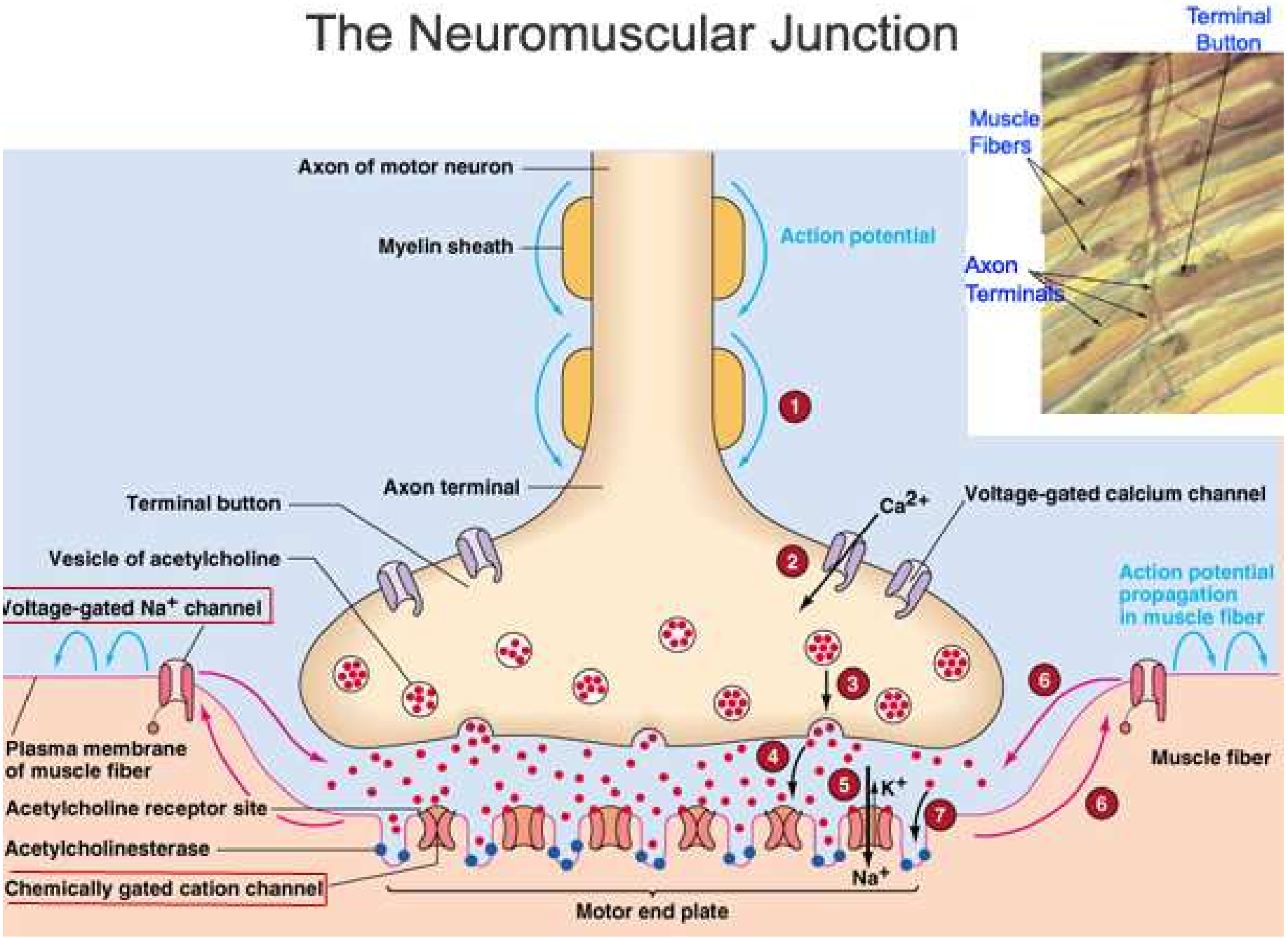
