Outline of class notes for Physiology

Objectives:
1. Briefly describe the three types of muscle tissue and their distinguishing characteristics.
2. Describe the functions and properties of muscle tissue.
3. Explain the connective tissue components of muscle.
4. Describe the anatomy of a skeletal myofiber.
5. Describe the components of a sarcomere and the Sliding Filament Model of a muscle contraction.
6. Describe how skeletal muscles are innervated and the structures of the neuromuscular junction.
7. Explain the steps involved in the contraction and relaxation of a skeletal muscle fiber.
8. Discuss the following conditions: Duchenne Muscular Dystrophy, Rigor Mortis, and Fibromyalgia.
9. Discuss the Clinical Applications from the study guide and assigned Applications to Health.

Part I, Muscular System Overview

- Muscle Tissue Types
- Properties and Functions
- Skeletal Muscle Anatomy
  - Myofiber (muscle cell)
  - Neurumuscular junction
- Events of a muscle contraction/relaxation

Muscles

- A Muscle is an organ
  - Contains nerves, blood vessels, various connective tissues, and muscle cells (muscle fibers).
- There are ~600 skeletal muscles within the body

Three Types of Muscle Tissue

1. Skeletal Muscle
2. Smooth Muscle
3. Cardiac Muscle

Skeletal Muscle

- Skeletal muscle
  - Location: Attached to bones – provides
  - Consist of long, cylindrical cells that are striated and multinucleate
    - Striations (light and dark bands) gives a banded appearance.
    - Under voluntary control and can grade (vary) its contraction strength.
Cardiac Muscle
- **Cardiac muscle**
  - Predominant tissue within the heart wall
  - Consists of *striated*, cylinder-shaped branching cells connected by *intercalated discs*
  - Cells contain 1-2 nuclei; single nucleus in most cells.

Smooth Muscle
- **Smooth muscle**
  - Located primarily in the walls of hollow organs (stomach, blood vessels, uterus, bladder, airways to lungs, etc.)
  - Consists of *non-striated* (smooth) spindle-shaped cells

Properties of Muscle Tissue
1. **Excitability**
   - Response includes the generation of an *electrical impulse (action potential)* that travels along the plasma membrane of the muscle cell.
   - Possible Stimuli: Neurotransmitter, hormone, stretch, $\Delta$pH, $\Delta$PCO$_2$, or $\Delta$PO$_2$. (*the symbol $\Delta$ means “a change in”*)

2. **Contractility**
   - The ability to shorten forcibly when adequately stimulated.

3. **Extensibility**

4. **Elasticity**
   - The ability to recoil and resume original length after being stretched.
Connective Tissue and Muscle

- Fibrous Connective tissue surrounds and protects muscular tissue.

- Fibrous CT (fascia) forms three layers within and around skeletal muscle:
  - **Epimysium**: Outermost layer that
  - **Perimysium**:
    - **Fascicle**: A bundle of skeletal muscle cells (muscle fibers),
    - **Fascicles may contain bundles of 10 to over 100 muscle cells**.
  - **Endomysium**:

Skeletal Myofiber Anatomy

- **Sarcolemma**:

- **Sarcoplasm**: Cytoplasm of a muscle cell
  - Sarcoplasm has lots of mitochondria, lots of glycogen granules (to provide glucose for energy needs) as well as myofibrils and sarcoplasmic reticuli.

- **T (transverse) tubules**: Tubular invaginations of the sarcolemma that extend through the cell.
  - Function to carry an action potential deep into the myofiber cytoplasm

- **Sarcoplasmic reticulum**: Muscle endoplasmic reticulum that surrounds the myofibrils.
  - Functions as a
    - **Terminal cisternae** are dilated end sacs of the sarcoplasmic reticulum that lie near the T tubules.

- **Triads**: Complex consisting of a central T tubule flanked on each side by terminal cisternae
• **Myofibrils**: Rodlike structures that
  - Composed of cylindrical bundles of **thick and thin myofilaments** arranged in repeating units called **sarcomeres**
  - The interaction of these proteins allow for muscle contraction.

