SMOOTH & CARDIAC MUSCLE TYPES

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Learning Objectives

1. Describe the structure and function of cardiac and smooth muscle types.
2. Explain how smooth muscle myofilaments are regulated.
3. Name three ways in which smooth muscle contraction is initiated.
4. Explain spontaneous electrical activity (pacemaker) in smooth muscle.
5. Contrast single unit and multiunit smooth muscles.
6. Explain how cardiac muscle myofilaments and contraction are regulated
7. Explain the contractile cardiac myocyte action potential.
8. Explain the absence of tetanus in the contractile cardiac myocyte.
9. Describe the structure of the heart.

SMOOTH MUSCLE

Smooth muscle fibers are cigar shaped cells that range in size from 20µm in the walls of the blood vessels to 200 µm in the wall of the intestine. As in striated muscle, the cytoplasm of the smooth muscle cell is filled with contractile proteins, actin and myosin. In smooth muscle the sarcomeres are not well ordered so no striated pattern is seen in light microscopy (Fig 1).

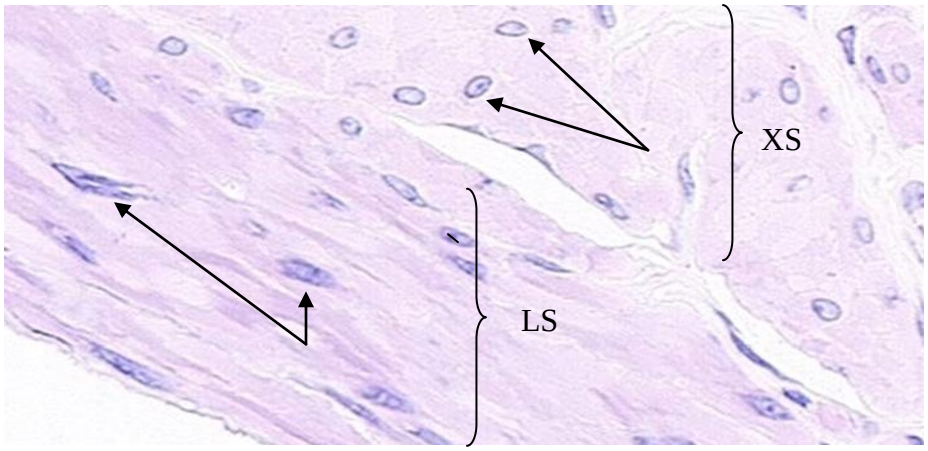

Figure 1. Light microscope image of longitudinal and cross sectioned smooth muscle shows close packed, cigar shaped cells with central nuclei (arrows) and no cross striations.

Thin filaments contain actin. They are attached to dense bodies which in turn are anchored to the plasma membrane.

Thick filaments contain myosin which has two subunits (heavy chain and light chain). The heavy chain contains the myosin ATPase activity. The light chain regulates this myosin ATPase. When the light chain is phosphorylated by an enzyme (myosin light chain kinase), cross bridges form between myosin and actin; contraction begins. The myosin light chain kinase is regulated by Ca++. Consequently, the thick filament regulates contraction in smooth muscle.

Smooth muscle myosin ATPase has a slow rate of hydrolysis. It hydrolyzes ATP at about 10% of the rate observed in skeletal muscle. Consequently smooth muscle produces slow, sustained contractions using only 10% of the ATP that skeletal muscle would require for the same work.

A special characteristic of smooth muscle is the **variability of the tension** it exerts at any given length. Some smooth muscles (blood vessels) will exert increased tension when stretched. In contrast, smooth muscle of the bladder shows little change in tension as the bladder fills but once full the bladder contracts forcefully.

Membrane activation
Contraction of smooth muscle, like skeletal muscle, is dependent on a rise of cytosolic Ca++ due to changes in the plasma membrane. However, smooth muscle does not have T tubules. Instead Ca++ enters from the ECF by diffusion through calcium channels in the plasma membrane. These Ca++ channels include: voltage-gated channels, ligand-gated channels and mechano-gated channels. The inputs that regulate contraction include:

1. Autonomic nervous system (parasympathetic, sympathetic and enteric) via voltage gated Ca++ channels.
2. Hormones via ligand-gated Ca++ channels.
3. Stretch via mechano-gated Ca++ channels.

At any one time, multiple inputs, some excitatory and others inhibitory, can be activated in a single cell. The net effect is dependent on the relative intensity of these inputs. Note that the intracellular Ca++ of smooth muscle can increase (or decrease) due to changes in the membrane potential from graded depolarization, hyperpolarization, or an action potential.

