Muscle Physiology

SKELETAL MUSCLE, SMOOTH MUSCLE
AND HEART MUSCLE

EVENING SEMINAR

Skeletal Muscle

Functions:
- Produces voluntary movement
- Produces rapid contractions
- Maintains posture & body position
- Maintains body temperature
- Stores nutrient reserves

Histology:
- Many nuclei per cell
- Long cylindrical cells
- No anatomical connection between cells
- Striated

Functional unit is the muscle fiber = cell
Skeletal Muscle Structure

Connective tissues
- Epimysium
- Perimysium
- Endomysium

Nerves
- From CNS

Blood vessels
- Supply large amounts of oxygen
- Supply nutrients
- Carry away wastes
- Transport heat

Skeletal Muscle Fiber

Internal organization of muscle fibers:
- Sarcolemma
- Sarcoplasm
- Transverse (T) tubules: transmit AP through the cell
- Myofibrils: contractile protein filaments
- Dystrophin (actin-binding protein)
- Sarcoplasmic reticulum (SR)
- Terminal cisternae: chambers of SR attached to T tubules
- Triad: formed by one T tubule and two terminal cisternae
**Sarcomere**

Sarcomeres
- The contractile units of muscle
- Structural units of myofibrils
- Give muscle striations
- Arranged between 2 Z lines

Regular organization of **thick filaments** (myosin) and **thin filaments** (actin)

- **I band**: light, only actin
- **A band**: darkest actin and myosin overlap
- **H band**: dark, only myosin
- **M line**: middle of sarcomere, only myosin tails

**Titin**
- Strands of protein
- Reaches from heads of thick filaments to the Z line
- Stabilizes the filaments
- Recolls after stretching

**Sarcomere – Thin Filament**

Thin filament proteins:

**Contractile protein:**
- F-actin (filamentous actin)
  - Is 2 twisted rows of globular (G) actin
  - The active sites on G-actin strands bind to myosin

**Regulatory proteins:**
- Nebulin
  - Holds F-actin strands together
- α-Actinin
  - Anchors the thin filaments to the Z-disk
- Tropomyosin
  - Is a double strand
  - Prevents actin-myosin interaction
- Troponin
  - A globular protein
  - Has 3 subunits (C, I and T)
  - C subunit binds Ca^{2+}
**Sarcomere – Thick Filament**

**Myosin molecule:**

- **Heavy chains (2):**
  - Tail
  - Binds to other myosin molecules forming bundles (like a double-headed arrow)
  - Head
  - Made of 2 globular protein subunits
  - Reaches the nearest thin filament
  - Has binding sites for ATP (ATPase) and for actin
  - Its position to the tail can vary between 45° and 90°

- **Light chains (4):**
  - Attached to the head of the heavy chains

**Sliding Filament Mechanism - Contraction**

1. Sarcomere relaxed
2. Sarcomere partially contracted
   - I bands are getting shorter
3. Sarcomere completely contracted
   - The I and H bands are disappeared

Note:
- The length of myosin filaments has not changed
- The thin actin filaments have moved closer together (toward the middle of the sarcomere)
- Shortening of the sarcomere produces the muscle contraction
Molecular Mechanisms of Contraction

Ca\(^{2+}\) is released from the SR
The Ca\(^{2+}\) ions bind to the troponin C
Troponin molecule changes position, rolling the tropomyosin away from the active sites on actin
Actin interacts with energized myosin heads
With the active sites on the actin exposed, the myosin heads bind and forming cross-bridges. ADP + P are bound to myosin head as myosin head attaches to actin.

ADP+P release causes head to change position and actin filament to move. “power stroke” occurs as the myosin pivots toward the M line.
When another ATP molecule attaches to the myosin head, the cross-bridge between the active site of the actin molecule and myosin head is broken. Thus freeing up the head to make another bridge and complete the contraction. ATP is necessary for the separation of actin and myosin.

Myosin splits the ATP into ADP + P and uses the released energy to re-cock the myosin head (reaching forward). Cycle can be repeated endlessly as along as calcium ion concentration remain high and sufficient ATP is present.
Summary of Muscle Contraction

1. Ca²⁺ is released from the SR.
2. Ca²⁺ binds to troponin C subunit
3. Myosin heads bind to the actin
4. The myosin head pivots towards the center of the sarcomere (45°)
5. The myosin head binds an ATP molecule and detaches from the actin
6. The free myosin head splits the ATP (ADP+P)

Neuromuscular Junction

- Large synapse between Aα motor neuron and the muscle fiber
- It is the location of neuronal stimulation (skeletal muscles contract only when get innervation from the nervous system!)
- Action potential (electrical signal) of the motor neuron travels along the axon and ends at synaptic terminal
- ACh neurotransmitter is released into the synaptic cleft and diffuse to the motor end plate (sarcolemma)
- ACh binds to nACh receptors of the motor end plate
Neuromuscular Junction II.

