NARCOTIC ANALGESICS: INTRODUCTION

I. Introduction and Opiate Receptors

Analgesics are primarily employed for their ability to reduce the perception of pain impulses by the CNS. Analgesic activity is mediated by opiate receptors in the CNS. Five major categories of opioid receptors are known: mu (µ), kappa (κ), sigma (σ), delta (δ), and epsilon (ε). Narcotic drugs occupy the same receptors as endogenous opioid peptides – enkephalins or endorphins – which are described in more detail below. Both the endogenous agonist and narcotic analgesics may alter the central release of neurotransmitters from afferent nerves sensitive to noxious stimuli. The actions of the narcotic analgesics now available can be defined by their activity at three specific opiate receptor types: mu (µ), kappa (κ) and delta (δ). Also, narcotic analgesics are classified as agonists, mixed agonist-antagonists, or partial agonists by their activity at opioid receptors as described later.

- µ-(mu) receptors mediate analgesia, euphoria, respiratory and physical depression, miosis, and reduced GI motility. These receptors have been further sub-typed as µ₁ which are supraspinal and mediate analgesia, and µ₂ which mediate respiratory depression. Enkephalins and endorphins are endogenous ligands for these receptors and morphine is an exogenous ligand. The µ₁ receptor is morphine selective.
- δ-(delta) receptors mediate spinal and supraspinal analgesia, dysphoria, psychotomimetic effects (eg, hallucinations), and respiratory and vasomotor stimulation caused by drugs with antagonist activity. Enkephalins are the endogenous ligand for these receptors and morphine is an exogenous ligand. These receptors have been sub-typed as δ₁ and δ₂ and are thought to be relatively unimportant in terms of analgesia.
- κ-(kappa) receptors mediate pentazocine-like spinal analgesia, sedation, and miosis and respiratory depression and dysphoria. Dynorphins are endogenous ligands at these receptors and morphine functions as an exogenous ligand. These receptors have been further subtyped as κ₁ which mediates spinal analgesia, κ₃ which mediates supraspinal analgesia and κ₂ whose function is unknown. These receptors are proposed to mediate a sedating analgesia with reduced addiction liability and respiratory depression, usually found linked to a-sites.
- σ- (sigma) sites have been implicated in psychotomimetic and dysphoric side effects of the opiates and possibly dilation of the pupil.

<table>
<thead>
<tr>
<th>Receptor Type</th>
<th>µ/δ</th>
<th>κ</th>
<th>σ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesia</td>
<td>Supraspinal/spinal</td>
<td>Spinal</td>
<td>-</td>
</tr>
<tr>
<td>Respiratory Depression</td>
<td>++</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Pupil</td>
<td>Constriction</td>
<td>-</td>
<td>Dilation</td>
</tr>
<tr>
<td>GI motility</td>
<td>Reduced</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Smooth Muscle Spasm</td>
<td>++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Behavior Effect</td>
<td>Euphoria ++</td>
<td>Dysphoria +</td>
<td>Dysphoria ++</td>
</tr>
<tr>
<td></td>
<td>Sedation ++</td>
<td>Sedation +</td>
<td>Psychomimetic</td>
</tr>
<tr>
<td>Physical Dependence</td>
<td>++</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
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II. The Endogenous Opiate Ligands

Discovery of endogenous opiate receptors suggested the existence of an endogenous opiate transmitters. Three types of endogenous opioid peptides called “endorphins” (endogenous morphines) have been identified, including the β-endorphins, the enkephalins (met- and leu-enkephalin) and the dynorphins (dynorphin and α-neoendorphin). These endorphins are formed from larger pro-endorphin peptides as indicated below:

- Proopio-melanocortin (POMC): β-endorphin precursor
- Proenkephalin A: Met- and leu-enkephalin precursor
- Proenkephalin B (Prodynorphin): dynorphin and α-neoendorphin precursor

All pro-endorphins are synthesized in the nucleus and transported to the nerve terminal by microtubule transport. At the nerve terminal they are cleaved by specific proteases. These protease recognize the double basic amino acid sequences positioned just before and after the opioid peptide. The peptides are released when the nerve fires and bind to post-synaptic receptors, stimulating second messenger systems. The action of opioid peptides is terminated by membrane-bound proteases which cleave the terminal Gly-3-Tyr-4 bonds.

Opioid peptides produce analgesia by interacting with spinal and supraspinal opioid receptors including µ (enkephalins and beta-endorphin), κ (beta-endorphin and dynorphins) and δ (enkephalins and beta-endorphin). After these opioid peptides (and opioid drugs) interact with opiate receptors, the neurons become hyperpolarized. This is thought to be due to both an increase in K+ conductance as well as a reduction of the inward calcium current that occurs during the action potential. It is believed that there is a direct interaction between the G-protein and the K+ and Ca +2 channels.

The pharmacological profile of methionine enkephalin is similar to that of morphine. Attempts to utilize this peptide as a therapeutic agent have been hindered by its polarity and metabolic lability. The basic structures of the opioid pro-endorphin and endorphin products are shown on the next page. Below is a more detailed drawing of Met- (top) and leu_(bottom) enkephalin:
III. Secondary Pharmacologic Actions of the Narcotics

The narcotics have a variety of secondary pharmacological effects, including the following:

- CNS depression (narcosis)
- CNS: Euphoria; drowsiness; apathy; mental confusion; alterations in mood; reduction in body temperature; feelings of relaxation; dysphoria. Nausea and vomiting are caused by direct stimulation of the emetic chemoreceptors located in the medulla. Hydromorphone increases CSF pressure.
- Cardiovascular: Peripheral vasodilation, reduced peripheral resistance, and inhibition of baroreceptors. Orthostatic hypotension and fainting may occur when the patient sits up.
Dermatologic: Histamine release, pruritus, flushing, and red eyes.

GI:
- Stomach: Decreases gastric motility, thus prolonging gastric emptying time. This may lead to esophageal reflux.
- Small intestine: Decreases biliary, pancreatic, and intestinal secretions and delays digestion of food in the small intestine. Resting tone increases and periodic spasms occur.
- Large intestine: Propulsive peristaltic waves in the colon are diminished and tone increases until it spasms. This, along with the inattention to the normal stimuli for defecation reflex, contribute to constipation.
- Biliary tract: The sphincter of Oddi constricts leading to epigastric distress or biliary colic.

GU: Increases smooth muscle tone in the urinary tract and can induce spasms. Urinary urgency and difficulty with urination may result.

Respiratory ($\mu_2$): Depressant effects first diminish tidal volume, then respiratory rate, because of reduced sensitivity of the respiratory center to carbon dioxide.

Cough: Depression of the cough reflex center of the medulla (antitussive activity)

Tolerance upon chronic use

Addiction and Physical dependence

IV. Classification of Narcotic Ligands

Narcotic agonists include natural opium alkaloids (eg, morphine, codeine), semisynthetic analogs (eg, hydromorphone, oxymorphone, oxycodone), and synthetic compounds (eg, meperidine, levorphanol, methadone, sufentanil, alfentanil, fentanyl, remifentanil, levomethadyl).

Mixed agonist-antagonist drugs (eg, nalbuphine, pentazocine) have agonist activity at some receptors and antagonist activity at other receptors; also included are the partial agonists (eg, butorphanol, buprenorphine).

Narcotic antagonists: Narcotic antagonists (eg, naloxone) do not have agonist activity at any of the opioid receptor sites. Antagonists block the opiate receptor, inhibit pharmacological activity of the agonist, and precipitate withdrawal in dependent patients.