Opioids

Opium is a naturally occurring opiate compound.

- Produced by the opium poppy (*Papaver somiferum*).
- Opium has been used for 1000s of years.
- First federally “controlled substance”.

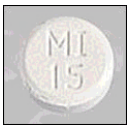
Effects of Opiates

- Analgesia - More effective for dull, throbbing pain.
- Euphoria - hul gil - “plant of joy”
- Constipation
- Cough Suppression
- Mild Sedation – Origin of “Narcotic”
- Nausea
- Respiratory Depression and Seizures

Types of Opioids.

2 *naturally occurring* opiates in opium:

- Morphine (10% of opium).
- Codeine (0.5% of opium).



Non Natural Opioids

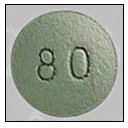
Semisynthetic compounds are produced by modifying morphine or codeine.

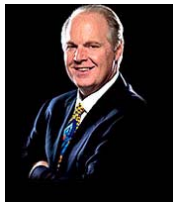
***Heroin* (diacetylmorphine)**

- Morphine + 2 acetyl groups.
- Much more lipid soluble than morphine.


Semisynthetic compounds ctd…

- Oxycodone – similar to codeine, but much more potent.
  - *OxyContin* – Oxycodone in time-release form.





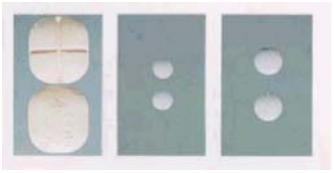
Synthetic compounds are produced from non-opioids.

Fentanyl (*Sublimaze*)

- 200X more potent than morphine.
- Short half life (1 hr vs 4 hrs for morphine).
- For preanesthesia (lollipop)
- For intense chronic pain (patch).
- Street drug: “China White”.

Methadone (*Dolophine*)

- Less potent.
  - Produces less euphoria.
- Longer half life (. 24 hours).
- Treatment for heroin addiction.



Opioids are often combined with other analgesics or anti-inflammatory drugs.

- hydrocodone + acetaminophen.
  - *Vicodin*
- hydrocodone + ibuprofen
  - *Vicoprofen*

Pharmacokinetics of Opioids

Absorption

- Oral absorption varies:
  - Morphine and heroin poor.
  - Codeine and methadone good.
- Other routes: injection, transdermal, suppository, inhalation.

Pharmacokinetics of Opioids

- Lipid solubility
  - The most potent forms are very lipid soluble (heroin, fentanyl).
  - Less potent forms aren't very lipid soluble (morphine, methadone).
    - 80% of morphine is metabolized *before* reaching the brain.
- Opioids are metabolized by the liver.

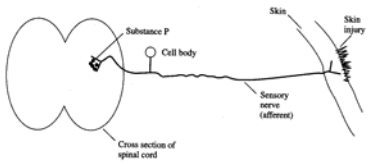
Pharmacodynamic Effects of Opioids

- Opioids are naturally found in 2 places:
  - In the opium poppy.
  - In the brain.
- Endorphins - endogenous opioid neurotransmitters.
  - Mediate pain transmission.

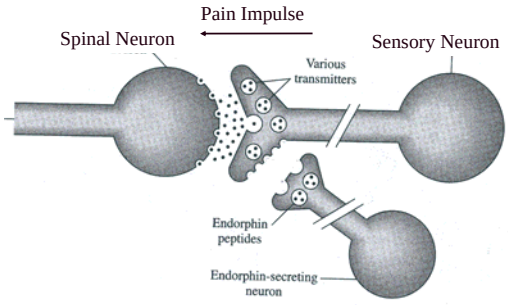
3 subtypes of opioid receptors.

- Mu receptor - mediates supraspinal analgesia, euphoria, respiratory depression.
  - Most potent site of action of most narcotic drugs.
- Kappa receptor – spinal analgesia, miosis, sedation, dysphoria.
- Delta receptor – mediates actions of endorphins.

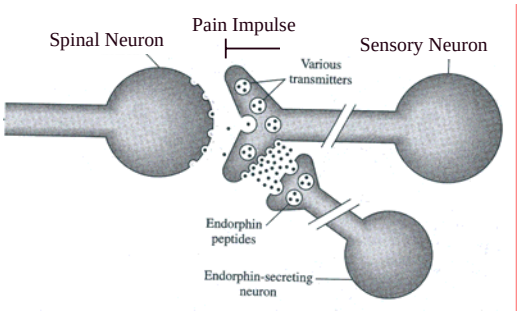
Physiology of pain transmission.



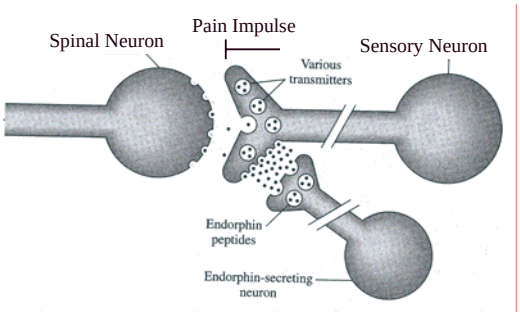
- Sensory neuron detects cellular damage and sends signal to spinal cord.
- Neurons in the spinal cord send the message to brain.



