

Muscle Relaxants

Overview of Muscle Relaxants

Mechanism of action

Centrally active

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

Peripherally active

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

Centrally Active Agents

- 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



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
- Multiple sclerosis, cerebral palsy, injuries of brain and spinal cord...

Centrally Active Agents

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

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

Overview of Muscle Relaxants

Mechanism of action

Centrally active

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

Peripherally active

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

Peripherally Active Agents

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 effect (10-30 min): alcuronium, atracurium
- Surgery – muscle relaxation in the operating field, or before mechanical ventilation (tracheal intubation)
- Oversedosing: 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 – repositioning 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