

Q24 Describe the mechanism of action of the analgesic effect of opiates (70% marks). Explain the mechanisms by which morphine causes respiratory depression and constipation (30% marks) (March 2010)

Opioid → any substance which acts at an opioid receptor

Opiate → a drug derived from the poppy plant *papaverum somniferum*

- Opioid receptors are serpentine structures which are linked to inhibitory G-proteins
- They are present both pre and post synaptically.
 - Presynaptically, activation causes closure of voltage gated calcium channels and a reduction in neurotransmitter rel
 - Post synaptically, activation causes stimulation of potassium efflux from the cell, leading to hyperpolarization of the membrane
- Overall this leads to a reduction in neuronal cell excitability, resulting in reduced transmission of nociceptive impulses.
- There have been 4 different opioid receptors identified:
 - Mu (MOP) – broad distribution with wide range of effects
 - Kappa (KOP) – contribute to analgesia at the spinal level; does not tend to cause respiratory depression
 - Delta (DOP) – less widely distributed; also contributes to analgesia
 - NOP – produces effects similar to MOP stimulation

- Morphine and other opiates bind primarily to Mu opioid receptors which are located throughout the CNS, including the cerebral cortex, spinal cord and periaqueductal grey, and peripherally. Stimulation produces analgesia via the mechanisms above, as well as sedation, euphoria and dysphoria (likely due to supraspinal actions, possibly at the level of the limbic system). The euphoria is often useful in attenuating the emotional aspect of pain.

MORPHINE

- High affinity for mu receptors, with some activity at kappa and delta
- Reduces chemoreceptor sensitivity to PaCO₂, hence causes respiratory depression. May also act on the pre-Botzinger complex in the respiratory centre of the medulla to alter respiratory pattern.
- Reduces GIT secretions and motility hence causes constipation via direct action on visceral smooth muscle, mediated by inhibition of the Auerbach (myenteric) nerve plexus involving all three (mu, delta, kappa) opioid receptors.