MUSCLE PHYSIOLOGY (PHS 213)

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Course Objectives:

To familiarize students with the principles and basic facts of Human Physiology and with some of the laboratory techniques and equipment used in the acquisition of physiological data. The emphasis will be on muscles physiology. Since the course will focus on muscle physiology, some cellular and molecular mechanisms will be discussed in order to present a current view of physiological principles of muscle. Where appropriate, basic chemical and physical laws will be reviewed in order to enhance and to promote student understanding. The laboratory component of the course is designed to reinforce the topics discussed in lecture, as well as to familiarize students with some of the laboratory techniques and equipment used in muscle research

Student Learning Outcomes:

Upon successful completion of lecture portion of this course, the students will be able to describe, identify, and/or explain:

- Structure and function of skeletal muscle, including excitation-contraction coupling, sliding filament mechanism, force generation, and isometric versus isotonic contractions.
- Structure and functions of the cardiovascular system, including the mechanical and electrical properties of cardiac muscle function.
- Structure and functions of smooth muscles including contraction of smooth muscle

Upon successful completion of the laboratory portion of this course, the students will be able to describe, identify, explain, perform, and/or measure:

- Computer simulations of the membrane potential, action potential, and synaptic neurotransmission.
- Skeletal muscle mechanics, and the electromyogram (EMG).

Required Course Materials:

- Any textbook of physiology (human or medical) published within the last four years will be appropriate.
- Emojevwe's *Lecture Notes on Physiology*. To obtain these notes as well as other supplementary materials, please visit the unimed portal

MUSCLE PHYSIOLOGY

Muscle is an excitable tissue. The human body has over 600 muscles which perform many useful functions and help us in doing everything in day-to-day life.

Classification of muscles: Muscles are classified by three different methods, based on different factors:

I. Depending upon the presence or absence of striations; the muscles are divided into two groups:

1. *Striated Muscle:* Striated muscle is the muscle which has a large number of crossstriations (transverse lines). Skeletal muscle and cardiac muscle belong to this category. **2. *Non-striated Muscle:*** Muscle which does not have cross-striations is called nonstriated muscle. It is also called plain muscle or smooth muscle. It is found in the wall of the visceral organs.

II. Depending upon the control

1. *Voluntary Muscle:* Voluntary muscle is the muscle that is controlled by the will. Skeletal muscles are the voluntary muscles. These muscles are innervated by somatic nerves.

2. *Involuntary Muscle:* Muscle that cannot be controlled by the will is called involuntary muscle. Cardiac muscle and smooth muscle are involuntary muscles. These muscles are innervated by autonomic nerves.

III. Depending upon the situation.

1. Skeletal *Muscle:* Skeletal muscle is situated in association with bones forming the skeletal system. The skeletal muscles form 40% to 50% of body mass and are voluntary and striated. These muscles are supplied by somatic nerves. Fibers of the skeletal muscles are arranged in parallel. In most of the skeletal muscles, muscle fibers are attached to tendons on either end. Skeletal muscles are anchored to the bones by the tendons.

2. *Cardiac Muscle:* Cardiac muscle forms the musculature of the heart. These muscles are striated and involuntary. Cardiac muscles are supplied by autonomic nerve fibers.

3. *Smooth Muscle:* Smooth muscle is situated in association with viscera. It is also called visceral muscle. It is different from skeletal and cardiac muscles because of the absence of cross striations, hence the name smooth muscle. Smooth muscle is supplied by autonomic nerve fibers. Smooth muscles form the main contractile units of wall of the various visceral organs.

In the preceding sections, I will be introducing you to the physiology of the skeletal, cardiac and smooth muscles.

SKELETAL MUSCLE

A skeletal muscle is a collection of muscle bundles or fascicles. Each fascicles is made up of a number cells or (myofibrils). Each muscle is cell compose of hundreds to thousands of myofibrils. Myofibrils are strings of the structural unit referred to as the sarcomere. The sarcomere is the functional unit of skeletal and cardiac muscle. The sarcomere contains the myofibrils; which are the proteins that are responsible for the contractile behavior of the muscle cell. In addition, the sarcomere contains structural proteins (which maintain the structural integrity of the sarcomere), as well as regulatory protein (which play an important role in the regulation of muscle contractile activity).

A mature skeletal muscle cell is a long cell, which comes about through the fusion of many embryonic muscle cells. Therefore, skeletal muscle cells are among the largest cells in the body, whose length can be as long as tens of centimeters. The diameter of a typical skeletal muscle cell is about 100 µm. Skeletal muscle cells are multinucleated, and they contain numerous mitochondria. The plasma membrane of skeletal muscle cells (the sarcolemma) is specialized in that it has invaginations that run deep into the muscle cell. These invaginations are referred to as transverse tubules (or tubules). It is important to say that the membrane of the t-tubule is continuous with the sarcolemma. Thus, t-tubules serve to allow muscle action potentials to reach deep into the muscle cell. It is also important to recognize that the lumen of the t-tubule is the extracellular fluid. Within the cytoplasm of the skeletal muscle fiber (myoplasm or sarcoplasm), there are numerous specialized structures, which we need to understand. A highly specialized endoplasmic reticulum referred to as the sarcoplasmic reticulum is tightly wrapped around individual myofibrils and functions to store a high concentration of Ca^{2+}. The release of Ca^{2+} from the sarcoplasmic reticulum is responsible for triggering muscular contraction. Another very important structure is the sarcomere. As mentioned above, the sarcomere is the functional unit of striated muscle, and it is discussed below.

