Local anaesthetics, general anaesthetics, major/narcotic analgesics

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General anesthesia

- Purpose: to reversibly switch off:
  - sensoric/motoric/vegetative reflexes
  - nociception,
  - awareness, consciousness.

- Its main components:
  - analgesia
  - amnesia (anterograde, retrograde)
  - muscle relaxation (immobility)
  - hypnosis (unconsciousness)
  - reduction/attenuation of sensory/autonomic functions (stability!)

General anesthesia

- Main periods/phases of anaesthesia:
  - premedication
  - anesthesia induction
  - anesthesia maintenance
  - recovery (= regaining consciousness)
  - postoperative

General anesthesia

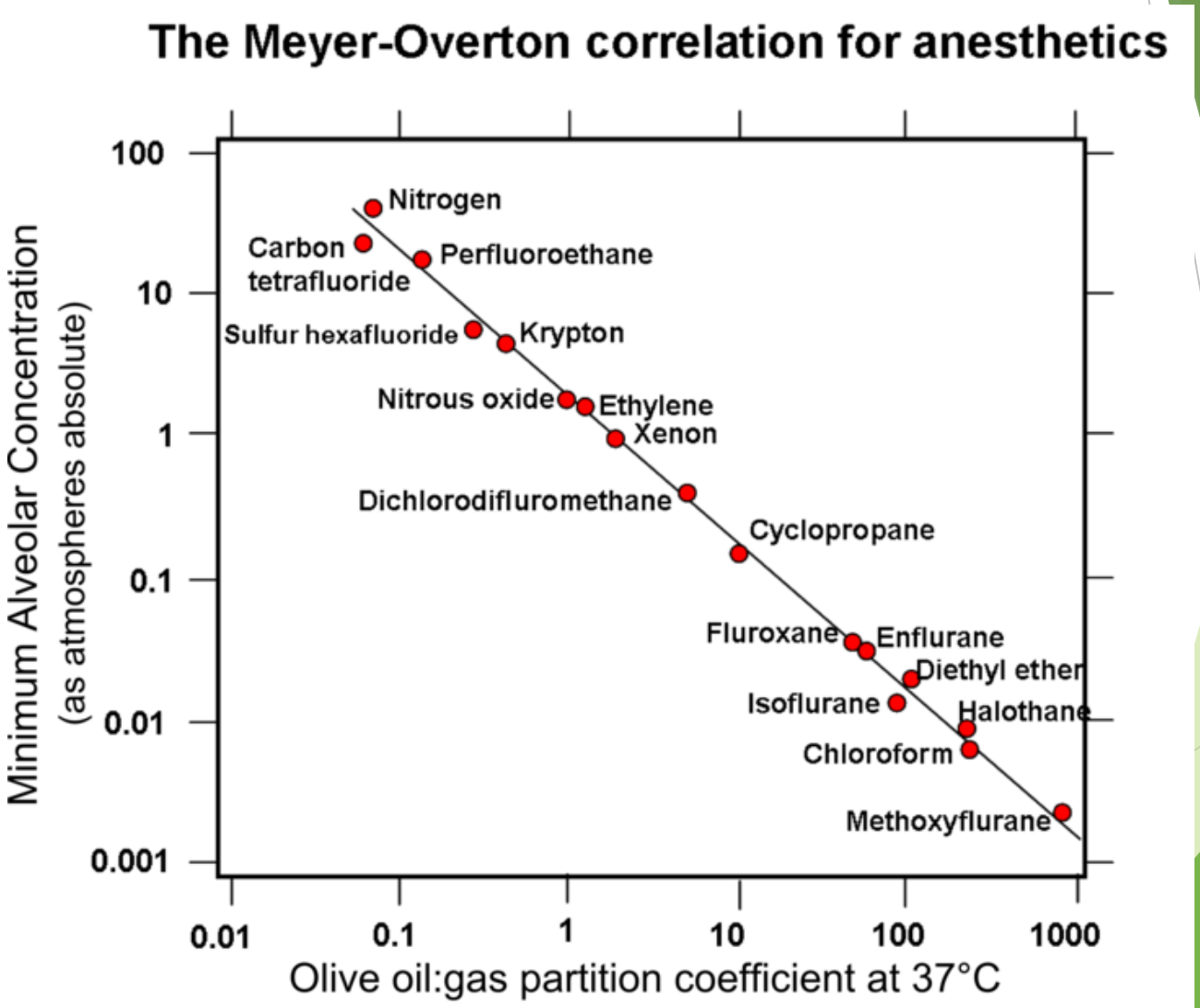
- History:
  - ancient Egypt: morphine, scopolamine
  - medieval ages: ethanol
  - 1842 –Henry Morton – diethyl ether
  - 1845 – Horace Wells - N_2O
  - 1847 – James Simpson – chloroform
  - 1935 – Lundy – barbiturates (thiopental)
  - 1956 – halothan
  - 1960 – benzodiazepines, etc (TIVA)

Drugs used in anesthesia

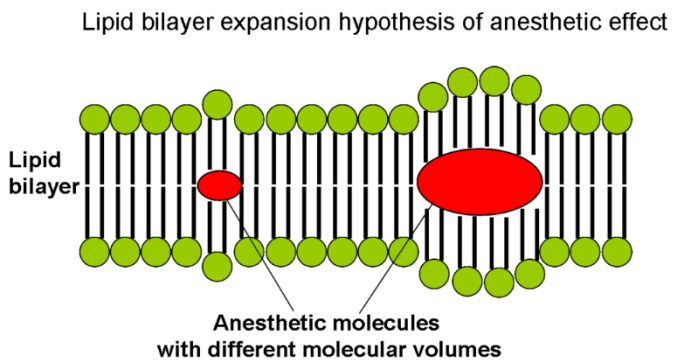
- **narcotics (anesthetics)**
  - intravenous narcotics
    - benzodiazepines
    - barbiturates
    - ethomidat
    - ketamin
    - propofol
  - inhalational narcotics
    - gasous narcotics
      - N_2O
    - volatile narcotics
      - halothan
      - sevofluran
      - enfluran
      - isofluran
- **maior analgetics**
  - fentanyl, sufentanyl
  - morphin
  - pethidin (meperidin)

- **muscle relaxants**
  - non depolarizing muscle relaxants
    - pancuronium
    - mivacurium
  - depolarizing muscle relaxants
    - succinyl-choline