  ![](image1)

**Thick Myofilaments**

• **Thick myofilaments**:
  - A single myosin protein resembles 2 golf clubs whose shafts have been twisted about one another.
  - About 300 of these myosin molecules are joined together to form a single thick filament.
  - The myosin heads (cross bridges) extend out toward the thin filaments.
  - Each myosin head contains an **ATP-binding site** and an **actin-binding site**
  - The ATP-binding site functions as a

  ![](image2)
**Thin Myofilaments**

- **Thin myofilament**: Composed of 3 different types of proteins: **actin** (main component), **troponin** and **tropomyosin**.
- **Actin filament** (F-actin): A polymer formed of 300 – 400 globular subunits (G-actin), arranged as a double row of proteins twisted to from a helix.
  - On each actin subunit, there is a
  - Under resting conditions, myosin binding is prevented by the **troponin-tropomyosin** complex.
- **Tropomyosin**: Consists of long strands of protein molecules that are located in the groves of the actin helix.
  - Covers the myosin binding sites and prevents actin-myosin interaction.
- **Troponin** binds to tropomyosin forming a **troponin-tropomyosin complex**.
  - **Troponin** is a complex of three proteins:
    - **Troponin I**: Helps inhibit cross bridge binding to actin
    - **Troponin T**:
    - **Troponin C**:
      - In resting muscle, intracellular calcium concentrations are low and the calcium binding site is empty.

**Sarcomeres**

- **Sarcomere**: The contractile unit in a striated muscle cell extending from
  - Each myofibril is made up 1000’s of repeating units known as **sarcomeres**
  - The portion of the sarcomere which contains the thick filament is known as the **A band**.
    - “A” stands for **anisotropic** which is a fancy way of saying that it
    - The “A” band contains a zone of overlap (between thick & thin filaments) and an **“H” zone** which contains only thick filaments
  - The portion of the sarcomere which does not contain any thick filaments is known as the **“I” band**.
    - The “I” band contains only thin filaments and
  - Note: One “I” band is actually part of two sarcomeres at once.
  - In the middle of the **H zone** is a structure called the **M line** which functions to hold the thick filaments to one another.
Other Muscle Proteins

- **Titin Filament**: An elastic protein that anchors a
  - Contributes to the elastic recoil of muscles in their return to resting length during relaxation.
  - It is like a molecular bungee cord.

- **Dystrophin**: A cytoskeleton protein that links thin filaments of the sarcomere to integral membrane proteins of the sarcolemma.
  - In connection with associated proteins, functions to reinforce the sarcolemma and help transmit the tension generated by the sarcomeres to the tendons

Muscular Dystrophy

- Refers to a group of inherited muscle-destroying diseases that cause progressive degeneration of skeletal muscle.
  - Characterized by the

- **Duchenne muscular dystrophy** is most common form
  - Little to no dystrophin protein made - sarcolemma lacks support
  - Results: Sarcolemma tears during muscle contraction and myofibers slowly rupture and die.
  - Disorder apparent between ages of 2-5 years
    - By age 12, are usually in a wheelchair
    - By age 20 – 30, death due to respiratory or cardiac failure
Muscle Contraction: The Sliding Filament Model

- Model describes the movement of thick (myosin) and thin (actin) filaments during contraction
  - During a contraction,
    - Thin filaments slide past thick filaments, extending more deeply into the A band, which remains at constant length
    - I bands and H bands decrease in length as Z disks are drawn closer together.
    - Sarcomere represents area between successive Z disks, therefore the sarcomere gets smaller during a contraction
  - When all the sarcomeres in a fiber do this the entire fiber gets shorter which pulls on the attached tendon and then pulls on the bone. Voila, we have movement.

