NEUROMUSCULAR BLOCKING AGENTS

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Learning Objectives:

1. Understand the physiology of the neuromuscular junction and the structure and function of nicotinic receptor
2. Understand the mechanisms by which competitive and depolarizing neuromuscular blockers cause paralysis.

I. NEUROMUSCULAR NICOTINIC RECEPTORS.

History: first receptor to be isolated, cloned. High concentration of receptors in electric eel, potent long lasting blocker: α-bungarotoxin. Five receptor subunits forming ion channel. Different subunit isoforms and composition define pharmacological differences among receptors in skeletal muscle, ganglia and CNS.

Active zones contain “docking” sites, quantal release of ACh (10⁴ molecules) causes miniature end plate potential (MEPP), which summate to EPP, trigger action potential in muscle.

ACh receptors are located on the ends of folds. Acetylcholinesterase (AChE) is located in folds. Binding of ACh to receptor leads to opening of ion channel (inward Na⁺, outward K⁺).

Figure 1. The motor endplate
II. **CLASSIFICATION OF NEUROMUSCULAR BLOCKING AGENTS**

See Tables 1,2,3 at end for characteristics of individual NMJ Blocking Agents

A. **Non-depolarizing (competitive) blocking agents** (ie. Tubocurarine)

B. **Depolarizing blocking agents** (ie. Succinylcholine)

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**Acetylcholine:** The binding of Ach to the NMJ N-receptor leads to membrane depolarization and opening of the ‘ion-channel’ allowing the outflow of K+ and inflow of N+ ions. Ach is rapidly metabolized by acetylcholinesterase and the membrane repolarizes leading to closure of the ‘ion-channel’. The triggered muscle action potential travels over the muscle surface and T-tubules to cause the release of calcium from the endoplasmic reticulum and subsequent muscle contraction.

**Depolarizing Drugs:** *Succinylcholine* is the only therapeutically useful neuromuscular blocker that acts as a depolarizing agent. It is effectively a more stable agonist than ACh, undergoing slow inactivation and hence having a much more prolonged duration of action than ACh. Initially, it causes persistent depolarization of the muscle end plate (synaptic target), yielding fasciculations. [This stage is referred to as phase I]. Maintained depolarization will block the ability of ACh to trigger muscle action potentials. With time, succinylcholine will desensitize the muscle nicotinic receptors, resulting in repolarization of the muscle, but the end plate remains blocked, most likely due to succinylcholine blocking the ion channel of the muscle nicotinic receptor. [Sometimes called ‘desensitization block’; this stage is referred to as phase II, clinically not important]. NMJ blockade cannot be reversed by increasing ACh concentration.

**Nondepolarizing Drugs:** The remaining NMJ blockers all act as basic competitive blockers, such as Tubocurarine for ACh at the muscle nicotinic receptors. NMJ blockade can be reversed by increasing ACh concentration (ie with AChE inhibitors). Relaxed, flaccid paralysis.
A. **Competitive (nondepolarizing) Neuromuscular Blocking Agents:**

- Compete with Ach for binding to receptor
- Muscle can still be stimulated directly
- Given intravenously, not well absorbed orally
- Flaccid, relaxed paralysis.
- Paralysis: small, rapidly moving muscles (eyes, fingers); then limbs, neck; last in respiratory muscles (recovery in reverse order)
- Some ganglionic blocking effect and histamine release, resulting in hypotension and tachycardia, bronchospasm. Vecuronium is devoid of these secondary effects.
- Neuromuscular block reversible by inhibitors of acetylcholinesterase e.g. neostigmine

1. **Tubocurarine** (curare: South America arrow poison)
   dimethyltubocarine (metocarine)
   - no effect on nerve transmission
   - in its presence muscle can still be stimulated
   - long onset, 4-6min; long-acting, 80-120min
   - can cause bronchospasm due to histamine release from mast cells
   - can block ganglionic receptors at high concentrations which can lead to hypotension

2. **Pancuronium**
   - more potent than tubocurarine (x5)
   - less histamine release than curare
   - lack of ganglionic blockade

3. **Others:**
   - **Gallamine:** no histamine release, no ganglion block, muscarinic block
   - **Mivacurium:** fast onset, 2-4min; short acting, 12-18min; some histamine release, good substitute for succinylcholine
   - **Rocuronium:** fast onset, 1-2min, short-intermediate, 30-40min, hypersensitivity, good substitute for succinylcholine
   - **Atracurium, Vecuronium, Alcuronium**
4. **Adverse effects and treatment**
   - apnea (loss of breathing)
   - ganglionic blockade (tubocurarine)
   - histamine release leads to bronchospasm (tubocurarine)
   - hypotension due to ganglionic block and secondary due to histamine release (tubocurarine)
   - no significant CNS effects
   - treatment of toxicity with AChE inhibitors (neostigmine)

![Figure 3](image)

**B. Depolarizing Neuromuscular Blocking Agents**

1. **Succinylcholine**
   - Initial depolarization (agonist, transient fasciculations) followed by paralysis.
   - Rapid onset, 1-2min
   - Brief duration (5-10min), due to breakdown by pseudocholinesterase 1/10,000 atypical pseudocholinesterase → long lasting inhibition.
   - Less effects at ganglia or on histamine release.