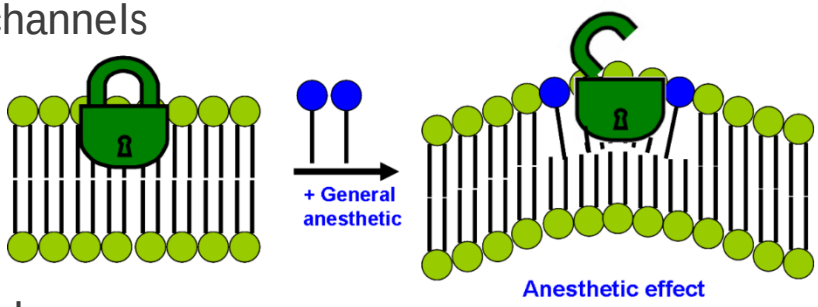
Theories for anaesthetic action



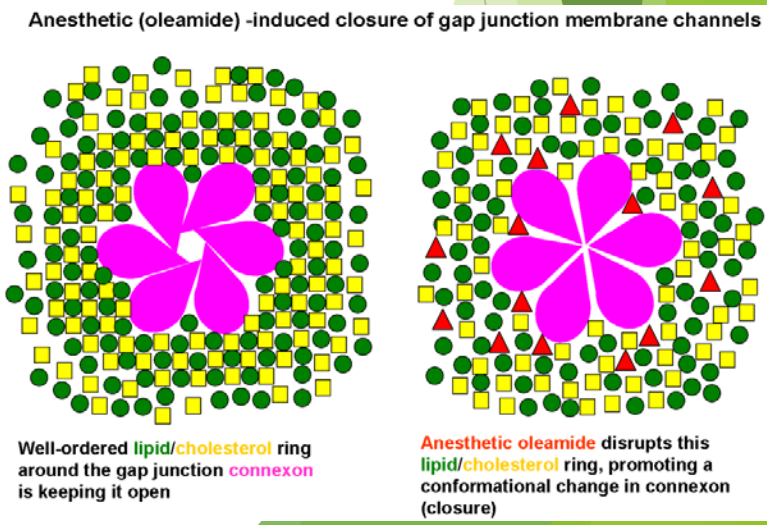
Theories for anaesthetic action



- Meyer-Overton lipid theory/expansion hypothesis
  - hydrophobic anaesthetics ➔ accumulate inside lipid membrane ➔ causing its distortion and expansion (thickening) (due to volume displacement) ➔reversibly alter function of membrane ion channels = anaesthetic effect.



- Modern lipid hypothesis
  - General anaesthetic changes membrane lateral pressure profile which determines conformation of membrane ion channel (green lock)
  - They may increase membrane fluidity, which may open/close ion channels



- Membrane protein hypothesis
  - general anaesthetics may also interact with hydrophobic protein sites of certain proteins most likely ion channels

General anesthesia

- **Mechanism of action of anesthetics:**
  - blocking VG Na^+ channels
    - general and local anaesthetics as well
    - BUT: no i.v. application of lidocain, procain
  - blocking T and L-type Ca^{2+} channels
  - NMDA R blocking (glutamate gated cation channels)
    - $Ca^{2+}\downarrow$
  - $GABA_AR$ agonism – (agonist vs. allosteric modulator)
    - inhaled narcotics
    - intravenous narcotics (BDZ, barbiturates)
  - mAChR blocking
    - halothan, isofluran, sevofluran

- **Sites of action:**

brain stem (formatio reticularis) – suppression of cardiovasc./respir. system, hypnoid effects, loss of consciousness

hyppocampus – amnesia, loss of awareness/consciousness

premotor cortex/spinal cord – muscle relaxant effect, reflexes↓

sensory cortex, thalamus, spinothalamic tract - analgesia

General anesthesia

- **levels of narcosis (ether narcosis)**

1. level of analgesia (stage of analgesia)
   - narcosis induction → disappearance of regular ventillation
   - analgesia, amnesia, finally losing of awareness/consciousness, small surgical procedures can be carried out
2. level of excitement (stage of excitement)
   - losing of awareness → regular ventillation
   - muscle tone↑, BP↑, HR↑
   - reflex↑ = violent reactions, escaping; especially in alcoholists, hyperthyreotic patients, and in drug abuse
3. level of tolerance (stage of surgical anaesthesia)
   - surgical procedures are performed in this phase
   - regular ventillation → asphyxia
   - muscle tone↓, reflex↓
   - general anaesthesia
     can be further divided into 4 sub-stages (next slide)
4. level of asphyxia/paralysis (stage of medullary depression)
   - overdosage
   - BP↓ bradycardia

	Pupil	Respiration	Muscle-tone	Reflexes
I. Stadium analgesiae	Normal Reacts well to light	-	-	-
II. Stadium excitationis	Dilated Reacts well to light	Rapid	Increases	-
III. Stadium tolerantiae				
III/1	Narrow/ Moderately dilated Reacts to light	-	-	Conjunctiva-reflex Ø, weakened swallowing, vomiting, caughing
III/2	Moderately dilated Reacts to light	Marked decrease of chest breathing	Decreases Surgical procedures!	Cornea-reflex Ø
III/3	Dilated Reacts barely to light	Chest breathing ceases, diaphragmic breathing	Decrease in *Smooth muscle*-tone	Reflexory glottis-closure Ø
III/4	Dilated No reaction to light	From paralysis of intercostal muscles, respir-atory arrest	-	-
Stadium paralyticum	Glassy look Dilated No reaction to light	Total paralysis of respiration	-	-

Factors affecting Inhalational general anesthesia

- minimal alveolar concentration (MAC)
  - relative potency
  - intraalveolar narcotic concentration (MAC_{50})
  - modified MAC: MAC_{EI50}

- Blood solubility (blood : alveolar gas partition coefficient)
  - low – rapid onset
  - high - slow onset

- Lipid solubility „1” (lipid : gas partition coefficient) – lipid hyptothesis/theory
  - high - fast onset
  - low - slow onset

- Lipid solubility „2” (fat : blood partition coefficient) – accumulation in fat
  - high: slow recovery
  - low: fast recovery

- „Brain solubility” (brain : blood partition coefficient)
  - high: rapid onset
  - low slow: onset

- Anaesthetic concentration in the inspired air (inhalational concentration)
  - Ficks’s law

- Pulmonary ventillation
  - anesthesia induction

Factors affecting the bioavailability of inhalational anaesthetics

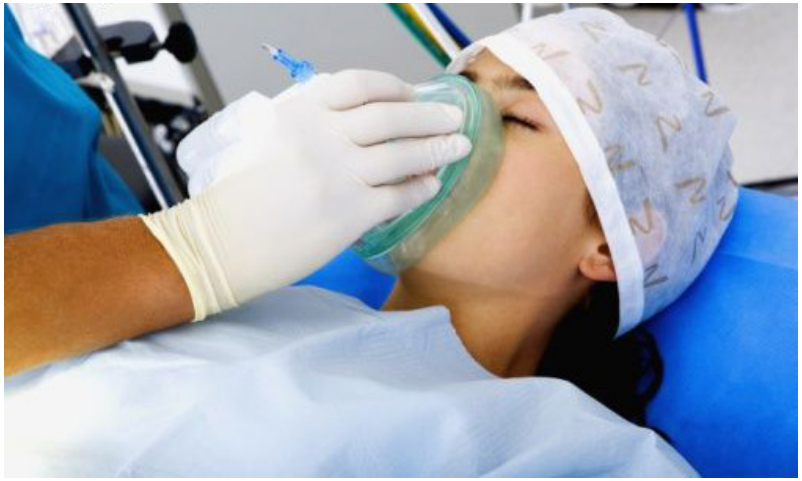
1. Partial pressure of anaeasthetic in mixture breathed
2. Alveolar ventillation (= respiratory minute volume)
3. Crossing of inhalational anaesthetic from the alveoli of lungs into the blood (= Condition of cellmembranes in the alveoli of the lungs)
4. Difference in venous and arterial partial pressure of anaesthetic (distribution in blood)
   (= cardiac output)
5. Crossing of anaesthetic through the blood-brain barrier (= Condition of cellmembranes in the tissue of the brain)
6. Solubility of anaesthetic in the blood/brain/fat (see former slide)
7. Age, individual sensitivity