1. AP spreads in the axon terminal
2. Voltage-gated Ca\(^{2+}\) channels open
3. ACh neurotransmitter release
4. ACh binds to nACh receptor
5. Na\(^{+}\) flows in the muscle fiber (EPP)
6. Depolarization opens voltage-gated Na\(^{+}\) channels → AP in the muscle fiber
7. ACh esterase in the synaptic cleft quickly breaks down ACh

Myasthenia gravis – a case history

Description of case:
• 18-year-old college woman complaining of progressive weakness
• Occasionally her eyelids droop
• She tires easily even when completing ordinary daily tasks such as brushing her hair
• She has fallen several times
• The symptoms improve with rest

Diagnosis:
• Blood test revealed elevated levels of antibodies to nACh receptors → myasthenia gravis (autoimmune disease)
• Antibodies block the ACh receptor, ACh cannot bind, depolarization of the motor endplate (EPP) will not occur and normal action potentials cannot be generated in the skeletal muscle, muscle weakness and fatigability ensue
• Not hereditary

Treatment:
• Incurable, only the symptoms can be alleviated
• Administration of AChE inhibitor pyridostigmine → ACh levels in the neuromuscular junction are maintained at a high level, prolonging the time available for ACh to activate the receptor → more normal EPP in the muscle fiber can be produced even though the many of the ACh receptors are blocked.
Excitation-Contraction Coupling

Events between the AP and muscle contraction

Excitation-Contraction Coupling II.

1. NMJ – Ach release
2. AP spreads along the sarcolemma into the T-tubules
3. DHP receptors of T-tubules change conformation
4. Ryanodin receptors of SR open – Ca\(^{2+}\) release
5. Ca\(^{2+}\) binds Troponin C
6. Acto-myosin complex is formed
7. Sarcomere shortens – muscle is contracted
Muscle fibers are organised in motor units.

**Motor unit:**
- One single Aα motor neuron and all the nerve fibers it innervates
- All motor fibers of the motor unit contract at once

Increasing muscle force by **recruitment**
- In a whole muscle or group of muscles smooth motion and increasing tension are produced by increasing the number of activated motor units
Increasing muscle force by **tetanic** contractions

Muscle response for APs

AP coming in quick succession → incomplett tetanus
Maximal AP frequency → complet tetanus (basis of normal muscle work)

**Muscle Contraction Types**

**Isotonic**

**Isometric**
Source of Energy - ATP

- ATP is the form of energy that muscle and all cells of the body use.
- The chemical bond between the last two phosphates has just the right amount of energy to energize myosin heads for other contraction (90°).
- Pulling of the end phosphate from ATP will release the energy.
- ADP and a single phosphate will be left over.
- When there is no more ATP (e.g., after death) myosin head can not release actin (stiffness of death).
- New ATP can be regenerated by reconnecting the phosphate with the ADP with energy from food.

Source of Energy – Creatine phosphate

Molecule capable of storing ATP energy

LOHMANN-reaction:
Creatine + ATP \( \longrightarrow \) Creatine phosphate + ADP
ADP + Creatine phosphate \( \longrightarrow \) ATP + Creatine

- immediate source
- used up very quickly (in case of an all-out-sprint in 4-6 seconds)
Source of Energy – Carbohydrate and Lipid Breakdown

<table>
<thead>
<tr>
<th>Aerobic metabolism</th>
<th>Anaerobic metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>In the presence of $O_2$ (from myoglobin)</td>
<td>Source of ATP: Creatine phosphate and anaerobic glycolysis</td>
</tr>
<tr>
<td>Carbohydrates: long term source <strong>36-38 ATP</strong> cover 95% of cell demand</td>
<td>Without $O_2$</td>
</tr>
<tr>
<td>Fats: slow, requires more $O_2$ <strong>129 ATP</strong></td>
<td>Produces: <strong>2 ATP</strong></td>
</tr>
<tr>
<td>Proteins: minor source, only few ATP</td>
<td>Provides substrates for aerobic metabolism</td>
</tr>
<tr>
<td></td>
<td>End product of pyruvic acid hydrolysis is <strong>lactic acid</strong></td>
</tr>
<tr>
<td></td>
<td>Lactic acid (acidic pH) fatigues the muscle</td>
</tr>
</tbody>
</table>

Metabolism

(a) Resting muscle: Fatty acids are catabolized; the ATP produced is used to build energy reserves of ATP, CP, and glycogen.
Metabolism II.

