Types of muscles

2 Types
- Striated muscle
- Smooth muscles

Skeletal muscles

Morphology (structure)

Skeletal muscles each contain muscle fibers each contains myofibrils each contains filaments

Myosin protein

2 Heavy chains
- Coil around each other \(\Rightarrow\) a helix

Tail

Body

2 Arms
- Has 2 hinges

Cross bridges

4 light chains
- 2 Heads
- Has 3 binding sites

One hinge with the body

2nd hinge with the head

Actin binding site

ATP binding site

Catalytic site (hydrolyzes ATP)

Thin filament proteins (3 types)

(1) Actin
- The backbone of thin filaments
- Formed of 2 chains (coil around each other \(\Rightarrow\) a helix)
- Each actin molecule has an active site with which cross bridges of myosin combine during muscle contraction

(2) Tropomyosin
- Long filaments present in the groove between the 2 chains of actin
- Covers the active sites on actin during relaxation

(3) Troponin
- 3 globular protein molecules
  1. Troponin I: has a strong affinity & binds with actin (I-band)
  2. Troponin T: has a strong affinity & binds with tropomyosin
  3. Troponin C: has a strong affinity & binds with Ca\(^{2+}\)

Tubular system: 2 networks

(1) Transverse (T) tubule
- Invagination on the surface of muscle membrane at the junction of A & I bands.
- Conducts action potential to the SR.
- Contains extracellular fluid.
- Contains a voltage sensitive (DHP) receptor that opens the ryanodine Ca\(^{2+}\) release channels on the SR membrane.

(2) Sarcoplasmic reticulum (SR)
- Networks of membranous channels surround each myofibril & run parallel with it
- It has high conc. of Ca\(^{2+}\) (for muscle contraction)
- The ends of SR (terminal cisternae) contact with T tubules by foot processes.
- SR membrane contains (ryanodine receptor) that contain foot process & Ca\(^{2+}\) release channel
Physiologic anatomy of neuromuscular junction

1- Axon terminals (end feet): contains A.Ch. vesicles.
2- Motor end plate (MEP) contains A.Ch. receptors
3- Synaptic cleft contains A.Ch. esterase enzyme.

Neuromuscular transmission

Sequence of events during N.M. transmission
1- The nerve impulse reaches the nerve ending ⇒ ↑↑ permeability to Ca^{2+}
2- Ca^{2+} enter the nerve endings ⇒ rupture of vesicles ⇒ exocytosis A.Ch.
3- A.Ch diffuses to the muscle ⇒ binds to its receptors in M.E.P. ⇒ activation of ligand-gated channels (Na\(^+\) entry > K\(^+\) exit) ⇒ depolarization at motor end plate (end plate potential "EPP") EPP is graded, non-propagated response
4- EPP depolarizes the adjacent muscle membrane to its firing level ⇒ action potentials are generated on either side of M.E.P & conducted in both directions initiate muscle contraction
5- A.Ch (dissociated from receptors) is hydrolyzed rapidly by choline esterase enzyme (to prevent it from causing multiple muscles contractions).

Miniature EPP: at rest, few vesicles containing A.Ch rupture spontaneously & release A.Ch ⇒ minute depolarization at MEP

The number of ruptured vesicles
α Ca^{2+} conc. & 1/α Mg^{2+} conc. at MEP

Properties of N.M transmission
(1) It is unidirectional: (in one direction only from the nerve to the muscle).
(2) There is a delay about 0.5 mSec: (represents the time for events of N.M. transmission)
(3) Easily fatigued: due to repeated stimulation & exhaustion of A.Ch vesicles.
(4) Effect of ions: Excess Ca^{2+} ⇒ ↑↑ release of A.Ch ⇒ ↑↑ transmission.
Excess Mg^{2+} ⇒ ↓↓ release of A.Ch ⇒ ↓↓ transmission.
(5) Effect of drugs:
(a) Drugs stimulate N.M transmission
(b) Drugs block N.M transmission

