Explain the mechanisms by which morphine produces analgesia (September 2016, 29%)

Introduction

Pain = unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage

Morphine
• Naturally occurring phenanthrene derivative and full agonist at mu and kappa opioid receptors
• Prototypical MOP agonist

Pain pathways

1) Ascending pathways
• Nociceptors transduce noxious stimuli to depolarisations that trigger AP → converted to release neurotransmitters at presynaptic terminal → conduction of AP to synapses
• Primary afferent fibres = Ad (myelinated, conduction velocity 6-30m/s) and C fibres (unmyelinated, polymodal, conduction velocity 0.5-2m/s)
• Dorsal horn- synapse with secondary afferent pathways in dorsal horn spinal cord (lamina I and II) → release excitatory mediators such as glutamate and substance P
• 2 main ascending pathways = spinothalamic and spinoreticular tracts
• Third order neurons ascend and terminate in somatosensory cortex + periaqueductal gray matter

2) Descending inhibitory control pathway
• Arise from periaqueductal grey in midbrain and rostral ventrolateral medulla (RVM)
• Project to dorsal horn and inhibit pain transmission
• Neurotransmitters = noradrenaline and serotonin (monoamines)

Opioid receptors

• Subtypes = Mu, Kappa, Delta and Nociceptin
• All Gi protein coupled receptors
  o Activation → Inhibits adenylate cyclase → decreased cAMP → inhibition of voltage gated Ca2+ channels → inhibition of neurotransmitter release (i.e. substance p)
  o Also causes activation of K+ channels and increased K+ efflux → hyperpolarisation of cells → inhibition of pain signals due to decreased neuronal excitability

Effect of Morphine on pain pathways
• Directly inhibits ascending transmission of nociceptive information from spinal cord dorsal horn
• Activates pain control circuits (descending pathways) from midbrain → RVM → Spinal cord dorsal horn

<table>
<thead>
<tr>
<th>Location</th>
<th>Effect of Morphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS</td>
<td><strong>Amygdala</strong> Inactivation of central nucleus of amygdala</td>
</tr>
<tr>
<td></td>
<td><strong>Locus coeruleus</strong> Likely to involve pathways in opioid withdrawal symptoms → can be managed by using a2 agonists (i.e. clonidine)</td>
</tr>
<tr>
<td></td>
<td><strong>Periaqueductal gray</strong> Potentiates inhibitory neuronal pathways in dorsal funiculus (increased noradrenaline &gt; 5HT release) → modulates ascending pain signals (i.e. Inhibits release of substance P from first order neurons- Ad and C fibres) → analgesia</td>
</tr>
<tr>
<td></td>
<td><strong>Rostroventral medulla</strong> Involved in neuropathic pain + modulation of pain via 5HT → potentiates inhibitory pain pathways → decreased pain signals from 1st order neurons</td>
</tr>
<tr>
<td>Local spinal</td>
<td><strong>Substantia gelatinosa</strong> - Opioids act at synapses pre- or post-synaptically - Opioid receptors abundantly expressed in substantia gelatinosa where substance P release from primary afferent neuron is inhibited by opioids → analgesia</td>
</tr>
<tr>
<td></td>
<td><strong>Peripheral</strong> May act on opioid receptors located on primary sensory neurons (some animal studies) → analgesia</td>
</tr>
</tbody>
</table>
Opioid Induced Hyperalgesia
- Phenomenon where using long term opioid (i.e. morphine) can increase sensitivity to noxious stimuli or even non-noxious stimuli
- Likely due to abnormal activation of NMDA receptors in CNS → risk can be reduced by using NMDA receptor antagonists (i.e. ketamine)

Tolerance
- Phenomenon whereby the same dose of morphine produces less antinociceptive effect- require dose escalation to maintain same effect
- Likely due to downregulation of receptors by endocytosis, increased metabolism of drug or alteration of receptors which have less intrinsic activity on activation
- Accompanied by increased MOP-mediated side effects

Examiners Report
29% of candidates achieved a pass in this question

The question essentially asks three things; the mechanism of action of morphine with as much detail about receptor and intermediate messenger pathways as possible, the anatomical location of mu opioid receptors, and the specific role of morphine in modifying pain pathways through its influence on the mu receptor at these locations. An example of this might be that morphine exerts influence at the periaqueductal grey through potentiation of inhibitory neuronal messaging through the mu receptor which then predominantly influences noradrenaline release to accentuate descending inhibitory control though the dorsal horn (more than serotonergic release which can exert some excitatory effects on pain pathways as well as inhibitory). In general the mechanism of morphine action was discussed well but the way in which this mechanism ties in with physiologic transmission of pain was handled less well.

Candidates who were able to discuss these three factors in detail achieved a good score with the question. Discussions of analgesic effects of morphine and potential mechanisms that explain longer term effects of tolerance and hyperalgesia were allowed and also attracted marks.

The following did not attract marks:
- Drawing the morphine molecule.
- Providing pharmacokinetic information.
- Discussing pain pathways without looking at how the morphine mechanism impacts on the pain pathways.
- Complex discussions of Fick's law of diffusion.
- Drawing diagrams of pain pathways and still needing to explain mechanisms on top of this; something which took up too much valuable time.

References
- Millers Ch 31
- FPM
- Power and Kam Ch13