Pharmacology of the Neuromuscular Junction (NMJ)

Edward JN Ishac, Ph.D.
Professor

Smith Building, Room 742
eishac@vcu.edu
828 2127

Department of Pharmacology and Toxicology
Medical College of Virginia
Campus of Virginia Commonwealth University
Richmond, Virginia, USA

Autonomic Nervous System

NERVOUS SYSTEM

Central Nervous System

Peripheral Nervous System

AUTONOMIC NERVOUS SYSTEM

Sympathetic
- Thoracolumbar
  - T1-12, L1-3
- "Flight or Fight"
  - TBP, THR, JGIT

Parasympathetic
- Craniosacral
  - Cranial N. III, VII, IX, X
  - Sacral S2-3
- "Feeding & Breeding"
  - JBP, JHR, JGIT

FUNCTIONS CONTROLLED
- Respiration
- Circulation
- Body Temperature
- Metabolism
- Sweating
- Secretions

CENTRAL INVOLVEMENT
- Hypothalamus - integration, body temp & water balance
- Medulla - BP, respiration
- Cerebral cortex - somatic NS & ANS integration

Afferent Division

Somatic Voluntary

Parasympathetic Nervous System

Sympathetic Nervous System

Efferent Division

Autonomic Voluntary Visceral Vegetative
Neurons of the ANS

Cardiac and smooth muscle, gland cells, nerve terminals

Parasympathetic

Sweat glands

Sympathetic

Cardiac and smooth muscle, gland cells, nerve terminals

Renal vascular smooth muscle

Somatic

Skeletal muscle

Neuromuscular Junction

FIG. 20 The Motor Endplate

MYELIN SHEATH
axon
NODE OF RANVIER
TERMINAL MEMBRANE
SUBNEURAL SPACE
POSTJUNCTIONAL MEMBRANE
SCHWANN CELL
MITOCHONDRIA
NUCLEUS
SARCOPHASM
MYOFIBRILL
TRANVERSE TUBULAR SYSTEM (TTS)

NERVE ACTION POTENTIAL (AP)
ACETYLCHOLINE RELEASE
DEPOLARIZATION (EPPI)
(INCREASED PERMEABILITY TO Na⁺ AND K⁺)
MUSCLE ACTION POTENTIAL (MAP)
SPREAD OF EXCITATION IN MUSCLE VIA TTS
MUSCLE CONTRACTION
Myasthenia gravis
Autoimmune disease

1:10,000 (250,000 USA)
- antibodies to NMJ nicotinic receptors leads to degradation
- simplified synaptic folds
- normal nerve terminal and transmitter
- wider synaptic junction

Diagnosis: Edrophonium (Tensilon, short acting) is used for diagnosis and determination of maintenance dose

Treatment: Neostigmine has direct (stimulates receptor) and indirect actions (inhibition of AchE). No CNS activity.

NMJ Nicotinic Receptor

Ion Channel
- pentamer
- Na⁺ in
- K⁺ out

Infant: α₂βδε
Adult: α₂βδγ
Paralysis: small rapidly moving muscles (eyes, fingers), then limbs, last is respiratory muscles (recovery in reverse order)

- **Competitive (non-depolarizing) agents (curare)**
  - compete with Ach for binding to receptor
  - flaccid, relaxed paralysis
  - non-NMJ effects: ganglia, muscarinic blocking, histamine release
  - NMJ block can be reversed by AchE inhibitors

- **Non-competitive (depolarizing) agents (succinylcholine)**
  - membrane depolarization
  - transient fasciculations followed by paralysis
  - desensitization
  - membrane repolarizes, hyposensitive to Ach
  - NMJ block not reversed by AchE inhibitors
Competitive (nondepolarizing) Blocking Agents - Curare

- **Tubocurarine, dimethyltubocarine (metocarine)**
  - no effect on nerve transmission
  - muscle can still be stimulated
  - 5-10mg (iv) produces flaccid paralysis
  - 10-20mg (iv) can produce apnea, not active orally
  - can cause histamine release (mast cells)
  - can block ganglionic receptors [higher concentrations]

Amazon hunter tips his darts with the poison curare

Sources of Curare

- Poison-arrow frogs
- Strychnos toxifera (Curare)
Competitive (nondepolarizing) NMBs - Others

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

- **Rocuronium**
  - fast onset (1-2min), 30-40min duration, hypersensitivity

- **Atracurium** (~10 isomers)
  - hydrolysis by AchE
  - replaced by **cisatracurium**, Hoffmann degradation, organ independent

- **Gallamine**
  - also some muscarinic block

- **Mivacurium**
  - fast onset (2-4min), short acting (12-18min), hydrolysis by AchE, some histamine release

Adverse Effects and Treatment

- **Adverse effects**:
  - apnea (loss of respiration)
  - ganglionic blockade (tubocurarine)
  - histamine release (tubocurarine)
  - muscarinic block (gallamine)
  - hypotension (histamine release & ganglionic block)
  - no significant CNS effects

- **Treatment of toxicity**:
  - Acetylcholinesterase inhibitors ie. neostigmine
Depolarizing NMJ Blocking Agents