Fine Details of the Sarcomere

The sarcomere is the functional unit of the muscle fiber. It is composed of overlapping units of two different filamentous proteins; the **thick** and the **thin filaments.** Movement of the thin filaments over the thick filaments brings about muscle shortening and force generation. Thus, the sarcomere is responsible for the contractile ability of muscle cells. In order to understand the function of the sarcomere, it is important that we first understand the protein composition of the sarcomere. The proteins found in the sarcomere can be placed into three proteins. As you read the following descriptions, be sure to examine the attached figures in order to achieve a better understanding.

a. Contractile Proteins
    i. Myosin (gives rise to the thick filaments) ii. Actin (gives rise to the thin filaments)

b. Regulatory Proteins
   i. Tropomyosin (in the absence of Ca^{2+} , it covers the myosin –binding site of actin)
   ii. Troponin (Ca^{2+} sensor)

c. Structural Proteins
   i. Titin (provide elasticity) ii. Nebulin (run closely with actin)
   iii. Dydrophine
   iv. Desmin (it binds z line with sarcomere)

Now let us discuss these proteins

Contractile Proteins

As their name suggest, contractile proteins are in fact responsible for muscles shortening (contraction). Myosin is the protein that makes up the **thick filaments** of the sarcomere. Myosin has two structural domains; a head region and a **tail** region. The head and the tail regions are connected through a **flexible neck region.** The tail region of myosin is used to join many myosin molecules together in order to give rise to the thick filament. In skeletal muscle, approximately 250 mysin molecules are intertwined to form a thick filament. The myosin head has an **actin-binding site** to which ATP binds (see cross – Bridge Cycle below). In a thick filament, the myosin molecules are arrange so that the myosin heads are clustered at the ends (facing the Z disks), and the central region of the thick filament is a bundle of myosin tails.

Actin is the protein that makes up the **thin filaments** of the sarcomere. An actin molecule is a globular protein (**globular actin** or **G-actin**)**.** Many G-actin molecules polymerize to form filamentous actin (F-actin). In skeletal muscle, two F-actin polymers intertwine to form a thin filament. Each G-actin molecule has a **myosin binding site.** Thus, the interaction of actin and myosin take place via the interaction of myosin binding site of Gactin with the actin binding site of the myosin of the myosin head group.

In order for the muscle to contract, the actin and the myosin molecules of the thin and thick filaments have to interact with one another. When the actin and myosin interact, they are said to be connected by **cross-bridges.** The cross-brides refer to the myosin head group that interact with a myosin-binding site on G-actin.

Microscopic Details

Under the light or electron microscope, the arrangement of the thick and thin filaments in a myofibril gives rise to a repeating pattern of alternating light and dark regions. One repeat in the pattern roughly corresponds to what is known as the functional unit of striated

muscle: the **sarcomere.** The special overlap of the thin and thick filaments within the sarcomere gives rise to the contractile and shortening capability of the muscle cell. The sarcomere has the following microscopic features:

Z Disks: Two adjacent Z disk along the myofibril mark the boundaries of a single sarcomere. The Z disk are the attachment sites for the thin filaments. Therefore, from each Z disk, thin filaments extend to two neighboring sarcomeres. When a muscle fiber contracts, the Z disks of a sarcomere move closer together (see Sliding Filament model of Contraction below). Thus, the sarcomere shortens as the muscle contracts.

A Band: The A Band is the entire length of the thick filament. At the outer edges of the A Band, the thick and thin filaments overlap and, therefore, this region is the darkest region of the sarcomere. The center of the A Band does not change as the muscle contracts.

H Zone: The H zone refer to the center of the A band where there is no overlap between the thick and the thin filaments. Therefore, in the H zone, the filaments consist only of the thick filament. The H zone becomes smaller as the muscle contracts because the overlap between the thick and the thin filaments increases (i.e., region of naked or non-overlap of the thick filament decreases).

I Band: This region is closest to the Z disk, and is the lightest region of the sarcomere. The I Band is occupied by the thin filaments only. Each Z disk runs through the middle of the I-band. Therefore, half of each I band belongs to one sarcomere, and the other half belongs to the neighboring sarcomere. The I-band also shortens as the muscle contracts.

M Line: The M Line is the attachment site for the thick filaments. The M line is in the middle of the A band and it is in the middle of the sarcomere.

In three dimensions, the sarcomere is a lattice of parallel and overlapping thick (myosin) and thin (actin) filaments. If a cross-section view is obtained from the outer edges of the A band where there is overlap between the thin and thick filaments, it can be seen that every thin filament is surrounded by three thick filament, and every thick filament is surrounded by six thin filaments.

