Topics Covered

Excitation-Contraction (E-C) Coupling.
- E-C Coupling in Skeletal vs. Cardiac Muscle.
- NMJ Transmission.
- Membrane Propagation of Action Potential (AP).
- Voltage Gated Ca2+ Channels.
- Calcium Release Channel (RYR-1).
**Membrane (Lipid Bilayer)**

**Transmembrane Signaling**

**PEP 8302 Module 2 (Class 1)**

Activation of Neurotransmitter Release by Synaptic Vesicle Fusion

Propagation of Muscle Action Potential (MAP) along sarcolemma/T-tubule

**E-C Coupling**

Differences in E-C Coupling Between Cardiac and Skeletal Muscle

**FIG. 2.** Models of muscle E-C coupling. Depicted are the mechanical coupling model for vertebrate skeletal muscle, and the calcium-induced calcium release (CICR) model for cardiac muscle.
Skeletal Muscle Excitation-Contraction Coupling

Spatial registration of the DHP tetrad structure on the T-tubule membrane with the RYR-1 receptors (feet) of the SR membrane in skeletal muscle.

Tetrads associated with every other RYR-1 “foot” group on skeletal muscle SR membrane.

Irregular non-tetrad arrangement of DHP receptors in cardiac T-tubule membrane. Not required due to trigger calcium influx.

SERCA I & II

DHP Receptor Tetrad

**Diagram Note:**

- T-tubule membrane
- RYR-1 receptors
- DHP tetrad structure
- SERCA I & II

**Text Note:**

- Calcium release from SR
- Conversion of ATP to ADP
- Movement of Ca^2+ across T-tubule
- Movement of calcium ions across SR membrane
- Reuptake of calcium ions
- Triggering of Ca^2+ in cytoplasm

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Voltage-Gated Calcium Channels

- multiple types of voltage-gated Ca2+ channels.
  - first distinguished on the basis of their voltage and time dependence single channel conductance properties as well as pharmacology.
  - also classified as low voltage-activated (LVA) and high voltage activated (HVA) channels depending on the degree of membrane depolarization required to activate the channel.
**Cultured Human Skeletal Muscle Myotubes**

Phase contrast micrograph of human skeletal myoblasts differentiated with horse serum to produce myotube structures.

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**α2-Subunit Expression In Mouse Dysgenic Myotubes**

Transfer cytoplasmic loop of the skeletal L-type channel to the cardiac L-type channel this rescues contractility in the myotube.

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**Compounds Capable of Blocking Voltage-Gated Calcium Channels**

L-type channels (skeletal, cardiac, smooth, neuronal, endocrine)
- dihydropyridines (DHP)

P/Q-type channel (neuronal, endocrine)
- Aga-IVA (funnel web spider)

P/Q- and N-type channels (neuronal, endocrine)
- conotoxin (marine snail)

T-type channels (α_{1G} neuronal)
- Kurotoxin (snake venom)
**Diseases Associated with Mutation of the α-Subunit of the Voltage-Gated Calcium Channel**

- familial hemiplegic migraine (FHM).
- episodic ataxia type 2 (EA-2)
- both involve mutation of the α1A subunit of the P/Q type channel

**Calcium Release Channel (RYR-1 Receptor) of the SR Membrane**

- calcium ion

**Compounds Capable of Modulating Calcium Release Channel (RYR-1) Activity**

physiological activation of RYR-1 in skeletal muscle is due to a mechanical interaction between the RYR-1 and DHP receptor.

RYR-1 can be activated directly using a number of agonists

- caffeine
- 4-chloro-m-cresol
- ryanodine (non-reversible activator)
Diseases Associated with Mutation of the Calcium Release Channel (RYR-1 receptor)

- central core disease (histological classification)
- central region of the myofiber contains no contractile apparatus
- associated with elevated myofiber calcium and subsequent calcium-dependent proteolysis within the myofiber

- malignant hyperthermia
- closely associated with central core disease but does not always coincide.
- usually diagnosed after inhalation anesthesia induces uncontrolled activation of the RYR-1 receptor followed by muscle contraction and a subsequent pathological increase in body core temperature.
- clinically treated using the RYR-1 blocker, dantrolene.
- clinically tested by caffeine challenge of muscle biopsy.

Malignant Hyperthermia

Number of cases, Mortality rate

- Dead
- Survive