General physiology
Second semester 2023-2024
Lecture 25
Neuromuscular junction and excitation contraction coupling in skeletal muscle

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Lecture objectives

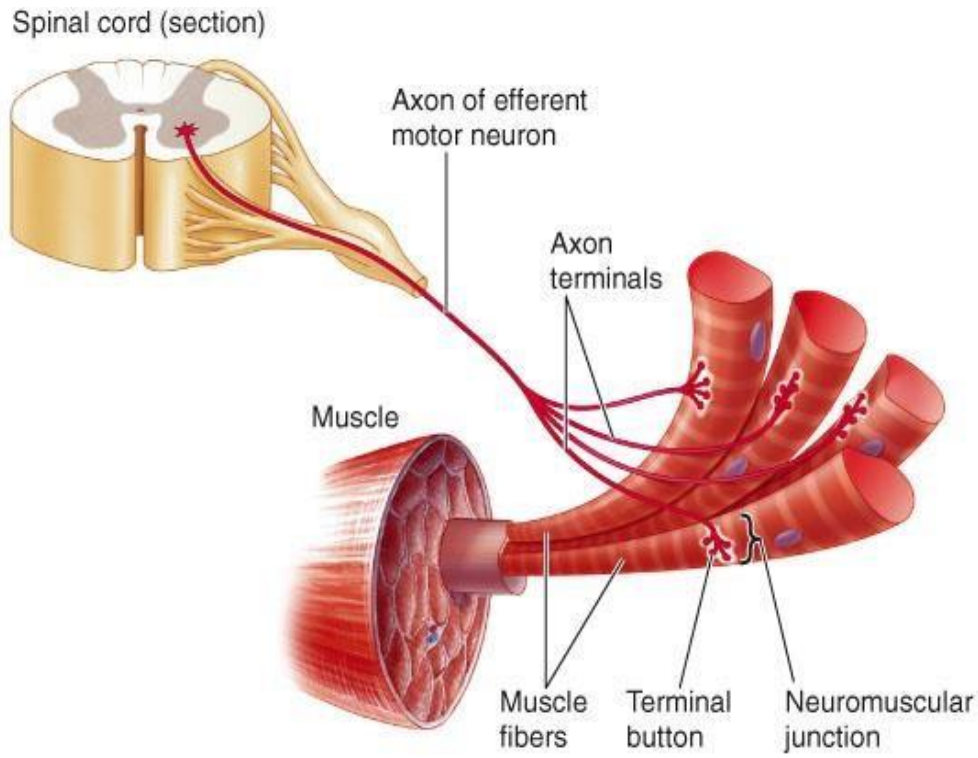
- Describe the motor describe innervation of skeletal muscle and define the motor units
- Identify the components of the neuromuscular junction and the physiological anatomy of NMJ
- Describe the sequence of events that leads to a propagation of action potential in the skeletal muscle and the neurotransmission across the NMJ
- Identify the neurotransmitter released at the neuromuscular junction , its synthesis and degradation
- Identify the type cholinergic receptors at the NMJ
- Define the motor end plate potential and identify its characteristics
- Explain how drugs or toxins affect neuromuscular transmission
- Describe the mechanism of excitation contraction coupling in skeletal and cardiac muscles
- Explain the pathophysiology of Myasthenia Gravis and malignant hyperthermia

Innervation of skeletal muscles :The Motor unit

- **Neuromuscular junction :** the synapse between motor neuron and muscle fiber is called the neuromuscular junction

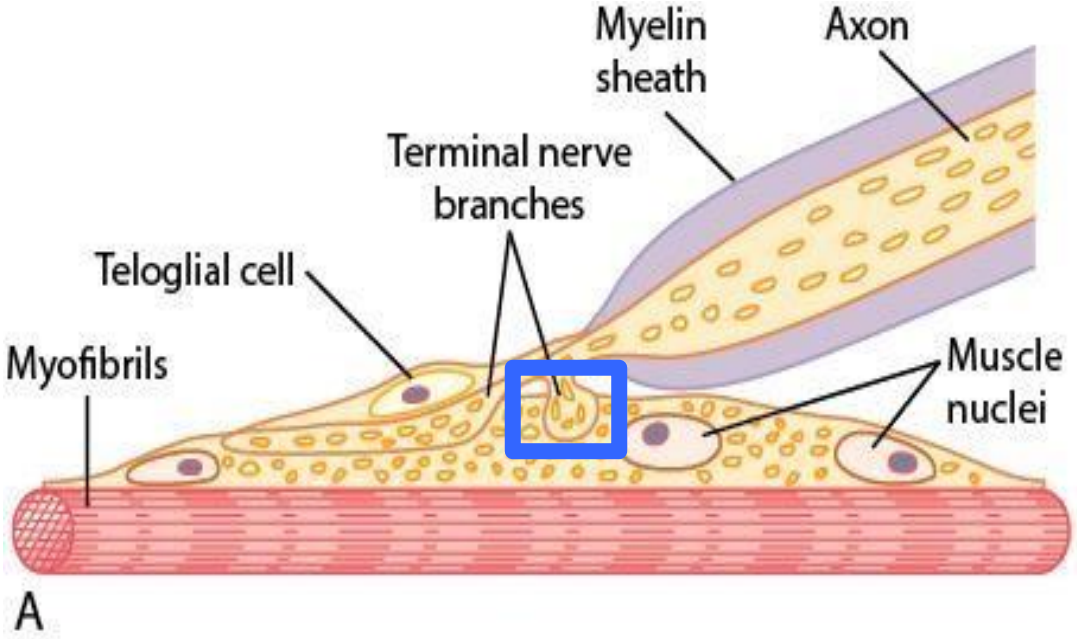
- **Motor neurons :** are the nerves that innervate muscle fibers

- **Motor unit :** single motor neuron and the muscle fibers it innervate



Component of neuromuscular Junction

- Specialized synapse between a motoneuron and a muscle fiber
- Occurs at a structure on the muscle fiber called the motor end plate *(usually only one per fiber)*
- Teloglia : Parasynaptic Schwann cells (also known as Terminal Schwann cells) are Neuroglia found at the Neuromuscular junction (NMJ)
- Function : synaptogenesis, and nerve regeneration.