(b) Moderate activity: Glucose and fatty acids are catabolized; the ATP produced is used to power contraction.

Metabolism III.

(c) Peak activity: Most ATP is produced through glycolysis, with lactic acid as a by-product. Mitochondrial activity (not shown) now provides only about one-third of the ATP consumed.
Smooth Muscle

- Fusiform (spindle-shaped) cells
- One nucleus per cell
- Non-striated (no sarcomeres)
- More actin than myosin (there is NO Troponin)
- Dense bodies instead of Z lines
- Has non-contractile intermediate filaments
- Involuntary (controlled by endocrine and autonomic nervous systems)
- Slow, wave-like contractions

Multi vs. Single-Unit Smooth Muscle

(a) Multi-unit smooth muscle

(b) Single-unit smooth muscle
Multi vs. Single-Unit Smooth Muscle

<table>
<thead>
<tr>
<th>Single-Unit</th>
<th>Multi-Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gap junctions (cells contract as single-unit)</td>
<td>Individual cells which are not electrically linked</td>
</tr>
<tr>
<td>Pacemaker cells with spontaneous depolarizations (without an external stimulus membrane potential)</td>
<td>Autonomic nervous system innervates</td>
</tr>
<tr>
<td>often associated with a basic <strong>slow wave rhythm</strong>. This is itself not an AP but a local property of the smooth muscle fibers</td>
<td>Each muscle cell is innervated by a single nerve ending</td>
</tr>
<tr>
<td>Only a few cells have innervation</td>
<td>Selective activation of cells (they contract independently of each other)</td>
</tr>
<tr>
<td>Can have inhibitory innervation</td>
<td>Cells are not spontaneously active</td>
</tr>
<tr>
<td>Myogenic tone</td>
<td>No inhibitory innervation</td>
</tr>
<tr>
<td>Level of contraction without relaxation</td>
<td>e.g. deferent duct, pilomotor muscles, intraocular muscles</td>
</tr>
<tr>
<td>Autonomic innervation modulates tension</td>
<td></td>
</tr>
<tr>
<td>Stretch may increase the activity (<strong>Bayliss effect</strong>)</td>
<td></td>
</tr>
</tbody>
</table>

e.g. bladder, uterus, urethra

Smooth Muscle Contraction – role of Ca\(^{2+}\)

- Poorly developed SR
- Thus, smooth muscle contraction is highly dependent on extracellular Ca\(^{2+}\) concentration

Ca\(^{2+}\) influx through:
- Voltage-gated Ca\(^{2+}\) channels
- Stretch-activated Ca\(^{2+}\) channels
- Ligand-gated Ca\(^{2+}\) channels (neurotransmitters and hormones)

Point to Note:
The main source of Ca\(^{2+}\) in smooth muscle is to greater extent the ECF and to a lesser extent the SR as compared to the skeletal muscles, where the greatest source of Ca\(^{2+}\) is the SR.

- MLC (myosin light chain) is a regulatory protein preventing formation of cross-bridges
- Ca\(^{2+}\) binds calmodulin, the complex activates MLCK
- MLC is phosphorylated
- Cross bridges are formed
- Muscle is contracted
Smooth Muscle Contraction

- **Ca²⁺ influx**
- **Ca²⁺ release**
- **Calcium-binding proteins**
- **Smooth muscle relaxation**

**Steps:**
1. **Ca²⁺ influx** via voltage-gated or receptor-gated channels.
2. **Ca²⁺ release** from intracellular stores.
3. **Calcium-binding proteins** interact with actin and myosin.
4. **Smooth muscle relaxation** occurs.

**Key Points:**
- Increased intracellular Ca²⁺ concentrations lead to contraction.
- Ca²⁺ binding to calmodulin (CaM) activates myosin light chain kinase (MLCK).
- MLCK phosphorylates myosin light chains, leading to contraction.
- ATPase activity decreases, resulting in increased muscle tension.