General anaesthesia

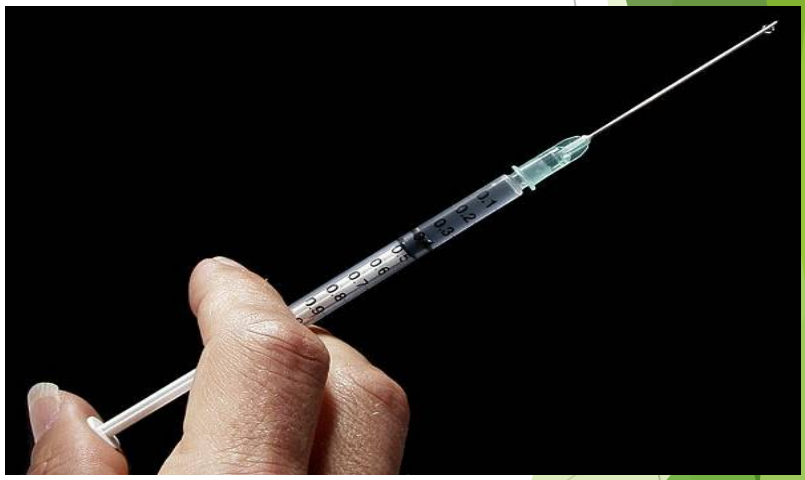
- Hazards in anaesthesia:
  - nausea, vomiting
  - aspiration (asphyxia, Mendelsohn's syndrome (=aspirational pneumonia))
  - hypotension (collapse of circulation)
  - negative inotropic effects
  - suppression of respiration
  - allergic reactions
  - hepatotoxic effects

General anesthetics

Inhalational anesthetics



Parenteral anesthetics



Inhalational narcotics

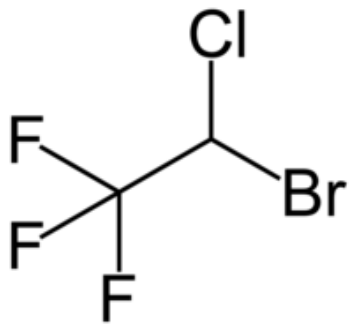
- N_2O (dinitrogene-oxid) – „laughing gas”
  - 25% O_2, 75% N_2O
  - low blood solubility (rapid narcosis induction)
  - rapid absorption from lungs (second gas effect) – advantage in anesthesia induction
  - diffusion hypoxia
    - O_2 displacement – relative hypoxia (at recovery)
  - Mechanism of effect:
    - stimulation of opioid neurons in limbic area
  - indication: analgetic effect
    - „demand mask”– analgesia at labour
  - adverse effect: > 6 h – methionine synthase inhib.→anaemia, leukopenia
  - contraindications: ileus, PTX – pressure rises in closed body cavities

Nitralgin: 50% N_2O; 50% O_2

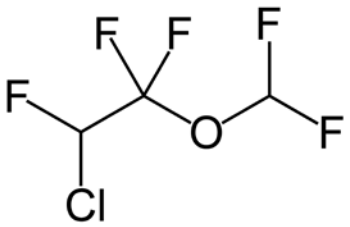
- ether
  - fluid at room temperature
  - „vitrum fuscum”
  - potent muscle relaxant effect
  - BP↑ (indirect sympathomimetic effect)
  - Obsolete

Inhalational narcotics

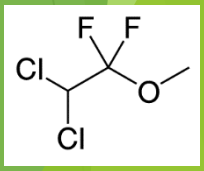
- halothan
  - halogenated compound, low cost
  - high blood solubility – slow induction
  - high lipid : blood partition coefficient – slow recovery
  - stimulation of CNS and n. vagus
    - bradycardia
    - hypotension
  - tocolysis (never appl. during delivery!!!)
  - bronchodilation
  - adverse effects:
    - arrhythmia (sensitization of myocardium to catecholamines – contraindications: pheochromocytoma)
    - halothane hepatitis
      - 1/100.000
      - trifluoracetate (metabolite)
      - in case of repeated exposure
    - malignant hyperthermia
      - excessive Ca^{2+} release
      - hyperpyrexia, convulsions, hypertonia, DIC, arrhythmia
      - therapy: danthrolen



- enflurane
  - halothan's alternative
  - similar pharmacokinetic features
  - metabolism: proconvulsive metabolites!
  - adverse effects: epileptiform convulsions

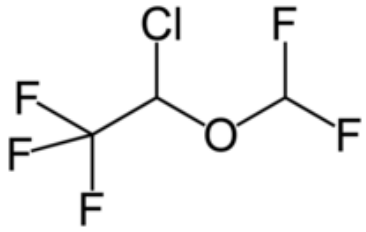


- methoxyflurane
  - no tocolysis – obstetrics!
  - metabolism: fluoride - nephrotoxic effect (chronic renal failure, diabetes insipidus)

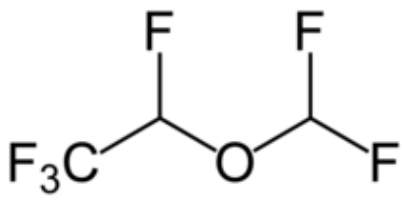


Inhalational narcotics

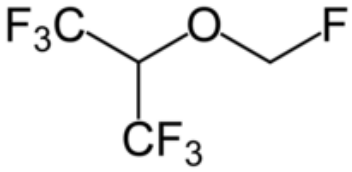
- isoflurane
  - low blood solubility (faster induction)
  - commonly used
  - arterial vasodilation
    - hypotonia
    - coronary steal effect (contraindic.: myocard. ischaemia)



- desflurane
  - low blood solubility (fast induction), low lipid : blood partition coefficient (fast recovery) ➔
  - ➔ „one day surgery”
  - struct. resemblence to isoflurane
  - airway irritation, broncho/laryngospasm (not used for induction)



- sevoflurane
  - low blood solubility, low lipid solubility
  - reduced adverse effect profile
  - CO formation (when CO_2 absorber is dehydrated in breathing machine)



Intravenous narcotics

- Classification
  - barbiturates (thiopental - Trapanal®)
  - ethomidate
  - propofol (Diprivan®)
  - BZD (midazolam - Dormicum ®)
  - ketamine (Calypsol ®)

- Barbiturates
  - thiopental
    - ultrarapid/ultrashort effect (20 sec./10-20 min.)
    - high lipid-solubility– repeated administration - accumulation!
      - only for induction!
    - respiratory depression
    - cardiovascular depression
    - indications:anticonvulsive effect,
    - adverse effects: in case of porphyria ➔ fatal attacks can be induced reason: induces ALA synthase

Intravenous narcotics

- etomidate
  - rapidly metabolised
  - no cardiovascular depression
    - Indication:
      In Acute Coronary Syndrome, in Left Ventricular Fibrillation (in patients with limited cardiovascular reserve)
  - chr. application→ suppresses adrenal cortex ➔ contraindicated in acute adrenal failure
  - dose: 0,3 mg/kg
- propofol
  - commonly used for anesthesia induction/maintenance
  - no accumulation – rapid metabolism→long term use
  - Blood pressure↓, has negative inotropic effect
  - dose: 2mg/kg
- ketamin
  - structural resemblence – phencyclidine (hallucinogenic)
  - Mechanism of effect: non-competitive NMDA antagonist, AMPA-agonist, D2-rec part. agonist, opioid rec. agonist, 5HT2A-rec agonist
  - dissociative anesthesia: amnesia, analgesia, but! intact consciousness
  - euphoria, hallucinations, nightmares (esp. in children)
    - supportive th.: BZD!
  - HR↑, BP↑, positive inotropic effect
  - ICP↑
  - analgetic effect:0,5 mg/kg
  - anesthesia ind.: 2 mg/kg

In low dose: $GABA_A$-PAMs
In high dose: $GABA_A$-agonists

Clinical phases of anesthesia

- Preoperative
  - premedication
    - anti-acid therapy (H_2R block, PPI)
    - PONV (postoperative nausea&vomiting) (metoclopramide, „-setron”s)
    - preoperative anxiolysis (diazepam i.m./p.o.)
    - cholinolytics/parasympatholytics
      - to decrease secretion
      - to prevent bradycardia

