Pharmacology of the skeletal muscles

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Classification of drugs acting on the skeletal muscles

- Constrictors
  - Tetanus toxin – very strong spastic contraction (inhibition of glycine release in the spinal cord – lack of inhibition on the peripheral motoneuron)
  - Strichnin – glicine-1 receptor antagonist, strong poison, spastic contraction
  - Activators of the genetically altered ryanodin receptor – halothan, succynylcholine, antipsychotics (see neurolpetic malignant syndrome)
  - Sympatomimetics – increase muscle strength
  - Centrally – any agent that may cause epileptiform convulsions

Classification of drugs acting on the skeletal muscles

- Relaxants
  - Centrally acting muscle relaxants – relieve spasticity
  - Peripheral muscle relaxants
    - Inhibitors of the neuromuscular junction
    - Botulinum toxin
    - Tetracyclines, aminoglycosids

Centrally acting muscle relaxants

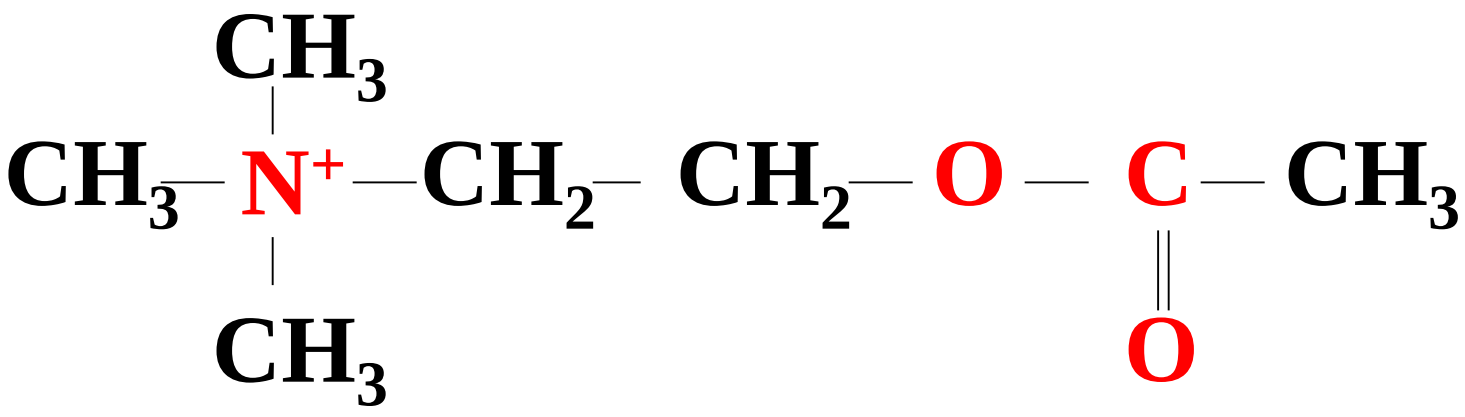
- They decrease pathologically higher muscle tone without affecting voluntary movements
  - Drugs for spasticity only
    - baclofen – $GABA_B$ agonist, highly sedative
  - Drugs for acute spasms only (unknown mechanism)
    - mephenesine, guaifenesine
    - chlorzoxazone

