Neuromuscular Blockers

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Objectives

After this lecture, you should be able to:

• Describe the physiology of the neuromuscular junction
• Differentiate the two types of neuromuscular blockers
• Identify the uses of neuromuscular blockers
History

- South American indigenous people used curare (extract of vines *Chondrodendron tomentosum* and *Strychnos toxifera*) on the tips of arrows and the darts of blowguns for hunting → death resulted from asphyxiation (respiratory arrest)
• In 1811, Brodie showed that curare is not lethal if the animal is ventilated
• In 1844, Bernard found that curare works by blocking conduction of nerve impulse to muscle fibre
• In 1935, King isolated the main active ingredient, d-tubocurarine, from a crude sample of curare and established its chemical structure
• In 1942, Griffith and Johnson in Montreal used curare to facilitate muscle relaxation in a patient undergoing an appendectomy (to supplement anesthesia)

“We continued to use the drug cautiously in selected cases, becoming increasingly confident that we had hit upon something to make the anaesthetist’s dream regarding relaxation come true.” (Griffith, 1945)
Skeletal Muscle Contraction

- Skeletal muscle is made up of elongated muscle fibres bundled together and has an abundant supply of blood vessels and nerves.
- Contraction of skeletal muscle is controlled by the somatic nervous system (voluntarily controlled).
- Signals originate from the brain and travel to motor neurons that innervate skeletal muscle fibres.
Neuromuscular Junction

• An intermediary between motor neurons and the skeletal muscle

• Neuromuscular junction consists of
  – Prejunctional motor nerve ending
  – Highly folded postjunctional skeletal muscle membrane (motor end-plate)
  – Synaptic cleft in between (~20 nm)

• The neurotransmitter at the neuromuscular junction is _________________
Acetyl-CoA + choline \[\rightarrow\] ACh

Ca & Mg compete same channel

Voltage-gated Na⁺ channel

Acetylcholine receptor site

Acetylcholinesterase

Chemically gated cation channel
(Nicotinic cholinergic receptor)

Motor end plate

Local current flow between depolarized end plate and adjacent membrane opens voltage-gated Na⁺ channels, reducing the potential to threshold and initiating an action potential in the adjacent membrane

Contractile elements within muscle fiber

Source: http://medicalkiss.blogspot.ca
Synaptic Transmission at the Neuromuscular Junction

1. An action potential conducted down the axon of a motor neuron ends in the prejunctional motor nerve ending
2. The arrival of an action potential leads to the opening of voltage-gated Ca\(^{2+}\) channels at the axon terminal
3. The resulting influx of Ca\(^{2+}\) causes exocytosis of ACh-containing vesicles into the synaptic cleft
4. The released ACh diffuses across the synaptic cleft and binds to nicotinic cholinergic receptors on the motor end-plate, which increases the channels’ permeability to Na\(^+\)/K\(^+\)
5. Net influx of Na\(^+\) causes the resting membrane potential (-90 mV) to increase, creating a local depolarization at the motor end-plate known as end-plate potential.

6. If the threshold potential (-55 mV) is reached, an “all-or-none” action potential is generated and propagated across the surface of skeletal muscle fibres via opening of voltage-gated Na\(^+\) channels outside the motor end-plate, resulting in muscle contraction.

7. ACh is rapidly hydrolyzed in the synaptic cleft by the enzyme acetylcholinesterase (within a few msec), allowing the membrane to restore (repolarize) to resting membrane potential.
End-plate potential is generated by opening of nicotinic cholinergic receptors, whereas action potential is generated by opening of voltage-gated Na\(^+\) channels.
Action of Neuromuscular Blockers

- Bind to nicotinic cholinergic receptors, which are ligand-gated cation channels, at the neuromuscular junction
- Only block synaptic transmission at skeletal muscles – do not affect nerve transmission and action potential generation

Cause temporary paralysis of skeletal muscles and muscle relaxation!!!
Structure

• Similar to ACh
• Contains 1-2 quaternary nitrogens – decreases lipid solubility and limits CNS penetration
• All administered parentally due to low lipid solubility
**Depolarizing Neuromuscular Blockers**

- **ACETYLCHOLINE**

- **SUCCINYLCHOLINE**
- **DECAMETHONIUM**

**Non-depolarizing Neuromuscular Blockers**

- **TUBOCURARINE**
- **PANCURONIUM**
Classification

1. Depolarizing neuromuscular blockers
   - succinylcholine (SCh)

2. Non-depolarizing neuromuscular blockers
   Isoquinoline derivatives - d-tubocurarine
   Steroid derivatives - pancuronium
Succinylcholine (SCh)