- **Succinylcholine** (decamethonium, not used)
  - Phase 1: depolarization, Phase 2: desensitization
  - fast onset (<1min), brief duration (5-10min)
  - metabolized by pseudocholinesterase
  - 'atypical' pseudo-AchE (1:10,000, long-lasting)
  - less histamine release than curare
  - less effect at ganglia than curare
  - not reversed by AchE inhibitors

Succinylcholine: Adverse effects & treatment

- **Toxicity:**
  - similar to competitive blockers with less effects at ganglia or histamine release

- **Treatment:**
  - Artificial respiration
  - use of AChE inhibitors will not reverse NMJ blockade

- **Adverse reactions:**
  - 'Atypical' pseudo-AchE (1:10,000, prolonged apnea, 2-3hr)
  - Hyperkalemia (esp. burn, trauma patients, response delayed 2-7 days)
  - Malignant hyperthermia (esp. with halothane)
Drugs Involved in Surgery Drug Errors

- Local anesthesia 9.3%
- Hypnotics 6.3%
- Epi 8.3%
- Cardiovascular agents 4.9%
- Antibiotics 3.9%
- Nondepolarizing NMBs 3.4%
- Opioids 11.7%
- Inhalational agents 13.2%
- Succinylcholine 17.1%
- Misc.* 22%

*The miscellaneous category includes insulin, potassium chloride, heparin, protamine and others.

Hyperkalemia

- burn & trauma
- usually small ↑K+
- cardiac arrest
- support: dialysis glucose / insulin

Hyperkalemia

<table>
<thead>
<tr>
<th>Concentration (mM)</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Normal</td>
</tr>
<tr>
<td>5</td>
<td>Mild</td>
</tr>
<tr>
<td>6.5</td>
<td>Moderate</td>
</tr>
<tr>
<td>7.0</td>
<td>Severe</td>
</tr>
<tr>
<td>8.0</td>
<td>Life-threatening</td>
</tr>
<tr>
<td>9.0</td>
<td>Cardiac arrest</td>
</tr>
</tbody>
</table>

Epi = epinephrine
NMB = neuromuscular blocker
Malignant Hyperthermia

- more likely with halothane
- 60% mortality
- $\uparrow$Ca++ $\rightarrow$ body temp
- tachycardia
- dysrhythmia
- $\uparrow$HR, muscle rigidity

Treatment:
- Dantrolene
- drug of choice
- $\downarrow$Ca++ release

Clinical Uses of NMJ Blocking Agents

- Muscle relaxation in surgery
  - decreases depth of anesthesia
- Orthopedics
  - dislocations, alignment of fractures
- Facilitate intubations
  - in mechanical artificial ventilation
- Facilitate internal examinations
  - laryngoscopy, bronchoscopy, esophagoscopy
- Prevent trauma
  - during electroshock therapy
- Diagnostic
  - tubocurarine (Myasthenia gravis), not commonly used not recommended, Edrophonium (Tensolin) better
NMJ Agents: Drug Interactions

Synergism with certain agents $\rightarrow \downarrow$ dose

Calcium channel blockers ie. verapamil
- $\downarrow$ Ach release

Aminoglycoside antibiotic ie. neomycin
- compete with Ca$^{++}$
- $\downarrow$ Ach release & stabilize membrane

Certain general anesthetic ie. halothane
- stabilize membrane

Direct Acting Neuromuscular Relaxant

- Dantrolene (Dantrium)
  - inhibits calcium release
  - significant liver toxicity
  - muscle weakness

- Clinical uses:
  - stroke
  - cerebral palsy
  - malignant hyperthermia (DOC)
  - multiple sclerosis

- Other agents
  - Benzodiazepines
### Comparison of Competitive (d-Tubocurarine) and Non-competitive, depolarizing (Succinylcholine) Agents

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

### NMJ Blocking Agents – Other Actions

<table>
<thead>
<tr>
<th></th>
<th>Ganglia</th>
<th>Muscarinic Receptors</th>
<th>Histamine Release</th>
</tr>
</thead>
<tbody>
<tr>
<td>Succinylcholine</td>
<td>Stimulates</td>
<td>Stimulates</td>
<td>Slight</td>
</tr>
<tr>
<td>Tubocurarine</td>
<td>Blocks</td>
<td>None</td>
<td>Moderate</td>
</tr>
<tr>
<td>Metaocurine</td>
<td>Blocks weakly</td>
<td>None</td>
<td>Slight</td>
</tr>
<tr>
<td>Gallamine</td>
<td>None</td>
<td>Blocks strongly</td>
<td>None</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>None</td>
<td>Blocks weakly</td>
<td>None</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Atracurium</td>
<td>None</td>
<td>None</td>
<td>Slight</td>
</tr>
<tr>
<td>Rocuronium</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Mivacurium</td>
<td>None</td>
<td>None</td>
<td>Slight</td>
</tr>
</tbody>
</table>
### Onset, Duration and Elimination of Neuromuscular Blocking Drugs

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

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**Succinylcholine**

"Boy! That new sleeping drug really works fast!"

Rapid onset and short duration, this sucks! What are we going to name it?