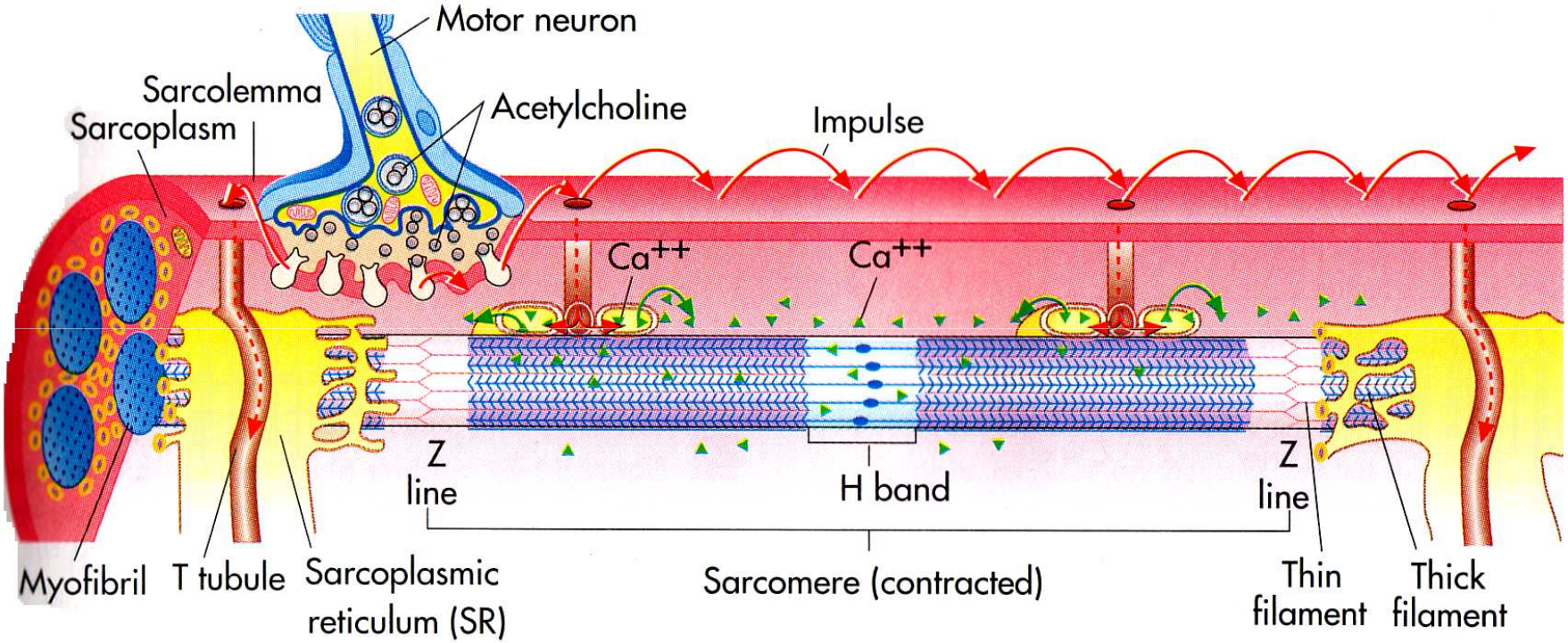
The Neuromuscular Junction




