Those who do not feel pain seldom think it is felt

Samuel Johnson
Overview

Morphine, the prototypical opioid agonist

The opium poppy is the source of crude opium

Sertturner in 1803 isolated morphine
History

Used medicinally from early Greek and Roman times

Opium and laudanum (opium combined with alcohol) were used to treat almost all known diseases

Morphine was isolated from opium in the early 1800’s and since then has been the most effective treatment for severe pain
Invention of the hypodermic needle in 1856 produced drug abusers who self administered opioids by injection

Controlling the widespread use of opioids has been unsuccessful because of the euphoria, tolerance and physiological dependence that opioids produce
**Terminology**

“opium” is a Greek word meaning “juice,” or the exudates from the poppy (\textit{Papaver somniferum})

“opiate” is a drug extracted from the exudates of the poppy

“opioid” is a natural or synthetic drug that binds to opioid receptors producing agonist effects
The major effects of the opioids are mediated by three major receptor families.

These are designated by the Greek letters (mu), (kappa), and (delta).
# Mu and Kappa Receptor Activation

<table>
<thead>
<tr>
<th>Response</th>
<th>Mu-1</th>
<th>Mu-2</th>
<th>Kappa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesia</td>
<td>⭐️</td>
<td>⭐️</td>
<td>⭐️</td>
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<tr>
<td>Respiratory Depression</td>
<td>⭐️</td>
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<tr>
<td>Euphoria</td>
<td>⭐️</td>
<td>⭐️</td>
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<tr>
<td>Dysphoria</td>
<td>⭐️</td>
<td>⭐️</td>
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<tr>
<td>Decrease GI motility</td>
<td>⭐️</td>
<td>⭐️</td>
<td>⭐️</td>
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<tr>
<td>Physical Dependence</td>
<td>⭐️</td>
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Natural opioids occur in 2 places:

1) In the juice of the opium poppy (morphine and codeine)

2) As endogenous endorphins

All other opioids are prepared from either morphine (semi synthetic opioids such as heroin) or they are synthesized from precursor compounds (synthetic opioids such as fentanyl)
Endogenous opioid peptides

Endogenous substances

They have opioid-like pharmacological properties

Three families:
Endorphins
Enkephalins
Dynorphins
<table>
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<tr>
<th>Receptor Subtype</th>
<th>Functions</th>
<th>Endogenous Opioid Peptide Affinity</th>
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<tr>
<td><strong>μ (mu)</strong></td>
<td>Supraspinal and spinal analgesia; sedation; inhibition of respiration; slowed GI transit; modulation of hormone and neurotransmitter release</td>
<td>Endorphins &gt; enkephalins &gt; dynorphins</td>
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<tr>
<td><strong>δ (delta)</strong></td>
<td>Supraspinal and spinal analgesia; modulation of hormone and neurotransmitter release</td>
<td>Enkephalins &gt; endorphins and dynorphins</td>
</tr>
<tr>
<td><strong>κ (kappa)</strong></td>
<td>Supraspinal and spinal analgesia; psychotomimetic effects; slowed GI transit</td>
<td>Dynorphins &gt; &gt; endorphins and enkephalins</td>
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</table>
Activation of the opioid receptor decreases Ca\(^{2+}\) influx in response to incoming action potential. This decreases release of excitatory neurotransmitters, such as glutamate.

Activation of the opioid receptor increases K\(^+\) efflux and decreases the response of the postsynaptic neuron to excitatory neurotransmitters.
Pure Agonist: has affinity for binding plus efficacy

Pure Antagonist: has affinity for binding but no efficacy; blocks action of endogenous and exogenous ligands

Mixed Agonist–Antagonist: produces an agonist effect at one receptor and an antagonist effect at another

Partial Agonist: has affinity for binding but low efficacy
OPIOID ANALGESICS AND ANTAGONISTS

STRONG AGONISTS
- Alfentanil
- Fentanyl
- Heroin
- Meperidine
- Methadone
- Morphine
- Oxycodone
- Remifentanil
- Sufentanil

MODERATE/LOW AGONISTS
- Codeine
- Propoxyphene

MIXED AGONIST-ANTAGONISTS AND PARTIAL AGONISTS
- Buprenorphine
- Butorphanol
- Nalbuphine
- Pentazocine

ANTAGONISTS
- Nalmefene
- Naloxone
- Naltrexone

OTHER ANALGESICS
- Tramadol
Morphine:

Organ systemic effects:

1. Central nervous system effects
   a. Analgesia
   b. Euphoria
   c. Sedation
   d. Respiratory depression
   e. Cough suppression
   f. Miosis
   g. Truncal rigidity
   h. Nausea and vomiting
   i. Temperature
2. Peripheral effects

Cardiovascular system:
No effect
Large dose: hypotension and bradycardia
Increase the cerebrospinal fluid (CSF) pressure

Gastrointestinal tract:
Constipation

Biliary tract:
Biliary colic
reflux of biliary and pancreatic secretions
Renal: Renal function is depressed by opioids.

