Neuromuscular blockers
(muscle relaxants)
Acetylcholine

- Acetylcholine is released from motor neurons in discrete quanta
- Causes “all-or-none” rapid opening of Na+/K+ channels (duration 1 msec)
- Development of miniature end-plate potentials (mEPP)
- Generate muscle action potential resulting in muscle contraction
- ACh is rapidly hydrolyzed by acetylcholinesterase; no rebinding to receptor occurs unless AChE inhibitor is present
Muscle relaxant

- Muscle relaxation could be achieved by:
  1. Blocking NM nicotinic receptors
    Nondepolarizing muscle relaxants:
    D-Tubocurarine (Curare) (prototype)
    Atracurium
    Mivacurium
    Pancuronium
    Gallamine
    Vecuronium
    Recuronium
Muscle relaxant

2. Desensitization of NM nicotinic receptors
   Depolarizing muscle relaxants:
   Succinylcholine (Suxamethonium)

3. Directly acting muscle relaxants (antispasticity agents):
   Baclofen
   Benzodiazepines (Diazepam=Valium®)
   Dantrolene sodium
Muscle relaxant

4. Centrally acting skeletal muscle relaxants

Carisoprodol
Chlorzoxazone
Cyclobenzaprine
Methocarbamol
Orphenadrine
Muscle relaxant

- **General clinical uses to muscle relaxants**
  - Provide muscle relaxation before major surgeries (↓ dose of general anaesthetic)
  - Provide muscle relaxation before intubation e.g. endotracheal intubation...
  - Prevent fractures and bone dislocation during electroconvulsive therapy
  - Spinal spasticity and spasticity associated with multiple sclerosis
  - Spasticity of malignant hyperthermia
Classification of Neuromuscular Blockers According to Mechanism of Action

- **Depolarizing**, Non competitive, agonist
  - *Succinylcholine*

- **Non depolarizing**, Competitive, antagonist
  - *Tubocurarine*
### Classification of Neuromuscular Blockers According Duration of Action

<table>
<thead>
<tr>
<th>Ultra-Short</th>
<th>Short</th>
<th>Intermediate</th>
<th>Long</th>
</tr>
</thead>
<tbody>
<tr>
<td>Succinylcholine</td>
<td>Mivacurium</td>
<td>Vecuronium</td>
<td>Pancuronium</td>
</tr>
<tr>
<td>Rapacuronium</td>
<td></td>
<td>Atracurium</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cis-a-tracurium</td>
<td>Rocuronium</td>
</tr>
</tbody>
</table>
**Nondepolarizing muscle relaxants**

Reversible competitive antagonists to Ach nicotinic receptors at NM junction

- In small doses they act predominantly at the nicotinic receptor site to block ACh
- At higher dose they can block prejunctional Na\(^+\) channels thereby decreasing ACh release

Because of their competitive nature, their effects could be reversed by antiCHE’s

Have no effects on muscarinic receptors
Nondepolarizing muscle relaxants

Do not enter CNS (quaternary ammonium; charged molecules)

Given IV; OOA 3-4 min → flaccid paralysis

1st muscles to be affected head & neck muscles, then limb muscles and finally respiratory muscles; recovery occurs in reverse
Nondepolarizing muscle relaxants

- **Clinical uses to nondepolarizing muscle relaxants**
  - Preanaesthetic medications
  - Prevention of bone fractures and dislocations that could be associated with electroconvulsive therapy
  - Control of spasm of tetanus

- **Side effects and drug-drug interactions to nondepolarizing muscle relaxants:**
  - Histamine release by mast cells $\rightarrow$ ↓ BP, skin rashes, & bronchospasm (newer drugs e.g. Pancuronium)
  - Partial block to symp. ganglia $\rightarrow$ ↓ BP
Nondepolarizing muscle relaxants

- Newborn and children are more sensitive to their effects due to lower No. of Ach receptors (need lower doses)

- Aminoglycosides and macrolide antibiotics increase their effects

Nondepolarizing muscle relaxants are mainly metabolized by liver and kidney (Pancuronium)
Mivacurium is metabolized by plasma cholinesterase
Most widely used nondepolarizing muscle relaxants:

**Pancuronium**
More potent than curare, does not release histamine; does not block symp. ganglia and has longer OOA & DOA

