I. THE NEUROMUSCULAR JUNCTION (NMJ)

Unique characteristics:
- a specialized chemical synapse between a motor neuron and a muscle fiber
- presynaptic terminal ALWAYS releases acetylcholine (ACh)
- postsynaptic membrane ALWAYS has nicotinic ACh receptors (in mammals)
- each muscle fiber only receives information from ONE motor neuron

Questions:
1) What is the biggest difference you can see in the above image that distinguishes the neuromuscular junction from any other synapse that uses ACh and nicotinic ACh receptors?

2) Is there a difference between the net results of synaptic transmission at the NMJ vs. a typical synapse? If so, what is the difference?

3) Why do you think this unique specialization of the NMJ exists?
**NMJ Questions:** Now that we’ve covered the general mechanics of synaptic transmission we’re ready to examine a few specific examples that apply those mechanics to the neuromuscular junction. So, using what you know about synapses and their effects on postsynaptic cells, answer the following questions.

<table>
<thead>
<tr>
<th>Action</th>
<th>Effect on NMJ Transmission?</th>
<th>Explain the effect?</th>
<th>Treatment?</th>
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<tbody>
<tr>
<td>Botulinum toxin</td>
<td>degrades SNAREs in presynaptic terminal</td>
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<tr>
<td>“Botox”</td>
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<td>Curare</td>
<td>Competitive nicotinic ACh receptor antagonist</td>
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<td>Hemicholinium</td>
<td>Blocks reuptake of choline into presynaptic terminal</td>
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<tr>
<td>Succinylcholine</td>
<td>ACh agonist that resists AChEase degradation</td>
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<tr>
<td>Myasthenia Gravis</td>
<td>autoimmune disorder in which ACh receptors are destroyed</td>
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II. Muscular Action Potential Transmission

Needs:

III. Transverse (T) Tubules

Dihydropyridine (DHP) Receptors

IV. Sarcoplasmic Reticulum (SR)

Ryanodine receptors (RyR)

Relationship between SR and muscle fiber
Striated Muscle Podcast Application Questions:

**Question:**
Given the events of the sliding filament model described in the podcast, explain why rigor mortis occurs. Why doesn’t rigor mortis start to occur until around 3-4 hours after death?

Dantrium (Dantrolene sodium) is a drug that acts as a ryanodine receptor antagonist. Explain the effects you would expect to see after its administration.

Certain anesthetics (e.g., halothane) can have the rare side-effect of initiating massive ryanodine receptor activation. What effects would you expect to see in a patient with this side-effect and what treatment would you use to help them?

V. Muscle Fiber Organization

Motor unit = a single motor neuron and all of the muscle fibers it innervates
VI. Basic motor unit characteristics

- Each time a motoneuron sends an action potential, ALL of its muscle fibers contract.
- The # of muscle fibers per motoneuron is referred to as the innervation ratio.
- Average innervation ratio is around 600 muscle fibers per motoneuron, but it ranges widely from as many as 2,000 in the quadriceps to as few as 5 in ocular muscles.

VII. Muscle mechanics

A) The length-tension relationship

- Demonstrates how the INITIAL length of a sarcomere affects the force elicited by an isometric twitch contraction at THAT length.
- Depends on initial cross-bridge availability, which is greatest at slight stretch from a neutral length. The ranges of motion for most joints are biomechanically organized to maximize this characteristic.
- In the scope of skeletal muscle, this relationship can be thought of as “mechanical advantage”. During movement, the neuromuscular system automatically tries to adjust our body position to maximize the length-tension relationship.
- In cardiac muscle, the length tension relationship plays an important role in the “contractility” of the heart. As the heart fills with blood during diastole, its muscle fibers are passively stretched into a more efficient length-tension orientation.
- The active portion of the length-tension curve from the sarcomere’s point of view
VII. Muscle mechanics (cont.)
A) The length-tension relationship (cont.)

Question: Describe situations in real-life movements where the limitations and advantages of the length-tension relationship are experienced.

B) The force-velocity relationship

- The faster a muscle is shortening (a concentric contraction), the less force it can produce either directly or in response to an imposed load.

- Conversely, the slower a muscle is shortening, the more force it can produce.

- When a muscle contracts while it is lengthening (an eccentric contraction) the amount of force generated increases briefly and then plateaus at a maximum.

- While the mechanism is still debated, the higher forces are likely a result of two effects. 1) activation of muscle spindles that initiate a strong reflexive contraction. 2) a proportion of myosin-actin cross-bridges that “lock” and prevent the sarcomere from lengthening. Combined, these yield a tensile stress that resists further lengthening.

Question: Studies show that eccentric exercise is the primary cause of “delayed onset muscle soreness”. Give some examples of eccentric exercises. What are the symptoms and signs of delayed onset muscle soreness?
VIII. SMOOTH MUSCLE

- The variety of smooth muscle forms and functions, from circular muscles that surround blood vessels, to sheets of muscle that line the gastrointestinal tract, suggest wide diversity of physiological regulation.

- Unitary vs. multi-unit

  - Unitary muscle is often spontaneously active; “pacemaker” activity controlled by hormones and neurotransmitters.

  - Vascular smooth muscle lies somewhere between the two examples.

*Excitation-contraction coupling in smooth muscle*

- Excitation can be from nerves/neurotransmitters, hormones, or simply spontaneous.

- Arrival at threshold can trigger:
  a) an inward Na⁺ current,
  b) a faster inward Na⁺ current and a slower inward Ca²⁺ current,
  c) just a slower inward Ca²⁺ current.

- All mechanisms increase [Ca²⁺]:
  - Opening membrane DHP Ca²⁺ channels triggers IP₃-gated SR Ca²⁺ release.

- Increased [Ca²⁺] leads to a conformational change in calmodulin, not the closely related troponin.
Additionally, calmodulin serves the role of rolling tropomyosin off of the binding sites on actin to allow myosin-actin interaction.

Activated calmodulin combines with myosin light chain kinase (MLCK) to open an ATPase site on MLCK.

Phosphorylation of smooth muscle myosin by MLCK energizes the myosin head which then participates in the process of contraction through its power stroke.

Myosin light chain phosphatase (MLCP) plays the role of removing the phosphate from the myosin head to allow relaxation. If MLCP is inhibited, the myosin head will stay bound to the actin and create a “latch bridge”. Smooth muscles can maintain a shortened length with reduced energy requirements as a result.

Unlike skeletal and cardiac muscle, smooth muscle does not have a sarcomere organization pattern.

Smooth muscle cells are surrounded by a mesh formed with lengths of actin that intersect with short myosin filaments.

Cross-bridging still occurs which shortens the distance between myosin intersection points and “shortens” the smooth muscle cell within the mesh.

Question: In skeletal muscle, chronic high loading leads to an increase in muscle fiber diameter (hypertrophy). Give an example of smooth or cardiac muscle responding in a similar manner.