

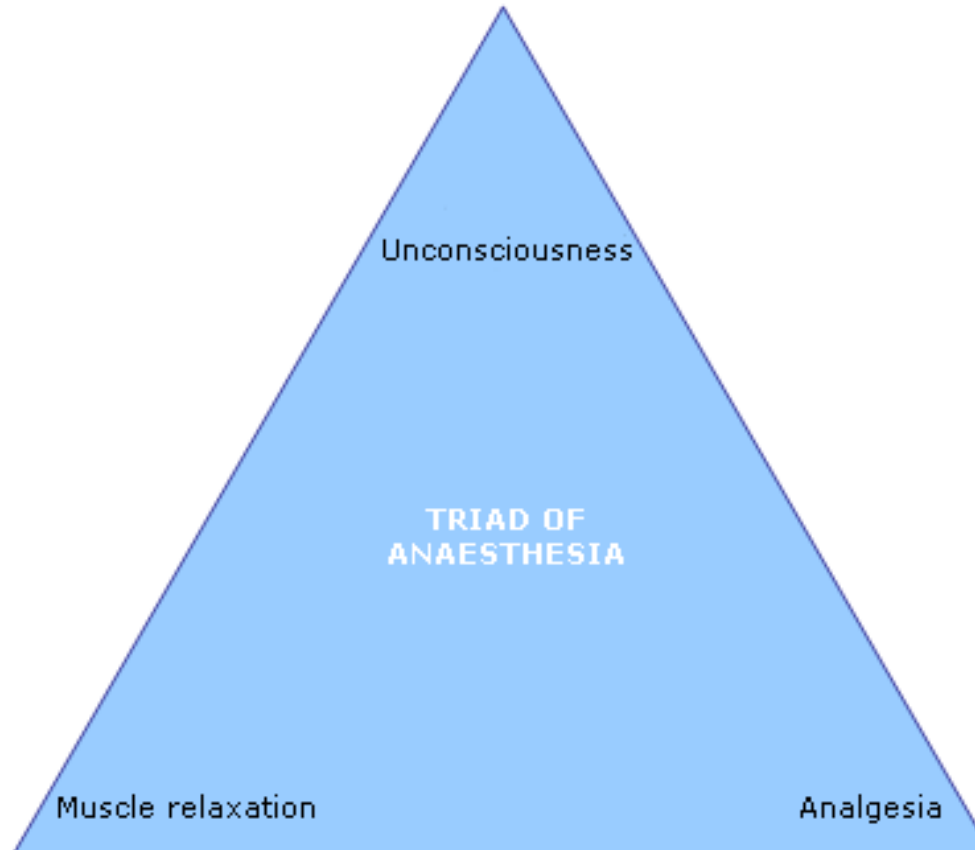


# PHARMACOLOGY OF ANAESTHETICS

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FN Brno, October 2013

# AIMS OF ANAESTHESIA



# Triad of anaesthesia

- **Neuromuscular blocking agents** for muscle relaxation
- **Analgesics**/regional anaesthesia for analgesia
- **Anaesthetic agents** to produce unconsciousness



Why unconscious patient require analgesia ?

# Overview

- Intravenous and inhalational anaesthetics
- Analgesics – simple, opioids
- Muscle relaxants
- Decurarization





# **INTRAVENOUS ANAESTHETICS**

# Stages of anaesthetics

- **Induction** – putting asleep
- **Maintenance** – keeping the patient asleep
- **Reversal** – waking up the patient



# Intravenous anaesthetics

- Onset of anaesthesia within one arm – brain circulation time – 30 sec
- Effect site → brain
  - Propofol
  - Thiopentale
  - Etomidate
  - Ketamine



# General anaesthetic-how do they work

- **TASK – EXPLAIN**
  1. Loss of conscious awareness
  2. Loss of response to noxious stimuli
  3. Reversibility
- Anatomical site of action
  - Brain : thalamus, cortex
  - Spinal cord