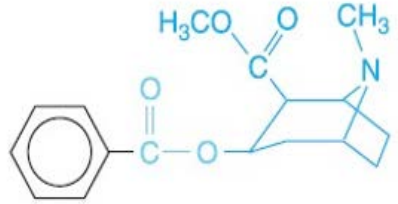
- Intraoperative phase (anaesthesia induction/maintenance, recovery)
  - iv. anaesthesia (TIVA =total intravenous anaesthesia)
  - inhalational anaesthesia (avoid irritative narcotics)
  - balanced anaesthesia
  - + opioid analgetics, muscle relaxants

- Postoperative phase
  - ANTIDOTUM (flumazenil, naloxon, neostigmin/physostigmin)
  - O_2
  - ChE blocking drugs

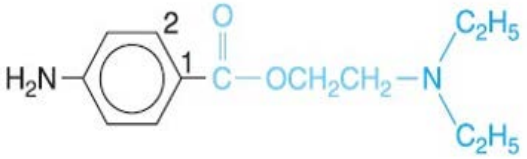
Local anesthetics

Structure of Local anesthetics

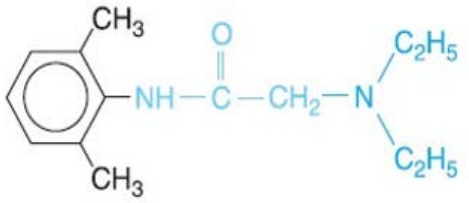
- Structure:
  - Esters: cocaine, procaine, tetracaine
  - Amides: lidocaine, bupivacaine, ropivacaine
  - hidrophobic structure (internal binding place of $VGNa^{+}$ channels)



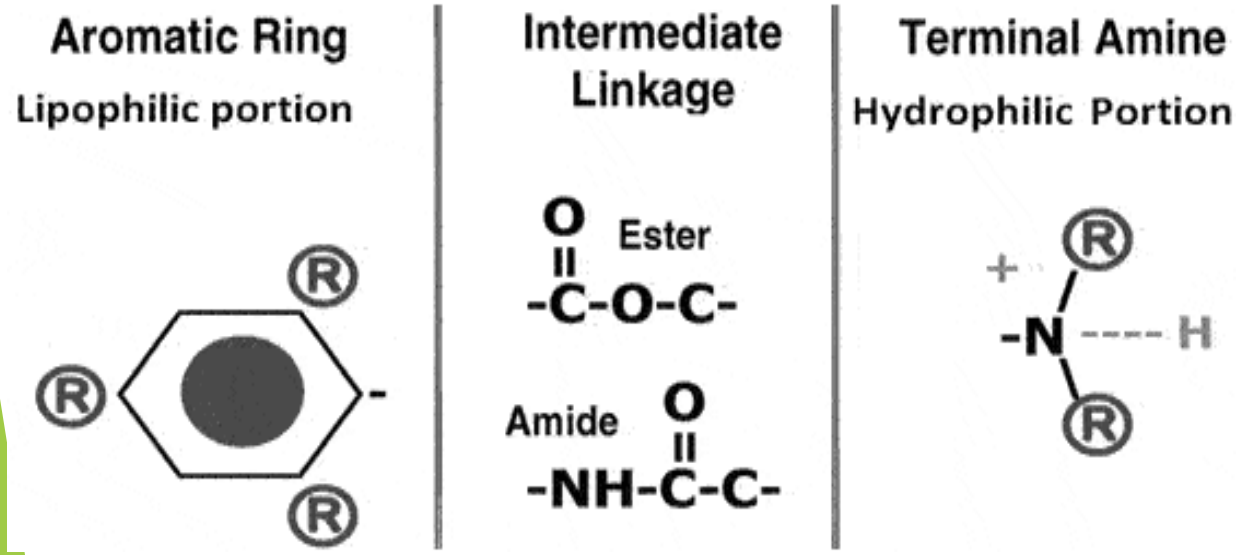
COCAINE



PROCAINE



LIDOCAINE



Classes: The rule of “i”

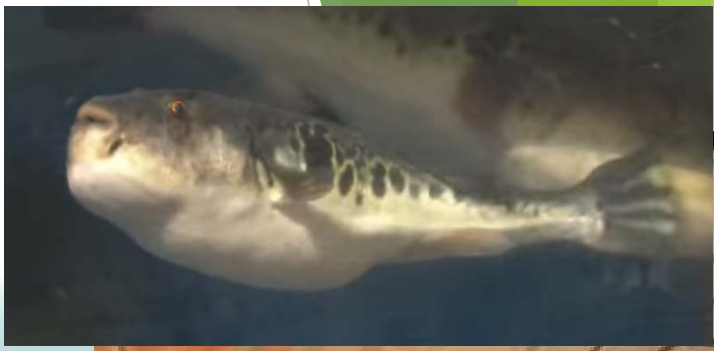
- Amides
  - Lidocaine
  - Bupivacaine
  - Levobupivacaine
  - Ropivacaine
  - Mepivacaine
  - Etidocaine
  - Prilocaine
- Esters
  - Procaine
  - Chloroprocaine
  - Tetracaine
  - Benzocaine
  - Cocaine

