# Opioids

## Background

- **narcotic analgesic:** drugs that can reduce pain w/o causing unconsciousness.
  - opioids are classified as narcotic analgesics.
- **Heroin:** increased ability to pass through the BBB b/c of ↑ lipid solubility.
  ↳ has 2 additional acetyl groups: increased permeability through the BBB.

## endogenous opioid system

- main endogenous opioid receptors in the body: **μ, δ, κ, and NOP-R** ⟶ all are metabotropic receptors.
- endogenous opioid R are found in the: brain and the gut.

### μ-receptors

- Found in various areas of the brain:
  - **brainstem:** cough, respiratory, circulatory control, vomiting.
  - **Locus coeruleus, PAG, SC, Raphei Nuclei, Thalamus:** pain regulation (analgesia)
  - **striatum, thalamus:** sensorimotor integration, motor learning
  - **Nucleus Accumbens:** feeding, +ve reinforcement, reinforcing aspects of salty/sweet foods.

### NOP-R

- doesn't respond to opioids: binding will cause a reduction in pain threshold.
  - **cortex, limbic system, striatum, Raphe nuclei, SC:** learning, motor function, neuroendocrine fcn, feeding.

### δ-Receptors

- mainly found in the same areas as the μ-receptors; distributed in the forebrain.
  - same distribution as μ-R: analgesia
  - other functions: olfaction, cognitive function, motor integration.

### κ-Receptors

- identified by binding to opioid analog **ketacyclozine**
  - **striatum, amygdala, hypothalamus:** involved in pain regulation, dysphoria, gut motility.

## SYNTHESIS

- opioids = synthesized as a large pro-peptide; cleaved into smaller AA sequence.
  - can be co-localized with other NT in the neurons.
    ↳ opioids have to be synthesized in the soma → the axon terminals don't have the cleavage enzymes required.

selective activation of the opioid receptors:

- **μ-receptors** → preferentially activated by **endorphins**, partially activated by **endomorphins**
- **κ-receptors** → preferentially activated by **dynorphins**
- **δ-receptors** → preferentially activated by **enkephalins**, **endorphins**

opioid receptors are all coupled to **Gi proteins** (↓ cAMP)

3 ways opioid R can act in circuits:

① **Axoaxonic**: inhibition of other neurons
↓ NT release
activate G protein to close $Ca^{2+}$ channel.

② **Post-synaptic**: activate G protein to open $K^+$ channel.

③ **Pre-synaptic**: reduce release of the NT. (co-localized).

## pharmacology

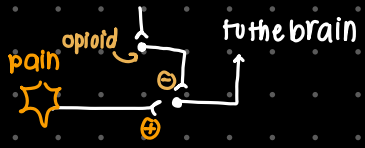
- **Buprenorphine**: partial agonist of opioids.
  ↳ ↓ chance of respiratory depression / dependence.
- **Naloxone, Naltrexone**: antagonist of opioid receptors
  ↳ reverse the effects of opioids @ the opioid receptors.
  ↳ same shape as opioids but no functional effect.

Naloxone / Naltrexone are used to tx opioid overdose: respiratory depression.

## opioids + pain

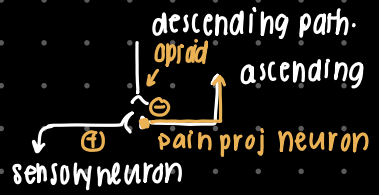
- 3 main locations where opioids can act to block pain in the body:

① In the SC



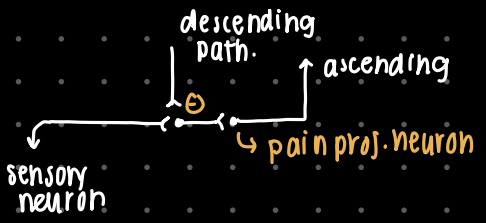

- blocking the pain projection neuron from ascending to the brain.

② In the Brain




- blocking the pain proj. neuron from sending signal to the brain.

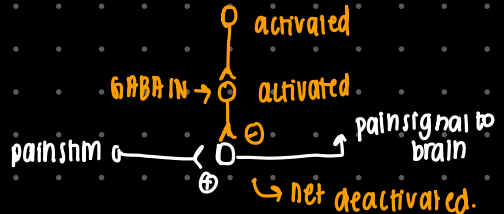
③ In the Brain




- blocking the interneuron that projects to the pain projection neuron.
- IN = usually excitatory.

- Activation of opioid R in 2 main descending projection neurons can also be analgesic.

Locus Coeruleus / Raphe nuclei are disinhibited




↳ net deactivated.

the 2 pathways are disinhibited when the **PAG** is activated.
↳ PAG projects down to those regions.