Neuromuscular Junction (cont.)

Synaptic trough: invagination in the motor endplate membrane

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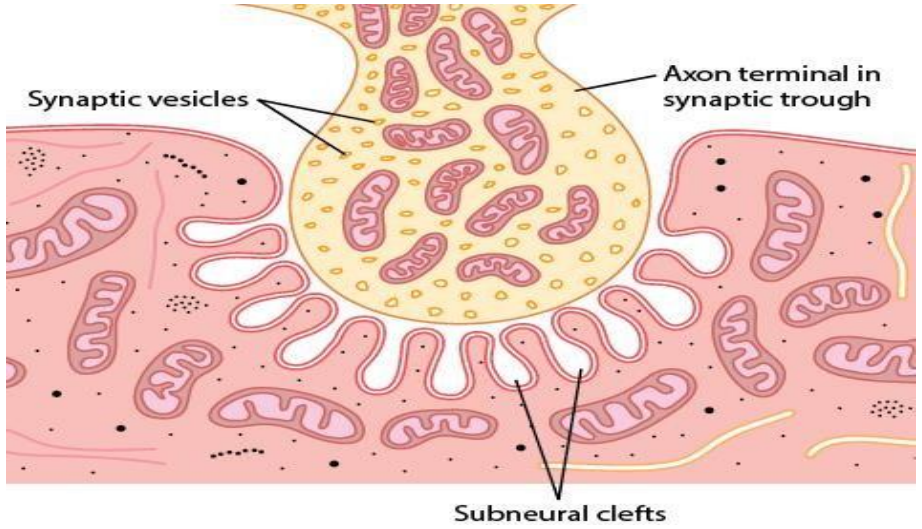
- **Synaptic cleft:**
  - 20-30 nm wide
  - contains large quantities of acetylcholinesterase (AChE
- **Subneural clefts:**
  - increases surface area of post-synaptic membrane



ACh Release - *details*

- **Ca^{2+} channels** are localized around linear structures on the pre- synaptic membrane called **dense bars**

- Vesicles fuse with the membrane in the region of the dense bars.

- Ach receptors located at top of subneural cleft.

- Voltage gated Na^{+} channels in bottom half of subneural cleft

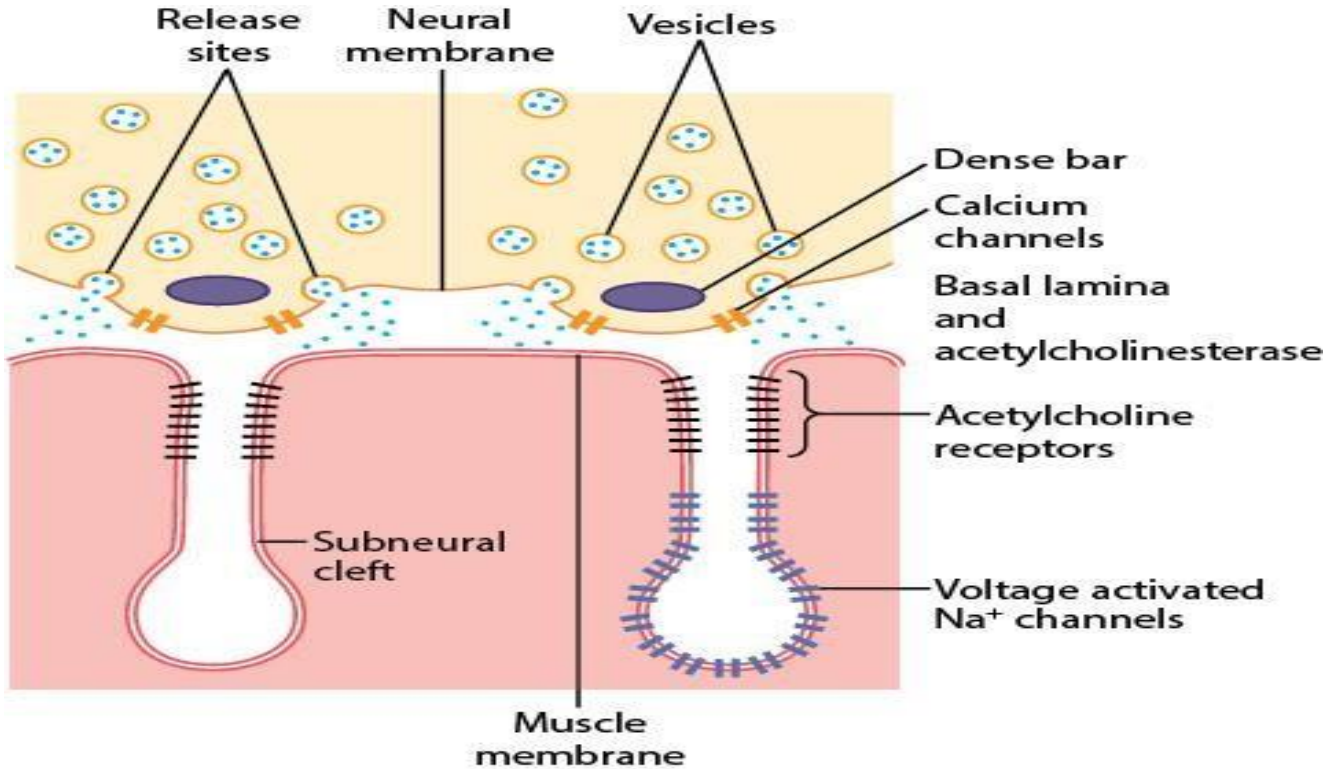
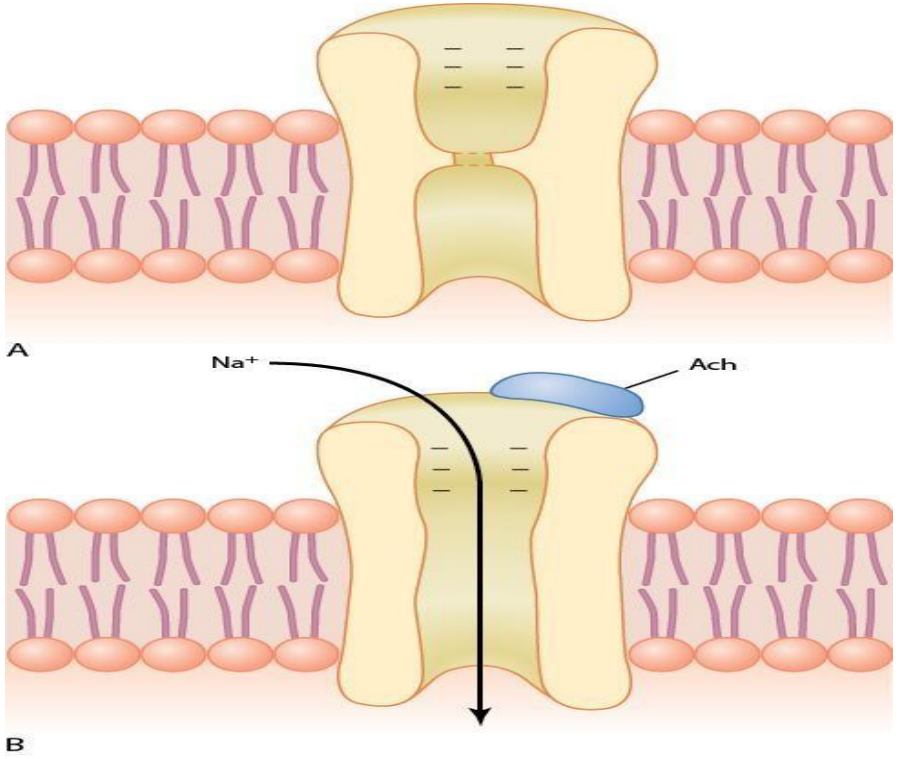