Regulatory Proteins

Two regulatory proteins closely interact with actin. A regulatory protein called **tropomyosin** spans over seven G-actin molecules and normally prevents the interaction of the myosin head group with g-actin. When the myoplasmic Ca^{2+} concentration is low at its resting level, tropomyosin covers the myosin binding site of G-actin. Tropomyosin also closely interact with **troponin**, which is a Ca^{2+} sensor. Binding of Ca^{2+} to troponin moves the troponin-tropomyosin complex out of the way exposing the myosin binding site. This allows the myosin head to interact with G-actin.

Structural Proteins

The structural integrity of the sarcomere is ensured by the presence of accessory structural proteins **titin** and **nebulin**. Titin is a very elastic protein that stretches from one Z disk to the M line. Its function is to bring the stretched muscle to its resting length. Nebulin is positioned alongside the thin filaments and stabilizes them. Nebulin is inelastic.

SLIDING FILAMENT MODEL OF CONTRACTION

This theory proposed by A. F. Huxley in 1957 states that muscle contraction result from the sliding of the thin filament over the thick filament. This explain how actin filament slides over myosin and form acto-myosin complex during contraction. Muscle contraction is an energy requiring event (ATP) that involves the movement of the thin filaments over the thick filaments. As the thin filament are connected to the Z disks, and as muscle contraction brings about movement of the thin filaments over the thick filaments and towards the center of the sarcomere (the M line), a shortening of the sarcomere takes place. This shortening brings the Z disks of a sarcomere closer together. During muscle contraction, the size of the A band remains the same, but the I-band and H zone become shorter as the thin filaments slide past the thick filaments.

A very important point to consider is that the tension generated in a muscle is directly proportional to the overlap between the thick and thin filaments. This extent of the overlap, of course, is a function of the number of myosin head groups that interact with thin molecules. Thus, the greater the overlap, the larger the tension that is developed by the muscle. However, it is possible for a muscle to generate tension without shortening. If one pushes against a wall, tension is generated without much skeletal muscle shortening. Note that this model is also called, **Canoe and paddle, Walk along** or **ratchet** theory of muscle contraction

CROSS BIDGE CYCLE

The movement of the thin filaments over the thick filaments involves a series of interactions between the myosin head groups of the thick filaments, and the actin molecules of the thin filaments. The interaction can be summarized in a cycle referred to as the crossbridge cycle. Cross-bridges refers to interaction site of the myosin head group and actin molecules. Each cross-bridge has 3 components hinge, arm and head.

During muscle contraction, each myosin head group attaches to one actin molecule of the thin filament. At a critical step in the cross-bridge cycle (**power stroke;** see below). At the end of a power stroke, the myosin head releases it bound actin, swing back and binds to a new actin molecule. As this process is repeated many times, the sarcomere shortens.
The cross-bridge cycle may be arbitrary divided into six steps:
Step 1: In this step, the myosin head interacts tightly with a G-actin of the thin filaments. The part of the myosin head group that interact with actin is referred to as the **actin-binding**

site. In this step, the myosin head makes a 45-degree angle with the thick filament. This is referred to as the **rigor state** because if there is no ATP present (such as after death), the thin and thick filaments maintain this tight interaction rendering the muscle very stiff (a condition called **rigor motis**)

Step 2: In addition to the actin-binding site, the myosin head also has a **nucleotide-binding site.** This is a site where ATP and ADP interact with myosin. The cytoplasmic ATP concentration in skeletal muscle cell is 3-5 mM. In this step, an ATP molecule bind to the nucleotide-binding site of the myosin head. Binding of ATP causes the release of the myosin head from the G-actin molecule.

Step 3: In this step, the myosin head coverts the bound ATP to ADP and P_i both ADP and P_i remain bound to the myosin head. Note that myosin is an ATPase (**myosin ATPase)** in that it has the ability to hydrolyze ATP to ADP and inorganic phosphate (P_i).

Step 4: The energy released from the hydrolysis of ATP is used to change the conformation of the myosin head, so that now it makes a 90-degree angle with the thick filament. This change in conformation "energizes" the myosin head (i.e., it places it in a high-energy state). At this point, if sufficient Ca^{2+} is present in the cytoplasm, the myosin head attaches to a G-actin one or two positions away from the one bound in Step1. If there is not enough Ca^{2+} present in the cytoplasm, the myosin head remains in this energized 90-degree angle. A rise in the cytoplasmic Ca^{2+} concentration is essential and evokes series of events that facilitates the binding of myosin head to G-actin again. Ironically, this step is referred to as the "relaxed state", meaning that the muscle is not contracting. Please note that the relaxed state refers to the muscle cell and not to the conformation of the myosin molecule.

At rest, most skeletal muscle fibers are in this "relaxed state".

Step 5: This is the **power stroke** step. Now, P_1 is released from the myosin head. As P_1 is released, the energized 90-degree angle myosin head begins to assume its original45degree angle. However, as it is bound to a G-actin of the thin filament, the change back to the 45-degree angle moves the actin filament toward the center of the sarcomere (M line).

