ANALGESICS

For Severe Pain	For Mild to Moderate Pain
Fentanyl	Codeine
Hydromorphone	Hydrocodone
Levorphanol	Oxycodone
Methadone	
Morphine Sulfate	
Oxycodone	
Oxymorphone	

Pentazocine (mixed agonist-antagonist)

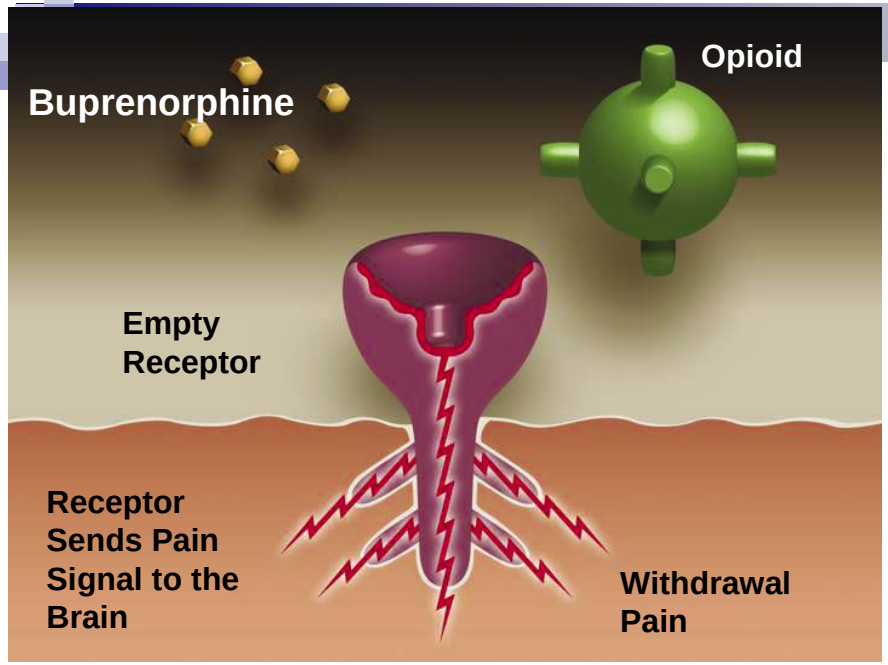
- In low doses, its potency and effects are very similar to those of morphine
- Increasing the dose does not cause a corresponding increase in the effects produced
- Therefore, at high doses, it causes only
  - slight respiratory depression
  - and it causes marked dysphoria, with nightmares and hallucinations, rather than euphoria