Motor neuron
Sarcolemma
Sarcoplasm
Acetylcholine
Impulse
Ca++
Ca++
Z line
H band
Z line
Myofibril
T tubule
Sarcoplasmic reticulum (SR)
Sarcomere (contracted)
Thin filament
Thick filament

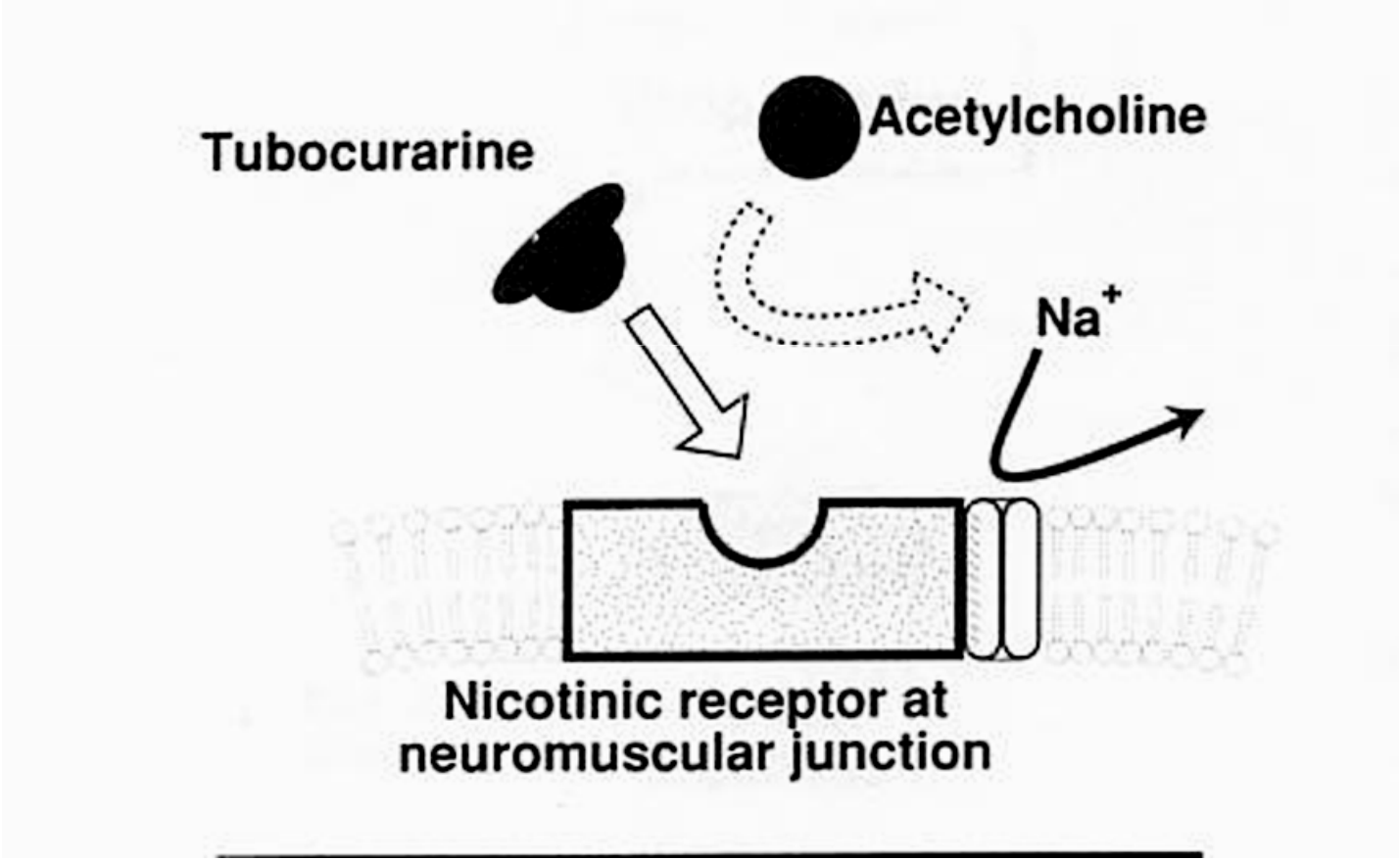
Major Events in Neuromuscular Transmission

- Motor neuron depolarization causes action potential to travel down the nerve fiber to the neuromuscular junction (1).
- Depolarization of the axon terminal causes an influx of Ca^{2+} (2) which triggers fusion of the synaptic vesicles (3) and release of neurotransmitter (Acetylcholine; ACh) (4).
- ACh diffuses across the synaptic cleft and binds to post-synaptic ACh receptor (AChR) located on the muscle fiber at the motor end-plate (5).
- Binding of ACh to AChRs opens the channels causing an influx of Na (5), depolarization of the sarcolemma that travels down the t-tubules (6) and ultimately causes the release of Ca^{2+} from the sarcoplasmic reticulum - CONTRACTION.
- Unbound ACh in synaptic cleft defuses away or is hydrolyzed (inactivated) by acetylcholinesterase (AChE) (7).

Two main Types of Neuromuscular Blocking Drugs

- Nondepolarizing (competitive)
- Depolarizing

Mechanism of Action of Nondepolarizing Neuromuscular Blocking Drugs



Non-depolarizing (competitive).

- Prototype of Non-depolarizing is tubocurarine (new generation: pancuronium and gallamine).
- Mechanism of Action: In small clinical doses they act the predominantly at the nicotinic receptor site to block ACh.
- At higher does they can block prejunctional Na channels thereby decreasing ACh release.

- Because of the competitive nature of the postsynaptic blockade, transient relief of the block can be achieved by increasing ACh levels at the synaptic cleft (i.e. use cholinesterase inhibitors).

