General anesthetics,
Local anesthetics,
Muscle relaxants

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General anesthesia

- „reversible” switch off period
  - sensoric/motoric/vegetative reflexes
  - nociception,
  - awareness, consciousness.

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

General anesthesia

- Main periods/phases of anaesthesia:
  - premedication
  - anesthesia induction
  - anesthesia maintenance
  - recovery
  - 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

General anesthesia

- **Mech. of action of anesthetics:**
  - blocking VG Na^+ channels
    - general-local anaesthetics
    - N.B.: no i.v. application (lidocain, novocain)
  - 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

brain stem (formatio reticularis) – suppression of CV/resp. syst., hypnoid effects, loose of consciousness

hyppocampus – amnesia, loose of awareness/consc

premotor cortex/spinal cord – muscle relaxants, reflexes↓

sensory cortex, thalamus, spinothal. tract - analgesia

General anesthesia

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

1. level of analgesia (stage of analgesia)
   - narcosis induction → disappearance of regular ventillation
   - analgesia, amnesia, loosing of awareness

2. level of excitement (stage of excitement)
   - loosing of awareness → regular ventillation
   - muscle tone↑, RR↑, HR↑
   - reflex↑

3. level of tolerance (stage of surgical anaesthesia)
   - surgical procedures are performed in this phase
   - regular ventillation → asphyxia
   - muscle tone↓, reflex↓
   - general anaesthesia

4. level of asphyxia (stage of medullary depression)
   - overdosage
   - RR↓ bradycardia

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) – Meyer - Overton lipid theory
  - high fast onset
  - 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

General anaesthesia

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

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) – anesthesia induction
  - th.: analgetic effect
    - stimulation of opioid neurons in limbic area
    - „demand mask”– analgesia at labour
  - expandive effect – alveolus
    - O_2 dilution – relative hypoxia (recovery)
  - a.e..: > 6 h – methionine synthase inhib.→anaemia, leukopenia
  - CI.: ileus, PTX – expandive effect

- ether
  - fluid at room temperature
  - „vitrum fuscum”
  - potent muscle relaxant effect
  - RR↑ (indirect sympathomimetic effect)
  - old-fashioned

Inhalational narcotics

- halothan
  - halogenated compound, low cost
  - high blood solubility – slow induction
  - high lipid : blood partition coefficient – slow recovery
  - CNS, stimulation of nucl. X.
    - bradycardia
    - hypotension
  - tocolysis (never appl. during delivery!!!)
  - bronchodilation
  - a.e.:
    - arrhythmia (sensitization of myocardiumto catecholamines – CI.: pheochromocytoma th.)
    - halothane hepatitis
      - 1/100.000
      - trifluoracetate (metabolite)
      - repeated exposure
    - malignant hyperthermia
      - excessive Ca^{2+} release
      - hyperpyrexia, convulsions, hypertonia, DIC, arrhythmia
      - th.: danthrolen

- enflurane
  - alternative drug (halothan)
  - similar pharmacokinetic features
  - metabolism: proconvulsive metabolites!
  - a.e.: epileptiform convulsions

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

Inhalational narcotics

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

- desflurane
  - low blood solubility, low lipid : blood partition coefficient
  - „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)

Intravenous narcotics

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

- Barbiturates
  - thiopental
    - ultrarapid/ultrashort effect (20 sec./10-20 min.)
    - ↑lipid-solubility– repeated administration - accumulation!
      - only for induction!
    - respiratory depression
    - CV depression
    - Th.i.:anticonvulsive effect,
    - a.e.: porphyria (fatal attacks), induce ALA synthase

Intravenous narcotics

- etomidate
  - rapid metabolism!
  - no CV depression!
    - ACS, LVF! (in patients with limited CV reserve)
  - chr. application→adrenocort. supp, acute adrenal failure
  - th.: 0,3 mg/kg

- propofol
  - commonly used for anesthesia induction/maintenance
  - no accumulation – rapid metabolism→long term use
  - RR↓, negative inotropic effect!!!
  - th.: 2mg/kg

- ketamin
  - structural resemblence – phencyclidine (hallucinogenic)
  - dissociative anesthesia: amnesia, analgesia, but!intact consciousness
  - euphoria, hallucinations, nightmares (esp. in children)
    - supportive th.: BDZ!
  - HR↑, BP↑, positive inotropic effect
  - ICP↑
  - analgetic effect:0,5 mg/kg
  - anesthesia ind.: 2 mg/kg

Clinical phases of anesthesia

- Preoperative
  - premedication
    - anti-acid therapy (H_2R block, PPI)
    - PONV (metoclopramide, „setrons”)
    - preoperative anxiolysis (diazepam i.m./p.o.)
    - cholinolytics/parasympatholytics
      - secretion↓
      - to prevent bradycardia