- Normally, the sensory neuron releases NT when a painful stimulus occurs.



- Endorphin release by a third neuron (axo-axonic synapse) inhibits the sensory neuron.



- Opioids therefore inhibit transmission of pain.

What is the purpose of the endogenous opioid system?

- Natural analgesia is likely adaptive.
  - Child birth.
  - Battling saber-toothed tigers?
- Endorphins are released into the bloodstream during periods of stress.
  - Rat model of stress induced analgesia.
  - Runners high?

Acute Toxicity of Opioids

- Death through respiratory depression or seizures.
- Abuse deaths may not be so simple.
  - Purity/potency/drug interaction issues.
  - Release of conditioned tolerance?

Chronic Toxicity of Opioids

- No dramatic life-threatening toxicity.
  - Maybe increases in cancer and liver disease.
- Suppression of immune system?

Chronic Toxicity of Opioids continued...

- Less serious chronic toxicity.
  - Inhibited sexual response.
  - Constipation.
- Indirect toxicity:
  - Sores and infections from needles.
  - Malnutrition
  - Risky behavior.

Tolerance

- Most opioids support rapid development of tolerance.
- Effects show different rates of tolerance.
  - Tolerance to constipation is slow (if at all).
  - Tolerance to analgesia is fast.
  - Tolerance to euphoria is very fast.

Tolerance continued...

Tolerance occurs due to:

- Enzymatic facilitation
- Nervous system changes
- Learning
  - Siegel -conditioned morphine tolerance.

Addiction

- Most opioids are very addictive.
- Opioids increase DA in nucleus accumbens.
- Addictiveness varies:
  - Heroin and fentanyl - very addictive.
  - Codeine and methadone - less addictive.

Addiction continued...

- Physical dependence marked by a withdrawal syndrome.
  - Restlessness
  - Dysphoria
  - Flu-like symptoms
  - Muscle spasms
  - Occurs within 6-12 hours for short duration drugs like heroin.

Treatment for Opioid Dependency

- Traditional approach: weaning.
- Methadone Maintenance
  - Methadone is substituted for heroin.
  - Methadone:
    - blocks the withdrawal symptoms.
    - produces less euphoria.
    - has a longer half life (~24 hrs).
    - tolerizes slower.
    - LESS DISRUPTIVE to normal life.

Treatment for Opioid Dependency continued...

- However, methadone therapy is controversial.
  - Not in my neighborhood!
  - Lessens the impact on society, but what about the addict?
- Buprenorphine (*Subutex*) now available as an office-based maintenance program.
  - Mu partial agonist.
  - Low overdose potential

Treatment for Opioid Dependency continued...

- Treatment with Opioid Antagonists.
  - Example: Re Via (naltrexone).
  - Antagonists:
    - block the effects of opioids in the brain.
    - displace opioids from the opioid receptor.
      - fast induction of strong withdrawal.
      - Short acting forms can be used for overdose.
    - don't block craving.
- Sublingual buprenorphine+naloxone (*Suboxone*) available for maintenance therapy.

Treatment for Opioid Dependency continued...

- RAAD (Rapid Anesthesia Aided Detoxification)
  - Antagonists are delivered during general anesthesia or sedation.
  - Controversial
    - Dangerous?
    - Doesn't treat the *addiction*.

Most Non Narcotic Pain Relievers are *Cyclooxygenase* (COX) Inhibitors.

- Often called Nonsteroidal Anti-Inflammatory Drugs (NSAIDs).

2 Types of COX:

- COX-1 produces *prostaglandins* important for normal GI and blood platelet functioning.
- COX-2 produces prostaglandins that activate pain receptors and produce inflammation.
  - COX-2 activated by tissue damage.

Aspirin, Ibuprofen (*Advil*), and Naproxen (*Aleve*) are *Nonselective COX Inhibitors*

- Affect both COX types.
- Produce analgesia.
- Anti-inflammatory effects.
- Reduce fever (antipyretic).
- Cause GI irritation/ulceration.
- Decrease platelet activity (cardioprotective, bruising, bleeding disorders),

Celecoxib (*Celebrex*) and Rofecoxib (*Vioxx*) are *Selective COX-2 Inhibitors*.

- Analgesia.
- Anti-inflammatory effects.
- No GI or platelet side-effects.
- No antipyretic actions.
- Mostly used for arthritis.

- Recent evidence of cardiotoxicity!

Acetaminophen (*Tylenol*) is in a class by itself.

- Nonselective COX inhibitor but only in CNS.
- Possesses analgesia, antipyretic effects.
- No anti-inflammatory, platelet, or GI effects.
- Especially hepatotoxic.
- Technically not an NSAID.