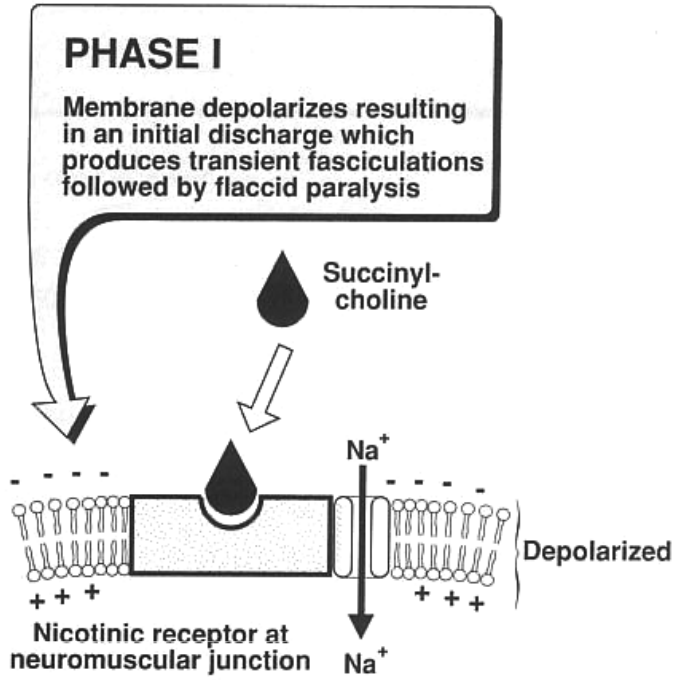
Nondepolarizing Agents

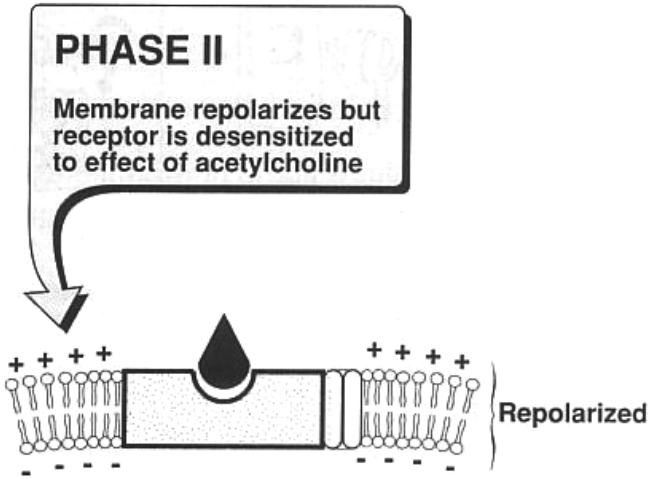
- **Therapeutic Use:** Adjuvant drugs in surgical anesthesia
- **Pharmacology:** Must be given by injection because they are poorly absorbed orally. Do not cross the BBB. Generally excreted unchanged (i.e. not metabolized).
- **Adverse Effects:** Tubocurarine causes release of histamine from mast cells – decrease in blood pressure, bronchospasms, skin wheals. Newer generation don't.

Drug Interactions:

- Cholinesterase Inhibitors decrease the effectiveness of nondepolarizing agents
- Aminoglycoside antibiotics (e.g. streptomycin) decrease ACh release by competing with Ca^{2+} – increase action of nondepolarizing drugs
- Calcium channel blockers increase the actions of nondepolarizing drugs by decreasing the amount of ACh released (i.e. increase action of nondepolarizing drugs)
- Halogenated carbon anesthetics (e.g. Isoflurane) enhance neuromuscular blockade by 1) decreasing excitability of motoneurons, 2) increasing muscle blood flow, and 3) decreased kinetics of AChRs (increase action of nondepolarizing drugs)