# Molecular theories

## Meyer Overton Correlation

HAL Halothane

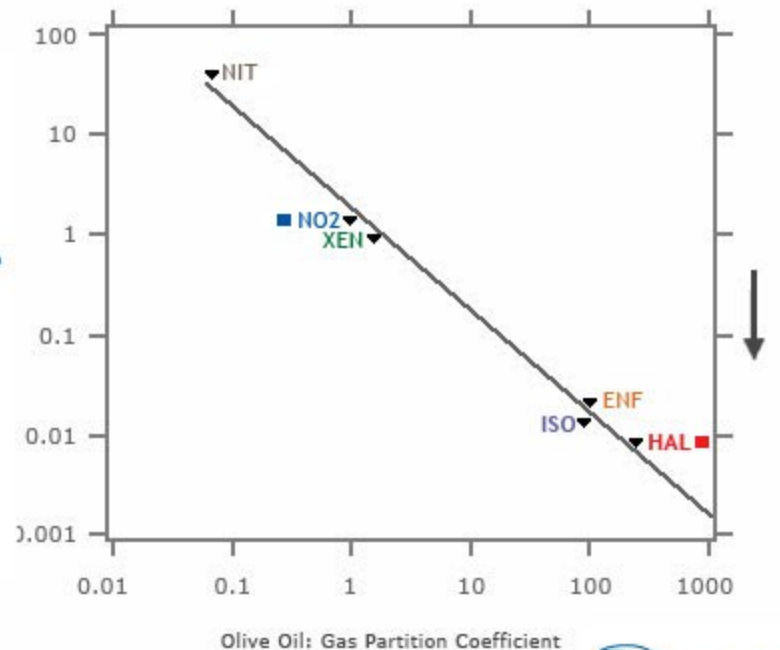
ISO Isoflurane

ENF Enflurane

NO2 Nitrous oxide

XEN Xenon

NIT Nitrogen

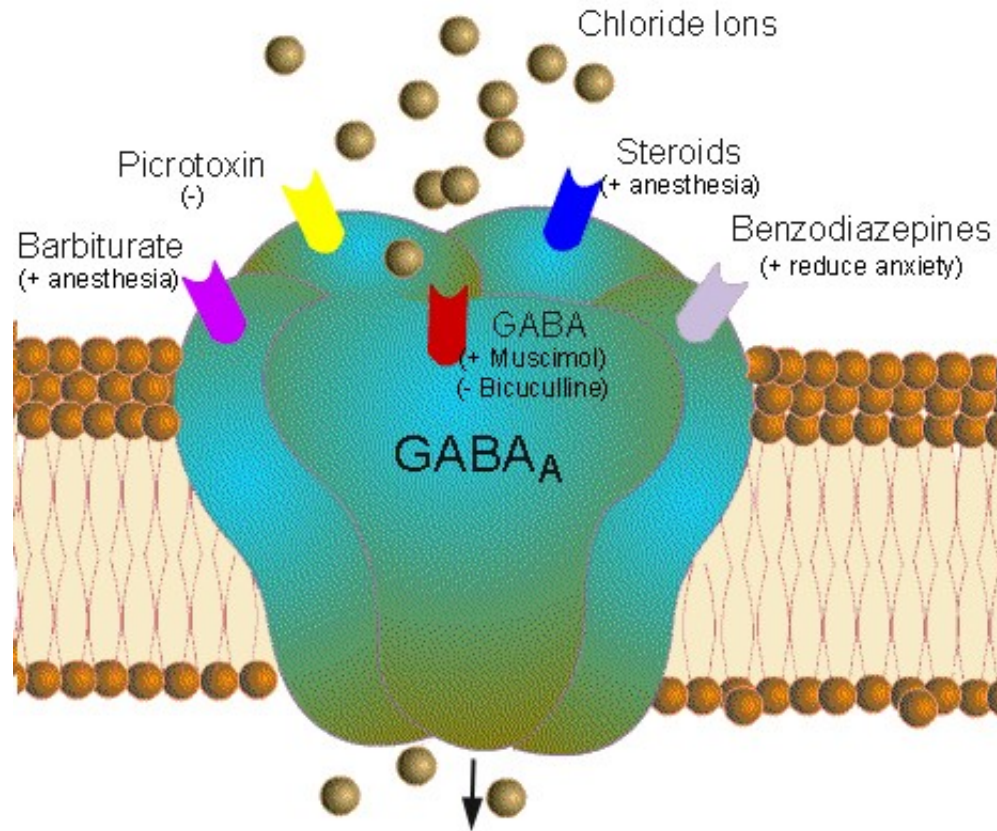


- Linear correlation between the lipid solubility and potency

# Molecular theories

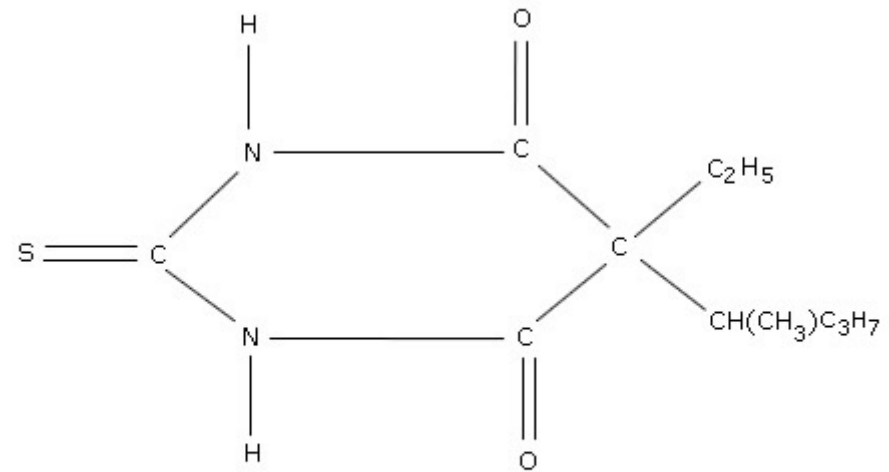
- Critical volume hypothesis
  - Disruption of the function of ionic channels
- Perturbation theory
  - Disruption of annular lipids assoc. with ionic channels
- **Receptors**
  - **Inhibitory** – GABA<sub>A</sub>, glycin ← enhance
  - **Excitatory** - nAch, NMDA ← inhibit

# GABA<sub>A</sub> receptor



# Thiopentale

- Barbiturate
- **Dose** 3-7 mg/kg
- **Effects** : hypnosis, antiepileptic, antanalgesic
- **Side effects**
  - CVS: myocardiac depression, ↓CO
  - Reduction in MV, apnea

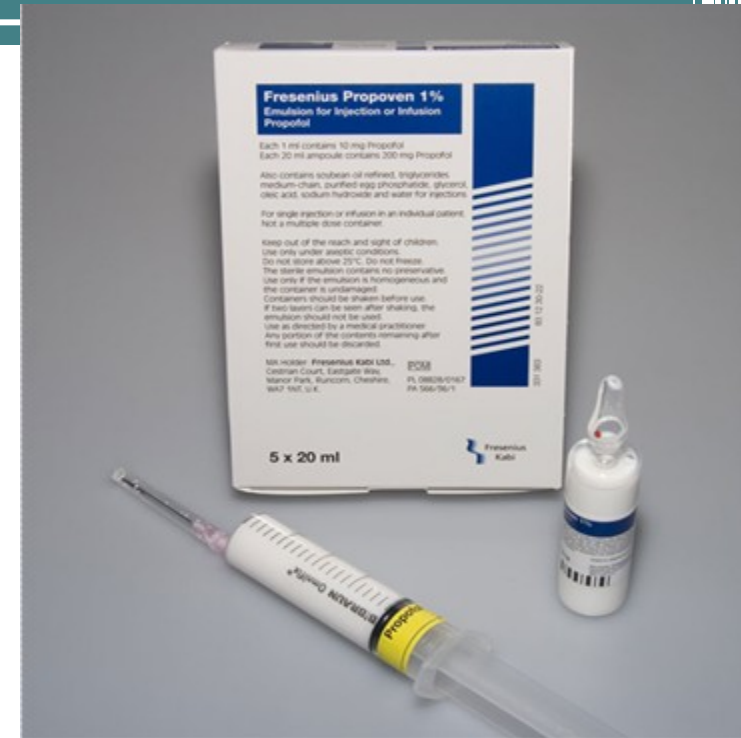


# Thiopentale

- **Problems with use**
  - Extremely painful and limbthreatening when given intra-arterially
  - Hypersensitivity reactions 1: 15 000
- **Contraindications**
  - Porphyria

# Propofol

- Phenolic derivative
- **Dose** 1- 2.5 mg/kg
- **Effects** : hypnosis
- **Side effects**
  - **CVS**: myocardiac depression, ↓SVR, ↓CO
  - Respiratory depression
  - Hypersensitivity 1 : 100 000



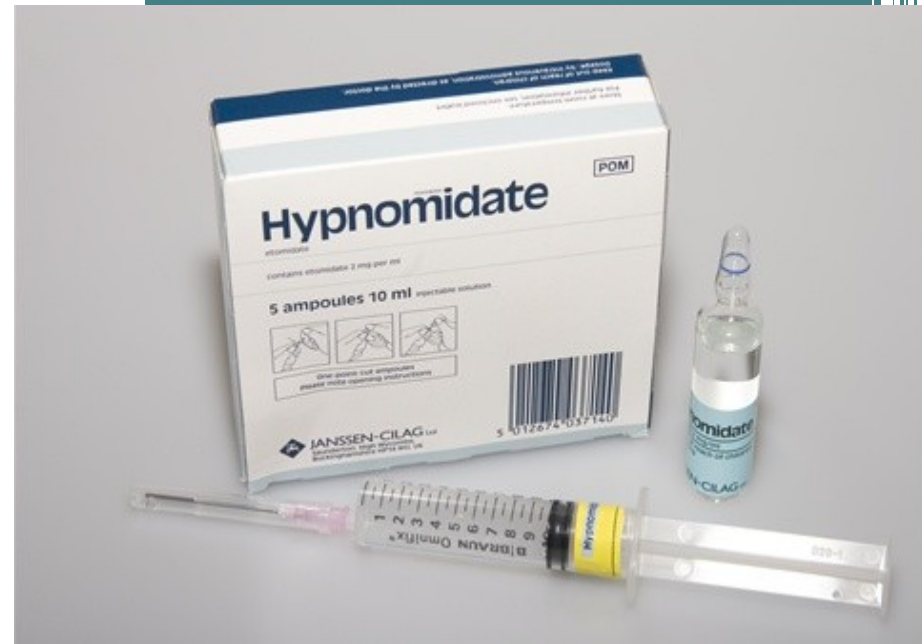
# Propofol



- Other effects
  - Pain on induction
  - Nausea and vomiting less likely
  - Better for LMA placement than thiopentale
- Relative **contraindications**
  - Children under 3

