Skeletal Muscle Relaxants

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The nicotinic Acetylcholine receptor

- Present at the neuromuscular junction, peripheral autonomic ganglia; and in the CNS.

- Distinct subtypes of nicotinic receptors exist at these sites.

- Several pharmacological agents discriminate between the receptor subtypes.

- The binding of ACh to the nicotinic ACh receptor initiates the end-plate potential (EPP) in muscle or an excitatory postsynaptic potential (EPSP) in peripheral ganglia.

- Classical studies of the actions of curare and nicotine defined the concept of the nicotinic ACh receptor over a century ago and made this the prototypical pharmacological receptor.

- Peripheral and then central nicotinic receptors were isolated and characterized.
Skeletal Muscle Relaxants

Neuromuscular Blockers:
- Nondepolarizing Drugs
- Depolarizing Drugs

Spasmolytics.

Directly Acting Drugs.
Neuromuscular Blockers

**Chemistry:**

- One or two quaternary nitrogens, i.e. poorly lipid soluble or highly polar compounds.

- Double acetylcholine molecules linked:
  - End to end.
  - Concealed, bulky semi-rigid ring systems.
Acetylcholine

Succinylcholine

Pancuronium
Neuromuscular Blockers

Pharmacokinetics:
– All given parenterally.
Neuromuscular Blockers

**Pharmacokinetics:**

- **Depolarizing Drugs:**
  - Extremely short duration (5-10 minutes).
  - Metabolized by cholinesterases in the plasma and liver.
  - Only a small percentage reaches the neuromuscular junction, where it diffuses away into the extracellular fluid.
  - Some patients have a genetically abnormal variant of plasma cholinesterase.
  - *Dibucaine Number:* is a measure of the ability of a patient to metabolize succinylcholine.
Table 27–1. Some properties of neuromuscular blocking drugs.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Elimination</th>
<th>Clearance (mL/kg/min)</th>
<th>Approximate Duration of Action (minutes)</th>
<th>Approximate Potency Relative to Tubocurarine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Isoquinoline derivatives</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atracurium</td>
<td>Spontaneous(^1)</td>
<td>6.6</td>
<td>20–35</td>
<td>1.5</td>
</tr>
<tr>
<td>Cisatracurium</td>
<td>Mostly spontaneous</td>
<td>5–6</td>
<td>25–44</td>
<td>1.5</td>
</tr>
<tr>
<td>Doxacurium</td>
<td>Kidney</td>
<td>2.7</td>
<td>&gt; 35</td>
<td>6</td>
</tr>
<tr>
<td>Metocurine</td>
<td>Kidney (40%)</td>
<td>1.2</td>
<td>&gt; 35</td>
<td>4</td>
</tr>
<tr>
<td>Mivacurium</td>
<td>Plasma ChE(^2)</td>
<td>70–95</td>
<td>10–20</td>
<td>4</td>
</tr>
<tr>
<td>Tubocurarine</td>
<td>Kidney (40%)</td>
<td>2.3–2.4</td>
<td>&gt; 35</td>
<td>1</td>
</tr>
<tr>
<td><strong>Steroid derivatives</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancuronium</td>
<td>Kidney (80%)</td>
<td>1.7–1.8</td>
<td>&gt; 35</td>
<td>6</td>
</tr>
<tr>
<td>Pipecuronium</td>
<td>Kidney (60%) and liver</td>
<td>2.5–3.0</td>
<td>&gt; 35</td>
<td>6</td>
</tr>
<tr>
<td>Rocuronium</td>
<td>Liver (75–90%) and kidney</td>
<td>2.9</td>
<td>20–35</td>
<td>0.8</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>Liver (75–90%) and kidney</td>
<td>3–5.3</td>
<td>20–35</td>
<td>6</td>
</tr>
<tr>
<td><strong>Depolarizing agent</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Succinylcholine</td>
<td>Plasma ChE(^2) (100%)</td>
<td>&gt;100</td>
<td>&lt; 8</td>
<td>0.4</td>
</tr>
</tbody>
</table>

\(^1\) Nonenzymatic and enzymatic hydrolysis of ester bonds.
\(^2\) Butyrylcholinesterase (pseudocholinesterase).
Neuromuscular Blockers

**Mechanism of Action**

- **Nondepolarizing Drugs:**
  - Compete with acetylcholine at the nicotinic receptor sites at the NMJ.
  - In high doses, can enter the pore of the ion channel to cause a more intense blockade.
  - Can also block prejunctional sodium channels to interfere with the mobilization of acetylcholine at the nerve ending.
Tubocurarine Acetylcholine

Nicotinic receptor at neuromuscular junction
d-Tubocurarine (no enteral absorption)

Pancuronium

Blockade of ACh receptors
No depolarization of endplate

Relaxation of skeletal muscles
(Respiratory paralysis)

Artificial ventilation necessary (plus general anesthesia!)