Step 6: At this point, ADP is released from the myosin head, and the myosin head remains tightly bound to the G-actin. This brings us back to the beginning of the cycle at Step 1. If there is ATP around (and if the cytoplasmic Ca^{2+} concentration is high; see below) the Cross-bridge cycle repeats itself again and again resulting in the sliding of the thin filaments over thick filaments, which will lead to muscle shortening.

It is important to emphasize that the cross-bridge cycle can take place only if the cytoplasmic Ca^{2+} concentration is high. Thus, when skeletal muscles are at rest and the cytoplasmic Ca^{2+} concentration is low, the cross-bridge cycle does not take place. Instead the myosin head groups remains in an "energized" state (see Step 4 of the cross-bridge cycle). When a motor neuron stimulates the skeletal muscle cell that it innervates, the

ultimate result is a rise in the cytoplasmic Ca^{2+} concentration, which then allows the crossbridge cycle to take place (see Excitation-Contraction Coupling below).

LENGTH TENSION RELATIONSHIP

The amount of tension developed by a muscle is directly proportional to the overlap between the thick and thin filaments. The greater the number of myosin head groups that interact with the actin filaments, the greater the amount of tension that the muscle cell can produce. This overlap between the thick and thin filaments, in turn, is a function of the length of the muscle. If the muscle is stretched so that at the level of the individual sarcomere, very little overlap exist between the thin and the thick filaments, very little tension can be developed. The muscle may also be forced to shorten to the point where the thin filaments extending from opposite Z disks begin to collide. This causes a reduction in the number of thin filaments that can effectively interact with the myosin heads. Therefore, again, little tension can be developed. Thus, there is an optimum length for the muscle to produce the maximum tension that it is capable of producing. At rest, most of our skeletal muscles are at their optimum length, and on average the sarcomere has a resting length of about 2.15µm. Tension developed by muscle tissue at rest is called passive tension, while tension generated during isometric contraction is called total tension. The difference between the total tension and the passive tension is called the active tension and it is the real tension developed during contraction. In the laboratory, a curve can be obtained using simple nerve preparation (gastrocnemius –sciatic preparation). This curve is called length tension curve.

Excitation-Contraction Coupling (E-C Coupling) in skeletal Muscle

A muscle contraction begins when a signal is sent to the muscle from the central nervous system. The activity of a somatic motor neuron leads to the release of acetycholine at the neuromuscular junction. Acetycholine binds with nicotinic acetylcholine receptors, causing them to open. Na^+ entry into the muscle cell leads to depolarization of the sarcolemma. The depolarization caused is always excitatory and is referred to as **end-plate potential.** The end-plate potential is always above threshold and leads to the activation of voltage-gated Na^+ channels in the sarcolemma. Therefore, a new muscle action potential is generated and travels along the sarcolemma. The action potential propagates deep into the muscle fiber along the t-tubules. At special regions within the muscle fiber, the t-tubule is flanked by the sarcoplasmic reticulum (also known as L-tubule). This arrangement is referred to as the **triad** (composed of one t-tubule and the flanked sarcoplasmic reticulum regions). Within the membrane of the t-tubule exits a voltage-gated molecule referred to as the **dihydropyridine receptor (DHP receptor).** The DHP receptors are very closely positioned to Ca^{2+} channel located in the membrane of the sarcoplasmic reticulum. These Ca^{2+} channels are referred to as the **ryanodine receptors.** When the muscle is at rest, a mechanical link between the DHP receptor and the ryanodine receptor keeps the ryanodine

receptors closed. Therefore, there is literally a "mechanical plug" (provided by the DHP receptor) that keeps the pore of the ryanodine receptor closed.

When an action potential propagates along the t-tubule, the depolarization caused by the action potential changes the conformation of the DHP receptor leading to the removal of the mechanical plug from the pore of the ryanodine receptor. Since Ca^{2+} is highly concentrated in the sarcoplasmic reticulum, it diffuses down its concentration gradient through the ryanodine receptor and into the cytoplasm. Usually, this leads to an increase in the cytoplasmic Ca^{2+} concentration from resting value of 70 nM to about 1 µm (i.e 0.110 µmol). The available Ca^{2+} can now bind with troponin in order to trigger the power stroke of the cross-bridge cycle. Recall that at low myoplasmic Ca^{2+} concentration, tropomyosin fully covers the myosin binding sites of the thin filaments. When the cytoplasmic Ca^{2+} concentration rises, Ca^{2+} binds with troponin causing the troponintropomyosin Ca^{2+} complex to move, thereby exposing the myosin binding sites of the thin filament. When this occurs, the myosin head groups can interact with the thin filaments and go through the cross-bridge cycle.