Depolarizing Agents





Depolarizing Agents

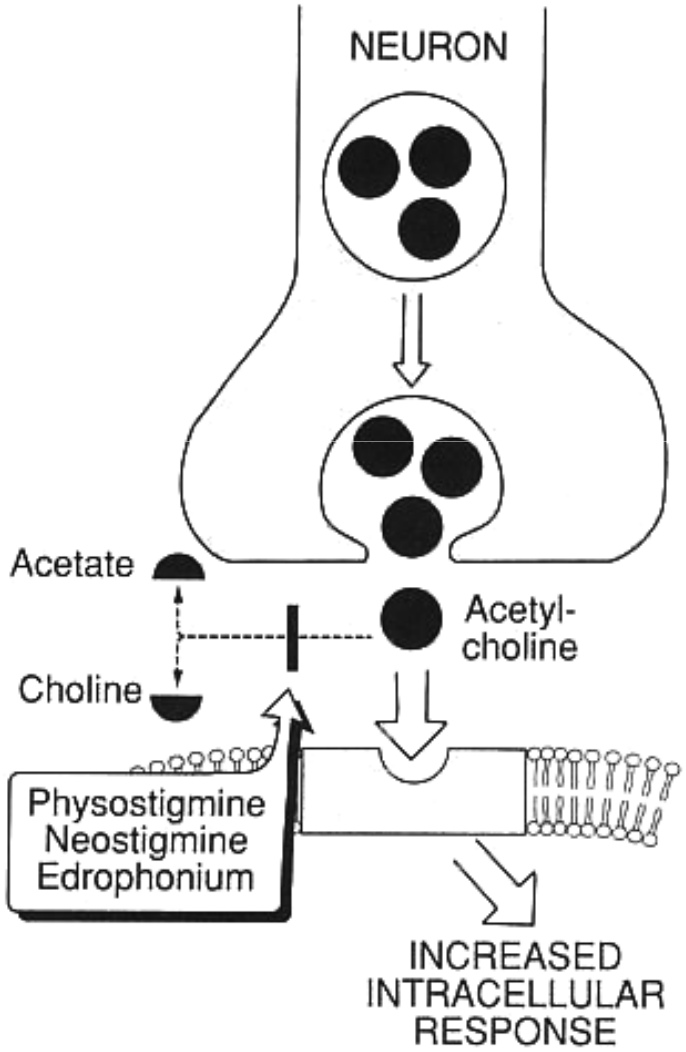
- Prototype of depolarizing agent is succinylcholine (only depolarizing drug in clinical use).
- Mechanism of Action: Similar action to ACh, but longer acting.
- **Phase 1**: Membrane is depolarized by opening AChR channels causing brief period of muscle fasciculation.
- **Phase II**: End-plate eventually repolarizes, but because succinycholine is not metabolized like ACh it continues to occupy the AChRs to "desensitize" the end-plate.

- Because of the mechanism of action of depolazing drugs is similar to ACh, their blocking effects are augmented by AChE inhibitors.

Depolarizing Agents

- **Therapeutic Use:** Adjuvant drugs in surgical anesthesia
- **Pharmacology:** Duration of action is short (several minutes) because it is rapidly broken down by plasma cholinesterases (must be administered by continuous infusion)
- **Adverse Effects:** When administered with halothane some genetically susceptible people (inherited autosomal dominant condition) experience malignant hyperthermia. Treatment: rapid cooling of the body and dantrolene

Cholinesterase Inhibitors



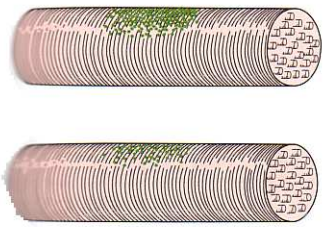
Cholinesterase Inhibitors

- Examples: Neostigmine, edrophonium.
- Mechanism of Action: Inhibit acetylcholinesterase

- **Therapeutic Use:**
- Antidote for nondepolarizing blockers
- Treatment of myasthenia gravis (neostigmine)
- Diagnosis of myasthenia gravis (edrophonium)

Myasthenia Gravis

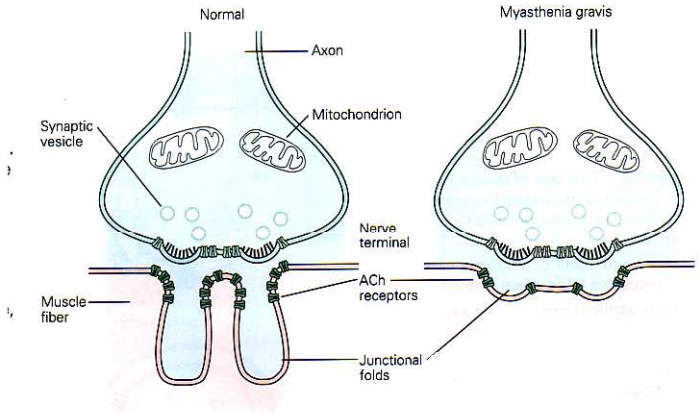
Myasthenia Gravis is an autoimmune Disease that is characterized by a decrease in number of AChR