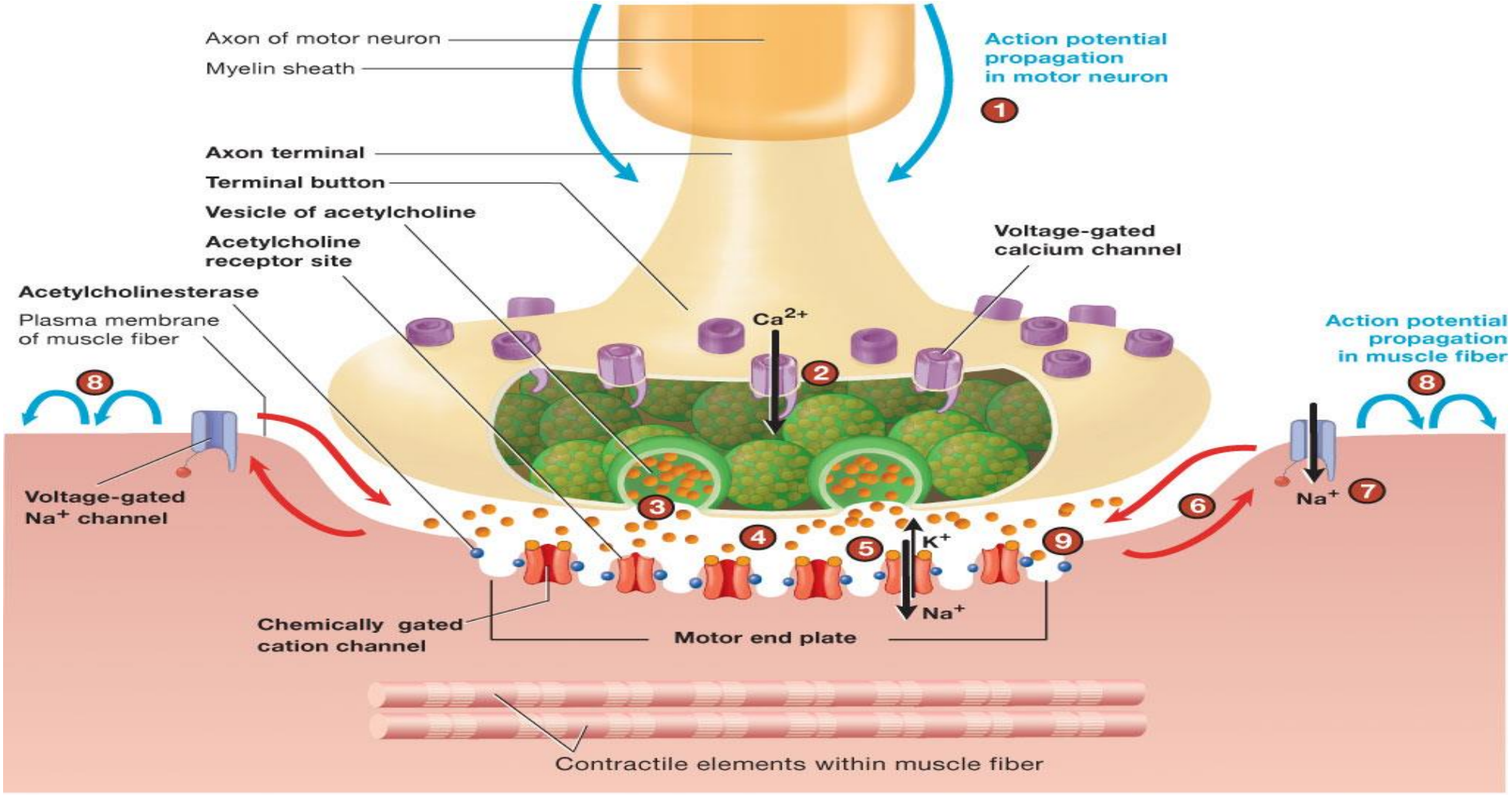
Figure 7-7

Acetylcholine gated channel

Acetylcholine-gated channel. **A,** Closed state.
B, After acetylcholine *(Ach)* has become attached and a conformational
change has opened the channel, allowing sodium ions to enter the muscle fiber and excite muscle cells and causing contraction. Note the negative charges at the channel mouth that prevent passage of negative ions such as chloride ions.