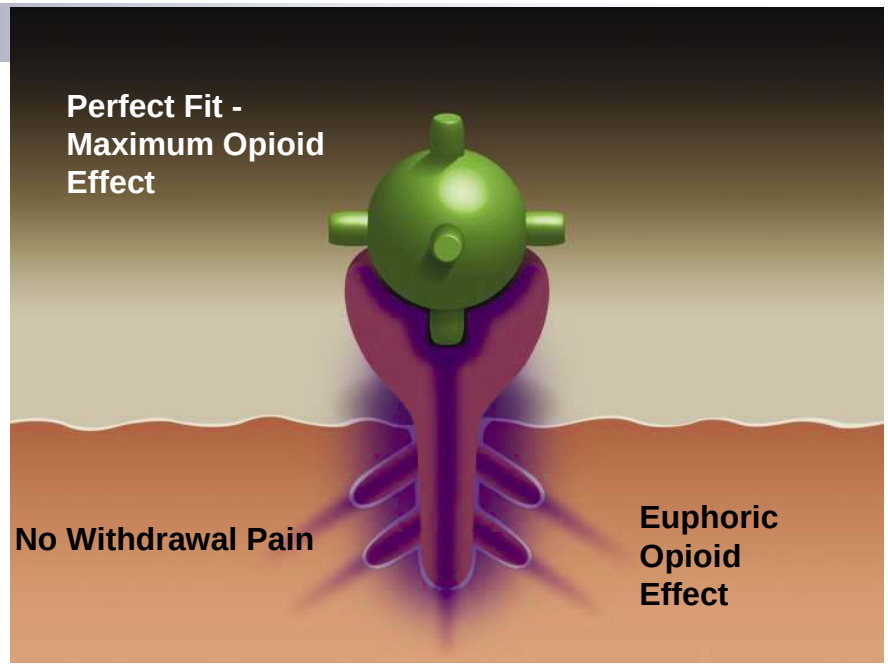
Pentazocine

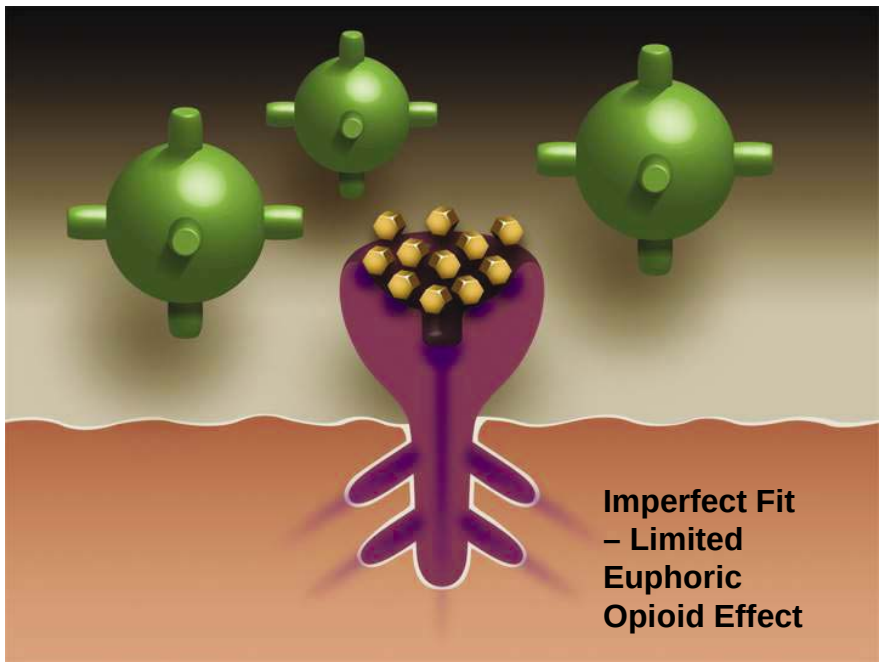
- Given concurrently with morphine, it reduces the analgesic and other actions of morphine
- It can even precipitate the withdrawal syndrome in morphine addicts
- Binding studies show that it has a higher affinity for κ- than for μ-receptors, and also acts on σ-receptors,
- Less tendency to cause dependence
- Its acute toxicity is much less than that of morphine

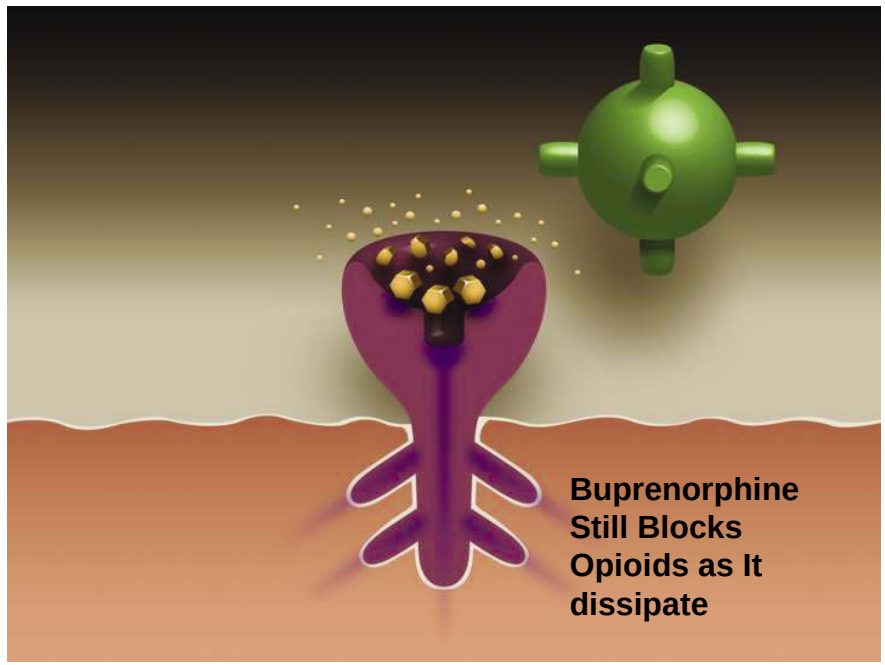
Buprenorphine

- A partial agonist on μ-receptors:
  - less liable to cause dysphoria
  - more liable to cause respiratory depression
- It has a long duration of action
- Its abuse liability is probably less than that of morphine


Buprenorphine
Opioid
Empty Receptor
Receptor Sends Pain Signal to the Brain
Withdrawal Pain