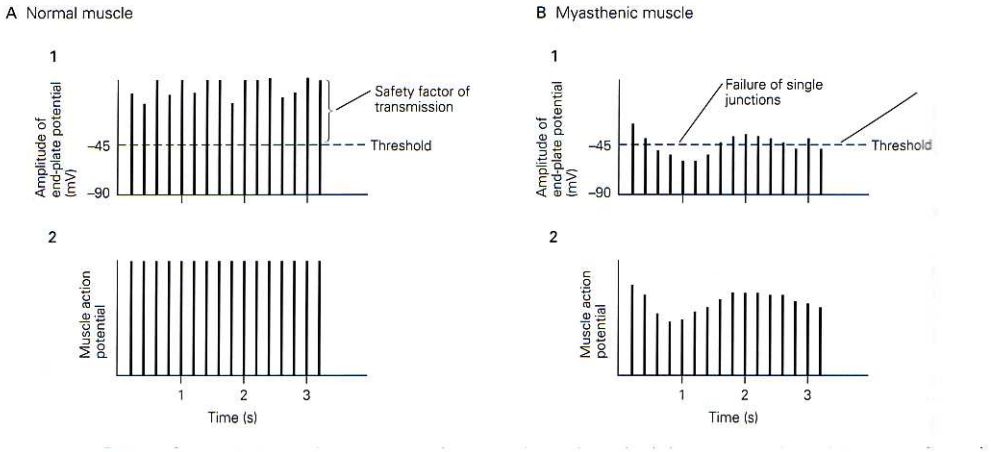
Normal

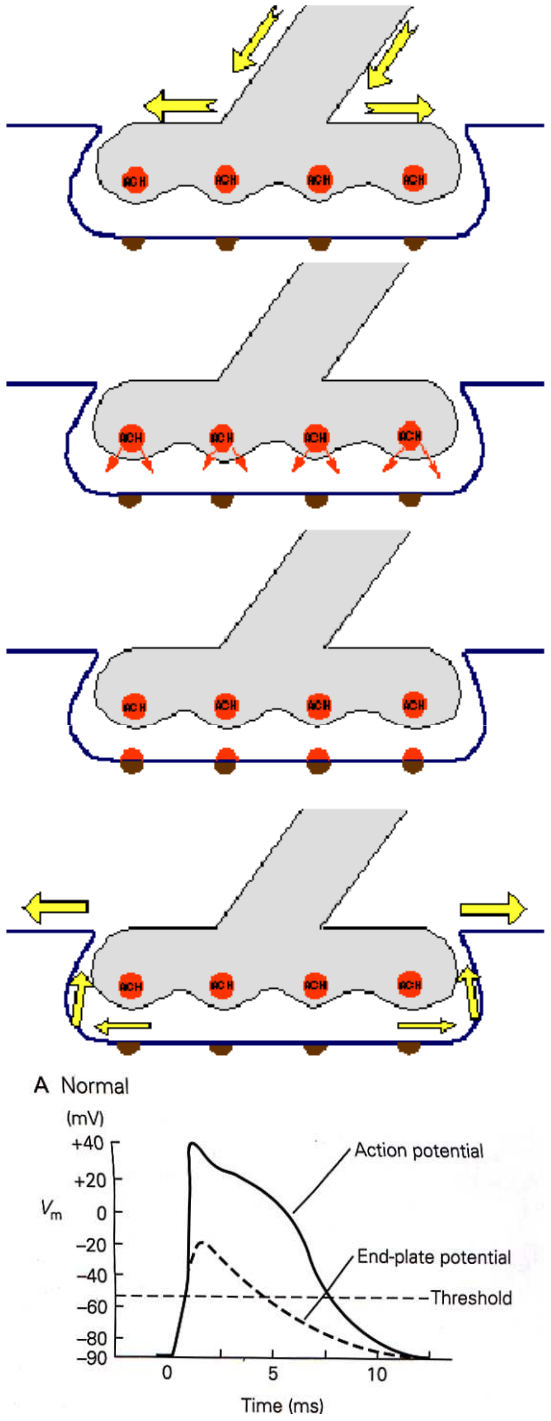
Myasthenia gravis

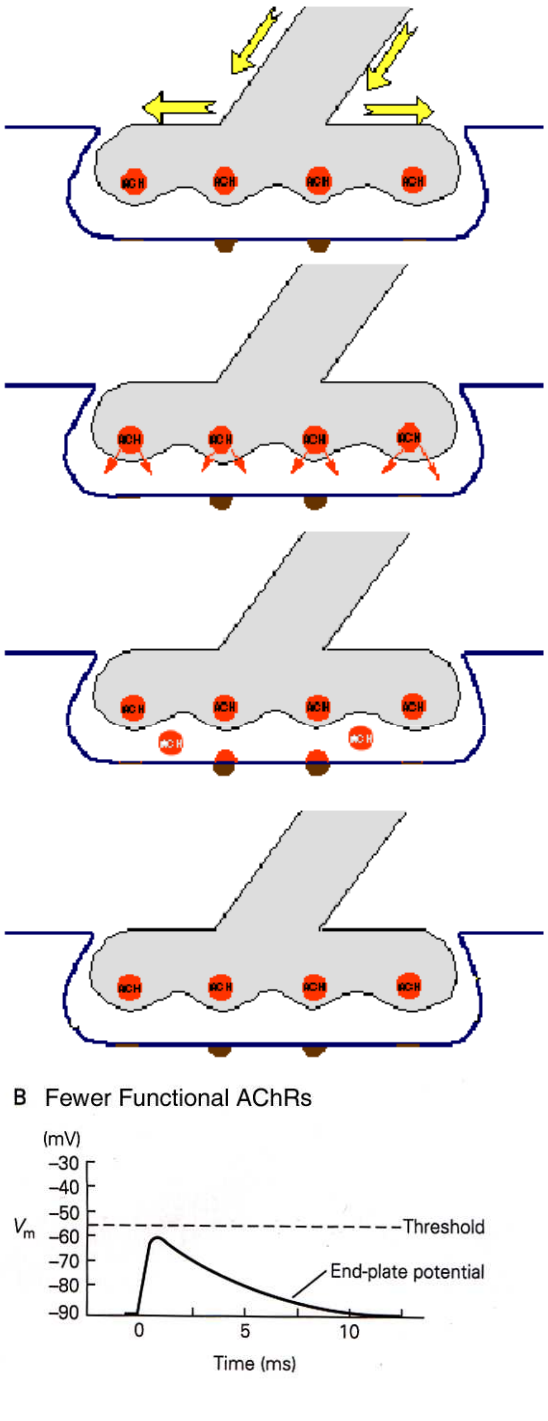
Because there are fewer AChR to bind to the end plate potentials (EPPs) are smaller.



With smaller EPPs the “safety factor” is reduced there is less chance