Uterus: The opioid analgesics may prolong labor.

Neuroendocrine: Opioid analgesics stimulate the release of ADH, prolactin, and somatotropin but inhibit the release of luteinizing hormone.
Pruritus: Therapeutic doses of the opioid analgesics produce flushing and warming of the skin accompanied sometimes by sweating and itching;

Miscellaneous: The opioids modulate the immune system by effects on lymphocyte proliferation, antibody production, and chemotaxis.
Therapeutic uses:

- Analgesia
- Treatment of diarrhea

Relief of cough: codeine or dextromethorphan are more widely used for this purpose.

Treatment of acute pulmonary edema:
1. reduced anxiety
2. reduced cardiac preload
3. reduced after load
Absorption of *morphine* from the gastrointestinal tract is slow and erratic.

*Codeine*, by contrast, is well absorbed when given by mouth.

Significant first-pass metabolism of *morphine* occurs in the liver.

When used orally, *morphine* is commonly administered in an extended-release form.
Distribution:

*Morphine* rapidly enters all body tissues, including the fetuses of pregnant women.

Infants born of addicted mothers show physical dependence on opiates and exhibit withdrawal symptoms if opioids are not administered.

Only a small percentage of *morphine* crosses the blood-brain barrier.
Fate:

- *Morphine* is conjugated in the liver to glucuronic acid. The conjugates are excreted primarily in the urine.

- The duration of action of *morphine* is 4 to 6 hours when administered systemically but considerably longer when injected epidurally.
Adverse effects:

- Severe respiratory depression.
- Other effects include vomiting dysphoria, and allergy-enhanced hypotensive effects.
- The elevation of intracranial pressure.
- In benign prostatic hyperplasia, *morphine* may cause acute urinary retention.
Sedation

Constipation

Nausea

Urinary retention

Potential for addiction

Respiratory depression
Tolerance and physical dependence:

Repeated use produces tolerance to the respiratory depressant, analgesic, euphoric, and sedative effects of morphine.

However, tolerance usually does not develop to the pupil-constricting and constipating effects of the drug.
Drug interactions:

The depressant actions of *morphine* are enhanced by phenothiazines, monoamine oxidase inhibitors, and tricyclic antidepressants.
Absolute contra-indication to meperidine and relative contra-indication to other narcotic analgesics because of high incidence of hyper-pyrexic coma

Increased CNS depression, particularly respiratory depression

MAO inhibitors

Sedative-hypnotics

Narcotic analgesics

Tricyclic antidepressants

Antipsychotic drugs

Increased sedation; variable effects on respiratory depression
Codeine

- The analgesic actions of *codeine* are due to its conversion to morphine.
- *Codeine* is a much less potent analgesic than *morphine*, but it has a higher oral effectiveness.

- *Codeine* shows good antitussive activity.

- It has a lower potential for abuse than *morphine*, and it rarely produces dependence.

- *Codeine* produces less euphoria than *morphine*. 
Analgesia

Sedation

Euphoria

Dry Cough
Pentazocine

*Pentazocine* acts as an agonist on kappa receptors and is a weak antagonist at mu and kappa receptors.

*Pentazocine* is used to relieve moderate pain.

*Pentazocine* produces less euphoria compared to *morphine*. In higher doses, the drug causes respiratory depression & constipation.

High doses increase blood pressure and can cause hallucinations, nightmares, dysphoria, tachycardia, and dizziness.
**Tramadol**

*Tramadol* is a centrally acting analgesic that binds to the μ-opioid receptor. It weakly inhibits reuptake of norepinephrine and serotonin.

It is used to manage moderate to moderately severe pain. Its respiratory-depressant activity is less than that of *morphine*.

**ADRs:**
- Anaphylactoid reactions
- Seizures
Naloxone

*Naloxone* is used to reverse the coma and respiratory depression of opioid overdose.

*Naloxone* has a half-life of 60 to 100 minutes.

*Naloxone* is a competitive antagonist at mu, kappa, and delta, receptors, with a 10-fold higher affinity for mu than for kappa receptors.
Binding of *naloxone* does not activate the receptor; therefore, *naloxone* reverses the effects of opioid agonists, such as *morphine* and *heroin*. 
Naltrexone has actions similar to those of naloxone.

It has a longer duration of action than naloxone,
Tolerance

1. Persistent activation of u receptors such as occurs with the treatment of severe chronic pain
2. Repeated exposure to agonist caused u receptors to be down-regulated by endocytosis.
3. Tolerance is due to a dysfunction of structural interactions between the u receptor and G proteins, second-messenger systems, and their target ion channels.
4. NMDA receptor, has been shown to play a critical role in tolerance development and maintenance
Which of the following statements about morphine is correct?

- A. It is used therapeutically to relieve pain caused by severe head injury.
- B. Its withdrawal symptoms can be relieved by naloxone.
- C. It causes diarrhea.
- D. It is most effective by oral administration.
- E. It rapidly enters all body tissues, including the fetus.