<table>
<thead>
<tr>
<th>(b) Drugs block N.M transmission</th>
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<tbody>
<tr>
<td>(Curariform drugs)</td>
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<tr>
<td>⇒ Prevent passage of impulses at MEP.</td>
</tr>
<tr>
<td>Curare: competes with A.Ch for the receptor sites on the membrane.</td>
</tr>
</tbody>
</table>

Myasthenia Gravis: Muscle weakness & easy fatigability:
• It is a serious & sometimes fatal disease (in case of respiratory muscles paralysis).
• It is an autoimmune disease (autoantibodies against patient’s A.ch receptors)
• Treatment: anticholine esterase (e.g. neostigmine) ⇒ ↑↑ A.Ch to affect normal muscles activity
Changes following skeletal muscle stimulation

1. **Electrical changes** following skeletal muscles stimulation similar to those in nerve but:
   1. Resting membrane potential (~90 mV.)
   2. Action potential precedes contraction by (2 mSec)
   3. Action potential lasts (2 – 4 mSec).
   4. Conduction velocity (5 m/sec).

2. **Excitability changes** following skeletal muscles stimulation similar to nerve:
   - ARP: coincides with the ascending limb & part of the descending limb of the spike potential
   - ARP: coincides with the latent period of the mechanical response.
   - As the muscle begins to contract, it regains its excitability.

3. **Mechanical changes** following skeletal muscles stimulation:
   Molecular mechanism of muscle contraction (the contractile response) (Excitation - Contraction (EC) coupling):
   - 4 steps
   1. **Release of Ca^{2+}**: propagation of A.P. into the T tubules ⇝ opening of the Ca^{2+} channels on terminal cisternae (TC) ⇝ Ca^{2+} flow out of the SR into the cytoplasm.
   2. **Activation of muscle proteins**: Ca^{2+} binds to troponin C (undergoes conformational changes)
      - Tropomyosin is moved away
      - Cross bridges from myosin combines with the binding site on actin & contraction begins

4. **Generation of tension**: by cycling of the cross bridges: 4 steps:

<table>
<thead>
<tr>
<th>1st step</th>
<th>2nd step</th>
<th>3rd step</th>
<th>4th step</th>
</tr>
</thead>
</table>
   | Binding of actin & myosin | Binding of cross bridges ⇝ sliding of actin over myosin
   - The energy needed for bending is obtained from hydrolysis of ATP | Release (detachment) of the cross bridges from actin
   - ATP is needed to ↓↓ affinity of cross bridges for active sites
   - If ATP is not available, the thick & thin filaments cannot be separated (muscle contracture) | Return of the cross bridges to their original site to act in another cycle
   - cycling continues as long as Ca^{2+} is attached to troponin & energy is available.

4. **Relaxation**: Ca^{2+} is removed by Ca^{2+} pump on the SR membrane ⇝ ↓↓ intracellular Ca^{2+} conc.
   - Troponin returns to its original conformational state.
   - Tropomyosin covers the binding site of actin & cycling stops.

**All or none law**

A single skeletal ms. fiber obeys all or none law

- The skeletal ms. fiber contracts maximally or does not contract at all.
- A threshold stimulus produces maximal contraction provided that other conditions remain constant

**The muscle twitch**: a brief contraction followed by relaxation caused by a single action potential
Types of contraction of skeletal muscles

<table>
<thead>
<tr>
<th></th>
<th>(1) Isotonic contraction</th>
<th>(2) Isometric contraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1- Ms. Length</td>
<td>Shortens</td>
<td>Constant</td>
</tr>
<tr>
<td>2- Ms. Tension</td>
<td>Constant</td>
<td>Highly increased</td>
</tr>
<tr>
<td>3- Time</td>
<td>More</td>
<td>Less</td>
</tr>
<tr>
<td>4- Energy</td>
<td>More</td>
<td>Less</td>
</tr>
<tr>
<td>5- Work</td>
<td>Done (load is moved)</td>
<td>Not done (load is not moved)</td>
</tr>
<tr>
<td>6- Mechanical efficiency</td>
<td>% of energy input converted into work</td>
<td>20 — 25 %</td>
</tr>
<tr>
<td>7- Force of contraction is measured by</td>
<td>Velocity &amp; degree of muscle shortening</td>
<td>Degree of developed muscle tension</td>
</tr>
<tr>
<td>8- Function</td>
<td>Movement of part of the body or the body as a whole</td>
<td>Tenses a part of the body &amp; maintains the body against gravity</td>
</tr>
<tr>
<td>Example</td>
<td>Contraction of biceps to lift an object</td>
<td>Contraction of quadriceps to stiff the knee joint</td>
</tr>
</tbody>
</table>