that the post-synaptic muscle fibres will be activated

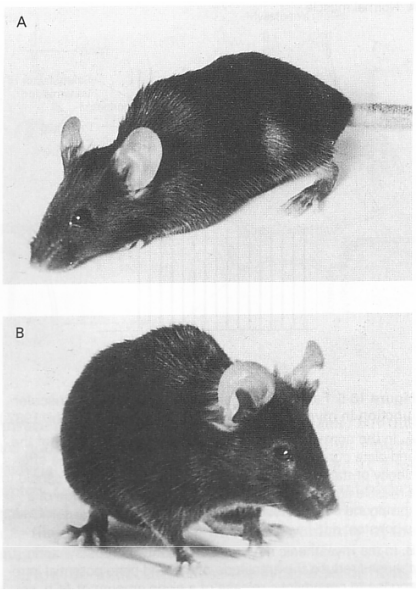


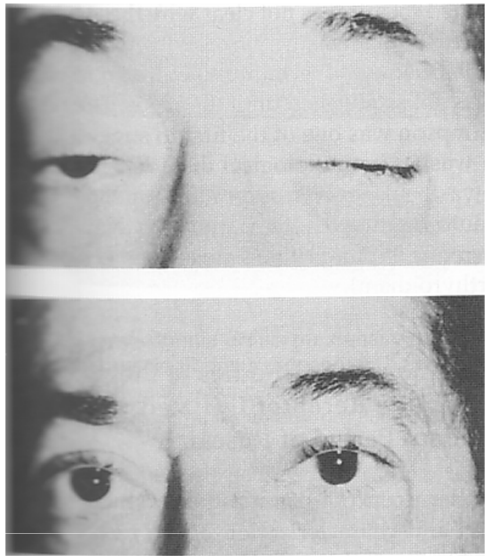


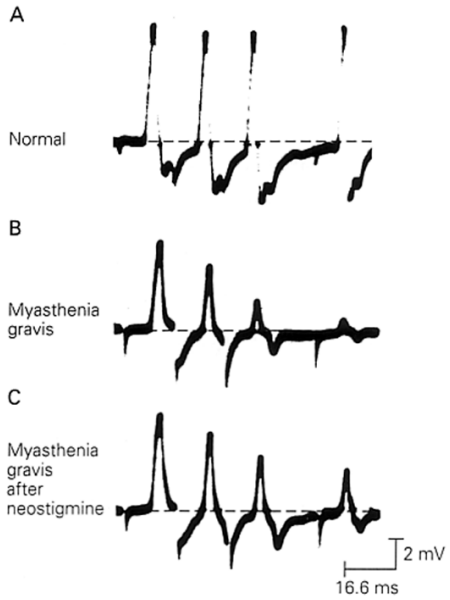


Note: The amplitude of the end plate-potential is directly related to the amount of ACh that binds to the post-synaptic AChRs.