**Vecuronium**
Similar to Pancuronium

**Rapacuronium**
Has rapid OOA (1.5 min) and short DOA (20 min), good for short procedures, releases histamine
Depolarizing muscle relaxants

- Act as strong Ach agonists
- Muscle relaxation is achieved through 2 steps:
  1. Phase I or depolarization block

An initial depolarization of end plate producing muscle action potential and fasciculation. Maintained depolarization leads to Na⁺ channel inactivation and hence action potential cannot be generated.
2. Phase II or desensitization block

In continued presence of the depolarizing agent, the membrane becomes repolarized, Na$^+$ channel inactivation will be reversed and membrane excitability is restored. But neuromuscular blockade continues due to desensitization of Ach receptors (Succinycholine is not metabolized like acetylcholine so it continues to occupy the Ach receptors to “desensitize” the end-plate)
Succinylcholine (Suxamethonium)

Succinylcholine is two acetylcholine molecules linked end-to-end

Depolarizing muscle relaxant (produce sustained contractions) given IV, good for minor procedures because has short DOA

Metabolized by plasma cholinesterase
Has no effects on autonomic ganglia or on muscarinic receptors
It does not enter CNS
It releases histamine
Succinylcholine (Suxamethonium)

- Actions of Succinylcholine are not reversed by antiCHE’s and may actually prolong the block
- Actions of Succinylcholine could be prolonged in:
  - Pts with liver disease (plasma cholinesterase is synthesized in liver)
  - Individuals with genetic defects leading to a decrease in plasma cholinesterase or presence of atypical enzyme with decreased affinity to Succinylcholine
Succinylcholine (Suxamethonium)

- **Succinylcholine side effects:**
  - Prolonged apnea
  - Fasciculation that could lead to myoglobinuria and postoperative pain
  - Hyperkalemia → cardiac arrhythmias
  - Increased intraocular pressure due to contraction of extra ocular muscles
  - Malignant hyperthermia
Directly acting muscle relaxants (spasmolytics):

- **Diazepam**
  - Acts at GABA$_A$ receptors in the CNS
  - Leads to sedation & addiction
  - Relieves muscle spasm

- **Baclofen**
  - Orally effective; drug of choice for treating spinal spasticity and spasticity of multiple sclerosis
  - Acts at GABA$_B$ receptors, resulting in hyperpolarization and presynaptic inhibition through reducing calcium influx
Action Potentials

Upper Motor Neuron (UMN)

Less release of Ca²⁺ ions

GABA-B

Inhibitory Interneurons

-70 mV

hyperpolarization

Baclofen

-for spasms from spinal injury

Lower Motor Neuron (LMN)

Activate Your Spinal Cord Function
Baclofen

Less sedative, but can cause drowsiness

Can be given intrathecally

Can reduce craving in alcoholics and in migraine
Tezanidine

- $\alpha_2$ adrenergic receptor agonist
- Congener of clonidine
- Results in presynaptic inhibition of motor neurons
- Has 1/10-1/50th potency as clonidine in lowering blood pressure
- Effective in treating spasms, cramping, and tightness of muscles caused by multiple sclerosis
- Given orally
- It is also prescribed for migrainous headaches, as a sleeping aid, and as an anticonvulsant
- Side Effects: Drowsiness, hypotension, dry mouth
Dantrolene sodium

Interferes with excitation-contraction coupling

Reduces release of Ca^{++} from the sarcoplasmic reticulum and thus blocks contraction

Uses: Cerebral palsy, multiple sclerosis and malignant hyperthermia

Given orally and IV

Side Effects: Muscle weakness, sedation, rare hepatitis
Ryanodine Receptor Channels (RyR2 Channels)

Sarcoplasmic Reticulum

Prevents muscle contraction

Extra-Cellular Fluid

Sarcolemma

Dihydropyridine Receptor (DHPR)

dantrolene
Centrally acting muscle relaxants

e.g. Carisoprodol...

Block pain sensations between the nerves and the brain

Depress spinal polysynaptic reflexes

Effective in muscle spasm associated with injuries

Have no over advantage above analgesic antiinflammatory agents

Have mild sedative & antianxiety properties

Combined with other analgesics (e.g. Aspirin) and with caffeine