Centrally acting muscle relaxants

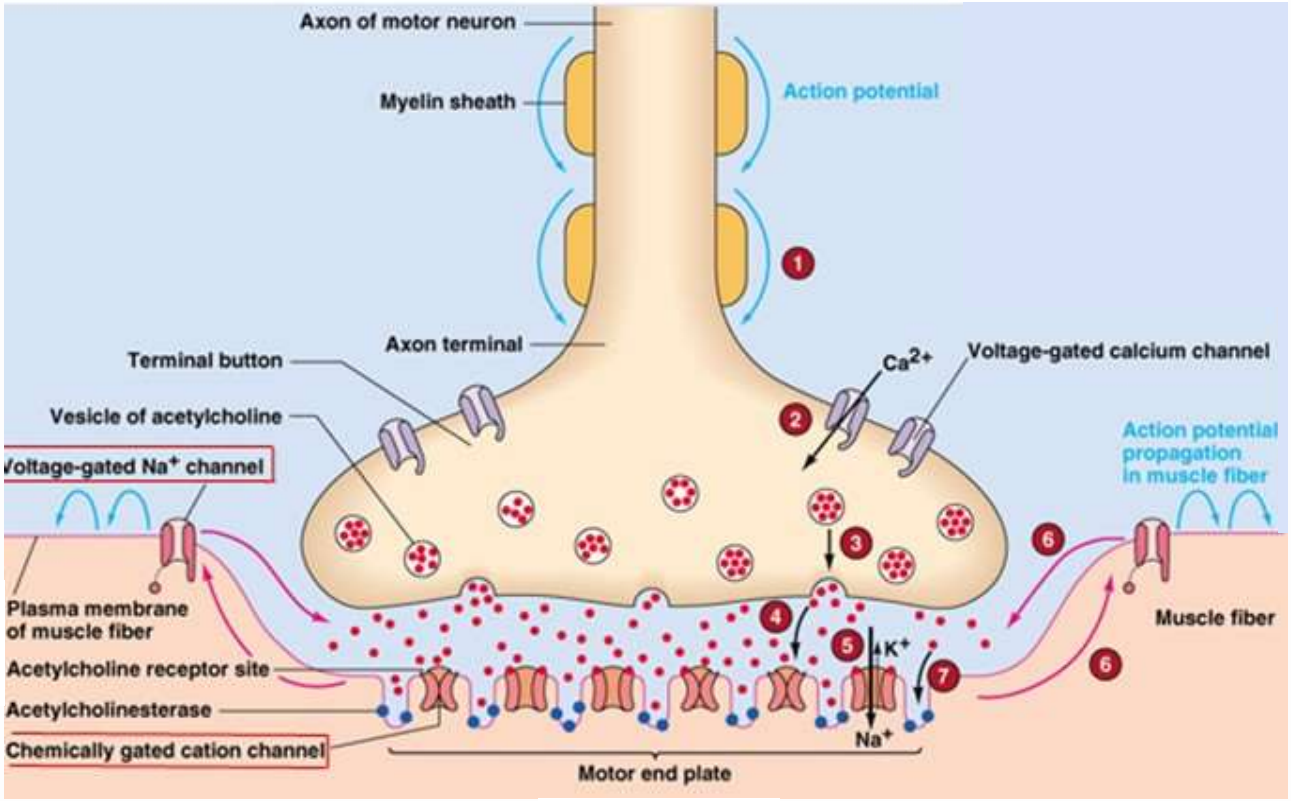
- Drugs for both acute and chronic spasms
  - diazepam – benzodiazepine
  - tizanidine – α_2 agonist, structural relative of clonidin (imidazoline core)
  - tolperisone – unknown mechanism
  - carisoprodol (its metabolite is meprobamate) – abuse potential, meprobamate is hepatotoxic

Neuromuscular junction

- The connection between the motoneuron endings and the skeletal muscles is called neuromuscular junction
- The neurotransmitter of the peripheral motoneuron is acetylcholine



The anatomy and the function of the NMJ



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Nicotinic acetylcholine receptors

- Kation-selective ion channel (Na^+, K^+)
- Two main types:
  - **N_N**, neuronal - α and β subunits
  - **N_M**, muscular - pentamer:($\alpha_2\beta\gamma\delta$)
- 2-5 acetylcholine molecules can bind (depending on the subunit structure – cooperative interaction)
- Continuous stimulation is not possible
  - Eventually a depolarization blockade develops (few seconds)

Possibilities to relax skeletal muscles

- Centrally acting muscle relaxants – decrease the tone of the skeletal muscles (spasmolytics)
- Peripheral muscle relaxants – paralyze the skeletal muscles (total relaxation)
  - Presynaptically acting drugs
    - Toxins: botulinumtoxin, ω-conotoxin (full relaxation)
    - Certain antibiotics: aminoglycosides, tetracyclines (muscle weakness)
  - Postsynaptically acting drugs
    - Curare derivatives
    - Depolarizing muscle relaxants
    - Ryanodine antagonists