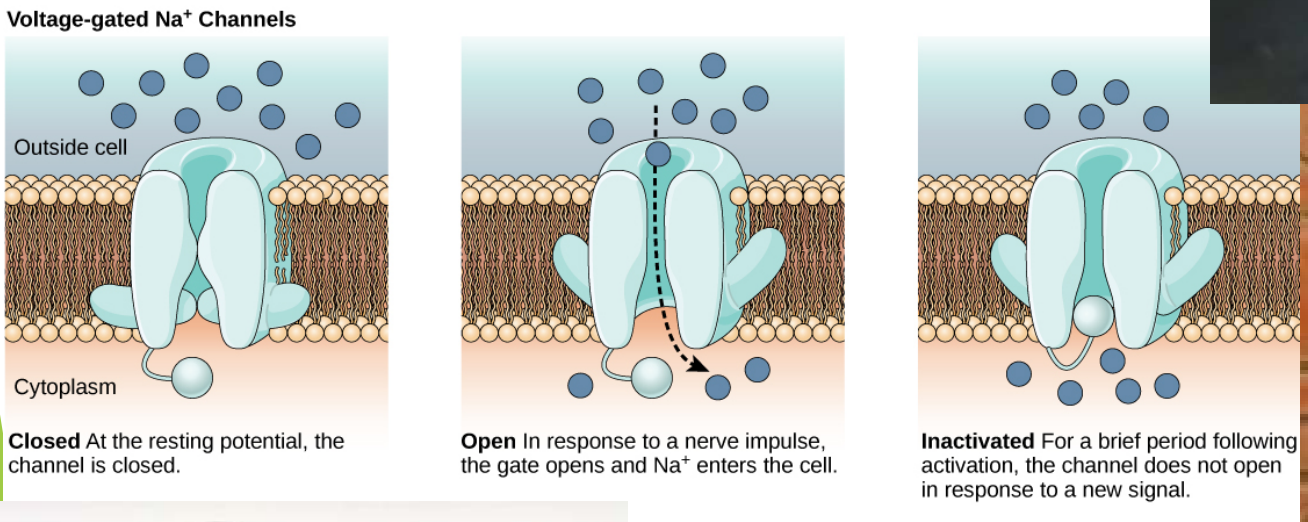
Potency, pK_a, Lipophilicity

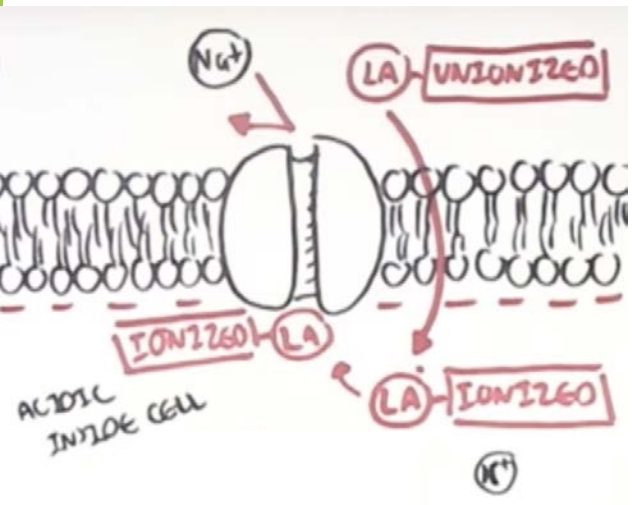
Drug	pK_a	Octanol/H2O
Low Potency		
Procaine	8.9	100
Intermediate potency		
Mepivacaine	7.7	130
Prilocaine	8.0	129
Chloroprocaine	9.1	810
Lidocaine	7.8	366
High potency		
Tetracaine	8.4	5822
Bupivacaine	8.1	3420
Etidocaine	7.9	7320
Ropivacaine	8.1	
Levobupivacaine	8.1	3420

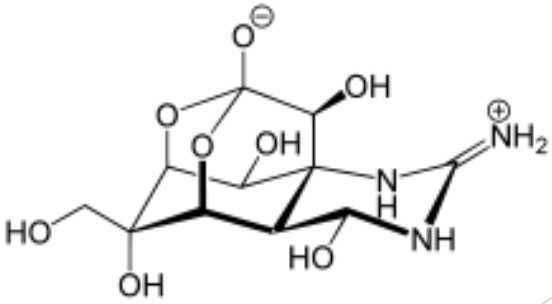
Mechanism of action of Local anesthetics

- Mechanism of action:
  - blocking VG Na^+ channels (from the inside)
  - use-dependent, voltage dependent effects
  - + adrenaline









tetrodotoxin

Susceptibility of nerves to Local anesthetics

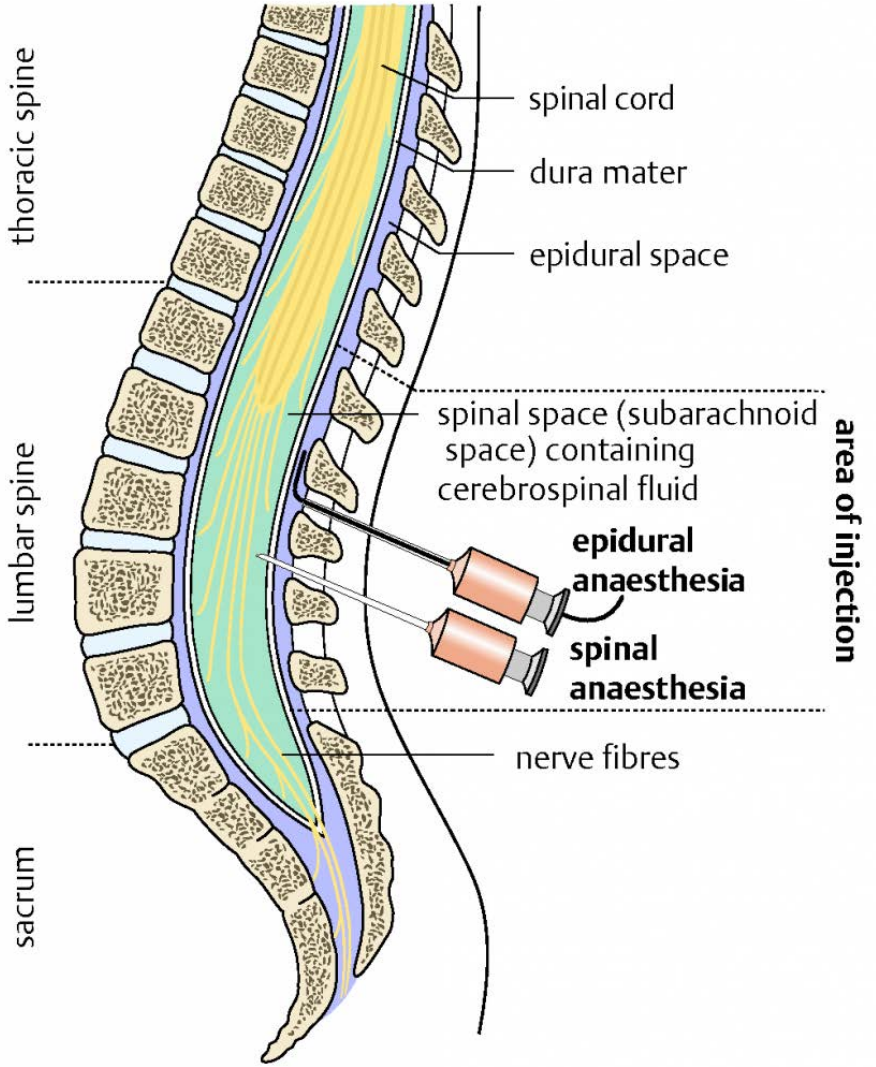
Table 14–1

Susceptibility to Block of Types of Nerve Fibers

Conduction Biophysical Classification	Anatomic Location	Myelin	Diameter (μm)	Conduction Velocity (m/sec)	Function	Clinical Sensitivity to Block
A fibers						
A α	Afferent to and efferent from muscles and joints	Yes	6–22	10–85	Motor and proprioception	+ ++
A β						
A γ	Efferent to muscle spindles	Yes	3–6	15–35	Muscle tone	++
A δ	Sensory roots and afferent peripheral nerves	Yes	1–4	5–25	Pain, temperature, touch	+++
B fibers	Preganglionic sympathetic	Yes	<3	3–15	Vasomotor, visceromotor, sudomotor, pilomotor	++++
C fibers						
Sympathetic	Postganglionic sympathetic	No	0.3–1.3	0.7–1.3	Vasomotor, visceromotor, sudomotor, pilomotor	++++
Dorsal root	Sensory roots and afferent peripheral nerves	No	0.4–1.2	0.1–2	Pain, temperature, touch	++++

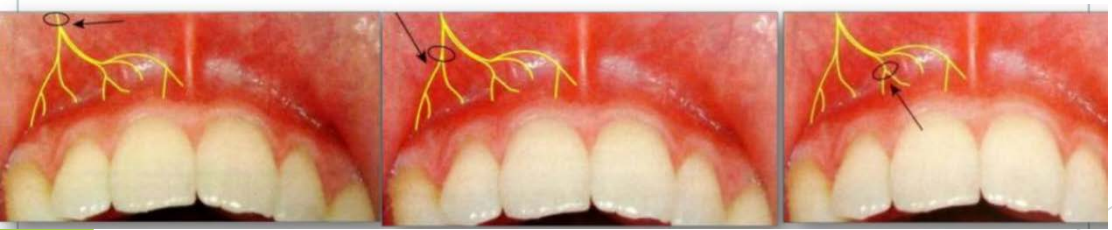
Indications of Local anesthetics

- Clinical use:
  - infiltrational anesthesia
  - nerve blockade
  - epidural anesthesia
  - spinal anesthesia