Sarcomere Structure and Contraction

- In the process of contraction:
  - Distance between the Z discs
  - Length of the A band
  - Length of the H zone
  - Length of the I band

Muscle Innervation

- In general each muscle is served by one nerve.
  - Nerve: A bundle of axons and/or dendrites carrying signals to the muscle or other structure.
  - Motor unit: A motor neuron and
    - Muscles that control small precise movements have many motor units with few muscle fibers.
      - Ex. Muscles of fingers, eyes
    - Muscles that cause large, powerful movements have few motor units with many muscle fibers per motor unit.
      - Ex. Gastrocnemius
  - Within the muscle, each axon will go its own way and eventually branch into multiple small extensions called telodendria.
    - Each telodendrium ends in a bulbous swelling known as the axon terminal or synaptic end bulb or terminal boutons.
  - Synapse:
Structures of the Neuromuscular Junction

- **Neuromuscular Junction:**
  - The *axon terminal* and *motor endplate* constitute the neuromuscular junction.
  - The minute space between the axon terminal and the sarcolemma is known as the *synaptic cleft*.
  - **Motor end plate**: Region (depression) of the sarcolemma that is adjacent to the *synaptic end bulbs*.
  - The nerve terminal is filled with vesicles that
    - The motor end plate has folds (*junctional folds*) that contain a number of *acetylcholine receptors (Nicotinic Receptors)*.
    - *Acetylcholinesterase* is an enzyme located in the *junctional folds*, it degrades acetylcholine, thus ending the depolarizing signal to the muscle cell.

**Contraction of Skeletal Myofibers**

- **Steps involved:**
  1. Excitation of the Nerve Terminal
  2. Excitation of the Myofiber
  3. Relaxation of the Myofiber

**Excitation of Nerve Terminal**

- A nerve
  - Depolarization of the axon terminal (presynaptic terminal) causes **voltage gated calcium channels** to open and extracellular calcium ions enter the axon
  - The rise in Ca$^{2+}$ triggers the *synaptic vesicles* to release *acetylcholine* into the synaptic cleft by exocytosis.
- **Acetylcholine (ACh)** diffuses across the synaptic cleft and binds to the ACh receptors (**nicotinic receptors**). These receptors are **ligand-gated Na+ channels**. ACh causes them to open.
  - Na+ will rush into the cell, making the local cell interior more positive.
  - This
  - If the depolarization reaches **threshold** an **action potential** is produced along the sarcolemma.
  - The **action potential** travels along the sarcolemma and into the **T tubules** which carry the wave of depolarization into the muscle cell. **This is really important!**
  - At the **triad**, action potentials of the **T tubules** cause the **voltage-gated dihydropyridine (DHP) receptors** to change shape (**conformational change**). The activated DHP receptors are attached to **calcium release channels (ryanodine receptors)** of the **terminal cisterns** of the **sarcoplasmic reticulum**.
    - This shape change causes the opening of **calcium release channels** allowing
  - The **sarcoplasmic reticulum Ca2+ release channels** open briefly
    - Allows calcium to enter the **sarcoplasm**.
• The Ca\(^{2+}\) interacts with the **troponin** causing a confirmational change in the **troponin-tropomyosin** complex, that exposes attachment sites for the **myosin head**.

• The **myosin head** (cross-bridges), previously activated by the hydrolysis of ATP to ADP and P, attaches to actin.
  
  – ATP hydrolysis provides the

• Once attached to actin, the myosin head undergoes a **power stroke** and pulls the thin filaments over the thick filament.
  
  – This results in the thin filament sliding along the thick filament.

• Myosin then remains bound to actin until it binds to another ATP. Attachment of fresh ATP provides the energy to “cock” the myosin head back and detach it from the actin molecule. The cycle can repeat as long a calcium remains attached to troponin and ATP is available

• Typically half the myosin molecules at any time are bound to the actin while the other half are preparing to bind again.

• A common analogy is climbing a rope hand over hand.