Muscles can contract both isometrically & isotonically (mixture of the 2 types)

Factors affecting skeletal muscle contraction

1. Type of muscle
2. Stimulus factor
3. Length – tension relationship
4. Load – velocity relationship
5. Muscle fatigue

(1) Type of muscle fibers (2 types)

1- Slow (red) fibers (type I)
   - Small muscle fibers.
   - Innervated by small slowly conducting motor neurons.
   - Contain: large numbers of oxidative enzymes
     - More mitochondria *(aerobic metabolism)*
     - More myoglobin (store O₂ for need).
     - More blood supply (supply more O₂)
   - Have: low ATPase activity
   - Slow contractile mechanism
   - High resistance to fatigue
   - e.g. back muscles & soleus muscle

2- Fast (pale) fibers (type IIb)
   - Large muscle fibers.
   - Innervated by large rapidly conducting motor neurons
   - Contain: large amount of glycolytic enzymes for glycolytic process *(anaerobic metabolism)*
     - Less myoglobin.
     - Less blood supply.
     - Less mitochondria.
   - Have: high ATPase activity – extensive SR
   - Rapid contractile mechanism
   - Less resistance to fatigue
   - e.g. muscles of the hand & extraocular muscles

(2) Stimulus factors

a- Strength of stimulus: ↑↑ strength of stimulus ⇔ ↑↑ no. of activated ms. fibers ⇔ ↑↑ ms. contraction

b- Frequency of stimulation: ↑↑ frequency of muscle stimulation ⇔ ↑↑ force of contraction (because ↑↑ Ca²⁺ release from the SR each time the muscle is stimulated)

According to frequency of stimuli, there are:

- Complete tetanus: (with high frequency) fusion of contractions with no relaxation
- Incomplete tetanus: (with moderate frequency) contractions with incomplete relaxation
- Separate twitches: progressive ↑↑ in force of contraction during each successive twitch until a plateau value (uniform tension)

Treppe “Stair case phenomenon”
cause: ↑↑ levels of intracellular Ca²⁺

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Example

Contraction of biceps to lift an object
Contraction of quadriceps to stiff the knee joint

Muscles can contract both isometrically & isotonically (mixture of the 2 types)
(3) **Length – Tension relationship**

**Starling’s law:**

*The greater* the initial ms. fiber length (preload), *the more* will be the active tension developed during its isometric contraction **within limits**

<table>
<thead>
<tr>
<th>Sarcomere length</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Maximal force occurs at 2.2μ</td>
</tr>
<tr>
<td>(b) More than 2.2 μ</td>
</tr>
<tr>
<td>(c) Less than 2.2 μ</td>
</tr>
<tr>
<td>At this length, there is a maximal number of cross bridges. This is the resting length of the muscles inside the body.</td>
</tr>
<tr>
<td>Some cross bridges do not have actin filaments to combine with ↓↓ force of contraction.</td>
</tr>
<tr>
<td>Ends of the 2 actin filaments overlap ↓↓ number of cross bridges ⇒ ↓↓ force of contraction</td>
</tr>
</tbody>
</table>

(4) **Load-Velocity relationship**

- ↑↑ after load ⇒ ↓↓ velocity & degree of muscle shortening.
- Maximal velocity of shortening (Vmax) occurs when there is no external load (zero load).
- Vmax is theoretical, because load can not be zero.