- The only depolarizing neuromuscular blocker in clinical use
- Very rapid onset of action (<1 min)
- Short duration of action (5-10 min)
- Acts as an ______ at the nicotinic cholinergic receptor (similar action to ACh, but longer acting)
• Hydrolyzed by butyrylcholinesterase or pseudocholinesterase, which are not found in the synaptic cleft (much slower than hydrolysis of ACh by acetylcholinesterase)

• Actions _________ by cholinesterase inhibitors (increase the level of SCh by preventing its degradation)

• Common side effects: bradycardia, hyperkalemia, muscle pain
Mechanism of Action

Phase 1: Depolarizing Block

• Muscle paralysis is preceded by initial series of muscle twitches (fasciculations)

• Blocks synaptic transmission by causing a relatively long-term, persistent depolarization (compared to ACh), as the nicotinic cholinergic receptors do not close immediately

• The depolarized membrane is unresponsive to subsequent impulses, since voltage-gated Na\(^+\) channels remain in the inactivated state
Voltage-gated Na\(^+\) Channel

- **Resting State**
  - (at resting potential / after repolarization)
- **Activated State**
  - (threshold potential reached)
- **Inactivated State**
  - (unresponsive to impulses)

Na\(^+\) only pass when both gates are open

Depolarizing block by SCh

Polarization of the resting motor end-plate and muscle (M) membrane

M Membrane

Motor End-Plate

M Membrane

Outside

Inside

A) Resting State

B) Activated State

C) Inactivated State

Depolarization of the end-plate triggers a wave of depolarization (action potential) to move down the entire muscle membrane

Source: Lehne et al. Pharmacology for Nursing Care, 8th edition, Chapter 16.
Phase 2: Desensitizing Block

- Observed after prolonged exposure to SCh
- Repolarization occurs, but because SCh is hydrolyzed more slowly than ACh, continuous activation by SCh can “desensitize” the receptors
- Receptors will become less sensitive to ACh even in the absence of SCh
- Mechanism by which desensitization occurs is not known
- Resembles blockade produced by non-depolarizing neuromuscular blockers
Non-depolarizing Blockers

- Slower onset (2-3 min) and longer duration (20-120 min) of action compared to SCh
- Act as _____________________ to block the nicotinic cholinergic receptors
- Prevent receptor activation by ACh
- Actions _______ by cholinesterase inhibitors (increase the level of ACh to re-establish neuromuscular transmission)
Non-depolarizing neuromuscular blockers prevent the end-plate potential from reaching threshold, therefore no action potential can be generated.

Isoquinoline Derivatives
(d-tubocurarine)

- High potency
- Lack of vagolytic effect
- Tendency to release histamine (i.e. cause hypotension, tachycardia, bronchospasm)
- Excreted by kidney
Steroid Derivatives
(pancuronium)

- High potency
- Exhibit vagolytic effects (i.e. cause tachycardia)
- Lack of histamine release
- Excreted by kidney and metabolized by liver
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<th>Drug</th>
<th>Effect on Autonomic Ganglia</th>
<th>Effect on Cardiac Muscarinic Receptors</th>
<th>Tendency to Cause Histamine Release</th>
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<tr>
<td>Succinylcholine</td>
<td>Stimulation</td>
<td>Stimulation</td>
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Clinical Uses

- Facilitate tracheal intubation
- Improve intraoperative surgical conditions by inducing muscle relaxation
- Decrease the dose of general anesthetics required during surgical procedures
- Manage critically ill patients requiring mechanical ventilation (by suppressing spontaneous ventilation)
Neuromuscular blocking agents improve intubating conditions and reduce vocal cord sequelae. The graph depicts the incidence of excellent and acceptable (defined as good or excellent) intubating conditions after atracurium or saline. The percentage of patients who reported hoarseness and those with vocal cord lesions documented by stroboscopy is also shown.

Surgeon's assessment of muscle relaxation during lower abdominal surgery. Rating goes from 1 (excellent) to 4 (poor). The incidence of poor rating was greater in patients not given vecuronium (29%) compared with those who received the drug (2%).

Points to Remember

• Neuromuscular blockers only produce skeletal muscle paralysis, not anesthesia
• Neuromuscular blockers act by binding to nicotinic cholinergic receptors at the neuromuscular junction
Neuromuscular Blockers

Non-depolarizing Blockers

- Competitive Antagonists
  - Isoquinoline Derivatives: d-tubocurarine
  - Steroid Derivatives: pancuronium

Depolarizing Blockers

- Agonists: succinylcholine