Persistent action induces depolarization, fasciculations (stimulation then paralysis)

Phase 1 block: -depolarization (potentiated by AChE inhibitors)

Phase 2 block: -desensitization (membrane repolarizes, hyposensitive to Ach)

![Figure 4](image)
3. **Adverse effects**
   
a. similar to competitive blockers
b. use of AChE inhibitors will not reverse NMJ blockade
c. **Malignant hyperthermia** (more likely with halothane)
   65% mortality, treat immediately with dantrolene (drug of choice, inhibits calcium release)
d. **Hyperkalemia** → cardiac arrest
   (more common in trauma and burn patients, develops slowly in 4-6 days)
e. **Prolonged paralysis** due to atypical or low circulating pseudocholinesterase
f. **Rocurarium** (liver metabolism) or **Mivacurium** are often used as substitutes when succinylcholine is not suitable

**Malignant Hyperthermia**: is a life-threatening disease, also referred to as a syndrome, which occurs when a person with malignant hyperthermia (MH) susceptibility trait is exposed to triggering factors, which include succinylcholine and most inhalational anesthetics (though not Nitrous Oxide). Classic Malignant Hyperthermia is characterized by hypermetabolism, (increased oxygen consumption and increased carbon dioxide production), increased calcium release, muscle rigidity, muscle injury, and increased sympathetic nervous system activity. Hypermetabolism reflected by elevated carbon dioxide production precedes the increase in body temperature. Halothane and Caffeine contracture tests used to examine patients suspected of being MH susceptible. Prompt administration of Dantrolene (DOC) required for treatment.

**Prolonged paralysis**: Succinylcholine is metabolized by plasma (pseudo) cholinesterase. Metabolism is normally complete within 5-10 minutes. Some patients lack this enzyme or have an altered enzyme that does not metabolize succinylcholine as rapidly. These patients may remain paralysed for many hours after a standard dose of succinylcholine, and must be kept anaesthetised and ventilated until the succinylcholine has been eliminated by other slower methods (ie. excretion).

**Hyperkalemia**: can occur in some patients after succinylcholine administration and can be severe and fatal. Up-regulation of ACh N-receptors can occur after burn injury, severe muscle trauma, upper or lower motor neuron denervation (e.g., stroke or spinal cord injury). The increased receptors can lead to excessive increase in plasma K+ levels due to membrane depolarization following succinylcholine administration. Develops in 4-6 days.

**Question**: Atypical pseudocholinesterase would cause problems with succinylcholine, does it increase the effects of non-depolarizing drugs such as mivacurium that are AchE metabolized.

**Answer**: Yes, if plasma cholinesterase activity is low (ie atypical pseudocholinesterase), then the actions of competitive NMJ blockers that are metabolized by AchE would also be prolonged. However unlike succinylcholine, the NMJ-blockade with the competitive NMJ blockers can be reversed with cholinesterase inhibitors such as neostigmine. This is not possible with succinylcholine, it would only make the blockade deeper. Rocurarium (liver metabolism) can be used as a substitute when use of succinylcholine.is not advised.
C. Clinical Uses of Neuromuscular Blocking Agents

1. Muscle relaxation in surgery
   a. Muscle relaxation decreases depth of anesthesia needed (decreases risk of respiratory and cardiovascular depression)

   Note synergism with certain agents necessitates dose reduction
   • calcium channel blockers (\(\downarrow\) Ach release)
   • aminoglycoside antibiotics (\(\downarrow\) Ach release & stabilize membrane)
   • certain general anesthetics eg. halothane (stabilize membrane)

   b. Orthopedics: dislocations, alignment of fractures

   c. Facilitate intubation in mechanical artificial ventilation

   d. Facilitation of laryngoscopy, bronchoscopy, esophagoscopy

2. Prevent trauma during electroshock therapy

3. Diagnostic (tubocurarine: myasthenia gravis ie. makes it worse, not recommended)

D. Direct Acting Neuromuscular Relaxant

   • dantrolene (Dantrium) inhibits calcium release from SR
   • significant liver toxicity, muscle weakness
   • used to treat malignant hyperthermia (DOC, drug of choice)
   • used in stroke, cerebral palsy, multiple sclerosis, muscle spasticity/rigidity