Spontaneous pacemaker potentials
Some smooth muscle exhibits spontaneous contractile activity in the absence of either nerve or hormonal stimuli. The plasma membranes of these fibers do not maintain a stable resting membrane potential. Instead the resting membrane potential gradually drifts towards threshold where it triggers an action potential (Fig 2). Following repolarization the membrane again begins to depolarize. This is property is called **pacemaker** activity. Pacemakers are found within the GI tract.

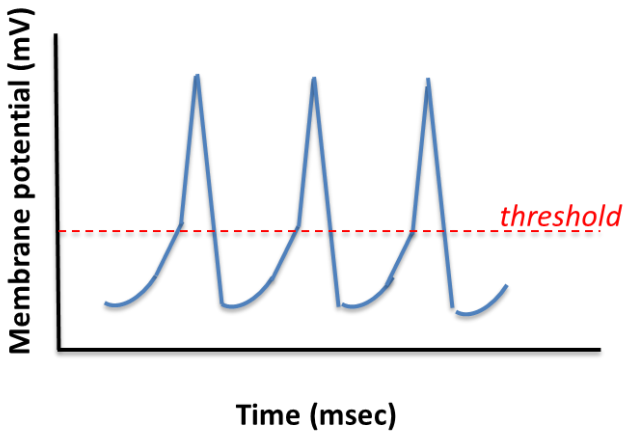

Figure 2. Pacemaker cells exhibit an unstable resting membrane potential leading to rhythmic states of depolarization followed by repolarization.

Single versus multi- unit fibers
Smooth muscle fibers do not have a specific neuro-muscular junction. Instead as the autonomic nerve enters the region of the smooth muscle it divides into many branches each containing a series of swellings (called varicosities) filled with vesicles of neurotransmitters.

In the **multi-unit smooth muscle**, each fiber is innervated independently. The fibers are not connected by gap junctions. Depolarization of one fiber is followed by contraction of that fiber only. These fibers are richly innervated by the autonomic nervous system. Nervous stimuli and hormones cause contraction (or relaxation) of these fibers, not stretch. The smooth muscle of the lung airways, in the walls of large arteries, and attached to the hair of the skin are multi-unit fibers.

In the **single unit smooth muscle**, the fibers are connected by gap junctions. Depolarization of one fiber triggers synchronous depolarization throughout the bundle followed by contraction of the fiber bundle. That is, many fibers act as one sheet. Single unit fibers are found in the walls of small blood vessels, the GI tract, and uterus where stretching of one fiber creates a coordinated contraction.

CARDIAC MUSCLE

Cardiac muscle is a striated fiber containing the same arrangements of contractile filaments as skeletal muscle**.** In addition, cardiac muscle fibers exhibit densely staining cross bands called intercalated discs (Fig 3). These intercalated discs join the muscle fibers end-to-end. They are highly specialized attachment sites which prevent the cells from pulling apart. On the lateral component of the intercalated discs are gap junctions which permit the cells to act as an electrical syncytium.

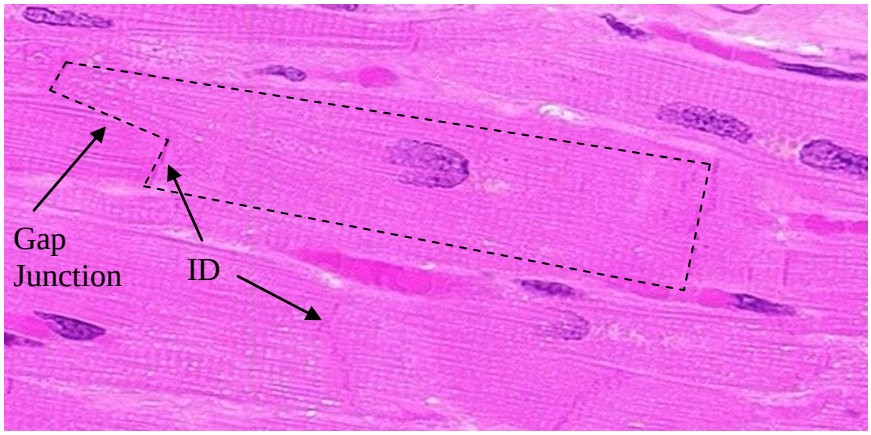

Figure 3. Cardiac myocytes are blunt ended with central nucleus (outline). Cells are mechanically coupled at the intercalated discs (ID) and electrically coupled by gap junctions.

There are two types of cardiac muscle cells: conducting and contractile.

Conducting cardiac muscle cells are ~ 1% of the cardiac muscle cells. These are large diameter cells that do not produce tension, instead they are specialized for excitation. They constitute a network in the heart known as a conduction system. They are connected to the contractile cells by gap junctions. The conducting fibers are filled mostly with glycogen and have few myofilaments.

These cells are the intrinsic pacemakers. We will deal with their action potentials in the next lecture.