# Etomidate

- Ester
- **Dose** 0.3 mg/kg
- **Effects** : hypnosis
- **Side effects**
  - **CVS**: very little effect on HR, CO, SVR
  - Minimal respiratory depression





# Etomidate

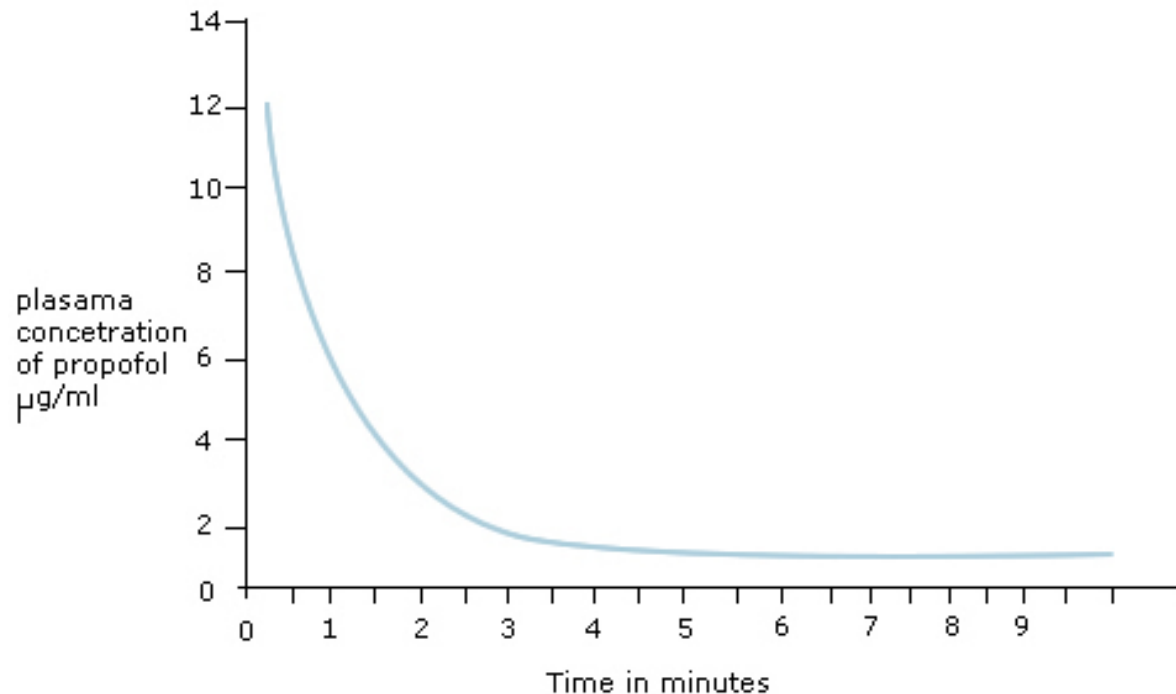
- **Problems with use**
  - Pain on injection
  - Nausea and vomiting
  - Adrenocortical suppression
  - Hypersensitivity reaction 1: 75 000
- **Relative Contraindications**
  - Porphyria

# Ketamine

- Phencyclidine derivative
- CV effects - ↑ **HR, BP**, CO, O<sub>2</sub> consumption
- RS - ↑ RR, preserved laryngeal reflexes
- CNS – **dissociative anaesthesia, analgesia, amnesia**
- Use – analgesic in Emerg. Med

# Pharmacokinetics

- Recovery from single bolus 5-10 min



# Choice of induction agent

- 1. Are any agents absolutely contraindicated ?
  - Hypersensitivity, porphyria
- 2. Are there any patient related factors ?
  - CVS status
  - Epilepsy
- 3. Are there any drug related factors ?
  - Egg allergy

# Intravenous anaesthetics

## Induction + maintenance



# SUMMARY - IV anaesthetics

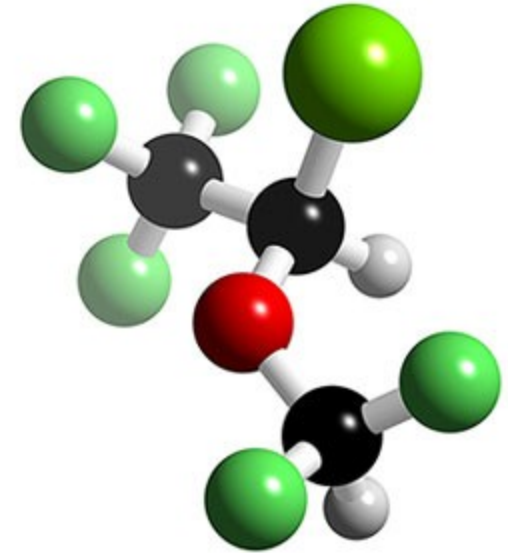
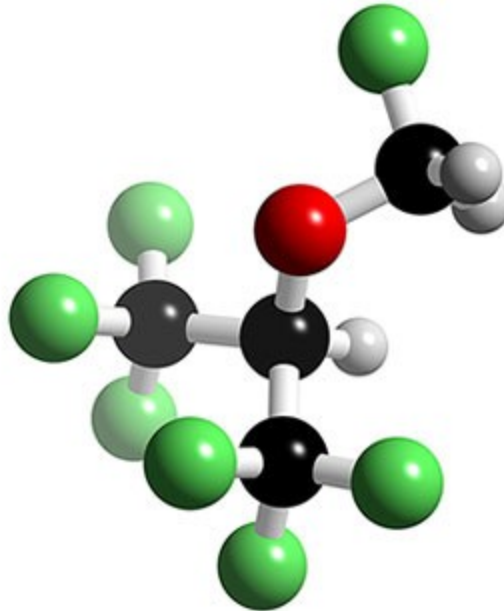
- Mechanism of action – via receptors
- Used for anaesthesia and sedation
- Used for induction
- Propofol used for maintenance as well
- Thiopentale, propofol, etomidate
- All cause CV and respiratory depression



# **INHALATIONAL ANAESTHETICS**

# Anaesthetic gases

- Isoflurane
- Sevoflurane
- Halothane
- Enflurane
- Desflurane
- $N_2O$  – nitrous oxide





## Anaesthetic gases

- Any agent that exists as a liquid at room temperature is a **vapour**
- Any agent that cannot be liquefied at room temperature is a **gas**
- Anaesthetic ‘gases’ are administered via **vaporizers**



## Potency

- MAC – that concentration required to prevent 50 % of patients moving when subjected to standart midline incision
- Sevoflurane      MAC 1.8 %
- Isoflurane      MAC 1.17 %



