

Pharmacology of the Neuromuscular Junction (NMJ)

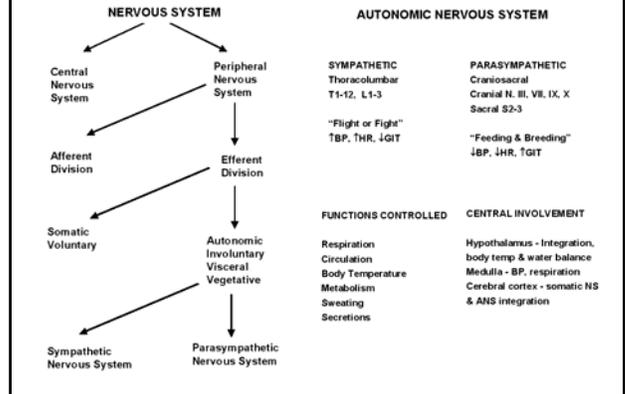
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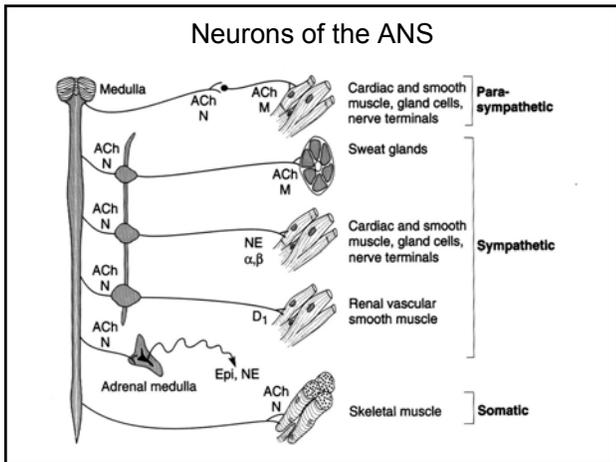


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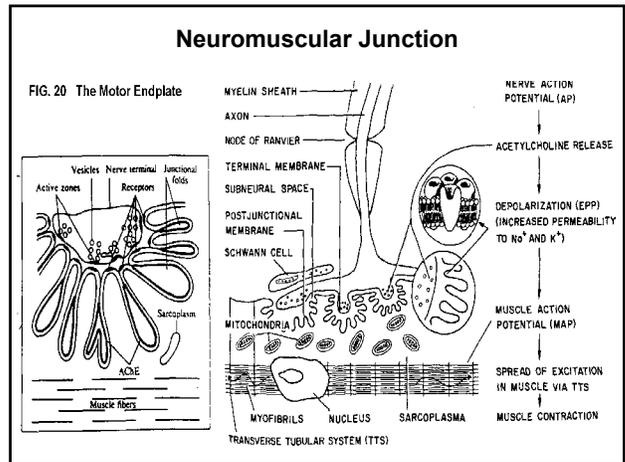
Autonomic Nervous System



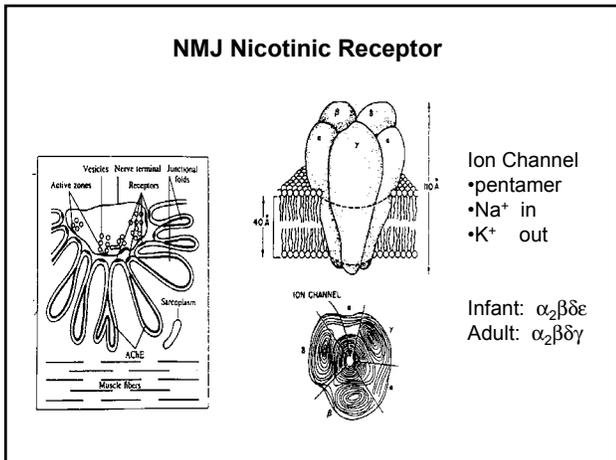
Neurons of the ANS



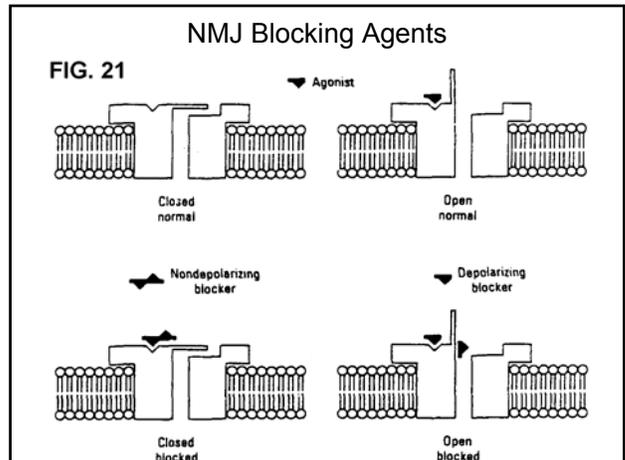
Neuromuscular Junction



NMJ Nicotinic Receptor



NMJ Blocking Agents



NMJ Blocking Agents

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)**
 - Phase 1 block:
 - membrane depolarization
 - transient fasciculations followed by paralysis
 - Phase 2 block:
 - desensitization
 - membrane repolarizes, hyposensitive to Ach
 - NMJ block not reversed by AchE inhibitors

