Opioids and opioid receptors

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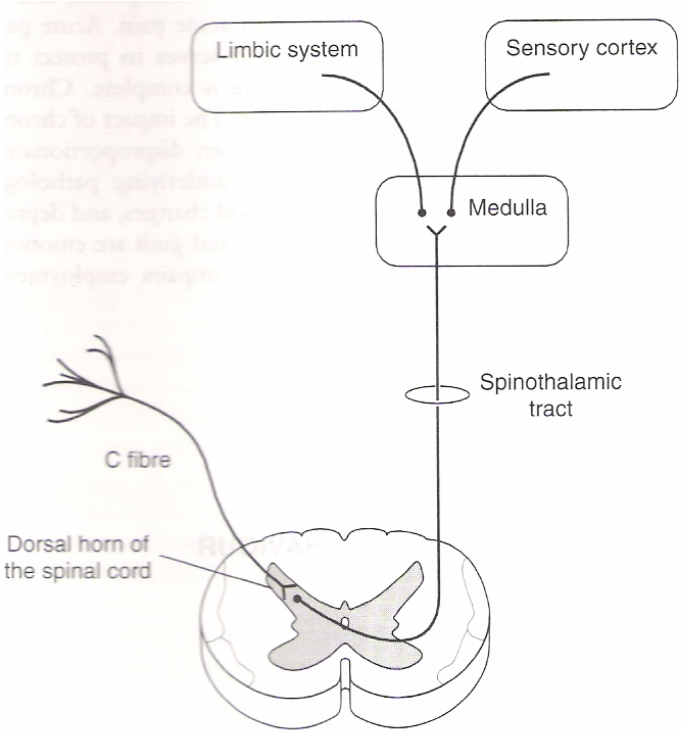
Introduction

- Throughout history humans have used plants and plant extracts to alleviate pain.
- Most prominent of these has been opium, a resinous substance obtained from poppy seeds used to produce euphoria, sleep and analgesia.

Pain pathway



- Cell bodies of C fibres synapse in the dorsal horn
- Mainly terminate in substantial gelatinise of Reed laminate
- Cross over to opposite ventrolateral side and ascend as either spinothalamic, spinoreticular or spinomesencephalic tracts

Opioids- sites of action

- Pre-synaptic terminal of primary nociceptive afferent
- Post-synaptic terminal of primary nociceptive afferent
- Periaquaductal grey matter
- (Peripheral receptors on sensory nerves)

Receptors

- μ receptors- thought to be responsible for action of *m*orphine
- κ receptors- mouse vas *d*eferens less responsive to morphine than other opioids
- δ receptors- responsible for range of actions of ketacyclazocine
- NB: σ receptors and nociceptin orphanin FQ peptide receptors

μ receptors

- Located throughout the central nervous system
  - cerebral cortex
  - basal ganglia
  - presynaptic primary afferent neurones in dorsal horn
  - periaquaductal grey
- Stimulation causes respiratory depression, inhibition of gastro-intestinal tract secretions and peristalsis

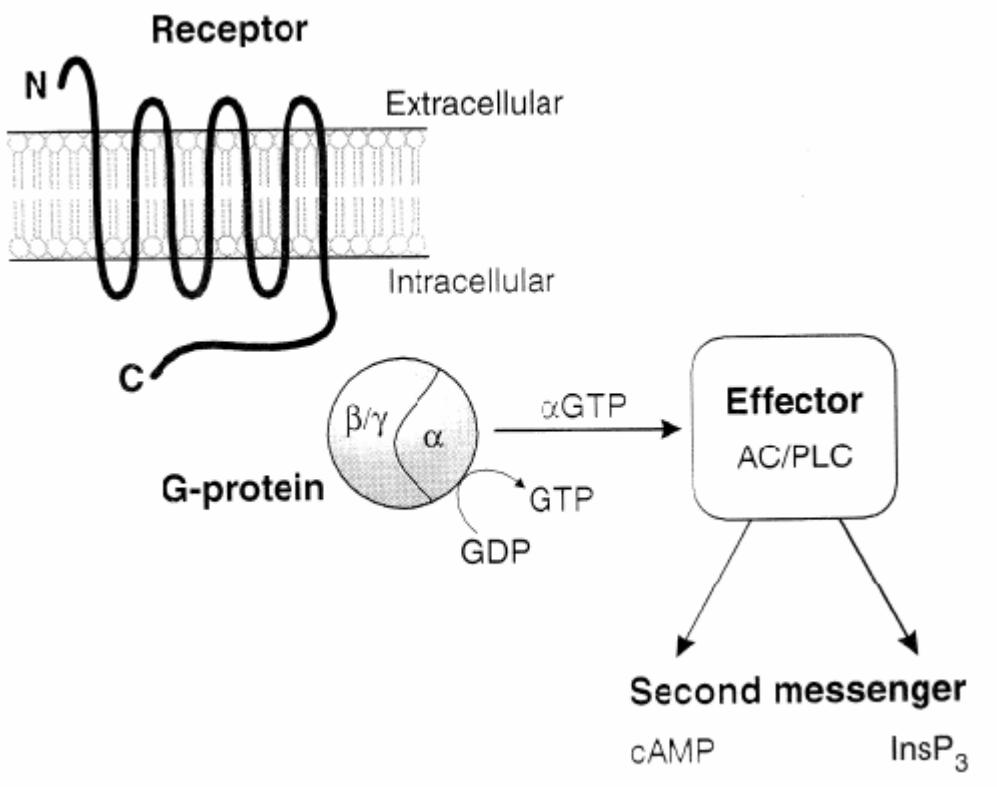
κ receptors

- Found in midbrain- nucleus raphe magnus- part of descending inhibitory control pathway
- Limited clinical use as produces side effects at doses lower than those required for analgesia
- Side effects include diuresis, sedation, dizziness, confusion and dysphoria