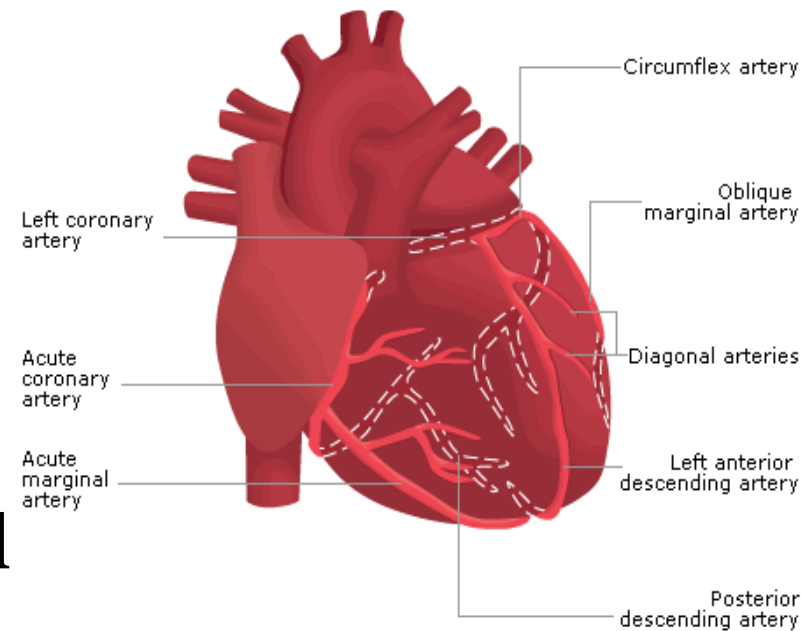
## Potency

- MAC – that concentration required to prevent 50 % of patients moving when subjected to standart midline incision
- Sevoflurane      MAC 1.8 %
- **Isoflurane**      **MAC 1.17 %**



## Respiratory and cardiovascular effects

- All volatile anaesthetics cause  $\downarrow$  MV and  $\uparrow$  RR
- Isoflurane is irritant vapour
- $\downarrow$  SVR, blood pressure falls,  $\uparrow$  HR
- Isoflurane - ? Coronary steal



# Metabolism and toxicity

- **Isoflurane** (0.2 %) and **Sevoflurane** (3.5%) are metabolized by liver
- **F<sup>-</sup>** ions are produced - ? Renal impairment
- Iso and Sevo trigger **malignant hyperthermia**
- **N<sub>2</sub>O**
  - Megaloblastic anaemia
  - Teratogenic
  - PONV

# SUMMARY - inhalational anaesthetics

- Mechanism of action – via receptors
- Used for induction (sevoflurane)
- And maintenance of anaesthesia
- Commonly used : Sevoflurane, Isoflurane
- Dose dependent CV and respiratory depression
- All, but N<sub>2</sub>O trigger malignant hyperthermia



# **NEUROMUSCULAR BLOCKING AGENTS**

# Neuromuscular blocking agents

- Exclusively used in anaesthesia and intensive care
- Two classes
  - Depolarizing
    - succinylcholine
  - Non depolarizing
    - Vecuronium - aminosteroid
    - Atracurium - benzylisoquinolinium





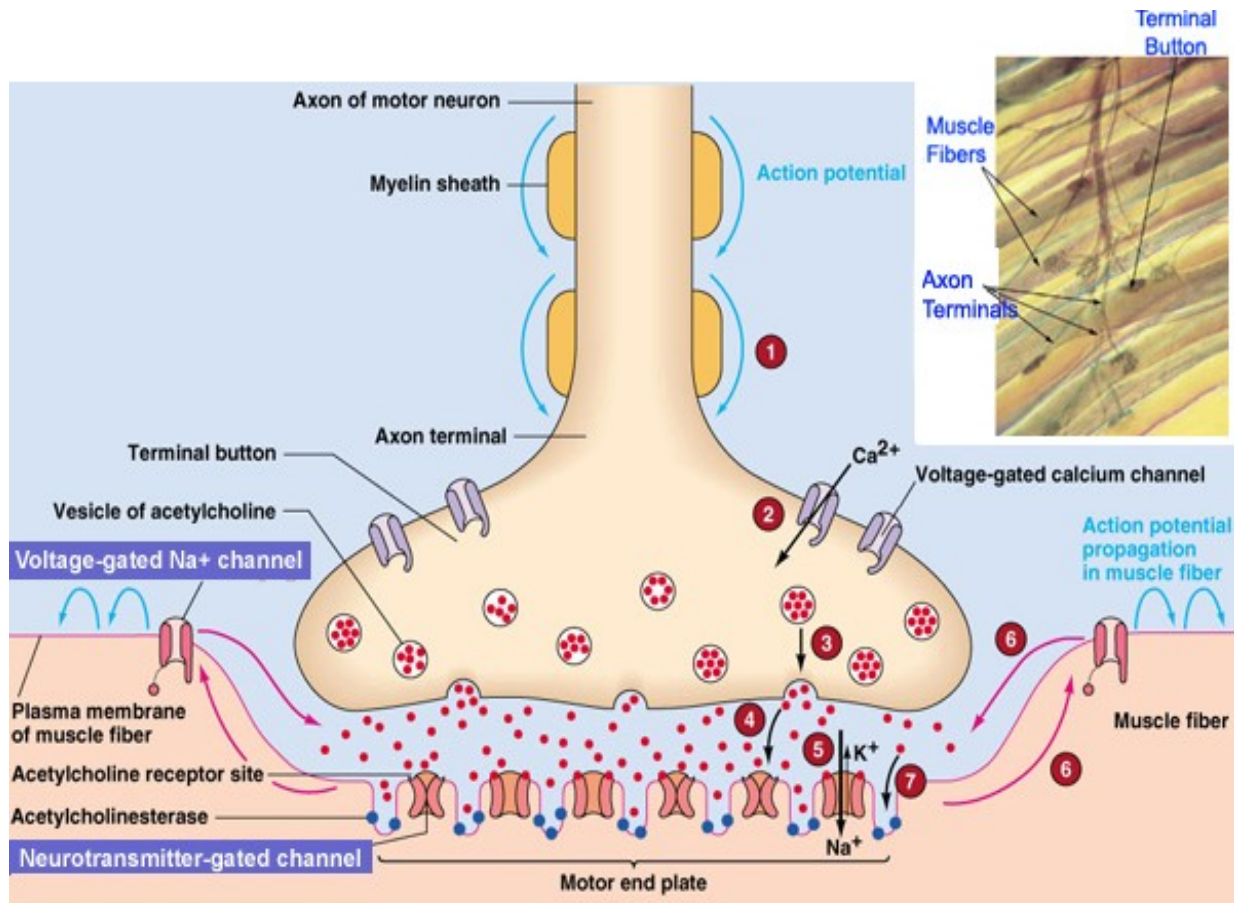
## Use of NMBs

- Tracheal intubation
- Surgery where muscle relaxation is essential
- Mechanical ventilation



# Neuromuscular blocking agents

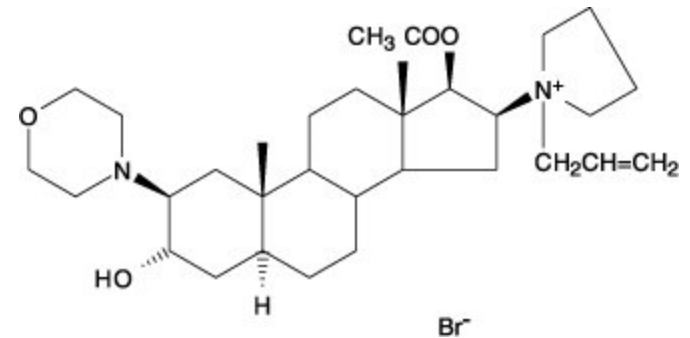
## Neuromuscular junction



## Neuromuscular blocking agents

### Mechanism of action

- Depolarizing
  - Structurally related to Ach
  - First activating muscle fibres, then preventing further response
- Non depolarizing
  - Compete with Ach at nicotinic receptor at the neuromuscular junction



