PRINCIPLES OF PHYSIOLOGY G6001

MUSCLE: EXCITATION-CONTRACTION COUPLING
LECTURE 10-9-2003
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Chapters 17 & 18

Topics to be covered:

1) Excitation-contraction coupling
2) Cardiac muscle vs skeletal muscle
3) Diseases of ECC

Myotubes in culture

Myofilaments
Skeletal muscle cross section EM

Sarcomeres

Thick filament II

Myosin heavy chain mutations in FHC

SR and T tubules in skeletal muscle fiber
Elements of hypertrophic cardiomyopathy

Structure of Thin Filament

Tropomyosin and Troponin

Nebulin and Titin

Intermediate filaments in the sarcomere: nebulin and titin

Emery-Dreifuss
Muscular dystrophy

Cardiac pacemaker
@18 y/o

Mutations in genes encoding nuclear membrane/lamina proteins emerin and lamin A/C

X-linked (emerin mut.)
Autosomal dom.
Myotonic stiffness

Becker's Muscular Dystrophy

Rest, tight fist 3 sec, relax (>10 sec)

Energy required for contraction comes from three main sources:

- Creatine phosphate
- Glycolysis
- Lactic acid cycle

Sliding filament model of muscle contraction:
actin and myosin filaments slide past one another
Filament Overlap Hypothesis

Neuromuscular Junction

Action Potential

Twitch

Role of Ca++ in contraction

Mechanics of Muscle Contraction
SPECIALIZED MUSCLE FIBRES

Different Muscle Fibre Types
Fatigue at Different Rates

Fast Oxidative Fibres
Fast Glycolytic Fibres
Slow Oxidative Fibres

Tension
Time (min)
(tetanus)

What causes muscle fatigue?

Muscle Fatigue
Characteristics:
- Tension
- Contraction Velocity
- Rate of Relaxation

Fatigue

Summation

Tetanus

TABLE 1 Duration of Key Steps in the Activation of a Fast-Twitch Skeletal Muscle

<table>
<thead>
<tr>
<th>Event/Step</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Action potential propagation along sarcomeres</td>
<td>0.10 ms</td>
</tr>
<tr>
<td>Action potential propagation in center of fiber along T-tubules</td>
<td>0.15 ms</td>
</tr>
<tr>
<td>Signal transduction at T-tubule junction &amp; T-tubule depolarization</td>
<td>&lt; 0.5 ms</td>
</tr>
<tr>
<td>Activation of RYR on SR</td>
<td>1-3 ms</td>
</tr>
<tr>
<td>Peak rate of Ca(^{2+}) release to peak Ca(^{2+}) binding to Titin (a motor of tension)</td>
<td>2-3 ms</td>
</tr>
<tr>
<td>Peak myotonic Ca(^{2+}) change to peak tension</td>
<td>13-23 ms</td>
</tr>
</tbody>
</table>

*Duration were calculated for a hypothetical long fiber of 30 mm diameter and 5 cm length, assuming a central end plate. Estimates refer to conduction velocity and diameter of intermediate steps (Stamenovic, 1971; Noreña and Dulay, 1996; Jong et al., 1998) were adjusted by 38 °C.

FIGURE 12 Relationship between charge movement (\(\Delta Q/\Delta t\)) and membrane potential (\(v_m\)). Charge moved at each potential was obtained by integrating the voltage-dependent capacity current, normalized to the fiber linear capacitance near the resting potential. Symbols represent the mean values of charge moved at the "on" and "off" of the pulse. The continuous curve is a fit of the data to a two-state Boltzmann function, with parameters \(V_{1/2} = -47.7 \text{ mV}, A = 8 \text{ mV}, \text{ and } Q_{\infty} = 21.5 \text{ nC/mF}\). (From Chandler et al., 1992.)
Sarcoplasmic Reticulum (SR) / T Tubule System

ECC membranes

Skeletal vs Cardiac ECC
T-tubule channel and RyR on SR: skeletal vs cardiac muscle
Heart Muscle Structure

Ion fluxing membranes in muscle

vertebrate skeletal muscle contraction

ECC
Voltage-gated ion channels

<table>
<thead>
<tr>
<th>Property</th>
<th>RyR1</th>
<th>RyR2</th>
<th>RyR3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sed coef.</td>
<td>30s</td>
<td>30s</td>
<td>30s</td>
</tr>
<tr>
<td>Ryan Kd</td>
<td>&lt;10 nM</td>
<td>&lt;10 nM</td>
<td>&lt;10 nM</td>
</tr>
<tr>
<td>Single ch. cond. (γ_{max}) Ca</td>
<td>~120 pS</td>
<td>~120 pS</td>
<td>~110 pS</td>
</tr>
<tr>
<td>Act by Ca^{2+}</td>
<td>mM</td>
<td>mM</td>
<td>mM</td>
</tr>
<tr>
<td>Act by caffeine &amp; ATP</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Inhibited by mM Ca^{2+} &amp; Mg^{2+}</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Mod by ryanodine</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

RyR

A T-tubule
B T-tubule

SR
VDCC
RyR1
RyR2
RyR2 is a macromolecular complex. RyR2 PKA phosphorylation dissociates FKBP12.6 & increases Ca\(^2+\)-induced activation of channel. RyR2 PKA hyperphosphorylation (3/4-4/4 sites) dissociates most FKBP12.6 & channels are “leaky”.

FKBP12/12.6 required for normal function of the ryanodine receptor calcium release channel.

RyR2 is a macromolecular complex. RyR2 PKA phosphorylation dissociates FKBP12.6 & increases Ca\(^2+\)-induced activation of channel. RyR2 PKA hyperphosphorylation (3/4-4/4 sites) dissociates most FKBP12.6 & channels are “leaky”.

Regulation of EC coupling by adrenergic signaling -- “fight or flight”.

FKBP12/12.6 required for normal function of the ryanodine receptor calcium release channel.

Planar lipid bilayer chamber.
RyR2/calcium release channel phosphorylated by addition of cAMP alone

A  

+  +  -  -  PKA     
-  -  +  +  PKA Inhibitor     
-  -  +  +  cAMP

PKA phos: RyR2

Left Ventricular Assist Device

Maladaptation of the fight or flight response in heart failure

Smooth muscle contraction
**Agonist**

- PM
- Ca
- CYTOSOL
- Fertilization
- Apoptosis
- Gene activation
- Transport
- Proliferation/Differentiation

**IP3 pathway**

**GnRH**

- K(Ca) current
- Indo-1 fluorescence

A. Normal heart in-systole
B. Normal heart in-diastole
C. Failing heart in-systole
D. Failing heart in-diastole