PAIN & ANALGESIA

Pain - subjective experience associated with detection of tissue damage ("nociception")

acute - serves as a warning

chronic - nociception gone bad

often accompanied by clinical depression

fibromyalgia, chronic fatigue, etc.

chicken or egg?

Physiological cause:

cyclooxygenase (COX) enzymes (a.k.a. prostaglandin synthetases)

COX 1, COX 2, and COX 3 (a variant of COX 1)

Each produces several hormones called prostaglandins
PAIN & ANALGESIA

COX-1: makes “good” prostaglandins that regulate GI tract and promote ability of blood platelets to clot in normal daily life

COX-2: activated in periphery and spinal cord by tissue injury
makes prostaglandin E2 (PGE2) and others
PGE2 at injury site activates dendrites of nociceptive neurons cell bodies in PNS (dorsal root ganglion) neurons become sensitized, firing spontaneously axons release substance P (“pain”) and glu into dorsal horn of spinal cord glu binds with NMDA-type glu receptors, sensitizing the neurons neural activity reaches cortex by way of ascending spinoreticular and spinothalamic tracts and is perceived of as “painful”
PAIN & ANALGESIA

Endorphins

Opiate Receptor

Pre-synaptic neuron

Substance P in the synapse

AND GLUTAMATE
Substance P receptor

Post-synaptic neuron

Dorsal horn of spinal cord

Pain signal from periphery

Pain signal to brain
“Pain” is caused by neural activity traveling from the periphery through the spinal cord to the cortex.

Therefore, we can pharmacologically reduce pain by:

- reducing the peripheral inflammatory response (NSAIDs)
- reducing glu release in spinal cord (opioids, cannabinoids)
- blocking NMDA-type glu receptors (ketamine, PCP, etc)
- inhibiting ascending spinal cord neurons by activating inhibitory neurons that release endorphins or GABA (opioids)
- inhibitory descending spinal paths (anti-depressants)
- reducing the unpleasant nature of the subjective experience (opioids, cannabinoids, depressants)
PAIN & ANALGESIA

2 main classes of analgesic drugs:

**opioids / narcotics**
- morphine, codeine, heroin, etc.
- act primarily on the CNS

**NSAIDs** (non-steroidal anti-inflammatory drugs)
- aspirin, ibuprofen, etc
- act primarily in the periphery

can be potentiated by anti-depressants and anti-convulsants, both of which have analgesic properties
Opiates and Opioids

- **Other name(s):** *morphine / codeine, heroin, fentanyl, oxycontin, junk, etc*
- **Class:** Phytochemical alkaloid and synthetic derivatives
- **Forms:** plant extracts (opium), pills, powder, “tar”
  - poppy flowers produce opium (“juice”)
  - opium contains the true “opiates”:
    - morphine (10%)
    - codeine (.5%)
Opiates and Opioids

History:

used and abused for thousands of years
smoked

laudanum = opium & alcohol

morphine synthesized in early 1800s
syringe invented in 1856
non-medicinal use banned in 1914

Current clinical usage: pain management
Opiates and Opioids

Effects:

euphoria

neurons in the Ventral Tegmental Area normally release GABA to inhibit neurons that release DA into the nucleus accumbens

endorphins / opiates inhibit GABA release, disinhibiting release DA into the nucleus accumbens

analgesia - primarily via endogenous endorphin system

block pain transmission (within the spinal cord)

reduce subjective response to pain

do not reduce damage / injury, just perception of pain

not very effective on chronic pain
Opiates and Opioids

Side effects:

- anxiolysis / lack of concern / sedation (cortex)
- receptors in brainstem areas
  - cough suppression
  - nausea induction
- depressed respiration - cause of overdose
- receptors in GI tract - peripheral anti-diarrheal (constipation)
  - diphenoxylate (“Lomotil”) and loperamide (“Imodium”) are both opioids that don’t cross the BBB
- histamine release - allergic reactions
- pupillary constriction (miosis)
THE OPIOIDS - MORPHINE

Pharmacokinetics:

Absorption: usually injected, but may be taken rectally, smoked, or orally (less effective),

injected straight into spinal cord (epidural)
crosses BBB slowly (more water soluble than fat soluble) - only about 20% reaches brain

heroin much more rapid and complete

a major metabolite is morphine-6-glucuronide

10-20x more potent as an analgesic

half-lives of both morphine & m6g ~3-5 hrs
THE OPIOIDS - MORPHINE

Pharmacodynamics

opioids are agonists for the endogenous “opioid” receptors

enkephalins, dynorphins, beta endorphins are endogenous opioids

runner’s high, shock, etc.

3 different metabotropic opioid receptors with different distributions throughout body:

* Mu
Delta
Kappa

Distribution of mu receptors
THE OPIOIDS - MORPHINE

Pharmacodynamics

mu

*activated by endorphin and associated with euphoria*

mu1 - analgesia + euphoria

mu2 - depressed respiration

  found in spinal cord / brainstem / thalamus / striatum / / nucleus accumbens

  very few in cortex

delta - not well understood (modulate mu receptors?)

kappa - modest analgesia, little euphoria, little respiratory depression

  found in cortex

salvia
THE OPIOIDS - MORPHINE

**morphine** - “pure” agonist at mu, and to a lesser extent, kappa and delta receptors

opioids and endorphins act at mu receptors on presynaptic terminals within dorsal horn of spinal cord to:

- reduce substance P and glutamate release
- stop transmission of pain info

![Diagram of opioid receptor action](image)
THE OPIOIDS - MORPHINE

Too much...

Tolerance:

  euphoria / analgesic effect rapidly declines with regular use

    50 mg/day can become 500 mg/day in 10 days

  purpose of use becomes avoidance of withdrawal

  cross-tolerance with other opioids

Withdrawal - opposite of pharmacological effects

  reduced DA release into nucleus accumbens

  not life-threatening - just feels like it
Other “pure” agonists:

- **codeine**: often combined with aspirin or acetaminophen, metabolized into morphine.
- **methadone**: synthetic mu agonist (similar to actions of morphine), orally effective, long acting, and resistant to tolerance, used in substitution for opiate dependence, “maintenance” medication.
- **diacetylmorphine (heroin)**: more lipid soluble, 3x more potent than morphine and faster acting.
- **oxycodone** ("Percodan", "OxyContin")
- **fentanyl** ("Sublimaze" / "China White") - synthetic opioid (much more potent than morphine).
THE OPIOIDS - OTHER AGONISTS

“partial agonists”

buprenorphine (long-acting partial agonist) bind to, but only partially activate, mu receptors

ceiling effect for analgesia - not as effective for pain

competitively inhibit pure agonists from binding
THE OPIOIDS - OTHER AGONISTS

“antagonists” - bind & stick to receptors (produces no action)

naloxone - antagonist at all 3

naltrexone (“Vivitrol”) – time release, chronic “control”

little to no effects in “normals” (non-addicts) but produces withdrawal response in addicts

(also reduces effects of ethanol ingestion)
THE OPIOIDS - OTHER AGONISTS

“mixed agonists / antagonists”

“Suboxone” = 4 pts buprenorphine : 1 pt naloxone

buprenorphine is active orally
but more potent when injected
naloxone only active if injected
mu receptors in gut “soak it up” if taken orally