Indications of peripheral muscle relaxants

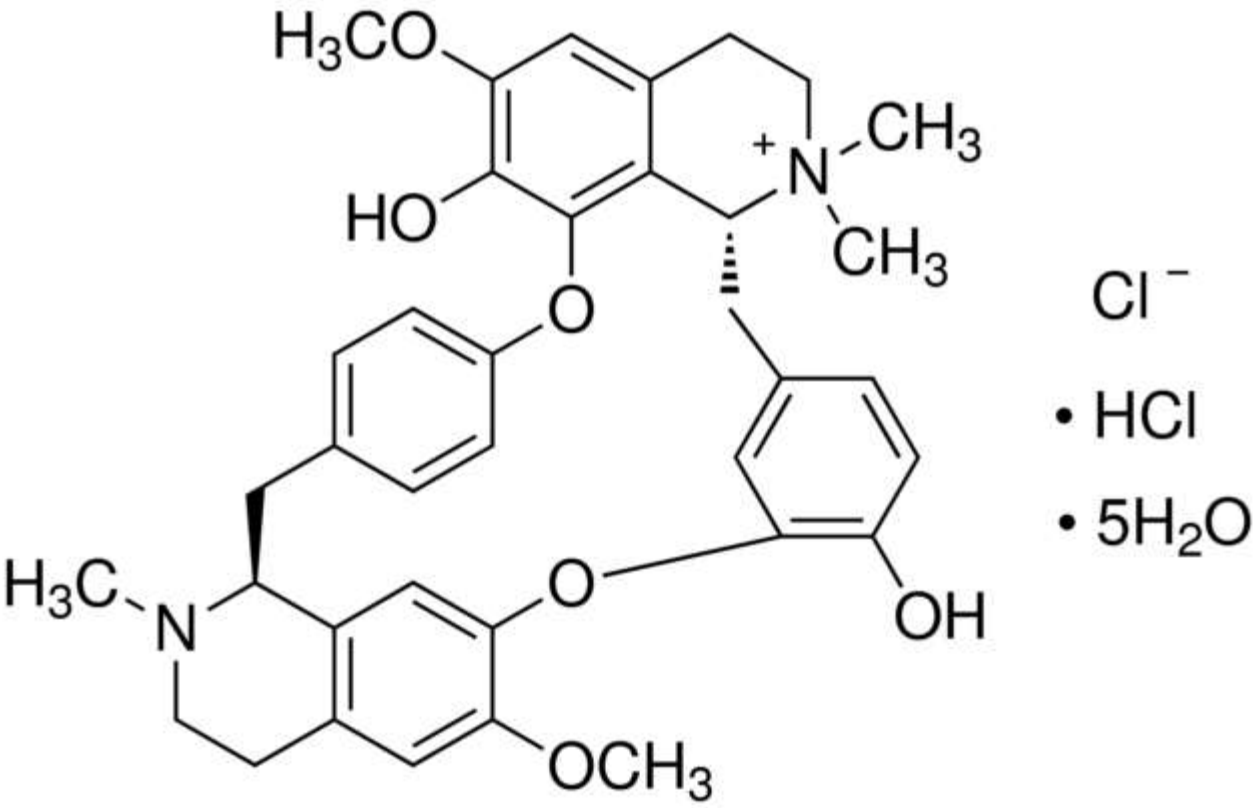
- Providing muscle ralxation during surgical narcosis
- Relaxing the muscles of artificially respired patients (eg. severe COPD)
- Electroshock
- Intubation
- Tetanus
- Epileptic seizure (convulsion) not responding to antiepileptics
- Intoxication (overdose) with certain medicines (theophyllin, amphetamin)

Curare type peripheral muscle relaxants

- Competitive antagonist of the N_M acetylcholine receptors in the neuromuscular junction
- Structure: bisquaternary ammoniumbases (Ø central effect!)
- Intravenously administered

d-tubocurarine

- The toxin of the South American poison dart frog (Dendrobates)
- Structure:



Time order of the curare induced muscle paralysis

- Outer eye muscles
- Facial muscles
- Pharyngeal muscles
- Extremities
- Truncal muscles
- Respiratory muscles (diaphragm)