Other agents used as muscle relaxants (e.g. benzodiazepines) will be discussed in the CNS portion of the course.
Table 1. Autonomic Effects of Neuromuscular Blocking Drugs

<table>
<thead>
<tr>
<th></th>
<th>Ganglia</th>
<th>Muscarinic</th>
<th>Histamine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Succinylcholine</strong></td>
<td>Stimulates</td>
<td>Stimulates</td>
<td>Slight release</td>
</tr>
<tr>
<td><strong>Tubocurarine</strong></td>
<td>Moderate block</td>
<td>None</td>
<td>Moderate release</td>
</tr>
<tr>
<td><strong>Metaocurine</strong></td>
<td>Blocks weakly</td>
<td>None</td>
<td>Slight release</td>
</tr>
<tr>
<td><strong>Gallamine</strong></td>
<td>None</td>
<td>Blocks strongly</td>
<td>None</td>
</tr>
<tr>
<td><strong>Pancuronium</strong></td>
<td>None</td>
<td>Blocks weakly</td>
<td>None</td>
</tr>
<tr>
<td><strong>Vecuronium</strong></td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td><strong>Atracurium</strong></td>
<td>None</td>
<td>None</td>
<td>Slight release</td>
</tr>
<tr>
<td><strong>Rocuronium</strong></td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td><strong>Mivacurium</strong></td>
<td>None</td>
<td>None</td>
<td>Slight release</td>
</tr>
</tbody>
</table>

Table 2. Comparison of Competitive (d-Tubocurarine) and Depolarizing (Succinylcholine) Agents

<table>
<thead>
<tr>
<th></th>
<th>d-Tubocurarine</th>
<th>Succinylcholine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase I</strong></td>
<td>An tagonistic</td>
<td>Additive</td>
</tr>
<tr>
<td><strong>Phase II</strong></td>
<td>Antagonistic</td>
<td>Augmented</td>
</tr>
<tr>
<td><strong>Addition of succinylcholine</strong></td>
<td>An tagonistic</td>
<td>Additive</td>
</tr>
<tr>
<td><strong>Addition of tubocurarine</strong></td>
<td>Additive</td>
<td>Antagonistic</td>
</tr>
<tr>
<td><strong>Effect of neostigmine</strong></td>
<td>An tagonistic</td>
<td>Augmented</td>
</tr>
<tr>
<td><strong>Initial effect on striated</strong></td>
<td>None</td>
<td>Fasciculations</td>
</tr>
<tr>
<td><strong>Response to tetanic stimulation</strong></td>
<td>Unsustained</td>
<td>Sustained</td>
</tr>
</tbody>
</table>

Table 3. Onset, Duration and Elimination of Neuromuscular Blocking Drugs

<table>
<thead>
<tr>
<th></th>
<th>Onset (min)</th>
<th>Duration (min)</th>
<th>Mode of elimination</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Succinylcholine</strong></td>
<td>1-2</td>
<td>6-8</td>
<td>Hydrolysis by AChE</td>
</tr>
<tr>
<td><strong>Tubocurarine</strong></td>
<td>4-6</td>
<td>80-120</td>
<td>Kidney, liver</td>
</tr>
<tr>
<td><strong>Metaocurine</strong></td>
<td>4-6</td>
<td>80-120</td>
<td>Kidney</td>
</tr>
<tr>
<td><strong>Gallamine</strong></td>
<td>4-6</td>
<td>80-120</td>
<td>Kidney</td>
</tr>
<tr>
<td><strong>Pancuronium</strong></td>
<td>4-6</td>
<td>80-120</td>
<td>Kidney, liver</td>
</tr>
<tr>
<td><strong>Vecuronium</strong></td>
<td>2-4</td>
<td>30-40</td>
<td>Kidney, liver</td>
</tr>
<tr>
<td><strong>Atracurium</strong></td>
<td>2-4</td>
<td>30-40</td>
<td>Hydrolysis by AChE</td>
</tr>
<tr>
<td><strong>Pipecuronium</strong></td>
<td>2-4</td>
<td>80-100</td>
<td>Kidney, liver</td>
</tr>
<tr>
<td><strong>Rocuronium</strong></td>
<td>1-2</td>
<td>30-40</td>
<td>Liver</td>
</tr>
<tr>
<td><strong>Mivacurium</strong></td>
<td>2-4</td>
<td>12-18</td>
<td>Hydrolysis by AChE</td>
</tr>
</tbody>
</table>