## Choice for tracheal intubation

| Elective surgery       | Emergency surgery        |
|------------------------|--------------------------|
| Standart induction     | Rapid sequence induction |
| Non depolarizing agent | Succinylcholine          |

## Intubating doses

|                 |             |
|-----------------|-------------|
| Succinylcholine | 1 – 2 mg/kg |
| Vecuronium      | 0.1 mg/kg   |
| Atracurium      | 0.5 mg/kg   |

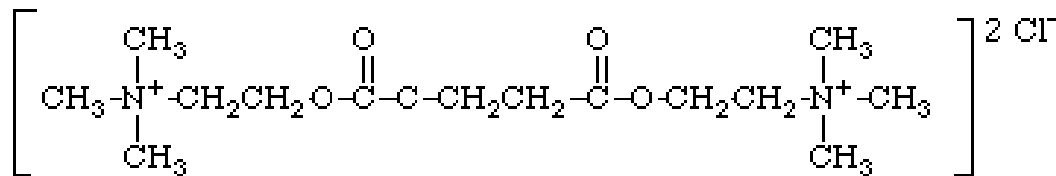
# To maintain paralysis

- Non depolarizing muscle relaxants

|                 |                   |
|-----------------|-------------------|
| Succinylcholine | No                |
| Vecuronium      | 0.02 – 0.03 mg/kg |
| Atracurium      | 0.1 – 0.2 mg/kg   |

# Succinylcholine pharmacokinetics

- Duration of action : 3 - 5 min
- Metabolism – plasma cholinesterase
  - Cave: suxamethonium apnea



# Succinylcholine - adverse effects

- Bradycardia
- Muscle pain – ‘sux’ pain
- Transient raised pressure in eye, stomach and cranium
- Raise in potassium

# Succinylcholine - contraindications

- Patient related contraindications
  - Malignant hyperpyrexia
  - Anaphylaxis to SCh
  - Succinylcholine apnea
- Clinical contraindications
  - Denervation injury
  - Penetrating eye injury



# Non depolarizing muscle relaxants

- Choice of NMBs
  - Personal preference
  - Atracurium better in renal or hepatic failure
  - Avoid atracurium in asthmatic patients

# Reversal

- Acetylcholine esterase inhibitor – neostigmine
  - Increases concentration of Ach at NMJ
- Neostigmine acts at all sites where acetylcholine esterase is present including heart



What effect this might have and how this can be overcome?

# Neostigmine

- Dose of neostigmine – 0.05 mg/kg
- In > 50 kg man 2.5 mg
- Given with atropine 0.5 mg

## Peripheral nerve stimulator

- Check the depth of neuromuscular blockade
- Determine that neuromuscular blockade is reversible
- Check that blockade has been reversed satisfactorily



# SUMMARY - muscle relaxants

- Mechanism of action – via acetylcholine receptor
- Used to facilitate tracheal intubation, mechanical ventilation and surgery
- Depolarizing – Succinylcholine
  - Lots of side effects
- Non depolarizing – Vecuronium, Atracurium
  - Minimal CV and Resp. effects



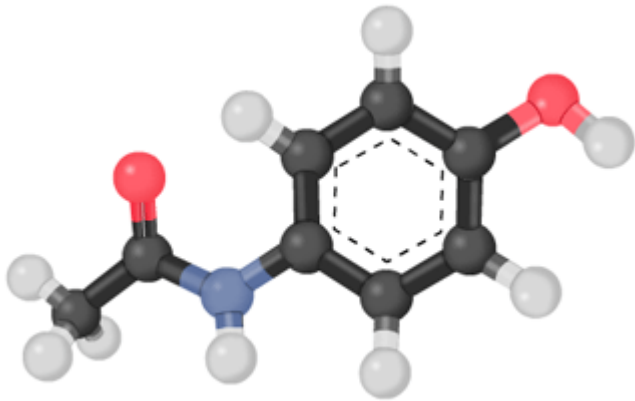
# ANALGESICS

# Analgesics

- Paracetamol, aspirin
- Other Non Steroid Anti Inflammatory Drugs
- Opioids
  
- Local anaesthetics
- Antidepressants
- Anti-epileptics
- Ketamine
- Clonidine

# NSAIDs - effects

- Antipyretic
- Anti-inflammatory
- Analgesic





1899

# Simple analgesics

- Antipyretic agents found in white willow bark and led to development of aspirin

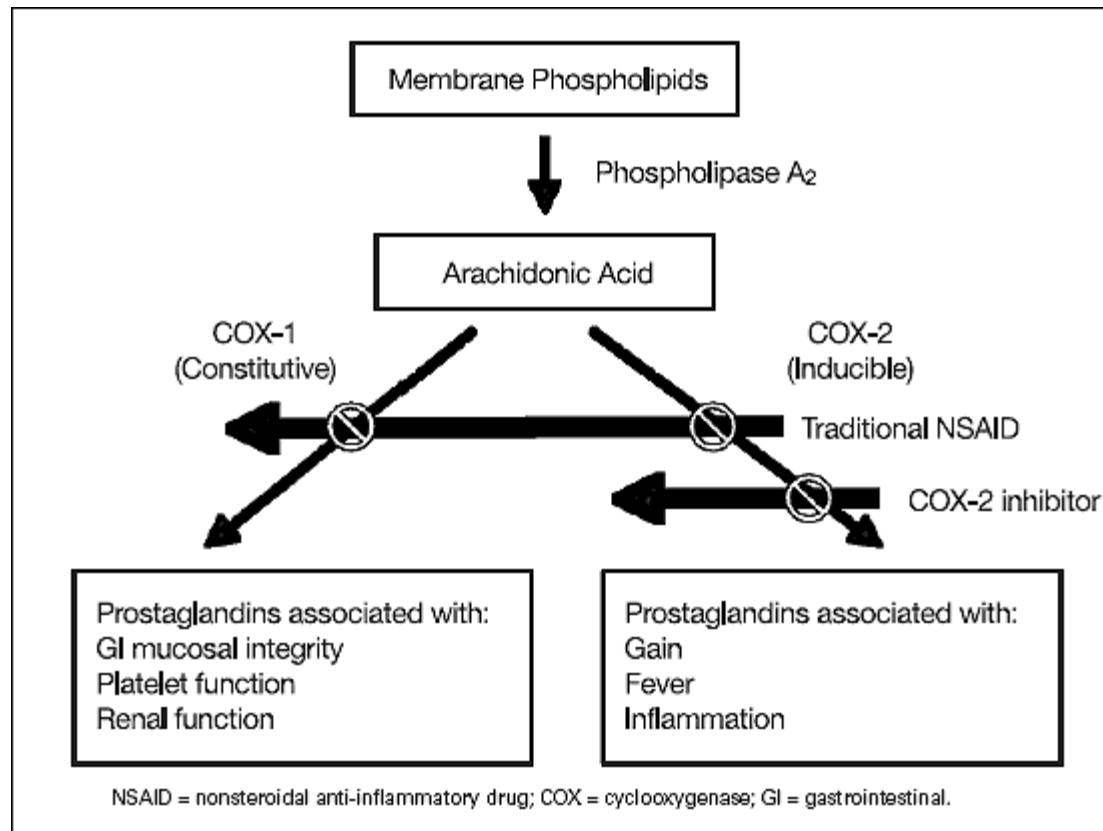


# Aspirin

- Anti-inflammatory agent in joint disease
- Cardiovascular – unstable angina
- Antiplatelet drug - prevention of stroke
- Radiation induced diarrhoea
- Alzheimer's disease