Summary of events at the neuromuscular junction

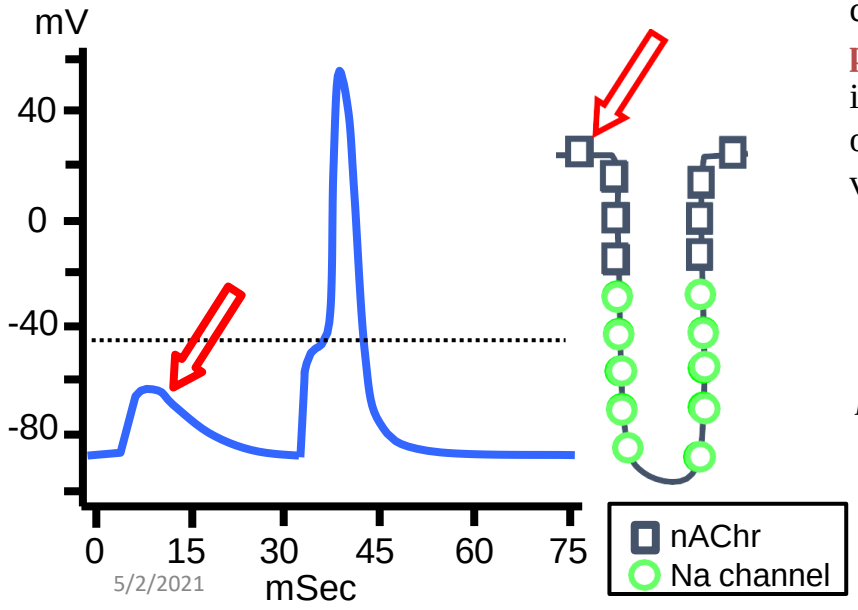


Summary of events at the neuromuscular junction

1. An action potential in a motor neuron is propagated to the terminal button.
2. The presence of an action potential in the terminal button triggers the opening of voltage-gated Ca^{2+} channels and the subsequent entry of Ca^{2+} into the terminal button.
3. Ca^{2+} triggers the release of acetylcholine by exocytosis from a portion of the vesicles.
4. Acetylcholine diffuses across the space separating the nerve and muscle cells and binds with receptor sites specific for it on the motor end plate of the muscle cell membrane.
5. This binding brings about the opening of cation channels, leading to a relatively large movement of Na^{+} into the muscle cell compared to a smaller movement of K^{+} outward.
6. The result is an end-plate potential. Local current flow occurs between the depolarized end plate and adjacent membrane.
7. This local current flow opens voltage-gated Na^{2+} channels in the adjacent membrane.
8. The resultant Na^{2+} entry reduces the potential to threshold, initiating an action potential, which is propagated throughout the muscle fiber
9. Acetylcholine is subsequently destroyed by acetylcholinesterase, an enzyme located on the motor end-plate membrane, terminating the muscle cell's response.

End plate potential and action potential at *the motor endplate* -

•ACh released into the neuromuscular junction binds to, and opens, nicotinic ACh receptor channels on the muscle fiber membranes (Na^+, K^+, Ca^{2+}).



•Opening of nACh receptor channels produces an **end plate potential,** which will normally initiate an AP if the local spread of current is sufficient to open voltage sodium channels.

•*What terminates the process?*

acetylcholinesterase

End plate potential

- When the ion channel on post synaptic membrane opens both Na^+ & K^+ flow down their concentration gradient.
- At resting potential net driving force for Na^+ is much greater than K^+ ,when Ach triggers opening of these channels more Na^+ moves inwards than K^+ out wards, depolarizing the end plate. This potential change is called end plate potential (EPP).
- EPP is not an action potential but it is simply depolarization of specialized motor end plate
- Small quanta (packets) of Ach are released randomly from nerve cell at rest, each producing smallest possible change in membrane potential of motor end plate, the MINIATURE EPP.
- When nerve impulse reaches the ending, the number of quanta release increases by several folds and result in large EPP.
- EPP than spread by local current to adjacent muscle fibers which depolarized to threshold & fire action potential

Drug Effects on End Plate Potential

- Inhibitors -

1. Balk widow spider venom

2.Organophosphates

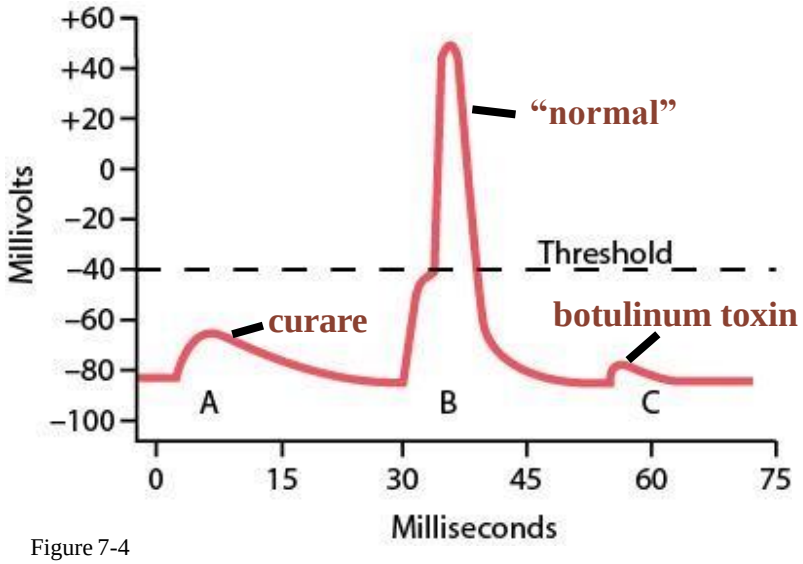


Figure 7-4

Curariform drugs (D-turbocurarine)

- block nicotinic ACh channels by competing for ACh binding site
- reduces amplitude of end plate potential therefore, no AP