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

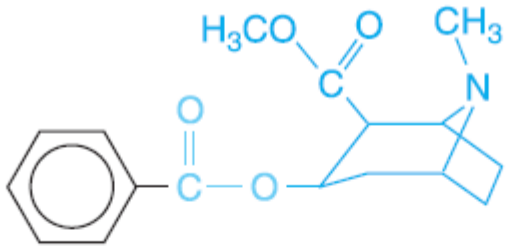
- Postoperative phase
  - ANTIDOTUM (flumazenil, naloxon, neostigmin/physostigmin)
  - O_2
  - ChE blocking drugs

Local anesthetics

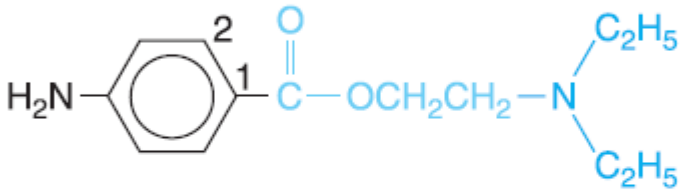
- Structure:
  - Esters: cocaine, procaine, tetracaine
  - Amides: lidocaine, bupivacaine, ropivacaine
  - hidrophobic structure (internal binding place of VGNa$^+$ channels)

- Mechanism of action:
  - blocking VG Na$^+$ channels
  - use-dependent, voltage dependent dependent effects
  - + adrenaline

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



COCAINE



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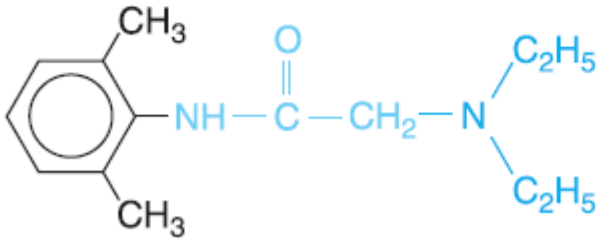