δ receptors

- Less widely distributed compared to other opioid receptors
- Found in caudate putamen, olfactory bulb and cerebral cortex
- Located presynaptically on primary afferents
- Shown to cause respiratory depression, mood changes and reduction in gastro-intestinal motility in animal studies

G-protein receptors



Endogenous and exogenous ligands

- Endogenous ligands
  - endorphins
  - enkephalins
  - dynorphins
- Exogenous ligands
  - agonists- opioids
  - antagonists- naloxone

Opioids and opiates

- The term *opioid* applies to any substance that produces morphine-like effects which can be reversed by an antagonist such as naloxone. This class includes synthetic analogues and neuropeptides whose structure may be different to morphine.
- The term *opiate* applies to morphine-like drugs with a close structural similarity to morphine.

Action of opioids

- Inhibition of calcium entry into the cell
  - closes voltage sensitive calcium channels
- Potassium efflux
  - resulting in hyperpolarisation
- Inhibition of adenylyl cyclase
  - reduces cAMP levels
- Overall result is reduced neuronal cell excitability with a reduction in nerve impulse transmission and inhibition of neurotransmitter release

Analgesia

- Two anatomically distinct sites for opioid-mediated analgesia
  - spinal- release of substance P, glutamate and other nociceptive neurotransmitters inhibited by activation of presynaptic receptors
  - supraspinal- mediates descending inhibition of nociceptive transmimssion

Respiratory depression

- Reduction in sensitivity of respiratory centre to carbon dioxide
- Depresses both medullary and peripheral chemoreceptors
- Respiratory rate affected more than tidal volume which may even increase
- Hypoxic drive also depressed by opioids

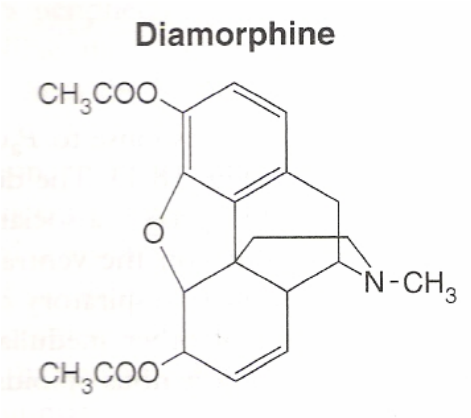
Other side effects

- Cardiovascular system- decreased central sympathetic outflow, vagal effects
- Emetic effects- stimulate chemoreceptor trigger zone leading to activation of the vomiting centre
- Gastro-intestinal effects- increase intestinal tone and decrease peristalsis
- Tolerance and dependance- mechanism of development uncertain

Opioids

- Phenanthrenes
  - Morphine
  - Diamorphine
  - Codeine
- Phenylpiperidines
  - Fentanyl
  - Alfentanil
  - Remifentanil

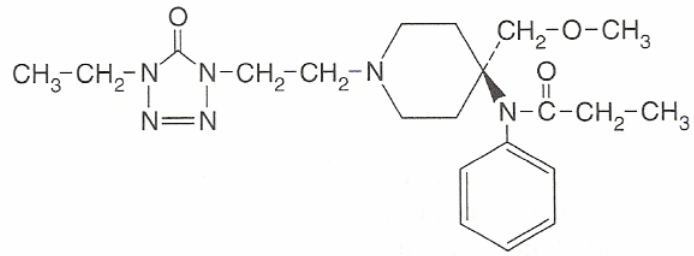
Phenanthrenes



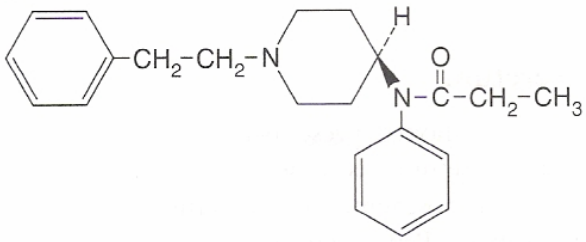
- Prototype drug is morphine
- Poorly lipid soluble due to the two hydroxyl groups that confer polar characteristics
- Cannot easily cross the blood brain barrier

Phenylpiperidines

Alfentanil



Fentanyl



- Synthetic opioids
- More lipid soluble due to groups on the piperidine ring, so more potent (despite lack of hydroxyl group on phenyl ring)

References

- Pharmacology for Anaesthesia and Intensive Care- Peck, Hill and Williams
- Textbook of Anaesthesia- Aitkinhead, Rowbotham and Smith
- Continuing Education in Anaesthesia, Critical Care and Pain- Vol 5, No 1. Feb 2005