Botulinum toxin

- decreases the release of Ach from nerve terminals
- insufficient stimulus to initiate an AP
- Causes muscle paralysis

Drug Effects on NMJ

- Black widow spider venom . Causes explosive release of Ach at all cholinergic synapses
- Prolonged depolarization May cause respiratory failure
- Acetylcholine esterase inhibitor
  - Organophosphates, insecticides, and nerve gas agents as a weapon.
- Theses substances are anticholinesterase agents thus prolong the action of acetylcholine at cholinergic synapses
- Symptoms of toxicity include :
- increased saliva and tear production, diarrhea, nausea, vomiting, small pupils, sweating, (autonomic effects), muscle tremors, and confusion.
  - The onset of symptoms is often within minutes, and it can take weeks to disappear

Excitation contraction coupling in Skeletal muscles

Transverse Tubule–Sarcoplasmic Reticulum System In Skeletal Muscles

T-tubules:

- Invaginations of the **sarcolemma** filled with extracellular fluid
- Penetrate the muscle fiber, branch and form networks
- Transmit AP's deep into the muscle fiber

Sarcoplasmic Reticulum:

- terminal cisternae and longitudinal tubules
- **terminal cisternae** form junctional "feet" adjacent to the T- tubule membrane
- intracellular storage compartment for Ca^{2+}

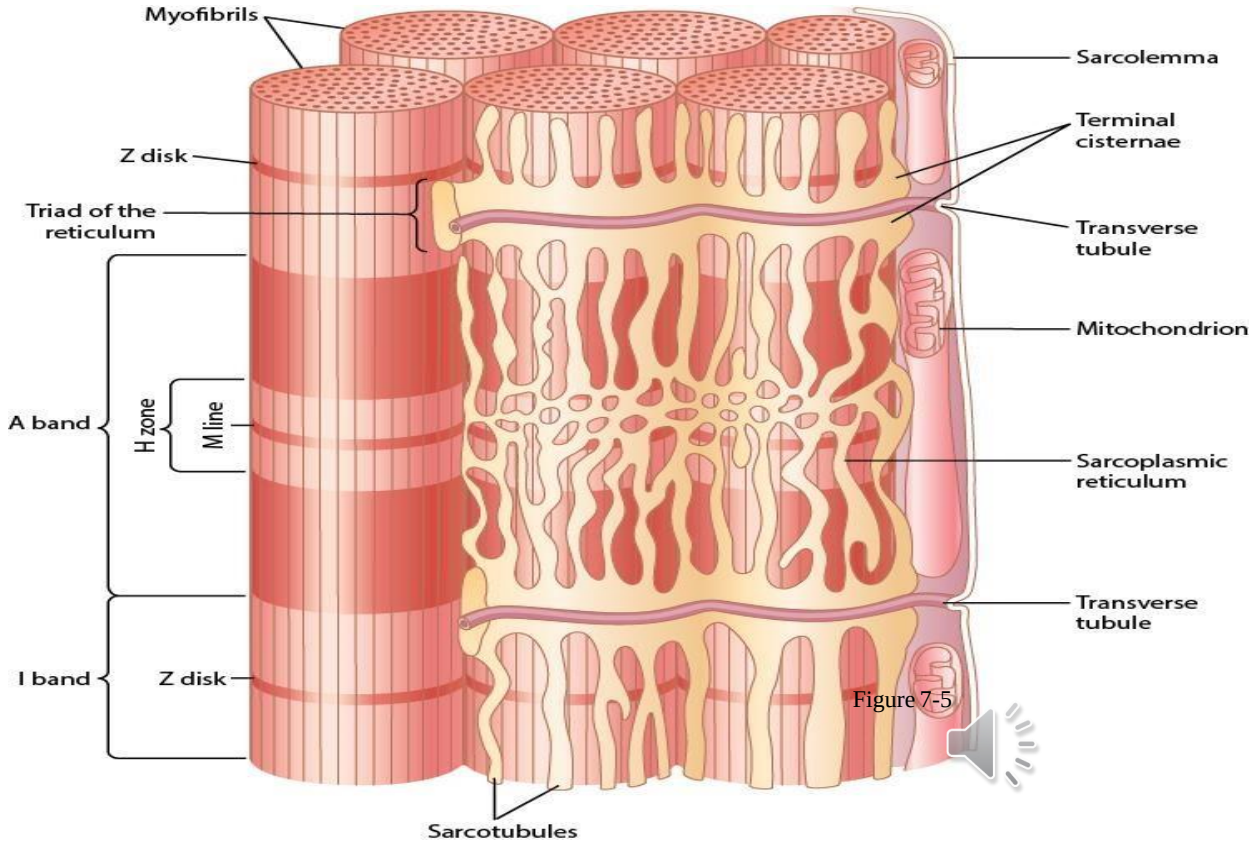


Figure 7-5

The spread of muscle action potential to through the triad and release of Ca during excitation contraction coupling

The "Triad"