(5) **Muscle fatigue**

- Prolonged & strong contraction of muscle ⇒ **muscle fatigue** (↓↓ strength of contraction, ↑↑ its duration & relaxation becomes incomplete).
- **Causes:**
  - (a) ↑↑ metabolites (as lactic acid) ⇒ ↑↑ intracellular acidity.
  - (b) ↓↓ muscle ATP, glycogen & creatine phosphate.
  - (c) ↓↓ blood flow ⇒ loss of nutrients & O₂ supply.
  - (d) ↓↓ transmission at N.M. junction.

(4) **Metabolic changes following skeletal muscles stimulation**

*(Energy sources & muscle metabolism)*

I- **During rest**  II- **During contraction**  III- **During recovery**

**I- During rest**  skeletal muscles consumes energy for:

- a- maintenance of RMP  
  - b- synthesis of chemical substances  
  - c- production of muscle tone

**II- During contraction**  Energy consumption is markedly ↑↑

- ATP is the only immediate energy source for contraction.
- ATP is hydrolyzed anaerobically into ADP. Myosin acts as the enzyme ATPase.
- ATP inside muscles is enough for maximal contraction for only (5 – 6 seconds).
- ATP is continuously reformed by 3 metabolic mechanisms:

<table>
<thead>
<tr>
<th>(1) Phosphocreatine</th>
<th>(2) Glycogen lactic acid system</th>
<th>(3) Aerobic system</th>
</tr>
</thead>
</table>
| **ADP + Creatine Phosphate** ⇒ **ATP + Creatine**  
  - Energy transfers from phosphocreatine to ATP within a small fraction of sec  
  - Phosphagen energy system (phosphocreatine + ATP) can provide maximal muscle power for (10 – 15 sec.) enough for 100m. running  
  - Creatine phosphate is later restored by the reverse reaction during muscle relaxation.  | **Glucose + 2 ATP (or glycogen + 1 ATP)**  
  - Anaerobic glycolysis  
    - Provides (30 – 40 sec.) excess muscle activity (10 – 15 sec.) provided by the phosphagen system.  
    - Enough for 200-800 meters running.  
    - Lactic acid ⇒ severe muscle fatigue  
  - Removal of lactic acid by:  
    - a- Some of lactic acid ⇒ pyruvic acid  
    - b- Much of lactic acid ⇒ glucose (by the liver) ⇒ glycogen stores in muscles  
    - c- It is used as a fuel in the heart. | **Glucose + 2ATP**  
  - (or glycogen + 1 ATP)  
  - 6CO₂ + 6H₂O + 40ATP  
  - Oxidation of food stuffs in the mitochondria to provide energy (glucose, fatty acids & amino acids).  
  - Provides unlimited time for ms activity as long as nutrients & O₂ are available. |
III. During recovery (Oxygen Debt) Extra post-exercise $O_2$ consumption:

**Definition:** Oxygen consumption during recovery (after exercise)
in excess of the resting basal oxygen consumption.

**This extra $O_2$ consumption is used for:**
1. Removal of excess lactate.
2. Reformation of ATP & creatine phosphate.
3. Refilling of myoglobin with oxygen.

Motor unit: the motor neuron & the muscle fibers supplied by it

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**Smooth muscles**

**Types (2)**

<table>
<thead>
<tr>
<th>Visceral (single unit) smooth muscles</th>
<th>Multiunit smooth muscles</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Site:</strong> in the walls of hollow viscera.</td>
<td><strong>Site:</strong> e.g. cilaiary muscle &amp; iris of the eye.</td>
</tr>
<tr>
<td>Fibers are aggregated &amp; have “gap junctions”</td>
<td>The fibers are separated</td>
</tr>
<tr>
<td>Action potential can spread from 1 cell to another</td>
<td>Action potential cannot spread</td>
</tr>
<tr>
<td>The whole muscle acts as one unit.</td>
<td>Each fiber contracts independently of others</td>
</tr>
<tr>
<td>The muscle is spontaneously active &amp; affected by hormones, chemical &amp; neuro-transmitters</td>
<td>The muscle is densely innervated &amp; contraction is under neural control</td>
</tr>
</tbody>
</table>

**Structure**

1. Thin, fusiform (spindle-shaped) cells (5 – 10 μ wide & 10 – 500 μ long).
2. No sarcomeres, no interdigitating thick & thin filaments ⇒ no striations,
3. No troponin-tropomyosin complex. No T tubules & SR is poorly developed,
4. The thin filaments are attached to dense bodies.
5. Cross-bridges cycle similar to that of striated ms.