Competitive (nondepolarizing) Blocking Agents - Curare

- **Tubocurarine, dimethyltubocurarine (metocurarine)**
 - 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 [high concentration]



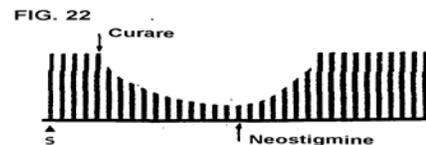
A Amazon hunter tips his darts with the poison curare

Competitive (nondepolarizing) Blocking Agents - Others

- **Pancuronium**
 - more potent than tubocurarine (x5)
 - reduced histamine release than curare
 - lack of ganglionic blockade
- **Gallamine**
 - also some muscarinic block
- **Mivacurium**
 - short acting, hydrolysis by AchE
- **Atracurium**
 - hydrolysis by AchE

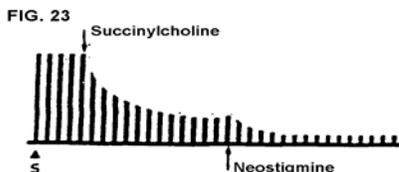
Adverse Effects and Treatment

- **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



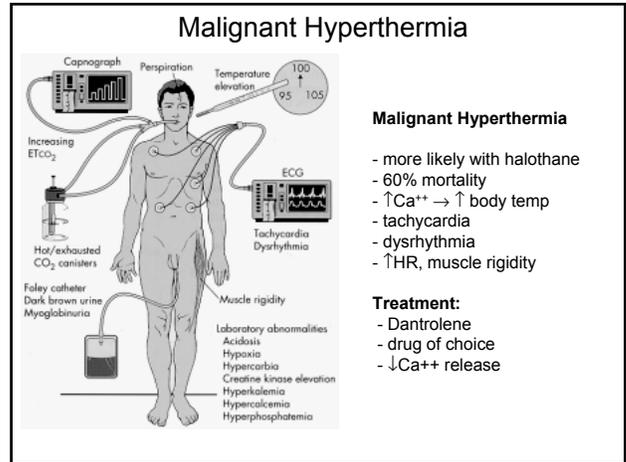
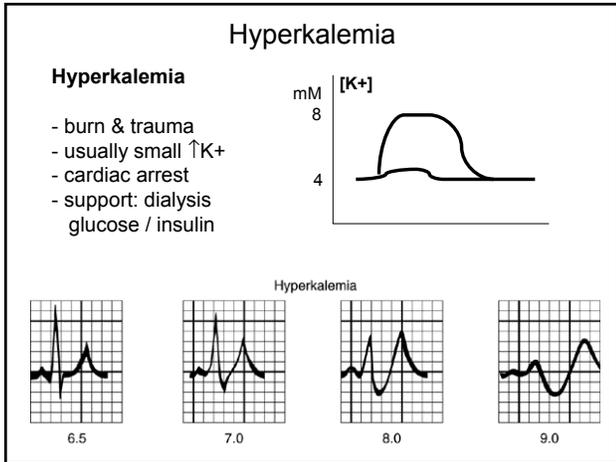
Depolarizing NMJ Blocking Agents

- **Succinylcholine** (decamethonium, not used)
 - Phase 1: depolarization, Phase 2: desensitization
 - 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

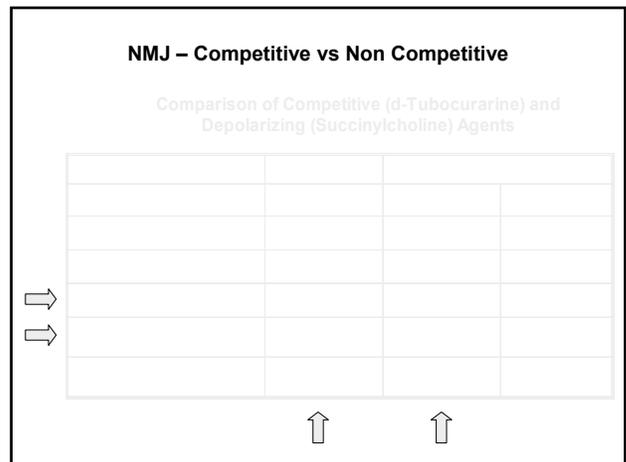
- **Toxicity:**
 - similar to competitive blockers with less effects at ganglia or histamine release
- **Treatment:**
 - Artificial respiration
 - use of AchE inhibitors will not reverse NMJ blockade
- **Adverse reactions:**
 - 'Atypical' pseudo-AchE (1:10,000, prolonged apnea, 2-3hr)
 - Hyperkalemia (esp. burn, trauma patients)
 - Malignant hyperthermia (esp. with halothane)



- ### 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



NMJ Blocking Agents – Other Actions

	Ganglia	Muscarinic Receptors	Histamine Release
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NMJ – Onset, Duration & Elimination

Onset, Duration and Elimination of Neuromuscular Blocking Drugs

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Succinylcholine