Contractile cardiac muscle cells are slow oxidative muscle fibers. These fibers form the walls of the heart, shorten and produce tension. They use glucose and fatty acids as substrates. We will consider their action potentials below.

Electrical –Contraction (E-C) Coupling
As in skeletal muscle, contraction in cardiac muscle is dependent on the entry of Ca++ from the T tubule (Fig 4). Depolarization of the T tubule membrane opens the voltage gated Ca++ channels (dihydropyridine receptor), permitting the entry of a small amount of Ca++. This Ca++ opens the Ca++ gated Ca++ channel (ryanodine receptor) on the sarcoplasmic reticulum (SR) thereby releasing a lot of Ca++ into the cytoplasm. In turn, Ca++ binds to troponin which unmasks the actin (thin filament), cross bridges form, and shortening occurs. With repolarization of the T tubule membrane, no further Ca++ enters the cells and the SR CaATPase removes Ca++ from the cytoplasm. This removal of Ca++ ends the contractile cycle and the muscle relaxes.
There are two other proteins located at the plasma membrane which help to return Ca++ to its basal level inside the cardiac muscle cell. The plasma membrane CaATPase uses ATP to actively pump Ca++ out. The Na+ - Ca++ exchanger transports Na+ into the cell for each Ca++ moved out of the cell (i.e., exchanges Na+ for Ca++).

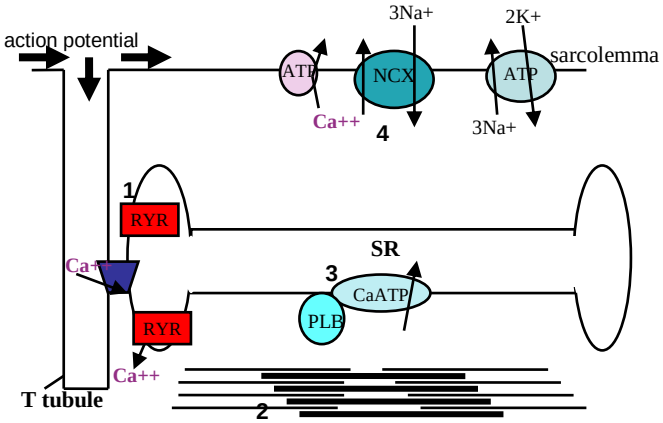

Figure 4. E-C coupling in cardiac muscle cells. Step 1, Ca++ entry via the voltage gated Ca++ channel, dihydropyridine receptor, causes the SR Ca release channel to open. Ca++ exits the SR. Step 2, myofilaments are activated by the binding of Ca++ to the thin filaments. Step 3. SR CaATPase removes Ca++ from the cytoplasm causing contraction to cease and the muscle relaxes. Step 4. The Na-Ca++ exchanger and the plasma membrane Ca++ ATPase help to remove Ca++ from the cytoplasm.

Membrane activation in contractile cardiac cells
The action potential of the contractile cardiac muscle fiber (Fig 5) is longer in duration (200-220 msec) than that seen in skeletal muscle (2 msec). In cardiac cells there are four phases to the action potential.

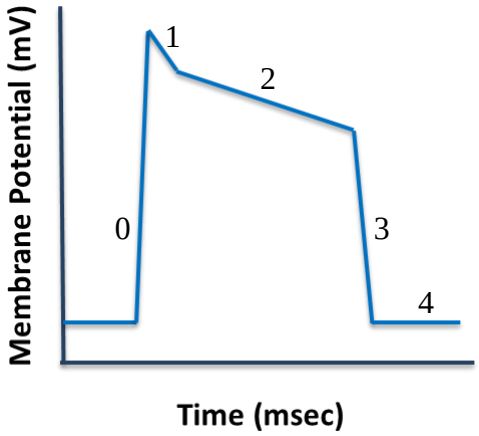

Figure 5. The action potential of the contracting cardiomyocyte is called the **fast action potential**. The plateau phase 2 is due to opening of the L type voltage gated Ca++ channel.

P**hase 0**, voltage gated Na+ channels open.
Phase 1, voltage gated Na channels inactivate and voltage gated K+ channels open.
Phase 2 (plateau), voltage gated Ca++ channels (L type) open and voltage gated K channels remain open.
Phase 3, only voltage gated K+ channels are open and cells repolarize.
Phase 4, all of the voltage gated channels are closed and the resting membrane potential is restored by the Na/K ATPase.

Note that the entry of Ca++ in phase 2 is essential for initiating contraction and triggering the opening of the Ca++ gated Ca++ release channel (ryanodine receptor). One other point, each action potential results in one contraction. One contraction (twitch) is ~250 msec, almost the same duration as the action potential (200 msec). This is due to the prolonged plateau phase 2.

