Excitation Contraction Coupling of Skeletal Muscles

Objectives:
• Importance of excitation for muscle contraction
• Neuromuscular endplate
• T-tubule system
• Ryanodine receptor and Ca++ release
• Ca++ removal and muscle relaxation

Excitation-contraction coupling refers to the process by which depolarization of sarcolemma produces contraction of the muscle cell.
Two single muscle fibers

Action potential produces muscular twitch contraction.
Skeletal muscles are excitable tissue. They have great similarities to neurons in terms of their membrane ionic channels for excitation. Na⁺ channels are the major players in excitation or the upstroke of APs.
The repolarization is produced by several ion channels including K⁺ and Cl⁻ channels.

- The density of Cl⁻ channels in skeletal muscles is much higher than that of K⁺ channels.
- Several different Cl⁻ channels have been identified. They are voltage-activated, Ca++-dependent, and cyclic nucleotide-gated Cl⁻ channels with single channel conductance range from 30pS to 300pS.

Players in Excitation

Motor neuron --- in the ventral horn of the spinal cord.
Myelinated axon --- most axons to skeletal muscles being myelinated and fast in conduction velocity.
Motor endplate --- the interface for neuro-muscular signal conversion.
ACh receptor --- nicotine receptor.
Ion channel --- Na⁺, K⁺ Cl⁻, and Ca++ channels. They are the final effector in the signal transduction.
FIGURE 11-19
Events occurring at a neuromuscular junction that lead to an action potential in the muscle fiber plasma membrane.
Autoantibodies inhibit receptor function in myasthenia gravis. In normal circumstances, acetylcholine released from stimulated motor neurons at the neuromuscular junction binds to acetylcholine receptors on skeletal muscle cells, triggering muscle contraction (left panel). Myasthenia gravis is caused by autoantibodies against the α subunit of the receptor for acetylcholine. These autoantibodies bind to the receptor without activating it and also cause receptor internalization and degradation (right panel). As the number of receptors on the muscle is decreased, the muscle becomes less responsive to acetylcholine.

Motor endplates and Myasthenia gravis

• Patients with this disease produce antibodies against their own nicotinic ACh receptors, leading to a mass loss of N-ACh receptor-gated channels.
• These patients respond to N-ACh receptor agonists and blockers of acetylcholinesterase.
T-tubule in invertebrate muscles: one per sarcomere.
T-tubule organization in vertebrate skeletal muscles: two per sarcomere.

Figure 16-7

EC Coupling
T tubules in a single muscle fiber

T tubules contact two sarcoplasmic reticula (SRs) in the skeletal muscle.
**Transverse tubular system**

- The T tubular system is an extension of sarcolemma.
- The content in the T tubules is interstitial fluid rather than cytoplasm.
- It forms extensive networks interior to the muscle cells and makes contact to two terminal cisternae of the SR.
- Its function is to spread excitation throughout the muscle cell.

**Depolarization activates the dihydropyridine sensitive Ca\(^{++}\) channels.**

![Graph showing depolarization and calcium current](image)
Dihydropyridine sensitive Ca\(^{++}\) channels

- Gene knockout of the L-type Ca\(^{++}\) channel eliminates skeletal muscle contraction.
- L-type Ca\(^{++}\) channel knockin resumes the muscle contraction.
- The muscle contraction is retained when Ca\(^{++}\) is removed from extracellular solution.
The dihydropyridine sensitive Ca\textsuperscript{++} channels are necessary for skeletal muscle contraction. However, Ca\textsuperscript{++} influx is not prerequisite for the muscle contraction.

Depolarization is critical for muscle contraction.
Release of Ca²⁺ stores mediated by ryanodine receptors (RYRs) in skeletal muscle. Voltagesensing dihydropyridine receptors in the plasma membrane contact ryanodine receptors located in the membrane of the sarcoplasmic reticulum. In response to a change in voltage, the dihydropyridine receptors undergo a conformational change; this produces a conformational change in the associated RYRs, opening them so that Ca²⁺ ions can exit into the cytosol.
• Ryanodine is a plant alkaloid.
• It blocks the Ca\textsuperscript{2+} release from the RyRs at a high concentration.
• At low concentration (<10\(\mu\text{M}\)), ryanodine locks the RyRs into a long-lasting subconductance state and eventually depletes the Ca\textsuperscript{2+} store.
Ryanodine Receptors (RYRs)

- The RYRs play a critical role in skeletal muscle contraction.
- The RYRs are located in the membrane of the sarcoplasmic reticulum.
- Depolarization is coupled to the RYRs by the dihydropyridine receptors in the plasma membrane through certain mechanical forces.
- The opening of the RYR channels leads to a release of Ca^{++} from the SR into the cytosol.
- The Ca^{++} rise initiates contraction.

Subtypes

- RyR1 is expressed in skeletal muscle.
- RyR2 is found in myocardium, responsible for the calcium induced calcium release.
- RyR3 is expressed in other tissues, especially in the brain.
Structure of the insect RyR

- RyRs are tetrameric homotetramers.
- Each subunit has six membrane-spanning helices.
- The pore loop is located near to the C terminal that is located in the lumen of SR.
- The large N terminal is located in the cytosol, containing receptors for ryanodine and Ca$^{2+}$ as well as DHPR coupling sites.

Structure highlights of RyRs
FIG. 5. Malignant hyperthermia. (a) Normal muscle contraction cycle. The Ca\(^{2+}\) release channel (shown here as square element) is a key element of the process known as excitation-contraction coupling or simply EC coupling. This is the chain of events beginning with the muscle AP, which invades the T-tubular membrane, causing movement of gating charge in the dihydropyridine-sensitive Ca\(^{2+}\) channel/voltage sensor (Fig. 4), which in turn, activates the Ca\(^{2+}\) release channel on the sarcoplasmic reticulum (SR), releasing Ca\(^{2+}\) from stores within the SR to initiate contraction. The exact means by which the voltage sensor of the T-tubular membrane couples with the release channel of SR is not yet fully understood. In addition, there are pumps and regulators which accumulate and store the Ca\(^{2+}\) for release. (b) MH muscle contraction cycle. Mutant calcium release channels can explain all of the basic mechanism of MH. The mutations produce a release channel that is more sensitive to specific stimuli and can cause rapid release, thus leading to the abnormally high calcium levels. Sustained Ca\(^{2+}\) levels in the fiber then causes contracture, increased glycolytic and anaerobic metabolism with...
Entry and removal of Ca\textsuperscript{++} ions in the cytosol

- The contraction is terminated by removal of Ca\textsuperscript{++} from the cytosol.
- This relies on the SERCA.
- The SERCA pump has Ca\textsuperscript{++} affinity higher than troponin, so that the troponin is deprived of Ca\textsuperscript{++} binding.
- Na\textsuperscript{+}/Ca\textsuperscript{2+} exchanger also plays a role in Ca\textsuperscript{2+} extrusion.