• **Excitation-contraction coupling**: Term used to describe the sequence of events by which
Relaxation of the Myofiber

- Cessation of action potentials stops the release of ACh
  - The **sarcoplasmic reticulum**
    - Without **calcium**, **Tropomyosin** moves over the **myosin binding site** on the **actin** filament preventing attachment of the **myosin crossbridge**.
- Note that ACh does not remain bound to the **ACh Receptor** for very long.
  - It quickly releases and is hydrolyzed by the enzyme **acetylcholinesterase** which exists as part of the sarcolemma and free within the synaptic cleft.

Summary of the Steps of a Muscle Contraction

1. An action potential travels along an axon membrane to a neuromuscular junction.
2. Voltage-gated calcium channels open and calcium enters the presynaptic terminal (nerve terminal) stimulating the fusion of Acetylcholine (ACh) containing vesicles.
3. ACh is released from the synaptic vesicles in the presynaptic terminal of the neuron by exocytosis.
4. ACh diffuses across the synaptic cleft and binds to nicotinic ACh receptors (ligand gated) located on the motor endplates of the sarcolemma, and stimulates the opening of these ligand gated sodium channels causing depolarization of the sarcolemma.
   - Sodium ions diffuse into the muscle cell and if the graded depolarization brings the sarcolemma (postsynaptic membrane) to threshold, an action potential is produced that is regenerated across the sarcolemma.
5. The action potential travels along the sarcolemma and into the T tubules which carry the wave of depolarization into the muscle cell.
6. Action potentials of the T tubules cause the voltage-gated dihydropyridine (DHP) receptors to change shape (conformational change). The activated DHP receptors are attached to calcium release channels (ryanodine receptors) of the terminal cisterns of the sarcoplasmic reticulum. This shape change causes the opening of calcium release channels allowing calcium to flow into the sarcoplasm.
7. Calcium released into the sarcoplasm binds to troponin molecules, causing a change in its structure.
8. The conformation change in troponin causes its attached tropomyosin to shift position on the actin filament, which exposes attachment sites for the myosin head.
9. The myosin head (cross-bridges), previously activated by the hydrolysis of ATP to ADP and P, attaches to actin.
10. Once attached to actin, the myosin head undergoes a power stroke and pulls the thin filaments over the thick filament. The ADP and P molecules are released.
11. Fresh ATP binds to the myosin head and are broken down to ADP and P which energizes the myosin head and allows the cross-bridge to detach from actin. The myosin head bends back to its resting position and will repeat the contraction cycle as long as calcium remains attached to troponin.
12. When action potentials stop being produced, the sarcoplasmic reticulum actively accumulates (sequesters) calcium via Ca2+-ATPase pumps and tropomyosin moves over the myosin binding site on the actin filament preventing attachment of the myosin crossbridge.

Rigor Mortis

- Upon death, muscle cells are unable to prevent calcium entry.
  - Since there is no ATP made postmortem, the myosin cannot unbind and the body remains in a state of muscular rigidity for a couple days.
**Muscle Hypertrophy**

- **Hypertrophy:**
  - **Muscle Hypertrophy:** Enlargement of existing myofibers due to increased numbers of:
    - increased numbers of myofibrils within the myofibers
      - Increases the strength of contraction.
    - Increased in mitochondrial number, sarcoplasmic reticulum, and nutrient storage (glycogen)
  - **Hyperplasia:** An increase in the number of fibers.
    - Rare to contribute to muscle hypertrophy after birth

**Muscle Atrophy and Fibrosis**

- **Atrophy**
  - In muscles, it's often caused by disuse or denervation.
  - Muscle fibers become smaller and weaker due to a decrease in the number of myofibrils within a muscle fiber.

- **Fibrosis**
  - Replacement of normal tissue with heavy fibrous connective tissue (scar tissue).

**Muscle Tone**

- **Muscle Tone:**
  - **Mechanism:**
    - Small number of motor units within the muscle are involuntarily activated to contract.
      - Their contraction does not produce enough tension to cause movement, but they do tense and firm the muscle.
    - There is a constant shift of activity among motor units to maintain muscle tone.
      - *Why do you suppose this is?*
  - Resting muscle tone stabilizes the position of bones and joints.