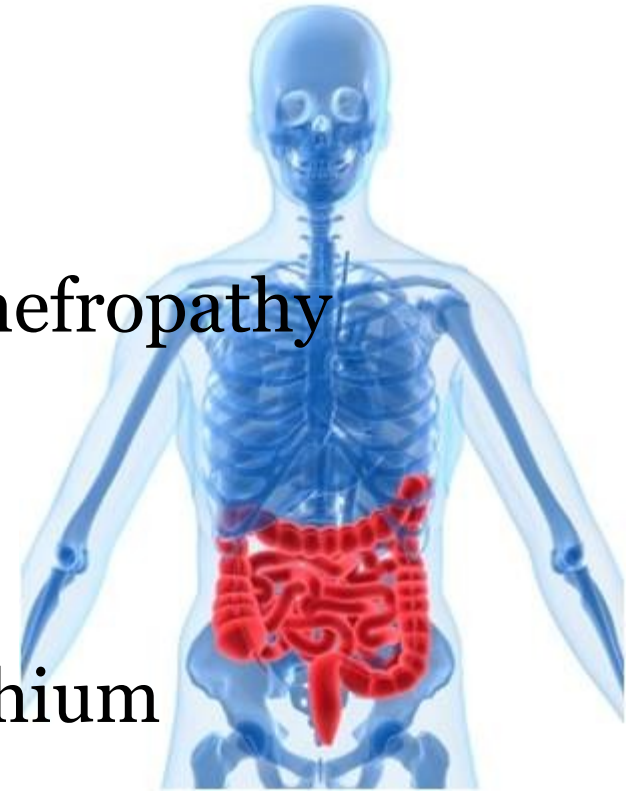
# NSAID - mechanism of action

- Inhibition of cyclo-oxygenase



# NSAID - side effects

- Gastric irritation
- NSAID sensitive asthma
- Renal dysfunction – analgesic nephropathy
- Antiplatelet function
- Hepatotoxicity
- Drug interaction – warfarin, lithium



## Simple analgesics

|                                | <b>Aspirin</b>              | <b>Paracetamol</b> |
|--------------------------------|-----------------------------|--------------------|
| <b>Chemistry</b>               | Acetic acid                 | Paraaminophenol    |
| <b>Mechanism of action</b>     | Inhibition of COX 1         | ? COX 3 inhib      |
| <b>Metabolism</b>              | Estrases in gut wall, liver | Liver              |
| <b>Toxicity</b>                | Hepatic/renal impairment    | GI upset           |
|                                | GI upset                    | Trombocytopenia    |
|                                | Rayes syndrome in kids      | Liver necrosis     |
| <b>Dose</b>                    | 300 – 900 mg every 6 h      | 1 g every 6 h      |
| <b>Route of administration</b> | orally                      | PO/PR/IV           |

# Other NSAIDs

- Ibuprofen – the lowest risk of GI upset
- Indomethacin, Diclofenac – mainly antiinflammatory effect
- Metamizole –Novalgin
- Aspirin and NSAIDs are not contraindicated for regional anesthesia

# SUMMARY - simple analgesics

- Aspirin, Paracetamol
- NSAID
- MOA – inhibition of COX
- Renal, gastric, hepatic side effects
- Can trigger NSAID sensitive asthma

# Opiods



- MORPHEUS- GREEK GOD OF DREAMS



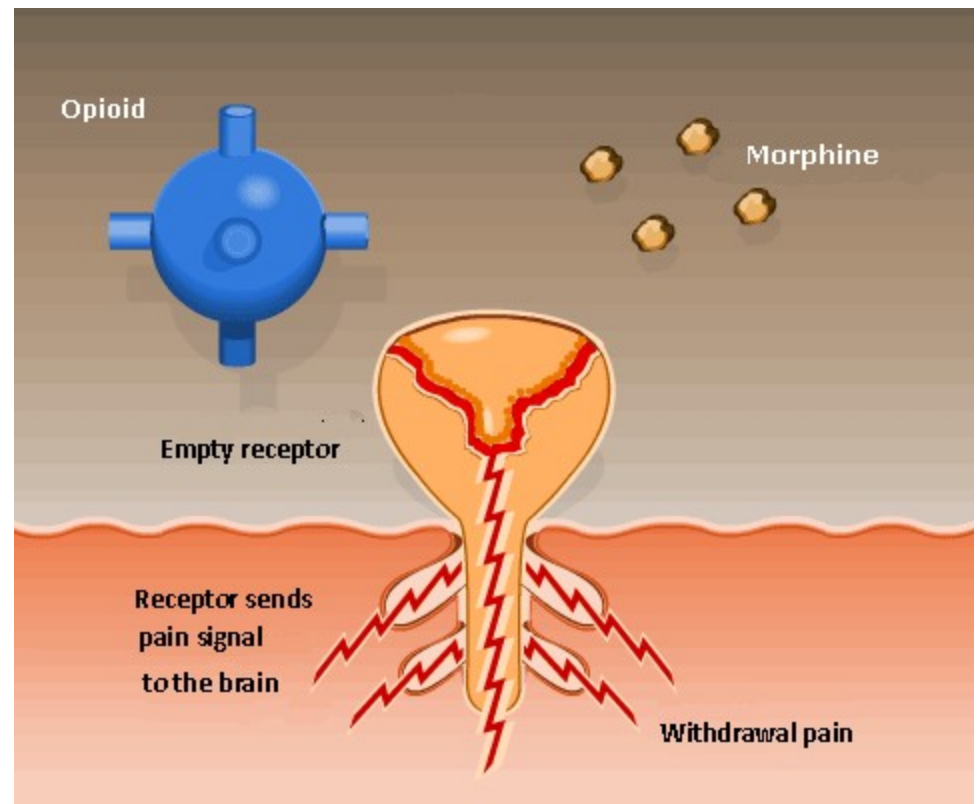
# Definitions

- **Opiate** : naturally occuring substance with morphine-like properties
- **Opioid** – synthetic substance
- **Narcotic** – from greek word ‘numb’