The junction between two terminal cisternae and a T-tubule

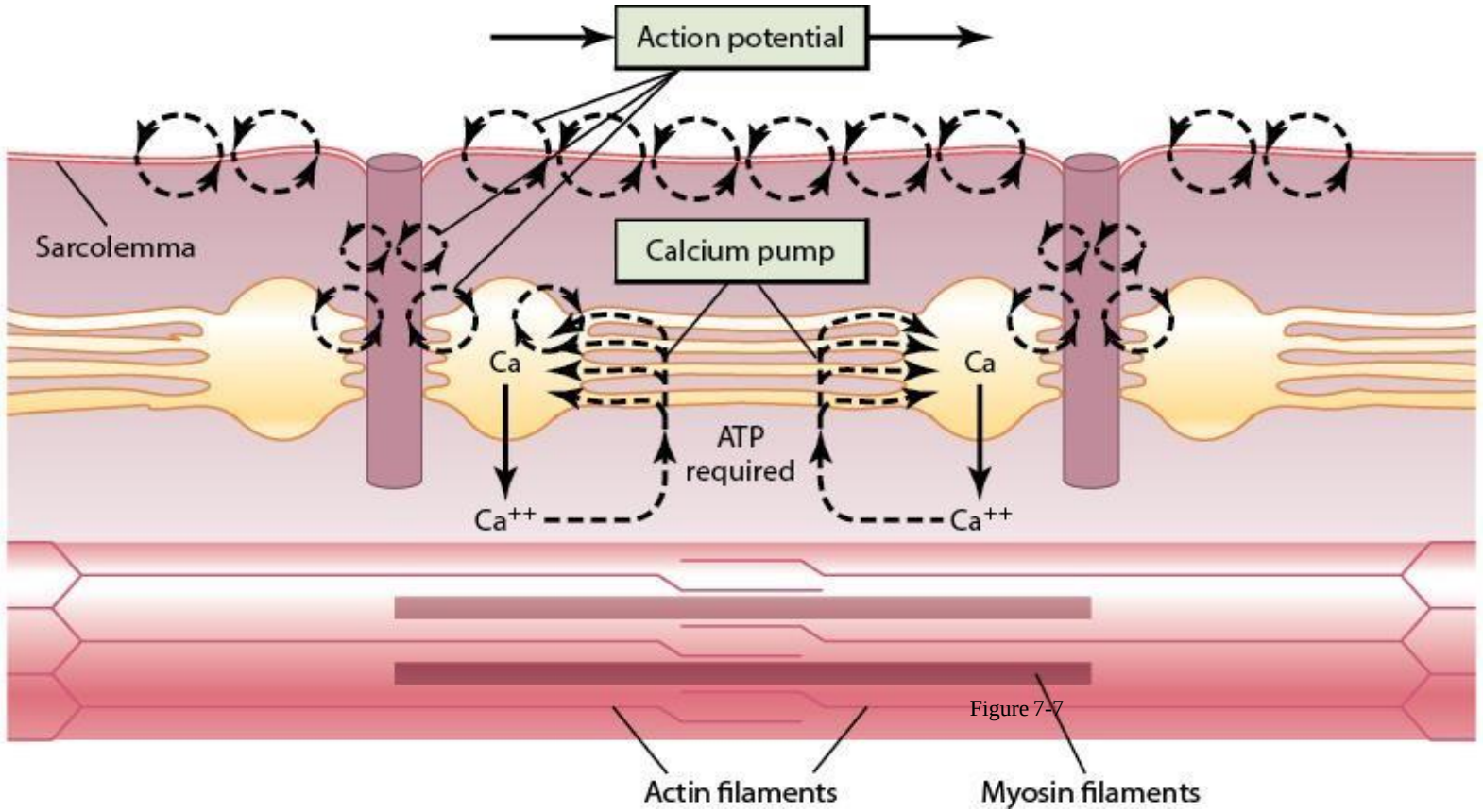
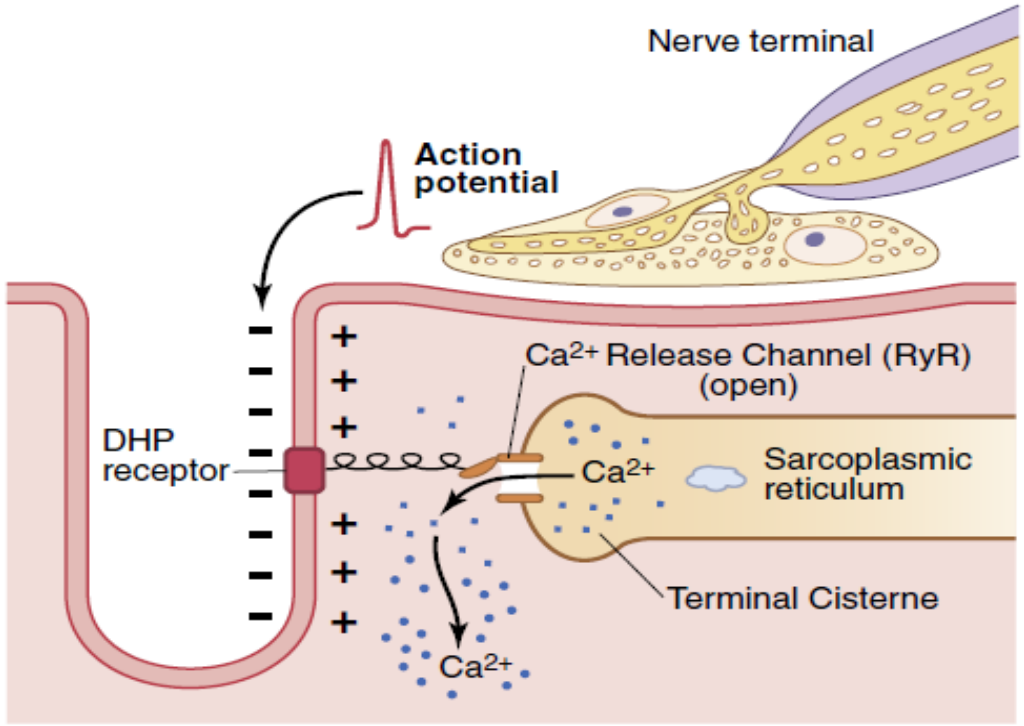