Myasthenia Gravis





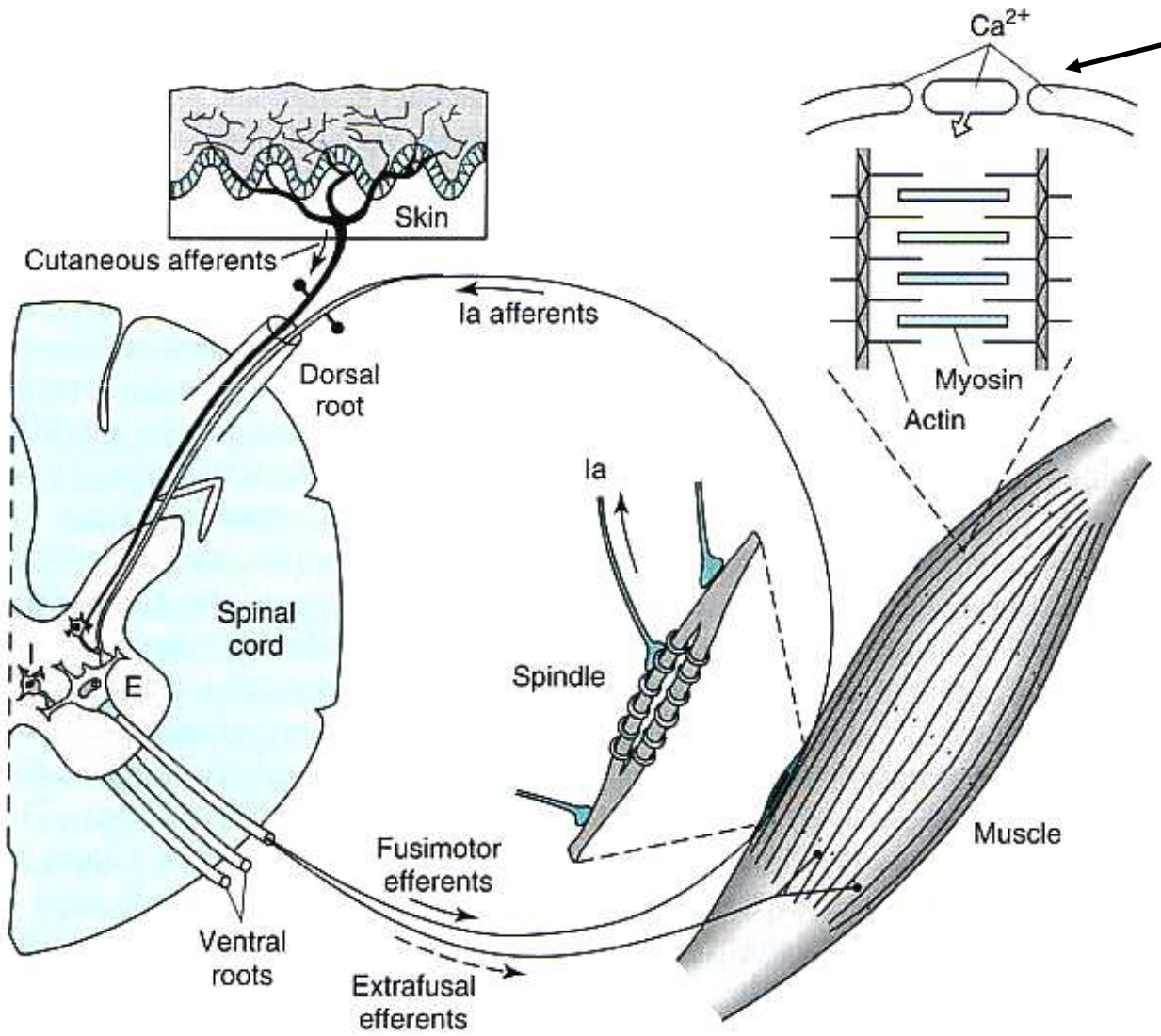


Adverse Effects

- Actions of generalized cholinergic activation (muscarinic and nicotinic).

- Abdominal cramping
- Diarrhea
- Flushing (transient redness of the face and neck)
- Increased salivation
- Miosis (contraction of the pupils)
- Incontinence
- Bronchospasms (can exacerbate bronchial asthma)

Malignant Hyperthermia



Dantrolene
(interferes with EC coupling by decreasing Ca exflux from the SR

Spasmolytic Drugs

Diazepam (A Benzodiazepine that probably facilitates the actions of $GABA_A$ in the CNS)

Baclofen ($GABA_B$ agonist – note error in your handouts)

Primarily used in the treatment of spastiticy associated with spinal cord injury