Summary of Events That Lead to Skeletal Muscle Contraction and Relaxation

1. Activation of a somatic motor neuron is normally a voluntary decision that made in the central nervous system.
2. Propagation of action potentials down the somatic motor neuron axon
3. Depolarization of the axon terminal of the somatic motor neuron, opening of voltage-gated Ca^{2+} channels and entry of Ca^{2+} into the axon terminal.
4. Fusion of synaptic vesicles with the pre-synaptic plasma membrane, and subsequent release of the neurotransmitter (acetylcholine) at the neuromuscular junction
5. Binding of acetylcholine to the nicotinic acetylcholine receptors located in the plasma membrane of the skeletal muscle cell. Acetylcholine binding leads to the opening of this ligand-gated ion channel.
6. Opening of the nicotinic acetylcholine receptor leads to the entry of N^{a+} into the myoplasm which leads to depolarization of the plasma membrane (sarcolemma) of the skeletal muscle cell. This depolarization is referred to as the end-plate potential.
7. At the neuromuscular junction, the end-plate potential is always excitatory and therefore, leads to the activation of voltage-gated N^{a+} channels in the sarcolemma. Activation of voltage-gated N^{a+} channel leads to the generation of muscle action potentials that travels along the sarcolemma.
8. Propagation of the action potential deep into the muscle cell down the t-tubules.
9. The depolarization caused by the action potential in the t-tubule changes the conformation of the dihydropyridine receptor. This change in conformation releases the plug that normally keeps the sarcoplasmic ryanodine receptors closed.
10. Ryanodine receptors are Ca^{2+} channels and their opening releases Ca^{2+} into the sarcoplasm.
11. Diffusion of calcium to the sarcomere units.

12. Binding of Ca^{2+} to the troponin complex.
13. Displacement of the troponin-tropomyosin unit to expose the myosin cross-bride binding site of G-actin.
14. Binding of myosin cross-bridges to the binding sites on G-actin molecules
15. Power stroke of the cross-bridges and movement of the thin filaments over the thick filaments.
16. Continued cross-bridge cycling for as long as ATP is present and Ca^{2+} concentration remain high in the myoplasm.
17. Muscle shortening and /or tension development
18. Muscle relaxation occurs when the train of motor neuron action potentials comes to an end. In the absence of motor neuron action potentials, no additional muscle action potentials are generated. The sarcolemma at the level of the t-tubules repolarizes to its resting value of -90 mV. This repolarization once again places the dihydropyridine plug over the ryanodine Ca^{2+} channels (closes it). Thus, no additional Ca^{2+} enters the cytoplasm.
19. Calcium concentration in the myoplasm is brought back to normal due to the activity of the sarcoplasmic Ca^{2+}-Mg^{2+} ATPase which pumps Ca^{2+} back into the sarcoplasmic reticulum.
20. Reduced Ca^{2+} in the myoplasm causes the troponin-tropomyosin complex to once again cover the myosin binding site of actin.
21. The myosin head "waits "in its relaxed state (ADP and P_i bound) for another rise in the Ca^{2+} concentration in the myoplasm.

Sources of Energy for muscle contraction: immediate source energy for muscle contraction is the hydrolysis of ATP. ATP → ADP + Pi+ Energy This can only sustain contraction for a fraction of time.

Other sources are from resynthesis of ATP from other sources which are:

Adenosine diphosphate, which is formed during ATP breakdown, is immediately utilized for the resynthesis of ATP. But, for the resynthesis of ATP, the ADP cannot combine with Pi. It should combine with a high energy phosphate radical such as creatine phosphate. ADP + CP → ATP + Creatine. Energy produced in this reaction is sufficient to maintain muscular contraction only for few seconds.

Other sources ATP synthesis is anaerobic glycolysis which yield 4molecules of ATP and aerobic glycolysis which yield 40ATP molecules.

Types of Muscle Contraction

a. **Isotonic contraction:** This is the type of muscular contraction in which the tension remains the same and the length of the muscle fiber is altered (iso = same: tonic = tension).Example: Simple flexion of arm, where shortening of muscle fibers occurs but the tension does not change.
b. **Isometric contraction:** Isometric contraction is the type of muscular contraction in which the length of muscle fibers remains the same and the tension is increased. Example: Pulling any heavy object when muscles become stiff and strained with increased tension but the length does not change.

Requirements for useful Muscular Contractions: A single action potential traveling down a motor neuron results in a single twitch in the skeletal muscle cell that the axon innervates. A single skeletal muscle cell twitch is not useful physiologically. Physiologically useful skeletal muscle contractions are **smooth and graded.** Smooth contractions allow are needed to avoid unwanted movements resulting from jerky twitches. Graded contractions allow an individual to adjust the amount of tension that needs to be developed. The amount of tension needed to lift a computer mouse is not as great as that needed to lift a computer. Two mechanisms allow whole organisms to have smooth and graded contractions. These are **tetanic contractions** (allow for smooth contractions) and **recruitment of motor units (**allow for graded contractions**).** These two requirements are discussed below.