- Full paralysis within 2 to 6 minutes

Structural classification of curare drugs

- **Izoquinolines**
  - D-tubocurarine
  - Doxacurium
  - Atracurium
  - Cisatracurium
  - Mivacurium
- **Steroids**
  - Pancuronium
  - Pipecuronium
  - Vecuronium
  - Rocuronium

Duration of action of curare derivatives

- Long acting (60-180 minutes):
  - Doxacurium (isoquinoline)
  - Pancuronium (steroid)
  - Pipecuronium (steroid) (60-90 minutes)
- Intermediate acting (20-40 minutes):
  - Vecuronium (steroid) (24-60 minutes)
  - Rocuronium (steroid) (dose-dependent: 15-110 minutes)
  - Atracurium (isoquinoline) (15-35 minutes)
  - Cisatracurium (isoquinoline) (20-30 minutes)
- Short acting(10-15 minutes):
  - Mivacurium (isoquinoline) (10-15 minutes)

Elimination of curare derivatives

- Filtration in the kidney (60-80%):
  - pancuronium, pipecuronium
- Metabolism in the liver (75-90%):
  - vecuronium, rocuronium
- Spontaneous metabolism (Hoffmann-elimination)
  - Atracurium, cisatracurium
- Metabolized by pseudocholinesterase
  - mivacurium

Adverse effects of curare derivatives

- Recurarization
  - After suspending the effect a reappearing muscle weakness (reason unknown)
- Ganglion blockade (d-tubocurarine, pancuronium)
  - hypotension, tachycardia
- Histamine release (isoquinolines: atracurium, mivacurium)
  - itching, bronchospasm, hypotension
- M_2 receptor blockade (pancuronium)
  - tachycardia
- Norepinephrine releaser and re-uptake inhibitor (pancuronium)
  - tachycardia
- The metabolite of atracurium (laudanosin) may cause muscle spasm - convulsions

Suspending / terminating the curare effect

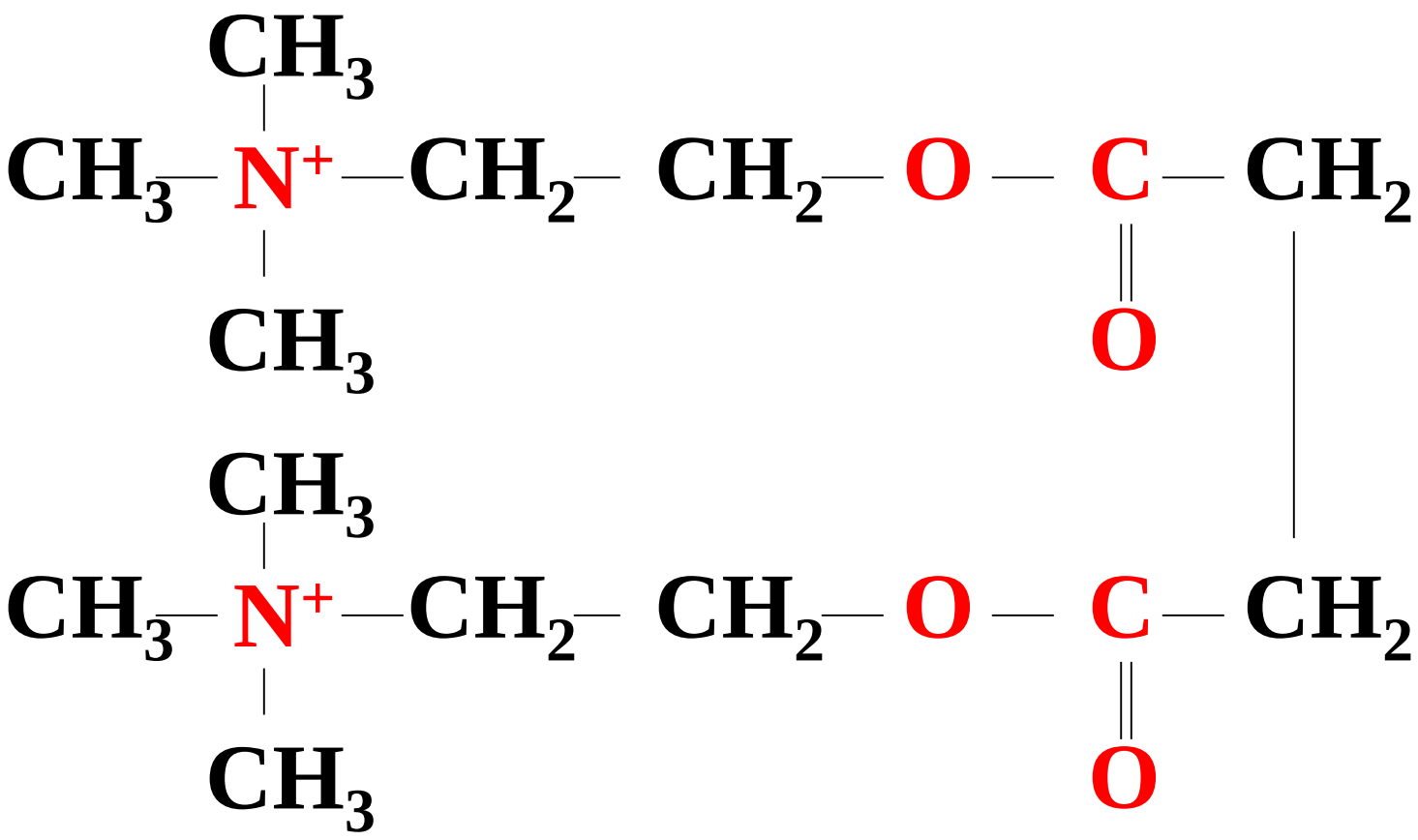
- Acetylcholinesterase inhibitors
  - neostigmine, distigmine
  - Coadministered with atropin in order to antgonize their parasympathomimetic effects
- Sugammadex
  - Neutralizes the steroid structures in the plasma