Perfect Fit - Maximum Opioid Effect
No Withdrawal Pain
Euphoric Opioid Effect


Imperfect Fit – Limited Euphoric Opioid Effect


Buprenorphine Still Blocks Opioids as It dissipate

Meptazinol and **dezocine**

- **Meptazinol**
  - short plasma half-life
  - Relatively free of morphine-like side-effects (advantages for obstetric analgesia)
  - Causing neither euphoria nor dysphoria, nor severe respiratory depression
  - It produces nausea, sedation and dizziness, and it has atropine-like side-effects
- **Dezocine**
  - A partial agonist at μ-receptors
  - Analgesic activity similar to that of morphine

Loperamide

- Does not enter the brain
- Therefore, lacks analgesic activity
- Like other opiates, it inhibits peristalsis, and it is used to control diarrhea

OPIOID ANTAGONISTS

- **Nalorphine** (first specific antagonist)
  - An antagonist action on μ-receptors (withdrawal syndrome in addicts)
  - Partial agonist action on δ- and κ-receptors (dysphoria)
  - In low doses, it is a competitive antagonist and blocks most actions of morphine
  - Higher doses, however, are analgesic and mimic the effects of morphine
  - Few clinical uses.

OPIOID ANTAGONISTS

- **Naloxone** (first pure opioid antagonist), IV.
- Its effect lasts only 2-4 hours (repeated doses)
- Affinity for all three opioid receptors
- It blocks the actions of:
  - Endogenous opioid peptides
  - Morphine-like drugs
- It produces a rapid reversal of the effects of morphine and other opioids, including partial agonists such as pentazocine and nalorphine (precipitates withdrawal symptoms in addicts).

OPIOID ANTAGONISTS (Naloxone)

- It has little effect on pain threshold under normal conditions
- Causes hyperalgesia under conditions of stress or inflammation, when endogenous opioids are produced

- The main clinical use of naloxone is
  - Treat respiratory depression caused by opioid overdosage,
  - Reverse the effect of opioid analgesics, used during labour
  - It can be used to detect opioid addiction

OPIOID ANTAGONISTS

- **Naltrexone**

- very similar to naloxone but with the advantage of a much longer duration of action (half-life about 10 hours).

OTHER ANALGESIC DRUGS

- **Tramadol**
  - Widely used as an analgesic for postoperative pain
  - It is a weak agonist at μ-opioid receptors and also a weak inhibitor of noradrenaline reuptake
  - It is effective as an analgesic and appears to have a better side-effect profile than most opioids

OTHER ANALGESIC DRUGS

- **Imipramine** and **amitriptyline** (tricyclic antidepressants)
  - Highly effective in relieving neuropathic pain in some, but not all, patients
  - Act centrally by inhibiting noradrenaline reuptake
  - Their action is independent of their antidepressant effects, and selective serotonin (5-HT) reuptake inhibitors are not effective.

OTHER ANALGESIC DRUGS

- Antiepileptic drugs such as **carbamazepine, gabapentin** and occasionally **phenytoin** are sometimes effective in neuropathic pain

- **Ketamine**
  - An anaesthetic
  - works by blocking NMDA-receptor channels
  - has analgesic properties
  - given intrathecally
  - its effects on memory and cognitive function are largely avoided

OTHER ANALGESIC DRUGS

- Intravenous **lidocaine**
  - a local anesthetic drug
  - short plasma half-life
  - can give long-lasting relief in neuropathic pain states
  - It probably acts by blocking spontaneous discharges from damaged sensory nerve terminals

COUGH

- A protective reflex mechanism that removes foreign material and secretions from the bronchi and bronchioles
- It can be stimulated by inflammation in the respiratory tract or by neoplasia (e.g. the dry painful cough associated with bronchial carcinoma or with inflammation of the pleura)
- In these cases, antitussive (or cough suppressant) drugs are sometimes used
- These drugs suppress the symptom without influencing the underlying condition

COUGH

- Antitussive drugs can cause harmful sputum thickening and retention in cough associated with:
  - Bronchiectasis (suppurating bronchial inflammation)
  - Or chronic bronchitis
- They should not be used for the cough associated with asthma

DRUGS USED FOR COUGH

- Antitussive drugs act in the brainstem by depressing 'cough centre'
- The narcotic analgesics have effective antitussive action in doses below those required for pain relief

CODEINE (methylmorphine)

- It decreases secretions in the bronchioles, which thickens sputum and inhibits ciliary activity; this reduces clearance of the thickened sputum

- **Pholcodine** is a non-analgesic opiate of the same chemical class as papaverine; it is also used as a cough suppressant.

DEXTROMETHORPHAN

- Dextromethorphan is related to levorphanol, a synthetic narcotic analgesic
- Its antitussive potency is equivalent to that of codeine
- It produces only marginally less constipation and inhibition of mucociliary clearance.