LIDOCAINE

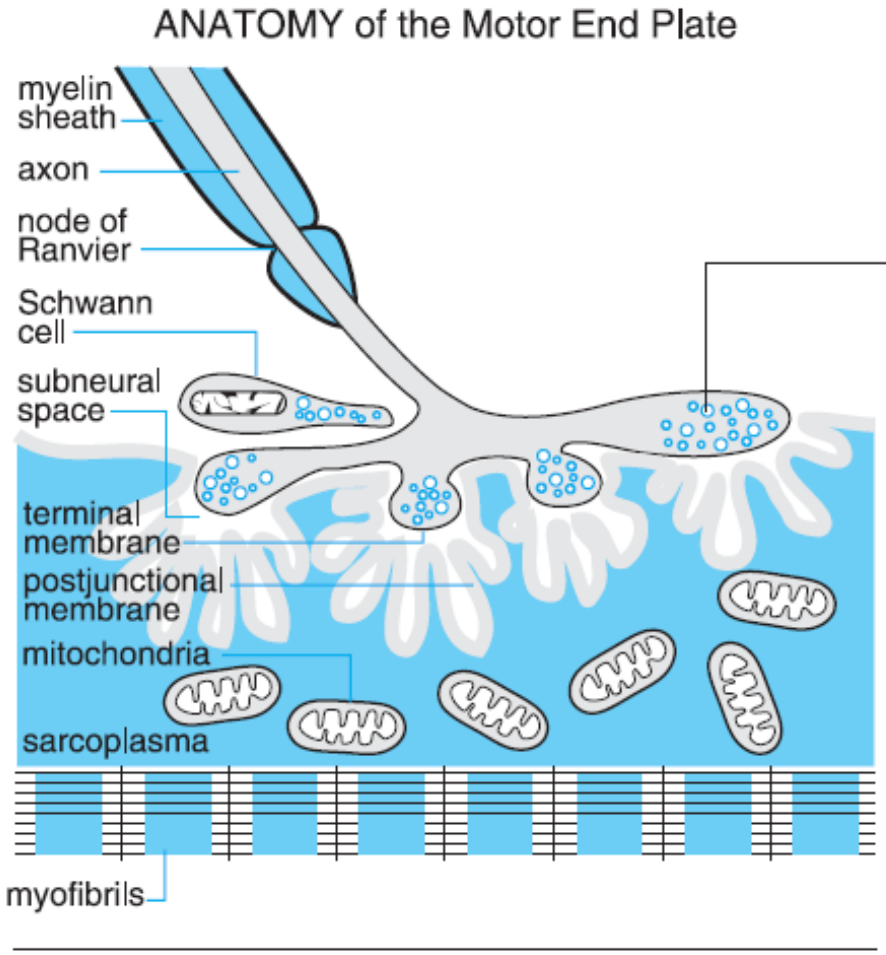
Local anesthetics

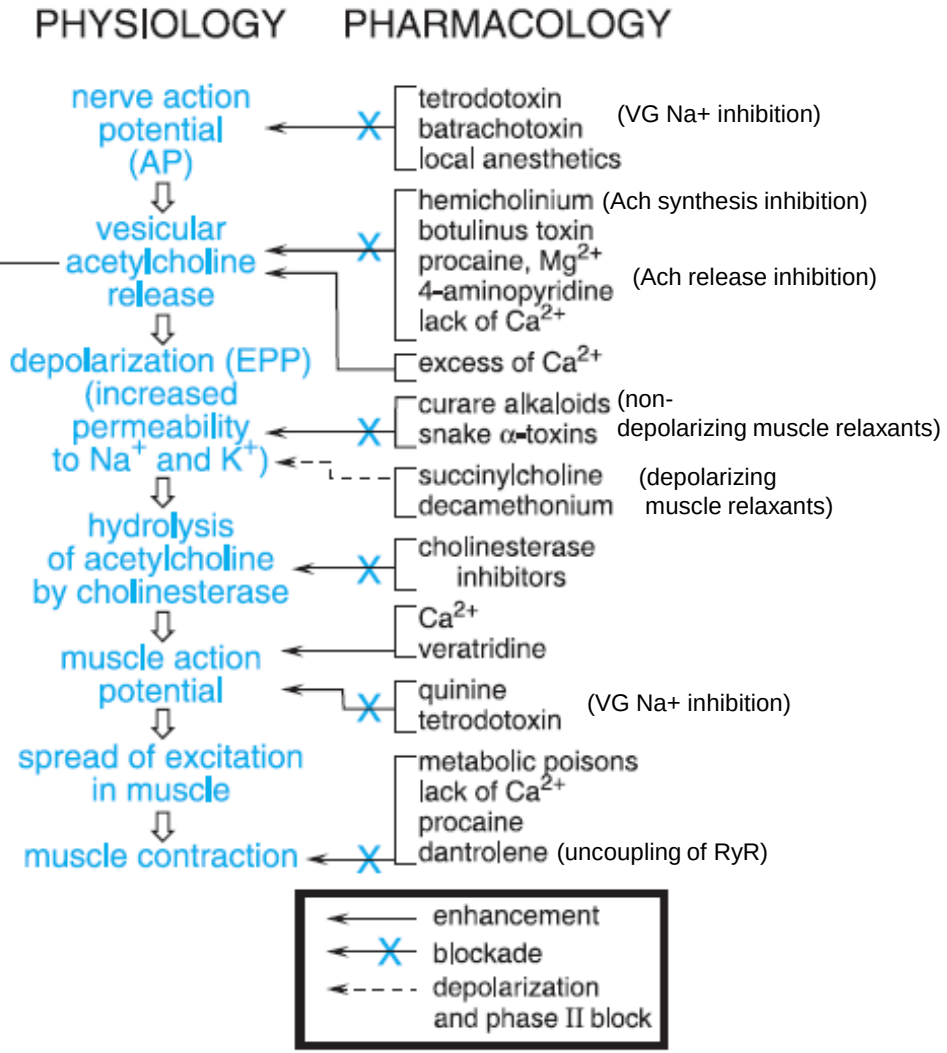
Table 14–1

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	++++

Muscle relaxants





Peripheral muscle relaxants

- Non depolarizing muscle relaxants
  - competitive antagonism on $nAch_mR$
  - structural resemblence to ACh
  - flaccid paralysis

  - d-tubocurarin (curare)
    - arrow poison, blocked motorium – but! intact sensory functions
    - hypotension (symp.ggl.block)

  - atracurium (Tacrium®)
    - spontaneous degradation
    - active metabolite: laudanosin (CNS effects, tachycardia)

  - cisatracurium
    - „most commonly used”
    - no laudanosine

  - pancuronium (Pavulon ®)
    - no sympathomimetic effect
    - no histamin release

Peripheral muscle relaxants

- Depolarizng muscle relaxants (Dual phase blockade)
  1. Depolarisatrion block (= large dose of Ach): FASCICULATION
  2. Desensitisation block (molecular conversion)

  - succinyl-choline:
    - ultrashort effect (5-10 min - 0,5-1mg/tskg)
    - BChE/PChE!!!
    - a.e.:
      - hyperkalemia (K+ release from ic. sites)
      - arrhythmia (digitalis th.)
      - malignant hyperthermia

- Clinical use of muscle relaxants
  - surgical relaxation, immobilization
  - endotracheal intubation
  - controll of ventillation (to reduce the chest wall resistance)
  - treatment of convulsions