Figure 7-7

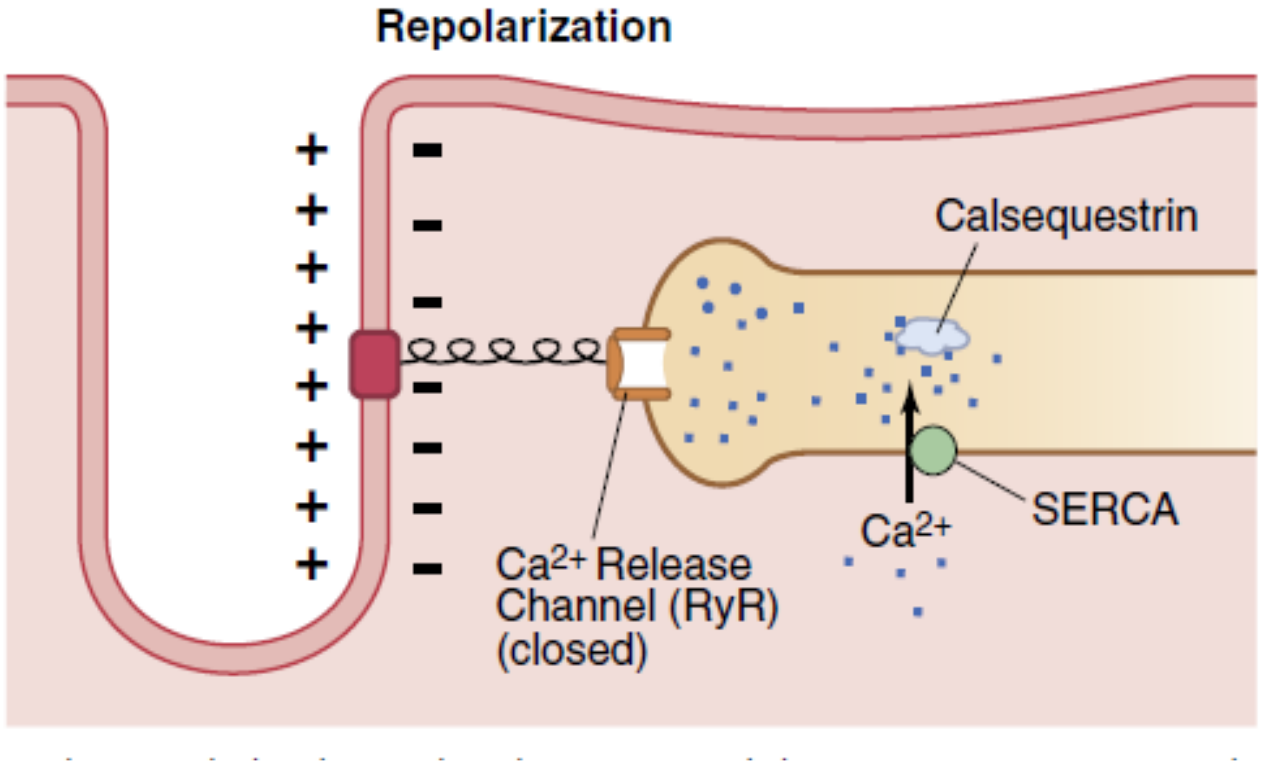
EC Coupling – *Skeletal muscle*

Following the excitation of muscles cells by acetylcholine release, an action potential in the transverse tubule that causes a conformational change in the voltage-sensing dihydropyridine *(DHP)* receptors, opening the Ca++ release channels in the terminal cisternae of the sarcoplasmic reticulum and permitting Ca++ to rapidly diffuse into the sarcoplasm and initiate muscle contraction

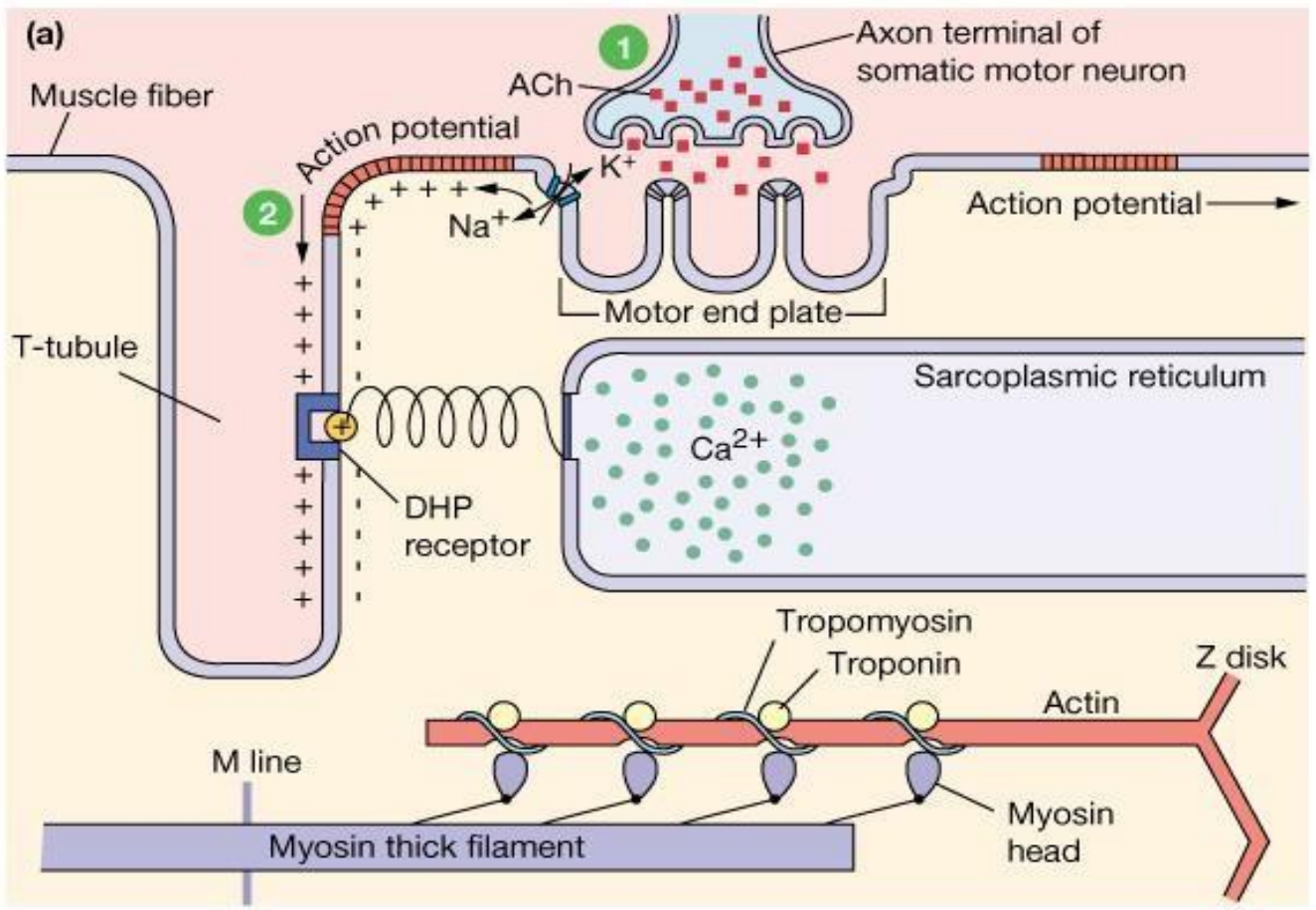


Reuptake of Ca ions released and termination of contraction

During repolarization *(* the conformational change in the DHP receptor closes the Ca++ release channels and Ca++ is transported from the sarcoplasm into the sarcoplasmic reticulum by an adenosine triphosphate–dependent calcium pump