**Electrical activity of smooth muscles**

- RMP is unstable (average – 50 to – 60 mV.)
- Waves are superimposed on the RMP (e.g. slow sine waves of the gut).
- These waves cannot cause muscle contraction.
- When wave potential reaches –35mV, action potential occurs.
- The action potentials of smooth muscle has (2 forms):

  1. **1- Spike potentials**
     - Duration of the spike (50 mSec).
     - Similar as in skeletal ms. or on top of slow waves or rhythmically (pace maker potential)

  2. **2- Action potential with plateau**
     - Like that of cardiac ms.
     - Plateau ⇒ delayed repolarization ⇒ prolonged contraction

**Contraction process of smooth muscles**

**Excitation – contraction (E – C) coupling:**

1. Binding of cytoplasmic Ca$^{2+}$ to calmodulin.
2. The calcium – calmodulin complex
   ⇒ activates myosin light chain kinase (MLCK)
   ⇒ phosphorylates the regulatory light chain on the head of myosin molecule
   ⇒ ATP hydrolysis & cross bridge cycling.
3. The phosphorylated cross bridges continue to cycle until they are dephosphorylated by myosin light chain phosphatase (MLCP) during relaxation.
4. Relaxation occurs when the intracellular Ca$^{2+}$ conc. fall & the MLCK becomes inactive
Mechanical properties of smooth muscles differ from those of striated muscles

(1) Smooth muscles contracts slower than skeletal muscles 
    (dependent on the phosphorylation of the myosin light chain)

(2) The dephosphorylated cross-bridges remain attached to actin
    latch-bridges: (smooth ms has the ability to maintain tone with little energy consumption)

(3) \( \text{Ca}^{2+} \) enter the cells in a variety of ways:
    a. During depolarization of the cell membrane ⇒ open voltage gated \( \text{Ca}^{2+} \) channels.
    b. When smooth muscle is stimulated by a neurotransmitter ⇒ open receptor activated \( \text{Ca}^{2+} \) channels
      or release \( \text{Ca}^{2+} \) from sarcoplasmic reticulum through inositol triphosphate (IP3) gated \( \text{Ca}^{2+} \) channels

(4) The level of cytoplasmic \( \text{Ca}^{2+} \) in smooth muscles is determined by:
    a. The rate of \( \text{Ca}^{2+} \) entry by \( \text{Ca}^{2+} \) influx & \( \text{Ca}^{2+} \) release from sarcoplasmic reticulum
    b. The rate of \( \text{Ca}^{2+} \) removal from cytoplasm of smooth muscle actively into SR or out of the cell

Characteristics of contraction of smooth muscles

(1) Spontaneous contractions (even, if there is no nerve supply)
    ⇒ rhythmic contractions or tetanic from (muscle tone).

(2) Role of nerve supply: do not initiate activity, but regulate the activity of smooth muscles

(3) Contraction are controlled by:
    a. Motor neurons
    b. Stimulatory factors:
       (1) Stretch: allows a hollow organ to contract & evacuate when it is distended.
       (2) Cold: ↑↑ contraction of plain muscles.
       (3) Local factors: Acid, ↑↑ \( \text{CO}_2 \) & ↓↓ \( \text{O}_2 \) cause relaxation.
          Alkali & ↑↑ \( \text{K}^+ \) cause contraction.
    (4) Humoral factors

(4) Relation of length to tension (plasticity)
    The smooth muscle is plastic i.e. if it is stretched ⇒ 1st the tension is increased.
    ⇒ Then the tension is gradually decreased to normal.
    Value: it allows hollow viscus to be filled without much increase in pressure.
    Cause: readjustment of the position of the myosin cross-bridges on the thin filaments.

(5) Smooth ms contraction uses less ATP than skeletal ms. ⇒ it is fatigue resistant