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Smooth Muscle Relaxation

- **Ca²⁺ efflux**
- **Myosin phosphorylation**
- **Myosin ATPase activity**

**Steps:**
1. **Free Ca²⁺** in cytosol decreases when Ca²⁺ is pumped out of the cell or back into the sarcoplasmic reticulum.
2. **Ca²⁺** binds to calmodulin (CaM).
3. **Myosin phosphorylation** decreases ATPase activity.
4. **Myosin ATPase activity** decreases, resulting in decreased muscle tension.

**Key Points:**
- Reduced intracellular Ca²⁺ concentrations lead to relaxation.
- Ca²⁺ bound to calmodulin (CaM) activates myosin phosphatase.
- Phosphatase removes phosphate from myosin, decreasing ATPase activity.
- ATPase activity decreases, leading to relaxation.
Latch Mechanism

It is a state in which the dephosphorylated myosin remains attached to actin for prolonged period of time. This produces sustained contraction without consuming ATP and thus enables the smooth muscle to sustain long-term maintenance of tone without fatigue. E.g. urinary bladder full of urine.

Cardiac Muscle

- Branching cells
- One/two nuclei per cell
- Striated
- Gap junctions between cells – functional syntitium
- Involuntary
- Medium speed contractions
Cardiac Muscle Contraction

- EC Ca$^{2+}$ is necessary for the contraction!
- DHPR of the sarcolemma are L-type Ca$^{2+}$ channels
- Entering Ca$^{2+}$ opens the RYR of SR (Ca$^{2+}$ induced Ca$^{2+}$ release)
- Without EC Ca$^{2+}$ the SR can not give down its Ca$^{2+}$ content
- 70% of the Ca$^{2+}$ signal comes from the SR and 30% from the ECF
- SERCA pumps back Ca$^{2+}$ in SR

**NO RECRUITMENT AND TETANUS** in the heart muscle
Force of contraction can be increased by increasing Ca$^{2+}$ content of the sarcoplasm (positive inotropic effect)

### Comparisons among muscle types

<table>
<thead>
<tr>
<th>Property</th>
<th>Skeletal</th>
<th>Smooth (single-unit)</th>
<th>Smooth (multi-unit)</th>
<th>Cardiac</th>
</tr>
</thead>
<tbody>
<tr>
<td>Situations (sarcomeres)</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Actin and myosin</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Level of control</td>
<td>Voluntary</td>
<td>Involuntary</td>
<td>Involuntary</td>
<td>Involuntary</td>
</tr>
<tr>
<td>Neural input</td>
<td>Somatic</td>
<td>Autonomic</td>
<td>Autonomic</td>
<td>Autonomic</td>
</tr>
<tr>
<td>Neuroeffector junction</td>
<td>Neuromuscular junction—specific</td>
<td>Variocities—diffuse</td>
<td>Variocities—diffuse</td>
<td>Variocities—diffuse</td>
</tr>
<tr>
<td>Hormonal control</td>
<td>None</td>
<td>Several, depending on location</td>
<td>Several, depending on location</td>
<td>Epinephrine</td>
</tr>
<tr>
<td>Source of calcium</td>
<td>SR</td>
<td>SR and ECF</td>
<td>SR and ECF</td>
<td>SR and ECF</td>
</tr>
<tr>
<td>Regulatory protein that binds calcium</td>
<td>Tropanin</td>
<td>Calmodulin</td>
<td>Calmodulin</td>
<td>Tropanin</td>
</tr>
<tr>
<td>Gap junctions</td>
<td>No</td>
<td>Yes</td>
<td>No (or few)</td>
<td>Yes</td>
</tr>
<tr>
<td>Pacemaker activity</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Myosin ATPase activity</td>
<td>Fastest</td>
<td>Slowest</td>
<td>Slowest</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Recruitment</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
Sample Test Questions

1. During which of the following steps in cross-bridge cycling in skeletal muscle is ATP bound to myosin? (1)
   a) rigor
   b) conformational change in myosin (45° → 90°)
   c) power stroke
   d) rest

2. Which of the following classes of drugs are contraindicated in a patient with myasthenia gravis? (3)
   a) nACh receptor antagonists
   b) inhibitor of choline-reuptake
   c) AChE inhibitors
   d) inhibitors of ACh release

3. A man is poisoned with curare. Which of the following agents would worsen his condition? (1)
   a) Pyridostigmine
   b) nicotine
   c) Botulinus toxin
   d) ACh

(1/1, 2-ab, 3-c)