Tetanic Contractions: One action potential that travels down a somatic motor neuron axon leads to the generation of one muscle fiber **twitch.** A **twitch** is a single contraction and relaxation of a single muscle fiber. Just like action potentials, a single skeletal muscle cell twitch is **all-or-nothing.** Depending on the skeletal muscle fiber type, a single twitch may last 10-100 ms. three different phases can be seen in a single muscle twitch:

i. ***Latent period:*** the time from the initiation of the muscle action potential at the neuromuscular junction to when the contraction of the muscle begins (about 1ms). This is the time requires for **excitation-contraction coupling** to take place
ii. ***Contraction period:*** this is the time during which the muscle fiber develop tension.
iii. ***Relaxation period:*** relaxation of muscle takes little more than the time it takes for contraction

Remember that a single skeletal muscle cell twitch is not useful physiologically. Physiologically useful skeletal muscle contractions are **smooth** and **graded.** In order to obtain smooth contraction lots of rapid muscle twitch have to take place. Since somatic motor neuron action potential leads to a single skeletal muscle twitch, multiple action potentials are then needed to establish multiple twitches. Multiple twitches fused together are referred to as **tetanus. Tetanic** contraction

It is important to note that tetanic contraction is not permitted in cardiac muscle, this is to ensure full relaxation of the heart before the next contraction.

Special note: ***Motor Unit***:- group of muscle fibers that function together and the motor neuron that controls their activities are collectively referred to as motor unit. It can also be defined as the motor neuron and the muscle fibers it innervates.

CARDIAC MUSCLE

Cardiac muscle cells within the myocardium are arranged in layers that completely encase the chambers of the heart. The contraction of these cells pressurizes the blood inside the chambers of the heart so that the blood can travel out of the heart to the rest of the body. Cardiac muscle contains elements of both striated skeletal muscle and smooth muscle. The striated structure of cardiac muscle is due to the arrangement of thick myosin and thin actin filaments which are similar to the arrangement of skeletal muscle. Compared to skeletal muscle, cardiac muscle is much shorter and has several branching processes. **Intercalated disks** join the ends of cardiac muscle cells to each other. **Gap junctions** are situated adjacent to intercalated disks which is similar to those found in many smooth muscle cells. The present of intercalated disc causes the cells to behave like a functional Syncytium. One percent of cardiac cells do not contract because the non-contracting cells have specialized features that aid in heart excitation. The non-contracting cells form a network known as the conducting system and contact other cardiac muscle cells at gap junctions. The conduction system begins the heartbeat and assists in spreading the contraction impulse rapidly. The present of intercalated disc causes the cells to behave like a functional Syncytium. The action potential of cardiac muscle is prolong due to presence of a plateau. Excitation contraction coupling is same as in skeletal muscles except for the fact that 20% of calcium needed for contraction enters the cell from the ECF during action potential. For more comparism please see the table at the end of this note

SMOOTH MUSCLE

Introduction to Smooth Muscle Function

There is no conscious control over the activity of smooth muscle rather its activity is under the control of the **autonomic nervous system;** therefore, its function is said to be involuntary. Although, little attention is given to smooth muscle, this is not because of their lack of importance, but mostly because of our lack of complete understanding of its function. In fact, the function of the majority of internal organs depends on smooth muscle. For example, the digestive system, the reproductive system, the respiratory system, the vascular system (but not capillaries because their walls are composed of only a single layer of endothelial cells), urinary bladder, as well as other organs all depend critically on smooth muscle. However, the function of smooth muscle is more difficult to examine due to several factors. First, due to lack of striation, smooth muscle ultrastructure is not as uniform and amenable to study as that of skeletal and cardiac myocytes. Second, the relatively weaker

forces of contraction generated by smooth muscle (primarily because these are smaller cells) prevented a thorough characterization (at least in the early years when instrumentation was not as readily available as today).

Smooth muscle cells are small fibers that lack sarcomeres and, therefore, the overlap of actin and myosin is not able to generate as much force as the much larger striated skeletal or cardiac muscle cells. In addition, twitches in smooth muscle cells can last much longer than those of skeletal and cardiac cells. An important feature of smooth muscle cells is that they do not fatigue easily. Because smooth muscle cells do not fatigue easily, they are able to maintain tension for long periods of time. In fact, sustained contractions of smooth muscle cells serve very important functions in the body. When smooth muscle cells undergo sustained contractions, they are said to have **tone**. Thus, when speaking of smooth muscle function, we must make distinction between tonic **contractions** and **phasic contractions**. Tonic contractions refer to some constant level of tension that is developed by the smooth muscle cell. An example would be in the walls of the arteries in which smooth muscle cells must tonically contract in order to maintain the tone of the artery wall. If the smooth muscle cells stimulated by the sympathetic nervous system (norepinephrine release), they will phasically contract in order to bring about vasoconstriction. Here, the force of contraction is increased transiently over its basal level.

Smooth muscle contractions are very slow. Skeletal muscle contractions and relaxations last around 10–100 ms. Contractions of cardiac muscle cells can last 200–300 ms.

Smooth muscle contractions last 0.5–5.0 s, or longer.

After damage to skeletal or cardiac muscle cells, the existing healthy cells in the tissue do not divide in order to replenish the lost cells. Unlike skeletal muscle and cardiac muscle, however, recent studies suggest that some smooth muscle cells are able to give rise to new cells. In fact, it is thought that it is this property of smooth muscle that gives rise to pathological conditions such as arteriosclerosis.