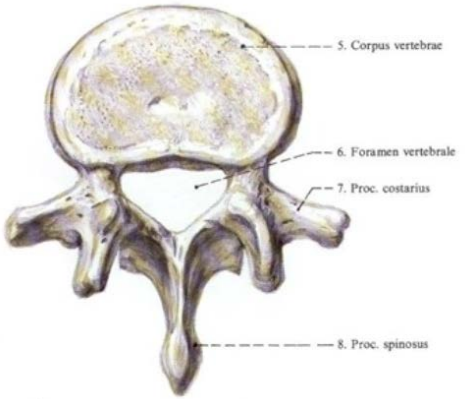


Types of Injection Procedures:

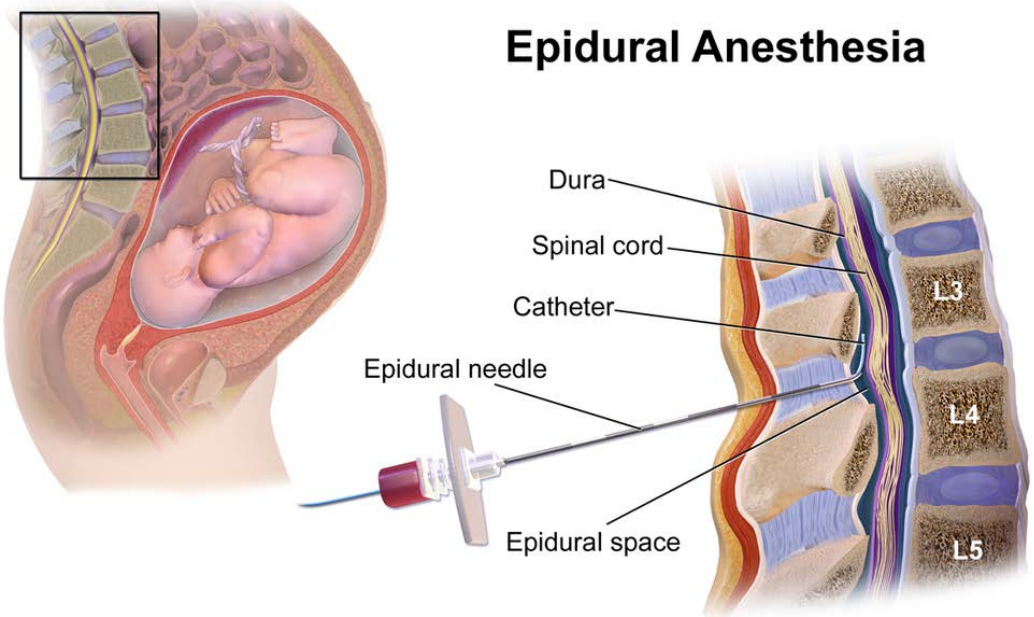
1. **Nerve block:** depositing the LA solution within close proximity to a main nerve trunk.
2. **Field block:** depositing a in proximity to the larger nerve branches.
3. **Local infiltration:** small terminal nerve endings are anaesthetized.

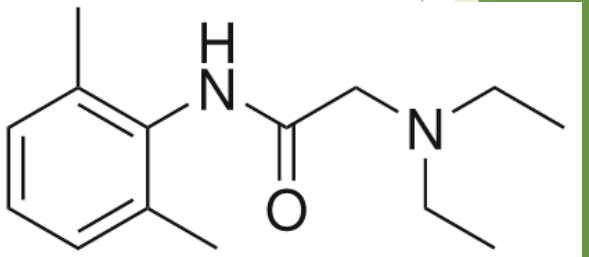


Epidural anaesthesia

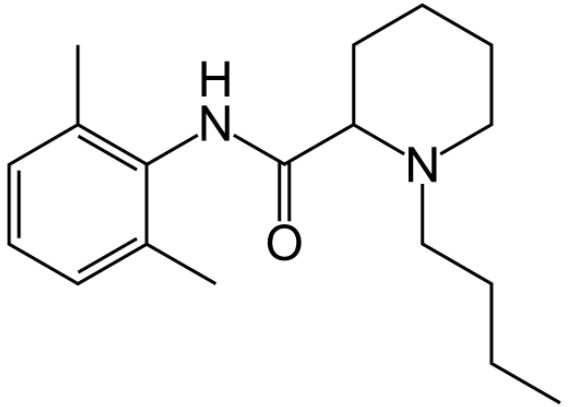


- Informed consent
- After 2 finger wide open cervix
- L2-L3, or L3-L4 vertebral space, G18 gauge needle
- Placing needle orifice at the epidural space by loss of resistance technique (physiologic salt solution)
- 2 ml 1% Lidocain test dose, then leg movement tested
- 10 ml 0,25% Marcain (bupivacain) (II.phase)
- 10 ml 0,125% Marcain (III.phase)





lidocain



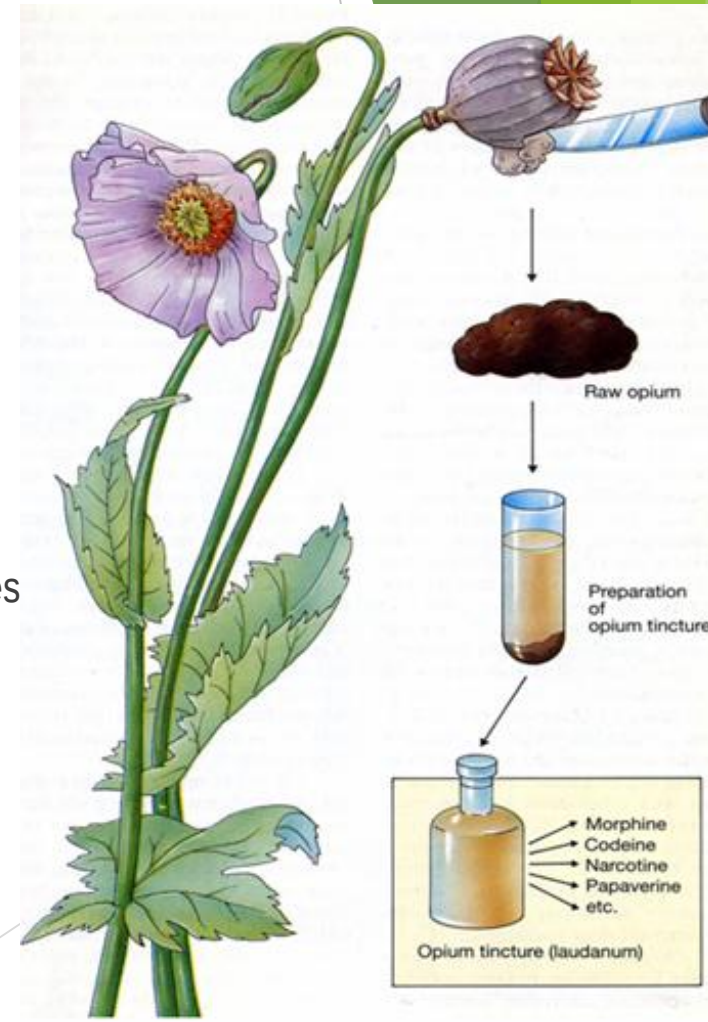
bupivacain

Epidural anaesthesia 1:18 – 3:40

Major/narcotic analgesics

Opioids

- Opioid drugs are used primarily for **the treatment of pain** (mostly chronic)
- Some of the CNS mechanisms that reduce the perception of pain also **produce a state of well-being or euphoria**
- Opiods/opiates are derivatives of morphine extracted from Opium poppy plant (Papaver somniferum) (from opium and poppy straw)
  - Opium (also called "raw opium") is the latex harvested by making incisions on the green capsules (seed pods).
  - Poppy straw is the dried mature plant except the seeds, harvested by mowing.