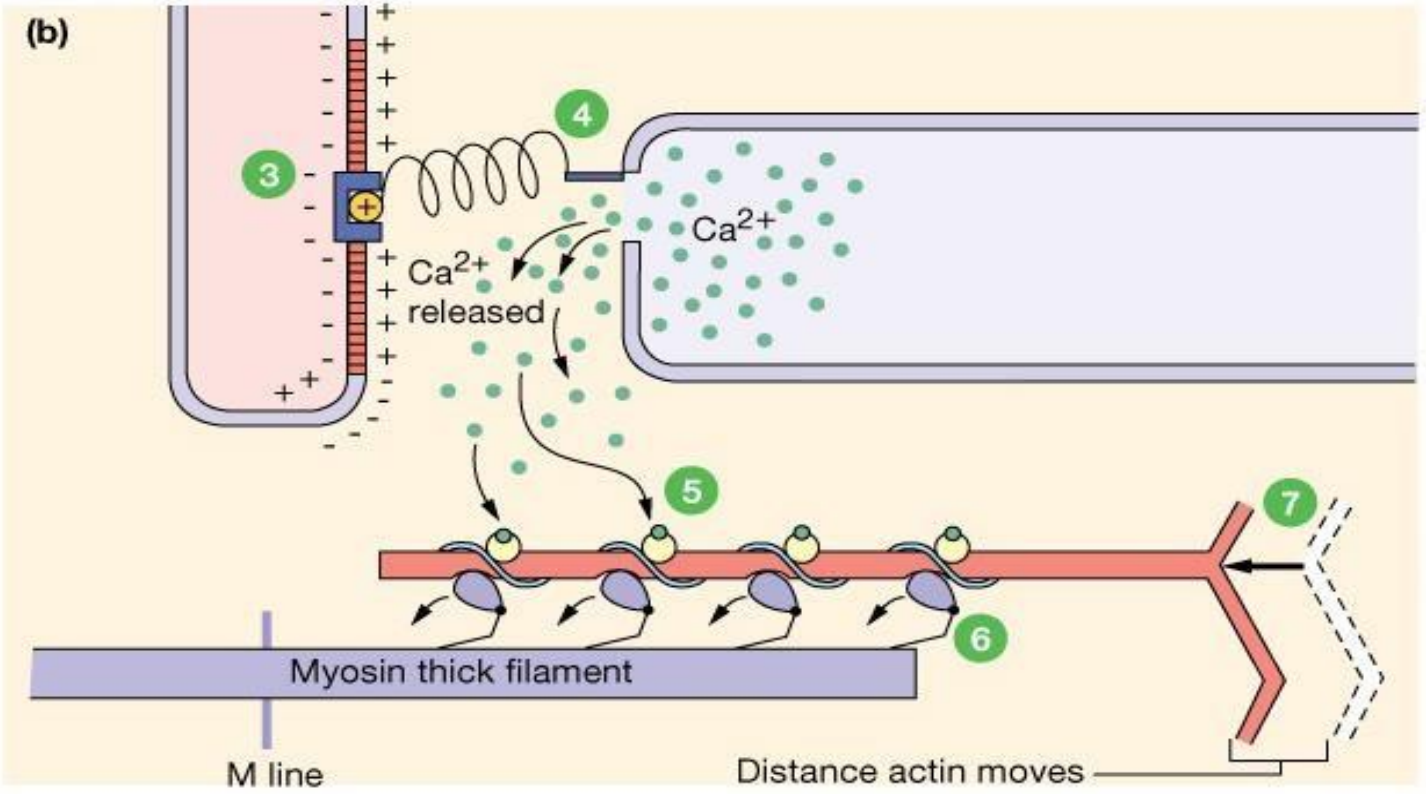
Excitation contraction coupling summary



1. Somatic motor neuron releases ACh at neuro-muscular junction.

2. Net entry of Na^+ through ACh receptor-channel initiates a muscle action potential.

Summary and Steps of Excitation Contraction Coupling



3. Action potential in t-tubule alters conformation of DHP receptor.

4. DHP receptor opens Ca^{2+} release channels in sarcoplasmic reticulum and Ca^{2+} enters cytoplasm.

5. Ca^{2+} binds to troponin, allowing strong actin-myosin binding.

6. Myosin heads execute power stroke.

7. Actin filament slides toward center of sarcomere.

Myasthenia Gravis

- **symptoms:**
  - paralysis - lethal in extreme cases when respiratory muscles are involved
- **Cause:**
  - autoimmune disease characterized by the presence of antibodies against the nicotinic ACh receptor which damages or destroys them This results in weak end plate potentials
- **Treatment:**
  - usually ameliorated by anti-AChE (neostigmine) The drug increases amount of ACh in NMJ

Malignant Hyperthermia

Symptoms:

- increased body temperature
- skeletal muscle rigidity
- lactic acidosis *(hypermetabolism)*

Cause:

- triggered by halogenated anesthetics (isoflurane, halothane)
- familial tendency - can be tested for by muscle biopsy
- constant leak of SR Ca^{2+} through ryanodine receptor

Why is so much heat generated?

Ans: our bodies are only about 45% energy efficient, 55% of the energy appears as heat.