Antidote: cholinesterase inhibitors e.g., neostigmine
Neuromuscular Blockers

**Mechanism of Action:**

- **Depolarizing Drugs:**
  
  *Phase I Block (depolarizing):* succinycholine reacts with nicotinic receptors to open the channel and cause depolarization of the motor end plate which will spread to adjacent membranes, causing contractions of muscle motor units.

  Can enter the channel to produce a prolonged “flickering” of the ion conductance.

  The depolarized membranes remain depolarized and unresponsive to subsequent impulses causing flaccid paralysis.

  This phase is augmented by cholinesterase inhibitors.
Neuromuscular Blockers

Mechanism of Action:

- Depolarizing Drugs:
  
  **Phase II Block (desensitizing):** with continued exposure, depolarization decreases and the membrane becomes repolarized and cannot be depolarized again because it is desensitized.

  This may be due to blockade of ion channel, which might be more important than the action of the agonist at the receptor, i.e. the channels behave as if they are in a prolonged closed state.

  This phase is reversed by acetylcholinesterase inhibitors.
A. Action of the depolarizing muscle relaxant succinylcholine

1. Rapid ACh cleavage by acetylcholine esterases
2. Repolarization of end plate
3. New AP and contraction can be elicited

Succinylcholine not degraded by acetylcholine esterases

Persistent depolarization of end plate

New AP and contraction cannot be elicited

Persistent depolarization

No repolarization, renewed opening of Na⁺-channel impossible
Table 27-2. Comparison of a typical nondepolarizing muscle relaxant (rocuronium) and a depolarizing muscle relaxant (succinylcholine).

<table>
<thead>
<tr>
<th></th>
<th>Rocuronium</th>
<th>Succinylcholine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administration of tubocurarine</td>
<td>Additive</td>
<td>Antagonistic</td>
</tr>
<tr>
<td>Administration of succinylcholine</td>
<td>Antagonistic</td>
<td>Additive</td>
</tr>
<tr>
<td>Effect of neostigmine</td>
<td>Antagonistic</td>
<td>Augmented</td>
</tr>
<tr>
<td>Initial excitatory effect on skeletal muscle</td>
<td>None</td>
<td>Fasciculations</td>
</tr>
<tr>
<td>Response to a tetanic stimulus</td>
<td>Unsustained (fade)</td>
<td>Sustained (no fade)</td>
</tr>
<tr>
<td>Posttetanic facilitation</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Rate of recovery</td>
<td>30–60 min</td>
<td>4–8 min</td>
</tr>
</tbody>
</table>

1. It is not known whether this interaction is additive or synergistic (superadditive).
2. The amplitude is decreased, but the response is sustained.
3. The rate depends on the dose and on the completeness of neuromuscular blockade.
Actions of Neuromuscular Blockers

Skeletal Muscle Paralysis:

- **Nondepolarizing Drugs:**
  - Onset of effect is very rapid.
  - Motor weakness followed by flaccidity.
  - Starts with small muscles, large muscles are more resistant to blockade and recover more rapidly. Diaphragm is last to be paralysed.
  - Effects last for 45-60 minutes.
Arrow poison of indigenous South Americans
Actions of Neuromuscular Blockers