Smooth Muscle Structure

Smooth muscle fibers (cells) are **spindle-shaped** structures of 10–500 μm long and 5–10 μm in diameter. Similar to cardiac muscle (but unlike skeletal muscle), smooth muscle fibers have a single nucleus. Single smooth muscle cells do not extend the full length of the muscle. Instead, smooth muscle cells are organized in groups which form sheets. Smooth muscle cells are called "smooth" because they do not have the distinct banding pattern (striation) seen in skeletal and cardiac muscle cells. **Sarcomeres** are absent in smooth muscle and, therefore, the striation apparent in skeletal and cardiac muscle is absent in smooth muscle. **Thin** and **thick filaments**, however, are present and function in a manner very similar to that described for striated muscle. Therefore, overlap of the thin and thick filaments leads to shortening (and rounding) as well as force generation in smooth muscle.

As mentioned, sarcomeres are absent in smooth muscle. *The thin and thick filaments in the cytoplasm are arranged in long bundles that tend to follow oblique lines (diagonal) with*

respect to the long axis of the cell. Therefore, contraction of smooth muscle leads not only to shortening of the cell, but also leads to rounding of the cell (i.e., after contraction the cell assumes a globular shape).

Both actin and myosin are present in smooth muscle. In addition, tropomyosin is present and associates with actin. However, *troponin* is absent in smooth muscle. Therefore, Ca^{2+} is not directly involved in triggering the cross-bridge cycle. However, Ca^{2+} is indirectly involved in this process. Within the cytoplasm, **actin** filaments are attached to **dense bodies**. Long actin filaments ultimately attach to the plasma membrane in regions referred to as **protein attachment plaques**. Smooth muscle **myosin** is arranged so that the myosin head groups cover the entire length of the thick filament. This arrangement allows for maximum overlap between the thin and thick filaments and, therefore, enables smooth muscle cells to generate tension over a much wider range of cell length (from about half of the resting length to about 2.5 times the resting length). This is not the case with striated muscle, as shortening or stretching leads to sub- optimal overlap between the thin and thick filaments.

Transverse tubules (**t-tubules**) are absent in smooth muscle cells. Because smooth muscle cells are much smaller than cardiac and skeletal muscle cells, t-tubules are not necessary to spread the wave of depolarization deep within the cell.

The **sarcoplasmic reticulum** of smooth muscle cells is not as well-developed as that of striated muscle. One reason for this is that Ca^{2+} is not the direct initiator of the crossbridge cycle. **Ca^{2+}** however, serves as a second messenger signal in the cell and is still indirectly required in order to activate a cascade of events that lead to cross-bridge cycling. The amount of Ca^{2+} that is released from the sarcoplasmic reticulum of smooth muscle makes a small contribution to the total amount of Ca^{2+} needed to bring about contraction. The majority of Ca^{2+} enters from the extracellular space through plasma membrane Ca^{2+} channels.

Smooth Muscle Types

Single-Unit Smooth Muscle (or Unitary Smooth Muscle)

1. The cells of this smooth muscle type are **electrically-coupled** via gap junctions. Electrical coupling allows the activity of a group of muscle fibers to become coordinated (similar to the activity of the atria and ventricles of heart).
2. Because the cells are electrically-coupled, individual cells in the group do not need to be innervated by the autonomic nervous system. Thus, innervation of only one or a few cells in the group is sufficient to control the activity of the entire group. The entire group that is connected by gap junctions is referred to as a **functional syncytium**.
3. The cells of this smooth muscle type exhibit **pacemaker potentials**. Note that pacemaker potentials are unstable potentials that gradually depolarize to the threshold

potential. Therefore, these cells exhibit spontaneous activity. Input of the nervous system is not required to initiate the contractions of these smooth muscle cells. In fact, every single-unit smooth muscle cell can act as a pacemaker to initiate an action potential (this is unlike the heart in which cells of a specific region act as pacemakers; SA node). Once the action potential gets under way in one cell, it sweeps across the sheet of muscle through the gap junctions, so that the whole muscle sheet will contract at once. Thus, during relaxation, the first cell to reach threshold becomes the pacemaker cell for the next contraction.

4. Although single-unit smooth muscle cells are capable of spontaneous contractions, the level of the activity of the cells can be modified by the autonomic nervous system, i.e., they can be either inhibited or stimulated.

5. Unitary smooth muscle lines the viscera (e.g., lining of the gastrointestinal tract, reproductive organs, urinary tract, and also some small blood vessels). Thus, it is also called **visceral smooth muscle**.

Multi-Unit Smooth Muscle

1. These smooth muscle cells are not coupled via gap junctions.
2. Multi-unit smooth muscle is found in the lining of blood vessels. Thus, it is also Called **vascular smooth muscle**. It is also found in the lining of large airways to the lungs, muscles of the eyes used for accommodation, iris of the eye, sphincters and the base of the hair follicles.
3. Muscular contraction is not spontaneous. Input from the autonomic nervous system is required for contraction. Each muscle cell has to be individually innervated. Therefore, contractile activity is said to be **neurogenic**. Both the parasympathetic and the sympathetic divisions of the autonomic nervous system are involved. The nervous input from these fibers can either inhibit or excite multi-unit smooth muscle cells.