History

Opium has been used for social and medicinal purposes for thousands of years as an agent to **produce euphoria, analgesia and sleep, and to prevent diarrhoea**.

- It was introduced in Britain at the end of the 17th century, usually taken orally as '**tincture of laudanum',**
- 19th century: **opium wars** (England and China)
- 20th century – discovery of receptors, partial agonists, antagonists, endogenous opioid peptides (endorphines)

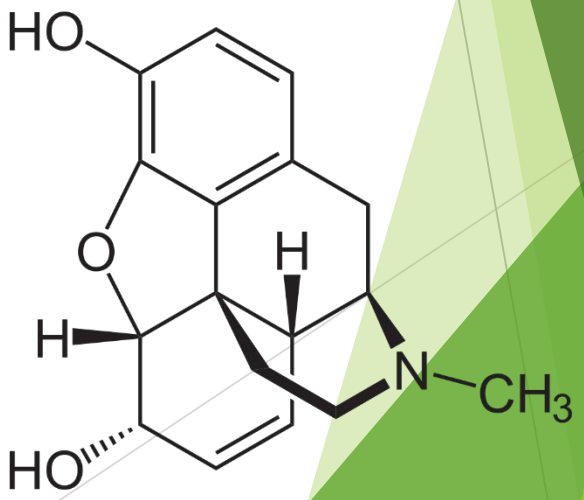
Major (Opioid) analgetics

History:

- opium (opos:"juice"), opiate, opioid
- obtained from"opium poppy" (Papaver somniferum)
- white substance→brown gum = OPIUM
- OPIUM contains alkaloids e.g.: morphine, narcotine, papaverine, etc.

Chemical structure:

- phenantrene derivative
- termed after Morpheus (God of dreams)
- two planar and two aliphatic rings
- N connected substitutive groups



morphine

Classification

- endogenous opioids
  - endorphins
  - enkephalins
  - dynorphins
- naturally occuring (morphine, codein, narcotin)
- semisynthetic (heroin, hydromorphone, oxycodone)
- synthetic (fentanyl, meperidine, methadon)

- based on chemical structure
  - phenantrenes
    - morphine, codeine, oxycodone
  - phenylheptylamines
    - methadone
  - phenylpiperidines
    - diphenoxylate, loperamide
    - fentanyl

Opioid receptors

μ R (MOR)
- cortex
- ventral/caudal thalamus
- medulla oblongata
- spinal cord (dorsal horn)
- peripherial tissue
- periaqueductal grey m.
- locus coeruleus
- GIT

→ inhibition of resp., sedation, GIT effect, modul. of neurotransmitter release

κ R (KOR)
- spinal cord
- hyppocampus, limbic area
- GIT

→ psychotomimetic effects, GIT effect

δ R (DOR)
- cortex
- brain stem
- peripherial tissues

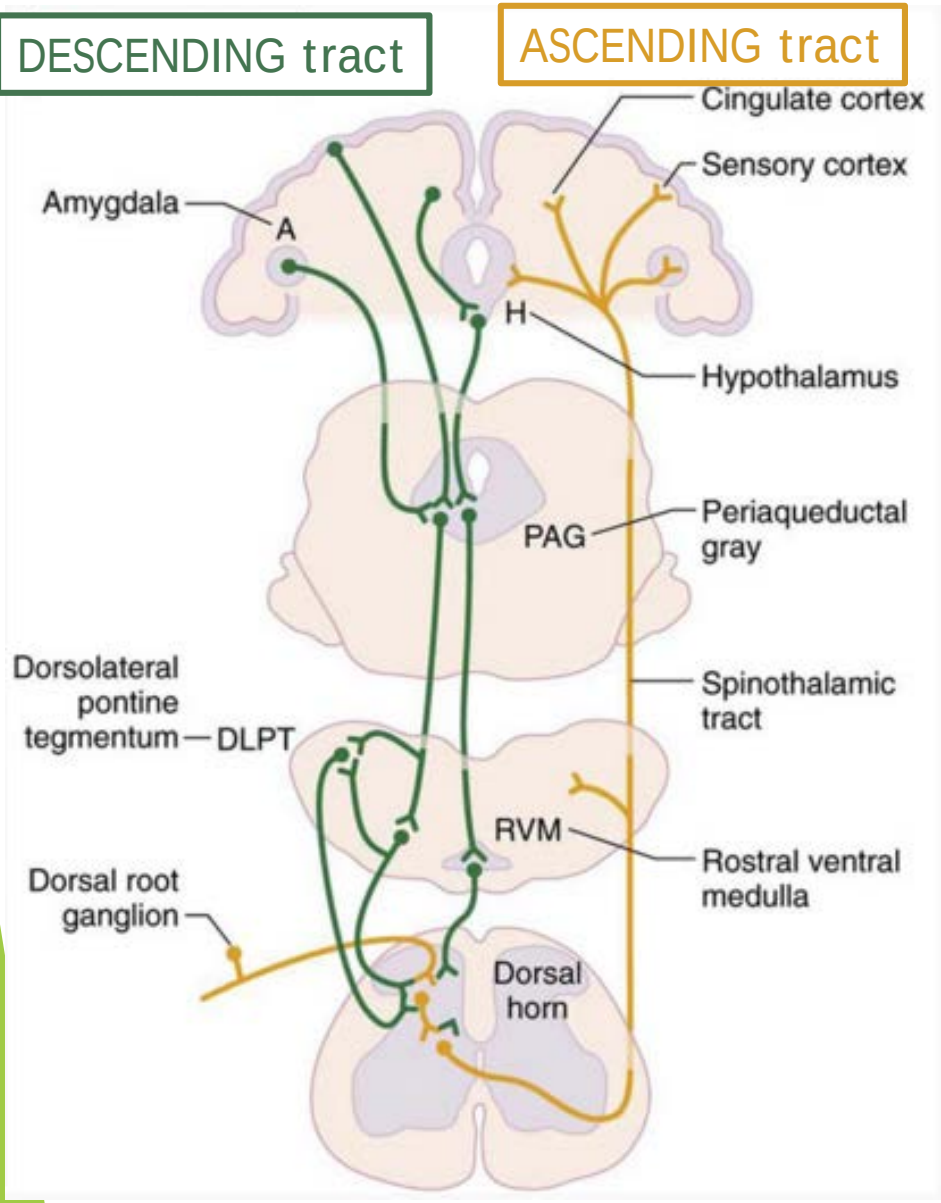
→ modulation of hormone and neurotransmitter release

Novel opioid receptor:
ORL1: orphanin opioid-receptor like subtype 1 (=nociceptin receptor (NOR))
endogenous ligand:
nociceptin (dynorphin like peptide)

Cellular actions:

- G protein coupled action→ Gi (blocking AC) →cAMP↓
  - blocking VG Ca2+ channels on presynaptic nerve terminals (↓ neurotransmitter release)
  - opening K+ channels on postsynaptic neurons (hyperpolarization)

Nociceptive pathways



<u>ascending pathway:</u>

peripherial tissue
dorsal horn
spinothalamic tract
thalamus
cortex (area postcentralis)

<u>descending (modulatory) pathway:</u>

periaqueductal grey,
raphe nucleus
NTs: serotonine, endogene opioids

locus coruleus
NTs: NA, A, D, Ach

inhibited by GABAerg interneurons
(tonic inhibitory effect)

Opioid analgetics (especially morphine)

Pharmacokinetic features:

- modest absorption from GIT
- ineffective per os
  - hydrophilic structures are absorbed poorly
  - high first-pass metabolism (except codein, oxycodone)
- highest concentrations in highly perfused organs
- metabolized in liver
  - Morphine-3-Glucuronide, effect on GABAerg receptors → higher concentration→seizures
  - Morphine-6-Glucuronide (10% of morphine degr.) 4-6x potency compared to morphine
    - It is also a metabolite of codeine (pediatric application?)