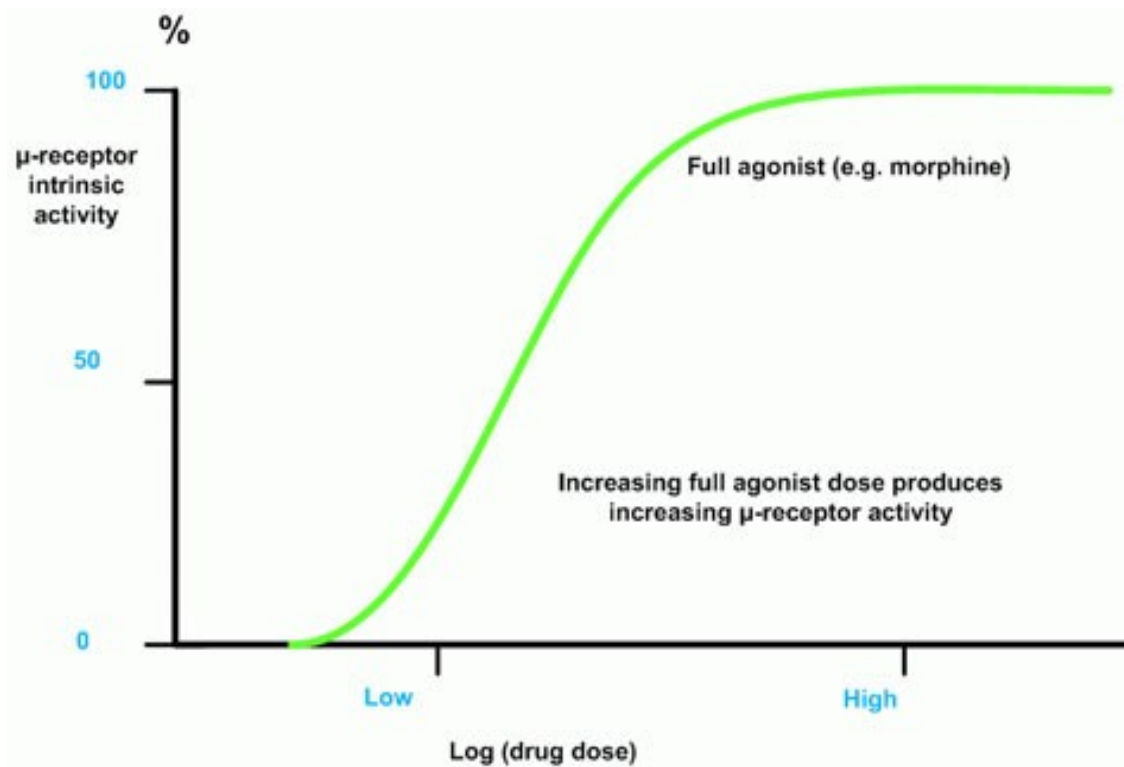


# Opioids - mechanism of action

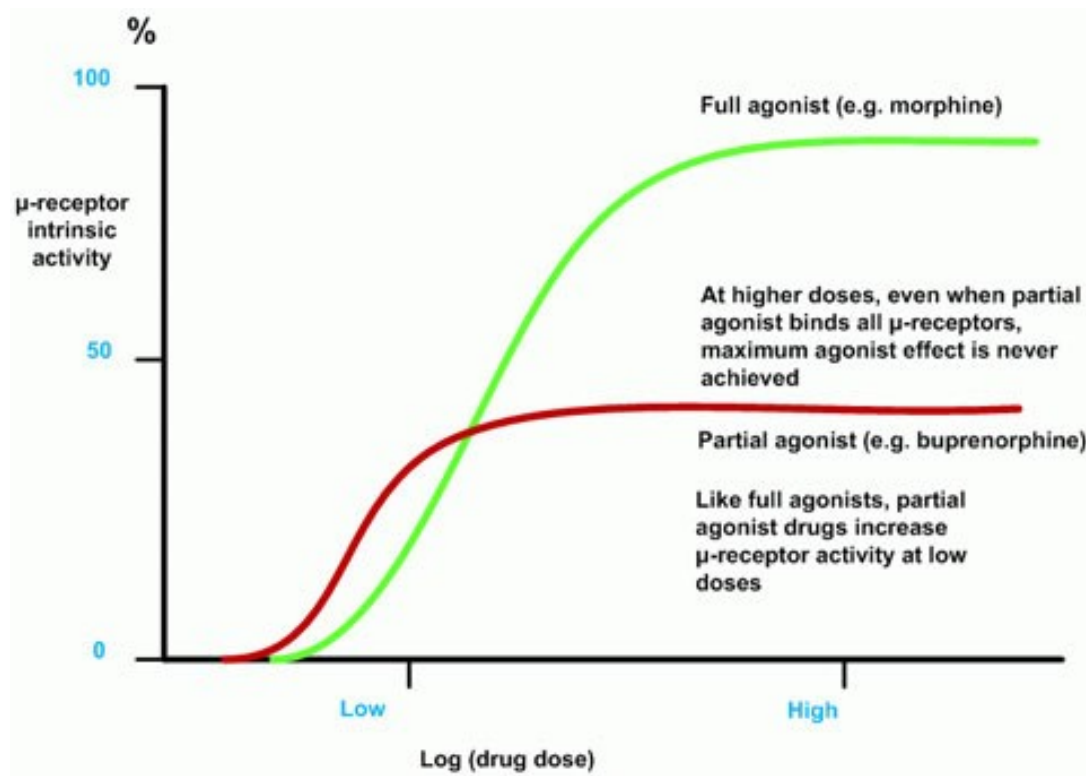
- Via opioid receptors
  - $\mu$  - receptor
  - $\kappa$  - receptor
  - $\delta$  - receptor



# Opioids - dose - response curve



# Opioids - dose - response curve

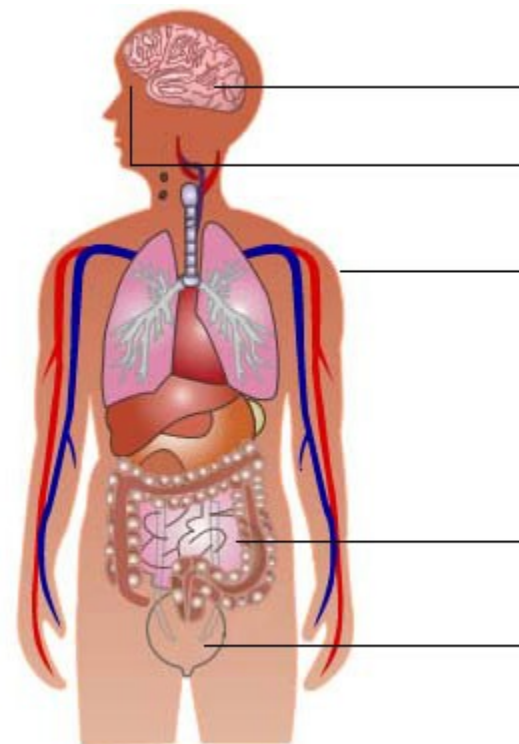


# Uses and routes of administration

- Analgesics
- Anti - tussive
- Anti – diarrhoea
  
- Intravenously
- Intramuscularly
- Oral, Buccal, rectal
- Transdermal - Patches
- Epidural/intrathecal

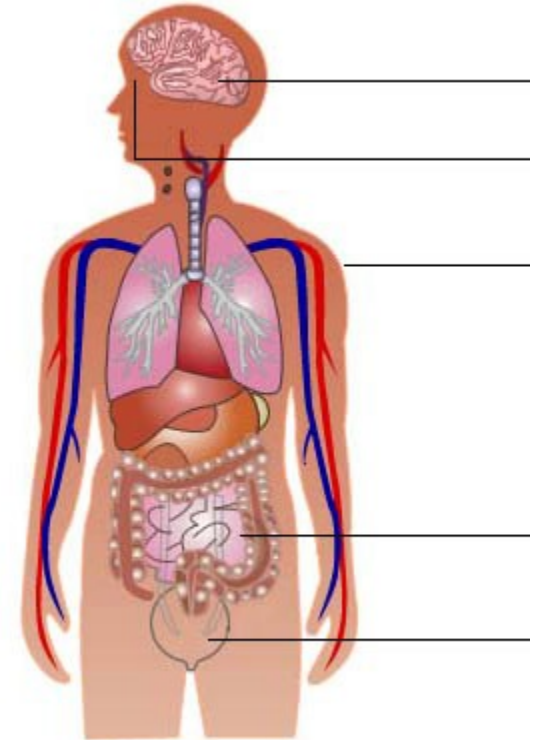
# Opioids - effects

- Brain:
  - Analgesia, sedation
  - Respiratory depression
  - Euphoria and dysphoria
  - Addiction, tolerance
  - Nausea and vomiting
- Eyes
  - Meiosis
- Cardiovascular system
  - Hypotension, bradycardia