Skeletal Muscle Paralysis:
- Nondepolarizing Drugs:
- Depolarizing Drugs:
  - Action starts by transient muscle fasciculations over the chest and abdomen within 30 seconds.
  - Paralysis develops rapidly (within 90 seconds); the arm, neck, and leg muscles; followed by the respiratory muscles.
  - Blockade lasts less than 10 minutes.
<table>
<thead>
<tr>
<th>Difference</th>
<th>Depolarizers</th>
<th>Non-Depolarizers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism of Action</td>
<td>These reach the neuromuscular junction, block receptors and cause depolarization Persistently.</td>
<td>Also called stabilizers. These compete with receptors to cause them not to depolarize and action potential is stopped.</td>
</tr>
<tr>
<td>Effects</td>
<td>First paralyze large muscles (Abdominal &amp; Limb) then Short  muscles (Face, ear, nose) and respiratory muscles in the end.</td>
<td>First paralyze short muscles followed by larger ones and respiratory muscles in the end.</td>
</tr>
<tr>
<td></td>
<td>Effect can not be antagonized.</td>
<td>Effect can be antagonized by reversible inhibitors.</td>
</tr>
<tr>
<td></td>
<td>These directly lead to flaccid paralysis (no tone in muscles).</td>
<td>These stimulate action potential initially for a short while then flaccid paralysis is followed.</td>
</tr>
</tbody>
</table>
Actions of Neuromuscular Blockers

Skeletal Muscle Paralysis.

Cardiovascular Effects:

- Mediated by autonomic or histamine receptors.
- Both sympathetic and parasympathetic ganglia and muscarinic receptors in the heart can be stimulated.
- Usually cause hypotension, which can be attenuated by antihistamines.
Actions of Neuromuscular Blockers

Skeletal Muscle Paralysis.

Cardiovascular Effects.

Hyperkalemia:
- In patients with burns, nerve damage, or neuromuscular disease, head injury, and other trauma.
- Can result in cardiac arrest.
Actions of Neuromuscular Blockers

**Skeletal Muscle Paralysis.**

**Cardiovascular Effects.**

**Hyperkalemia:**

**Increased Intraocular Pressure:**
- Due to tonic contraction of myofibrils or transient dilation of ocular choroidal blood vessels.

**Increased Intragastric Pressure:**
- In obese, heavily muscled, diabetics, traumatic patients, fasciculations of succinylcholine can cause regurgitation and aspiration of gastric contents.

**Muscle Pain:**
- Due to unsynchronized contractions of adjacent muscle fibers just before the onset of paralysis.
Drug Interactions of Neuromuscular Blockers

- **Anesthetics:**
  - Mostly with isoflurane, and least with nitrous oxide.
  - May be due to a central action, increased muscle blood flow.
  - Can cause **Malignant Hyperthermia**.

- **Antibiotics:**
  - Depress release of acetylcholine by blocking specific P-type calcium channels.

- **Local anesthetics and antiarrhythmic Drugs**

- **Other Neuromuscular Blockers**
Spasmolytic Drugs

Diazepam:

- Acts at GABA\textsubscript{A} receptors in the CNS.
- Facilitates GABA- mediated presynaptic inhibition.
- Sedative.
Spasmolytic Drugs

Baclofen:

- Acts at GABA$_B$ receptors, resulting in hyperpolarization and presynaptic inhibition through reducing calcium influx.

- Can also reduce spasticity by inhibiting release of substance P in the spinal cord and other excitatory transmitters.

- Less sedative, but can cause drowsiness.

- Can be given intrathecally.

- Can reduce craving (التوق الشديد); in alcoholics and in migraine.
Spasmolytic Drugs

- **Tizanidine:**
  - Related to clonidine.

- **Gabapentin:**
  - An antiepileptic.

- **Others**
Botulinum Toxin

Produced by *Botulinum* bacteria.
Inhibits acetylcholine release.

Food poisoning; caused by this bacteria; can result, within 12-36 hours, in diplopia, dysphagia, dysarthria, and dyspnea.

Toxin is used for opthalmic purposes, local muscle spasms, and in the cosmetic treatment of facial wrinkles around the eyes and mouth, as well as for generalized spastic disorders like cerebral palsy.
Directly Acting Drugs

Dantrolene:

- Related to phenytoin, an antiepileptic.
- Interferes with excitation-contraction coupling in the muscle fibers by interfering with the release of activator calcium by binding with the ryanodine receptor (RyR) channel of the sarcoplasmic reticulum.
- Can cause weakness, sedation, and hepatitis.
Malignant Hyperthermia

- Rare heritable disorder triggered by a variety of stimuli, including general anesthetics and neuromuscular blockers.
- Patients have a hereditary impairment of the sarcoplasmic reticulum to sequester calcium.
- The trigger can cause sudden and prolonged release of calcium, with massive contraction, lactic acidosis, and increased body temperature.
- Treatment is by cooling, correcting acidosis, and dantrolene to reduce calcium release.