Opioid analgetics

CNS effects:

- analgesia
  - reduce sensory and emotional (affective) components of pain
- euphoria
  - pleasent floating sensation with lessened anxiety and distress
- sedation
  - drowsiness
  - clouding of mentation
- respiratory depression
  - depressed response to CO_2 challenge (=Pa_{CO2}↑)
  - dose-related
  - Pa_{CO2}↑→cerebral vasodilation→ICP↑
  - dangerous in high ICP, COPD, asthma
- cough supression
  - supression of cough reflex
  - airway obstruction!
- miosis
  - no tolerance develops (see later)→diagnostical symptom in opioid intoxication
- truncal rigidity
  - spinal cord action, failure in ventillation
- nausea and vomiting
  - area postrema-chemoreceptor trigger-zone
- hyperthermia
  - anterior hypothalamus – μR agonism

Opioid analgetics

Extracranial effects:

- Cardiovascular system
  - hypotension
    - central depression of vasomotor system
    - release of histamin
  - tachycardia
    - meperidine (pethidine)
- GIT
  - spastic obstipation
    - tone (=persistent contraction)↑
    - motility (=rhythmic contr. and relax.)↓
- Biliary tract
  - contraction of biliary smooth muscle
  - contraction of Oddi sphincter
- Renal
  - antidiuretic effect, RBF↓
- Uterus
  - reduce uterine tone
  - labour prolongation

Opioid analgetics

Therapeutical application:

- Analgesia
  - severe, constant pain (cancer, terminal illnesses)
  - fentanyl transdermal system (fentanyl patch, Durogesic®)
  - Patient Controlled Analgesia vs. fixed interval administr.
- Acute pulmonary oedema (Acute Left Ventricular Failure)
  - preload↓
  - afterload↓
  - reduce anxiety, generalised sympatic tone↓
  - decreases hyperventillation, resp. panic
- Anaesthesia
  - sedative, anxiolytic, analgesic properties
  - premedication, ET intubation: 100µg Inj. Fentanyl
  - epidural/subarachnoideal administration
- Supression of cough (antitussive agents)
  - codeine, oxycodone
- Diarrhoea
  - never if diarrhoea is associated with infection

Opioid analgetics

Routes of administration

- i.v. application
  - rapid effect
  - respiratory depression
- rectal suppositories
  - morphine, hydromorphone
- transdermal patch
  - fentanyl TTS
- intranasal application (in migraine)
  - avoiding first pass metabolism
  - butorphanol
- PCA (patient controlled analgesia)
  - demanded application of preprogrammed dose
- i.m. injection

Endogenous opioids:

- endorphins
  - hypophysis: POMC→ACTH + α-MSH + β endorphin
    - μR affinity is highest
    - supraspinal/spinal analgesia, sedation, inhibition of respiration
- dynorphins
  - dynorphin A, dynorphin B
    - κR affinity is highest
    - supraspinal/spinal analgesia, slowed GIT motility
- enkephalins
  - met-enkephalin, leu-enkephalin
    - δR affinity is highest
    - supraspinal/spinal analgesia, slowed GIT motility
    - modulation of hormone and neurotransmitter release

Met-enkephalin is Tyr-Gly-Gly-Phe-Met.
Leu-enkephalin has Tyr-Gly-Gly-Phe-Leu.

Opioid analgetics

- diamorphine (heroin)
  - diacetyl derivative of morphine (lipophylic structure!!!)
  - rapid crossing of blood-brain barrier→rush↑
  - less emetic
  - dependence!
- codeine
  - analgesic potency 20%
  - no euphoria, no addiction
  - antitussive activity
  - But active metabolite: Morphine-6-Glucuronide
  - combined with paracetamol, acetaminophen
- methadone
  - bioavailability↑→oral application
  - long term acting
  - potent analgesic effect
    - μR agonism
    - blocking NMDA R
    - blocking monoamine reuptake system
  - lower euphoriac effect
  - used treating morphine/heroin addiction

Opioid analgetics

- pethidine (meperidine):
  - no sedative effects (restlessness)
  - antimuscarinic action
  - Local anesthetic effect due to resemblence to esther type LA-s
  - hallucinogenic, convulsant effect (active metabolite-normeperidine) ➔ no chronic use only acute
  - no uterus relaxation (analgesia during labor)
  - adverse effects: Serotonin syndrome (co-applied with MAO-inhibitors)

- fentanyl, sufentanyl, remifentanyl
  - 100x analgesic effect
  - anaesthesia practice
  - PCA (patient controlled analgesia), patch (TTS)

- tramadol
  - weak μR agonist
  - less potent (analgesia) than morphine
  - no resp. depressive effect
  - nausea, vomitus!

- buprenorphine
  - partial μR agonism, κR antagonism
  - long-term action
  - detoxification of heroine abusers
  - respiratory depression!

Opioid analgetics

- diphenoxylate, diphenoxin, loperamide
  - peripherial effect, no pass to CNS
  - Exclusively obstipant effect, against diarrhoea of travellers
  - diphenoxylate + atropin= Reasec®
  - obstipation

- Opioid antagonists
  - μR, δR, κR antagonism
  - ANTIDOTUM!
  - naloxone
    - 0,1mg-0,4mg i.v.
    - short half-life (intox. relapse)
    - „over-shoot" effect (after decay of antagonist effect, more severe morphine-effects)
    - 10 mg naloxone : antagonises 25 mg heroin
  - naltrexone
    - half-life: 10 hours → prolonged effect
    - oral application

Opioid analgetics

1. tolerance
   - 2-3 weeks at therapeutic dose
   - background: persistent activation of opioid receptors
     - up regulation of cAMP system
     - receptor recycling
       - receptor endocytosis
     - receptor uncoupling
       - structural dysfunction in opioid receptors
   - tolerance to euphoriac effect, analgesic effect, anxiolytic effect
   - no tolerance to obstipation, miosis, convulsive effects!

2. physical dependence
   - withdrawal/abstinence syndrome (lasting days)
     - autonomic: rhinorrhea, lacrimation, mydriasis, diarrhea, vomitting, piloerection
     - seizures, myoclonus
     - hyperthermia

3. psychologic dependence
   - compulsive use/craving (drug seeking behaviour)
   - elevated incidence at MD's!!!

Opioid analgetics

- Detoxication methods
  - supportive therapy
    - fluid/electrolyte suppl.
    - anticonvulsive agents: BZD
    - antipsychotics
    - antihypertensive:
      - clonidin (α_2R agonism)-central acting sympatholytic drug
      - β-blockers
  - methadon substitution
    - long acting μR agonist
    - less euphoriac effect
    - receptor occupancy ➔ no effect of morphine/heroin applied
    - dose reduction
  - naltrexon therapy
    - long acting μR, δR, κR antagonism
    - p.o.
    - application after withdrawal symptoms
  - Ultra short opioid detoxification
    - i.v. naloxone/naltrexone
    - massive withdrawal symptoms
    - supportive therapy !!!!