Muscle Relaxants

Overview of Muscle Relaxants

Mechanism of action

Centrally active
Spasmolytics

- Baclofen
- Benzodiazepines:
  - Tetrazepam
  - Diazepam
  - Clonazepam
- Thiocolchicoside
- Mephenoxalone
- Tizanidine
- Guaifenesin
- Orphenadrine

Peripherally active
Neuromuscular blockers

- Presynaptically active: botulinum toxin
- Postsynaptically active:
  - Depolarizing blocking agents (suxamethonium)
  - Non-depolarizing blocking agents (atracurium, vecuronium, pancuronium etc.)

Centrally Active Agents (Spasmolytics)

- Attenuate transmission of motoric impulses in **spinal cord** and **CNS**
- Decrease muscle tone, do not influence intentional contractions → weaker muscle relaxant activity
- **AE:** depression of CNS → sedation, somnolence, confusion…
- **Acute and chronic painful spasms** – p.o., parenterally
  - Spastic rheumatism
  - Damage of *n. ischiadicus* (spasms of deep paravertebral muscles, compressions in intervertebral space etc.)
  - Spastic disorders associated with cerebral palsy, multiple sclerosis, injuries of brain or spine…

Centrally Active Agents (Spasmolytics)

Mechanism of action:

- Increase effects of inhibitory neurotransmitter **γ-aminobutyric acid** (GABA) in **CNS** and **spine cord**

Baclofen

- Attenuates the activation of motor neurons in the spine cord
- $GABA_B$ receptor agonist
- Activation of $GABA_B$ receptors → opening of K^+ channels → change in ion homeostasis → hyperpolarization, decrease of Ca^{2+} influx → inhibition of neurotransmitter release presynaptically
- Multiple sclerosis, cerebral palsy, injuries of brain and spinal cord…

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MoA: Enhance of GABAergic transmission – $GABA_A$ receptors

Psychiatric medication with 5 effects:

Anxiolytic

Hypnotic

Muscle relaxant

Anticonvulsant

Amnestic

Low doses have expectorant effect, Higher doses have muscle relaxant and anxiolytic effect

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Peripherally Active Agents (Neuromuscular Blockers)

- Influence neuromuscular junction
- Inhibits impulse transmission to myofibrils:

1.) Presynaptically active agents
  - Decrease ACh release
  - **Botulinum toxin**

2.) Postsynaptically active agents
  - Act on nicotinic receptors (N_M)
    - Non-depolarizing
    - Depolarizing

Non-depolarizing agents

- Firstly described in 15th century by european explorers in S. America
- Used by natives as arrow poisons
- Tubocurarine – natural alkaloid

- Competitive N_M receptors antagonists
- **AE:** release of histamine (bronchoconstriction, hypotension, syncope – fainting)
- Progressive relaxation: eye muscles → muscles of mastication → neck and limbs → trunk → diaphragm
- Administered parenterally
- Effect weakens and is **reversible** – **competition of receptors**

Non-depolarizing Agents

- With long effect (1-2 h): tubocurarine, pancuronium, pipecuronium, vecuronium
- With short efect (10-30 min): alcuronium, atracurium

- Surgery – muscle relaxation in the operating field, or before mechanical ventilation (tracheal intubation)

- Ovedosing: antidote = acetylcholinesterase inhibitors (neostigmine, pyridostigmine…)

Depolarizing Agents

- N_M receptor agonists
- Open Na^+ channels → cause long-term depolarization → resistancy to activation by ACh = **depolarization blockade**
- Remain on the receptor for a longer time, resistant to AChE
- Fasciculation (muscle twitches)

  → muscle relaxation (paralysis)
- **AE:** cardiac arrhythmias, hyperkalemia, increase of intraocular pressure (IOP)

  + **malignant hyperthermia !**

Depolarizing Agents

- Decamethonium
- Suxamethonium (succinylcholine)
  - Short-term muscle relaxation (3-5 min)
  - Mechanical ventilation (tracheal intubation)
  - Orthopedic manipulations – repositiong of dislocated joint, fractures

Malignant Hyperthermia

- Rare AE of depolarizing MR and/or volatile general anesthetics

Mechanisms:

- Defect of **RYR receptor** – controls release of Ca^{2+} from sarcoplasmic reticulum
- Increase of Ca^{2+} in myocyte → uncontrolled increase of contractions, aerobic/anaerobic metabolism
- Symptoms: hyperthermia, cramps and rigidity, ↑ heart rate and breathing, cyanosis, lactate acidosis, rhabdomyolysis...
- 60 % of untreated cases are lethal (5 % of treated)
- Therapy: dantrolene, intensive cooling

Dantrolene

- Peripherally active muscle relaxant
- Blocks the release of Ca^{2+} from sarcoplasmic reticulum by interaction with RYR
- Do not affect smooth muscle and myocardium

- Malignant hyperthermia
- Spastic disorders associated with spinal cord injury, stroke, cerebral palsy and multiple sclerosis
  - Advantage: no CNS depression