Factors infulencing the curare effects

- Enhancing the effects
  - General anesthetics (fluranes have significant skeletal muscle relaxing effetcs)
  - Aminoglycosides, tetracyclines
  - Local anesthetics
  - Myasthenia gravis (autoimmune disease, antibodies against the NMJ)
- Attenuating the effetcs
  - Acetylcholinesterase inhibitors
  - Motoneuron lesions

Depolarizing muscle relaxants

- Succynylcholine (suxamethonium)



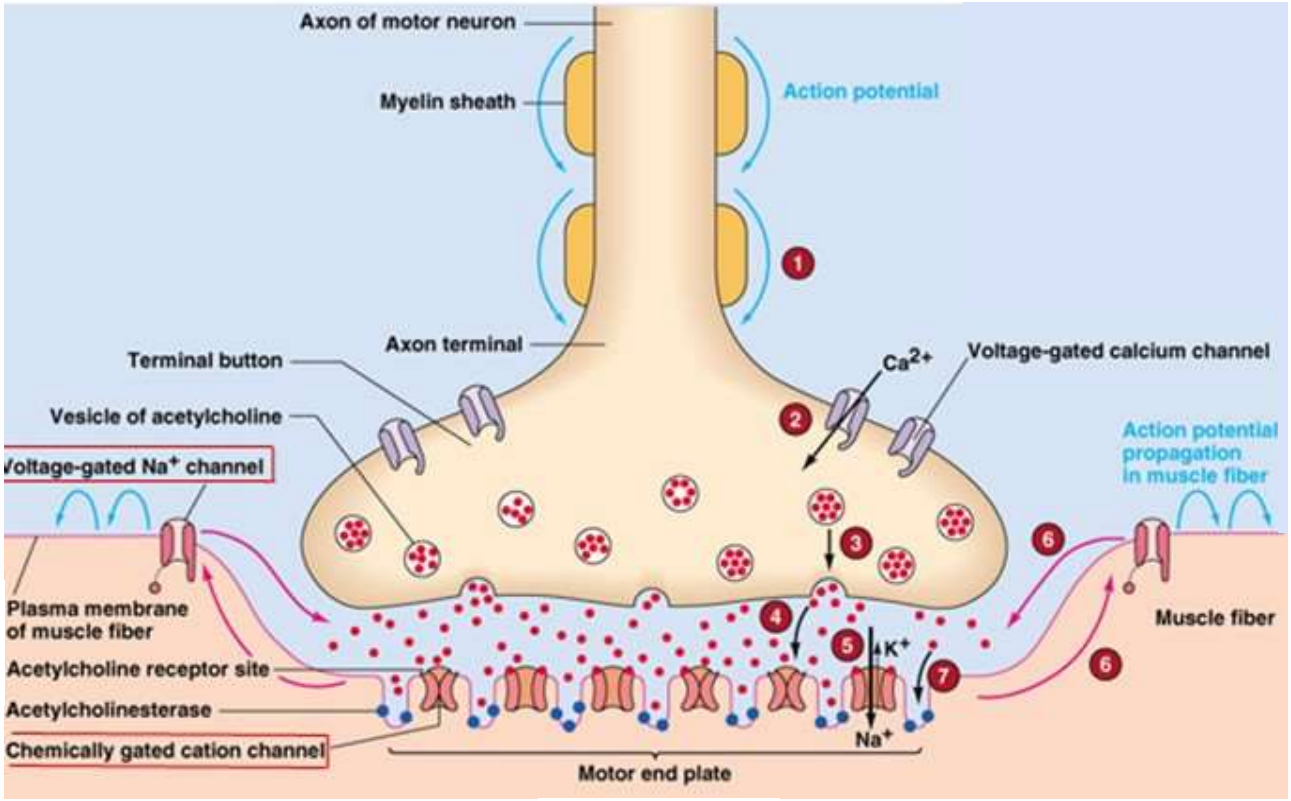
Succynylcholine (suxamethonium)