(Remember that skeletal muscle cells have only excitatory synapses at the neuromuscular junction).

Muscle Excitation-Contraction Coupling in Unitary Smooth

Excitation-contraction coupling in smooth muscle can be summarized as the following:

1. Opening of Ca^{2+} channels in the plasma membrane leads to Ca^{2+} entry into the myoplasm.

2. The majority (80%) of Ca^{2+} needed in smooth muscle contraction enters the cell from the extracellular fluid while Some (20%) Ca^{2+} is released from the sarcoplasmic reticulum through **Ca^{2+}-induced Ca^{2+} release**.

3. Ca^{2+} in the cytoplasm binds to the regulatory protein **calmodulin** to form **C^{a2+}-calmodulin complex**

4. Calmodulin by itself cannot activate **myosin light chain kinase**, but the **Ca^{2+}-calmodulin complex** can bind to the myosin light chain kinase to change its state from inactive to active.
5. Activated myosin light chain kinase activates myosin ATPase by phosphorylating the myosin head group. Therefore, myosin A T P a s e becomes active only when hosphorylated by myosin light chain kinase.
6. Activated myosin ATPase can initiate the cross-bridge cycle. Once the myosin ATPase is activated, the cross-bridge cycle is very similar to that seen in striated muscle cells.
7. Muscle relaxation is a multi-step process. Cytoplasmic Ca^{2+} concentration is reduced back to normal through the activity of sarcoplasmic and plasma membrane Ca^{2+} ATPase pumps. In addition, the plasma membrane Na^{+}/Ca^{2+} exchanger extrudes Ca^{2+} from the cytoplasm.
8. Reduced cytoplasmic Ca^{2+} concentration leads to the dissociation (i.e., release) of Ca^{2+} from calmodulin. Therefore, inactivation of myosin light chain kinase ensues.
9. Myosin ATPase becomes inactive when the phosphate group (the phosphate added by myosin light chain kinase) is removed by **myosin light chain phosphatase**. After myosin ATPase is dephosphorylated, ATPase activity is again inhibited and the cross- bridge cycle comes to a halt (i.e., contraction is stopped).

Contraction in Multi-Unit Smooth Muscle

Activities are triggered by nervous stimuli. Nerve secretes ACH or Noradrenaline which depolarizes the membrane slightly leading to contraction. Action potential does not occur but contraction is due to local depolarization or excitatory junction potential. Local depolarization is developed because the multiunit smooth muscle fibers are too small to develop action potential. This local depolarization travels throughout the entire smooth muscle fiber and causes contraction

Comparison of Important Features of Skeletal, Cardiac, and Smooth Muscle

Muscle Feature	Skeletal Muscle	Cardiac Muscle	Smooth Muscle
Location	Mostly attached to the skeleton; sphincter of some organs	Heart	Walls of hollow organs and tubes; sphincter of some organs

General morphology	Multinucleate; large, cylindrical fibers	Uninucleate; branching fibers	Uninucleate; small spindle-shaped fibers
Nervous control	Voluntary	Involuntary	Involuntary
Nervous input	Somatic motor neuron	Autonomic motor neuron	Autonomic motor neuron
Endocrine (hormonal) Control	None	Multiple hormones Epinephrine from adrenal medulla	Multiple hormones Epinephrine from adrenal medulla
Important cellular structures	T-tubules and sarcoplasmic reticulum	T-tubules and sarcoplasmic reticulum	No t-tubules; small sarcoplasmic reticulum
Initiation of contraction	Input from motor neuron	Autorhythmic	Single-unit is autorhythmic, multi- unit is not
Contractile proteins	Actin and myosin	Actin and myosin	Actin and myosin
Regulatory proteins	Tropomyosin and troponin	Tropomyosin and troponin	Tropomyosin, calmodulin, and myosin light chain kinase
Arrangement of actin and myosin contractile filaments	Sarcomere	Sarcomere	Longitudinal and diagonal bundles
Trigger of cross-bridge cycle	Ca^{2+} and troponin	Ca^{2+} and troponin	Ca^{2+} and calmodulin activating myosin light chain kinase
Termination of cross- bridge cycle	Ca^{2+} ATPase pumps Ca^{2+} back into sarcoplasmic reticulum	Ca^{2+} ATPase pumps Ca^{2+} back into sarcoplasmic reticulum and out of the cell; Na^{+}/Ca^{2+} exchanger extrudes Ca^{2+} from the cell	Myosin phosphatase; Ca^{2+} ATPase pumps Ca^{2+} back into sarcoplasmic reticulum and out of the cell; Na^{+}/Ca^{2+} exchanger extrudes Ca^{2+} from the cell
Contraction speed	Fastest (10–100 ms)	Intermediate (200–300 ms)	Slowest (0.5–5 s)
Twitch force	All-or-nothing	Graded (depends on the amount of Ca^{2+} available)	Graded (depends on the amount of Ca^{2+} available)
Electrical coupling	None	Via gap junction channels of intercalated disks	Via gap junction channels (single-unit)