- supraspinal regions of opioid activity:
  - limbic system
  - hypothalamic regions
  - sensory regions

these regions are responsible for the regulation of other aspects of pain (ie, emotional, neuroendocrine, autonomic).

- **Accupuncture**: works via stimulation of the endogenous opioid system.
  ↳ opioid antagonist = ↓ in efficacy of accupuncture.

# effects of opioids

## Therapeutic Effects

- pain relief
- usually given IM/orally; slow absorption.

## Recreational Effects

- IV / inhalation (fast methods of absorption).
- euphoric effects

## At low doses of opioids:

- constricted pupils
- drowsiness
- inability to concentrate
- analgesia
- dreamy sleep.

## At high doses of opioids:

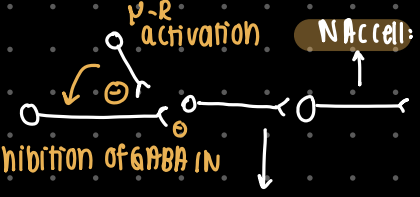
- euphoria
- abnormal state of elation

↓

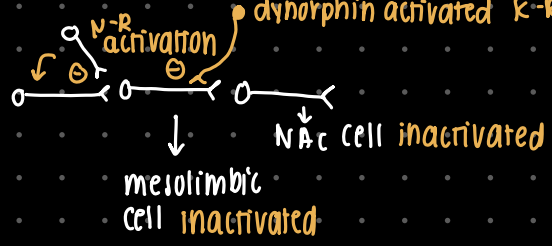
highest doses can cause unconsciousness, death, respiratory depression.

## DA and opioids

- increased DA via. activation of the **mesolimbic system.**




- If the K-receptors are activated: it can ↓ the release of DA.




## Aversive Effects:

- paranoia, restlessness, anxiety, nausea.
- can cause ↓ gut motility → constipation.
- many negative effects are due to the injection of the drug
  - ↳ collapsed veins, kidney dmg, infection.
- can have prolonged cognitive deficits.

**μ-receptors** can inhibit GABA IN
**k-receptors** inhibit mesolimbic cell →
↓ NAc DA release.

- **Agonist of μ-R** will ↑ self-admin of drugs
  **Agonist of K-R** will ↓ self-admin of drugs

opioid activation of mesolimbic system contributes to reinforcement of opioids.

# tolerance & withdrawal

- Tolerance to diff effects of opioids develop @ different rates.
  - euphoria = develops fast
  - pupil constriction / constipation = slow

  } main mechanism of tolerance: pharmacodynamic.

- **Cross-tolerance of opioids:** tolerance to one type of opioid = will also have tolerance to another opioid drug similar to it.
- withdrawal symptoms = dependent on the drug taken
  - buprenorphine / methadone: not as severe
  - morphine / heroin: severe.

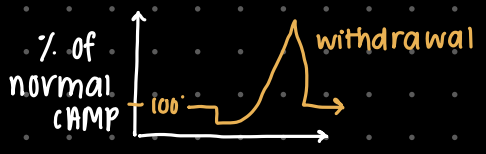
Main symptoms:
- rebound of CNS activity; worst day 3, gone by day 7.

- Precipitated withdrawal symptoms:
  - **emotional withdrawal** symptoms = via. injection of opioid antagonist into the **NAc, Amygdala**
  - **physical withdrawal** symptoms = via. injection of opioid antagonist into the **PAG, locus coreulus.**
  - systemic injection of naloxone = withdrawal symptoms.

## CELLULAR LEVEL OF WITHDRAWAL

- opioids does 2 things @ a cellular level: ① reduction in the cAMP production
  ② overall ↓ cellular firing.

**cAMP Decrease**




- inhibition of cAMP due to opioid usage.
- **tolerance** of drug: the cAMP levels return to normal
- **withdrawal** of drug: cAMP levels higher than usual. (above 100%)
  - remove opioid / add naloxone = ↑ in cAMP (withdrawal).

**Firing Rate**


- Drug ↓ the basal cell firing.
- naltrexone / the removal of the drug will cause withdrawal: rebound in cellular firing.
  ↳ increased firing rate in the **LC cells**.

# TREATING OPIOID ADDICTION

① **Detoxification** → done via. giving **$\alpha_2$ agonist**
  - reduce the hyperactivity in the LC cells.
  - prevention of hyperactivity.

③ **Maintenance** → methadone / Naltrexone.

Detoxification
↓
Maintenance

**Methadone**
- can develop cross tolerance to euphoria.
- decrease cravings
- taken orally.
  ↳ taken IV can cause high: need to have someone supervise.

**Naltrexone**
- can't reduce cravings.
- longer lasting effects
- for people who are more motivated.