- Provides depolarizing blockade that cannot be antagonized by acetylcholinesterase inhibitors
- Duration of action: after iv. admnistration 5 to 10 minutes
- Order of paralysis: arms, neck, legs, respiratory muscles, facial muscles, pharyngeal muscles
- Metabolism: pseudocholinesterase in the blood then in the liver
- Indications: short surgical interventions; intubation; electroshock; short, invasive diagnostic procedures (e.g. bronchoscopy)

Development of depolarization blockade

- Succynylcholine is the selective agonist of the N_M receptor and the acetylcholinesterase does not metabolize it
  - In the beginning short time muscle fasciculations
  - Due to the longer stimulus of the receptor Na^+ influx is higher resulting the depolarization of the surrounding membrane
  - In the surrounding depolarized membrane the voltage gated Na^+-channels cannot return to the resting closed state instead they remain in inactive state $\rightarrow$ action potential generation stops, the muscle becomes paralyzed
  - This paralysis cannot be antagonized by acetylcholiesterase inhibitors in the beginning

The anatomy and the function of the NMJ



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2nd phase: desensitization block

- Succynylcholine diffuses quckly out of the NMJ $\rightarrow$ continous receptor stimulation ends
- The muscle restores the normal ion balance (see Na^+/K^+-ATP-ase)
- The muscle can be stimulated with high amount of acetylcholine for a while
- Reason: desensitization of the N_M receptors

Adverse effects of succynylcholine

- Muscle pain (postoperative, fatigue fever like pain – muscle strain)
- Arrythmia – mainly bradycardia (cave digitalis!!!)
- Hyperkalemia – nicotinic receptor conducts outward K^+ current
- Vomiting
- Higher intraocular pressure (contraction of the myofibers or dilation of choroidal vessels)
- **MALIGNANT HYPERTHERMIA!!!**

Malignant hyperthermia: reason and symptoms

- Genetic disorder – affects ryanodin receptors
- For unknown reason (idiosynchrasia) succynilcholine makes ryanodin activation permanent, continously high amount of Ca^{++} flows out of the sarcoplasmic reticule
- Continuous muscle shivering $\rightarrow$ heat production $\rightarrow$ hyperthermia
- Lactacidosis
- Myoglobinaemia, myoglobinuria, acute renal failure

Treatment of malignant hyperthermia – dantrolene

- Dantrolene
  - Ryanodin receptor antagonis, inhibits Ca^{++} release in the skeletal muscle
  - Main indication: malignant hyperthermia
  - Most dangerous side effect: hepatotoxicity (1-2%), when develops lethality is 20-30%
- Other
  - Bicarbonate infusion to acidosis
  - Physical cooling of the patient