# Opioids - effects

- Respiratory system
  - Anti tussive effect
- GI tract
  - spastic immobility
- Skin
  - Pruritus – histamine release
- Bladder
  - Urinary retention



## Commonly used opiods

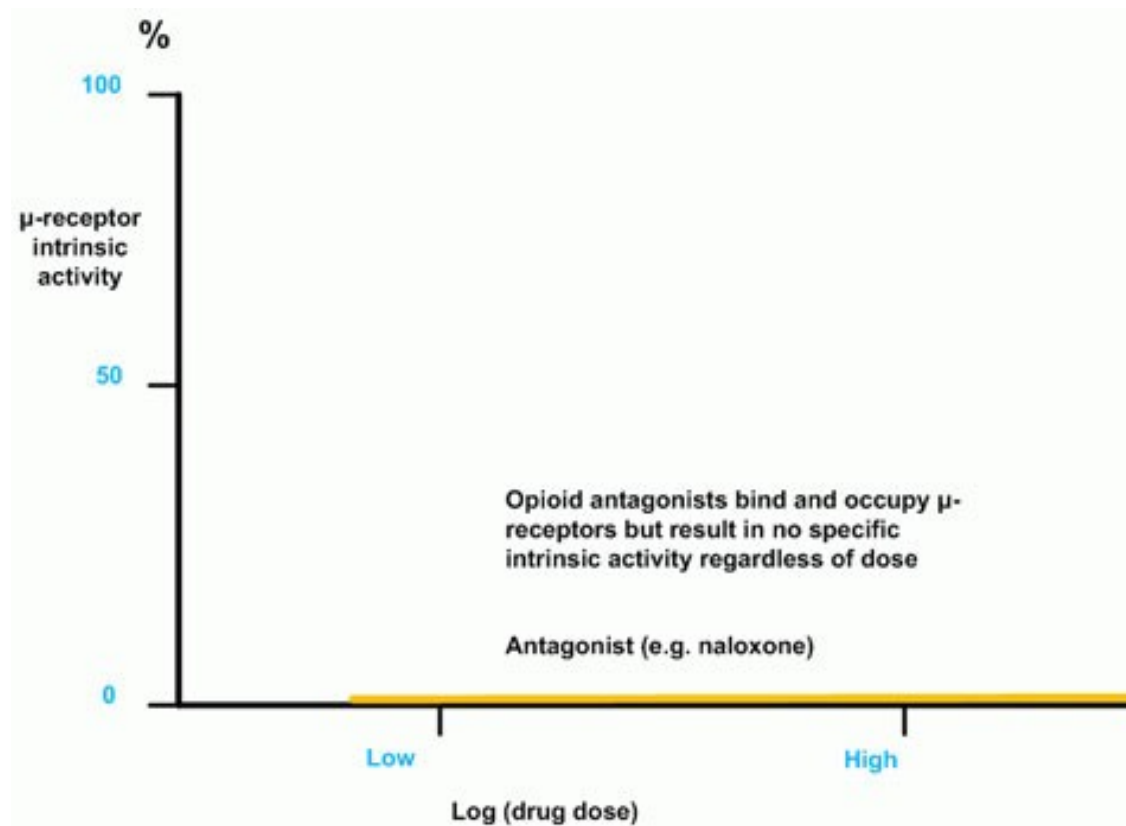
|                     | Dose              | Elimination<br>1/2 life | Metabolism                        | Comment   |
|---------------------|-------------------|-------------------------|-----------------------------------|---|
| <b>Sufentanyl</b>   | 0.1 µg/kg         | 50 min                  | liver                             | Faster onset<br>then fentanyl                               |
| <b>Fentanyl</b>     | 1-2 µg/kg         | 190 min                 | liver                             | Neurosurgery,<br>patches                                    |
| <b>Alfentanyl</b>   | 5 – 25 µg/kg      | 100 min                 | liver                             | Faster onset<br>then<br>sufentanyl                          |
| <b>Remifentanyl</b> | 0.05 – 2<br>µg/kg | 10 min                  | Plasma and<br>tissue<br>esterases | Infusion only,<br>very short<br>context sensit.<br>1/2 life |



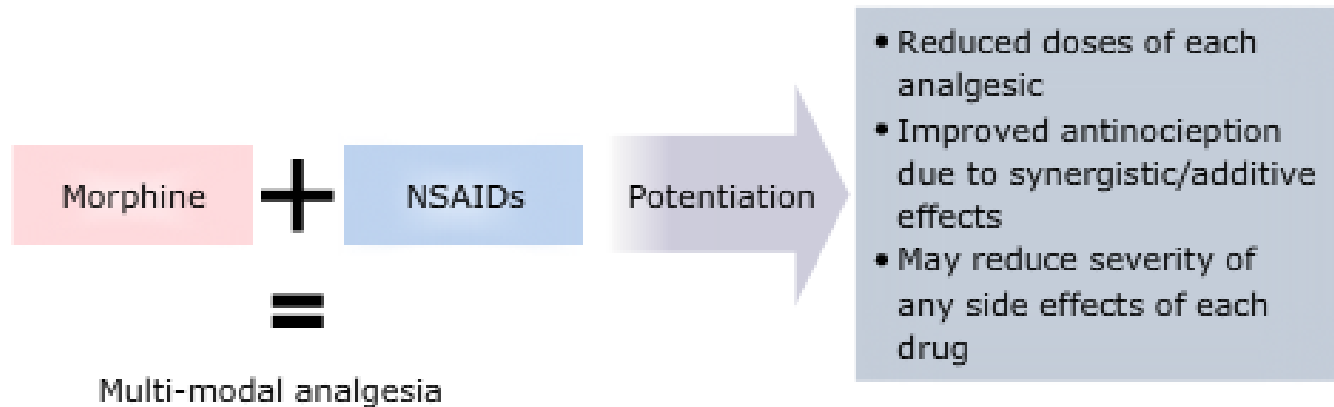
# Naloxone

- Pure opioid antagonist at  $\mu$ ,  $\delta$  and  $\kappa$  - receptors
- Used in opioid overdose
- Dose : 1- 4  $\mu\text{g}/\text{kg}$
- Duration of action 30 – 40 min
- ! Often shorter than duration of action of opioid, need for repeated doses

# Naloxone - dose - response curve



# Multimodal analgesia



# SUMMARY - opioids

- Morphine, Fentanyl, Sufentanyl, Alfentanyl
- MOA – via opioid receptors
- Used for analgesia, anti – tussive, anti – diarrhoea
- Side effects : respir. depression, tolerance, constipation, nausea + vomiting
- Opioid overdose reversal – Naloxone
- Multimodal analgesia – simple analgesics + opioids

# SUMMARY

- Triad of anaesthesia
  - Analgesia
  - Anaesthesia
  - Muscle relaxation
- Choice depends on
  - Patient factors
  - Type of surgery
  - Whether the surgery is elective or emergency

# Questions ?