Refractory period and absence of tetanus
Recall that these voltage gated Na+ channels must undergo a conformational change from an "inactivated" state to a "closed" state before they can reopen and initiate another action potential. As a consequence of phase 2, the voltage gated Na+ channels remain "inactivated" for an extended period of time and do not "close" until repolarization in phase 3 (~180 msec). This time period during which the voltage gated Na+ channels are inactivated is called the **absolute refractory period** (Fig 6). No amount of stimulus can cause an action potential during the absolute refractory period.

Note that the **absolute refractory period** (180 msec) is almost equal in duration to the action potential (200-220 msec). From ~180 msec to 200 msec is called the **relative refractory period.** During this time period, a second action potential can be fired but the stimulus required is greater than normal. This is because there are fewer voltage gated Na channels in the "closed" state and therefore it is harder to reach threshold.

An important point regarding the refractory period is that contractions cannot sum and therefore there is no fused tetanus (summed contractions). Fused tetanus in the heart would lead to death as it would prevent the rhythmic pumping of blood.

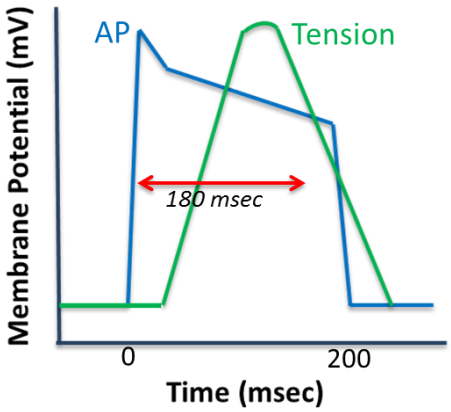

Figure 6. The absolute refractory period of the cardiac muscle action potential refers to the time interval when the voltage gated sodium channels are inactivated. The absolute refractory period lasts ~180 msec. The action potential lasts 200-220 msec. A single contraction is 250 msec.

Absence of muscle fiber recruitment
The contractile cells of the heart act as an electrical syncytium with all of the cells contracting during a single beat. Therefore it is not possible to increase the force of contraction by fiber recruitment. Instead the heart has developed other strategies to increase the force of contraction which we will consider below and in the cardiovascular lectures.

Muscle fiber length and tension
The relationship between initial fiber length and total tension in cardiac muscle is similar to skeletal muscle; there is a fiber length at which tension development is maximal. However in the heart, the length of the cardiac muscle fiber is determined by the filled state of the heart chamber. At the beginning of diastole when the heart begins to fill with blood, the muscle fibers are relaxed and the sarcomeres are not at optimal length for generating tension (Fig 7). Filling the heart with blood stretches the muscle fibers. This stretching produces optimal overlap of the myofilaments (optimal sarcomere length) and enhances contraction. This is known as Starling's Law of the heart.

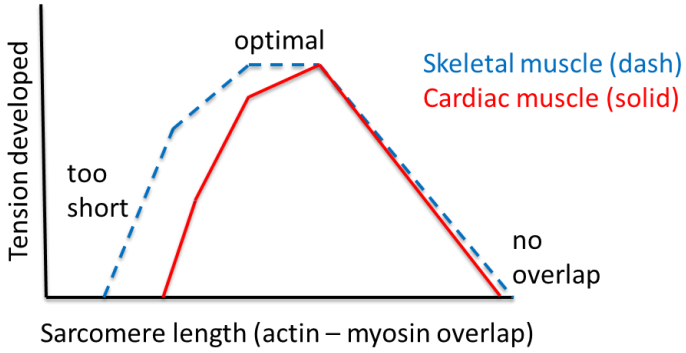

Figure 7 Diagram depicts the correlation between muscle fiber length and tension in the heart. Filling of the heart increases sarcomere length such that optimal force is generated. In contrast the resting length of skeletal muscle in the body provides optimal overlap of the thick and thin filaments to generate tension. Less tension is generated when the sarcomere is "too short" or when there is little or no overlap of the myofilaments.

HEART STRUCTURE

Cardiac muscle comprises the walls of the heart. The inner surface facing the blood is lined by a thin epithelium called endothelium. The heart is divided into right and left halves. Each half contains upper chamber called the atrium and a lower chamber called the ventricle. Located between the atrium and ventricle are valves (A-V valves) which permit blood to flow in a unidirectional manner from the atria to the ventricles. There are two other valves: the pulmonic valve permits blood to flow from the right ventricle to the lung circulation and the aortic valve (aorta) allows blood to flow from the left ventricle to the systemic circulation (every organ).

All of the valves open and close depending on the pressure differences across them. In each heart beat, blood moves from the right side of the heart to the lung to pick up oxygen, returns to the left side of the heart from which it is pumped to the systemic circulation for delivery of oxygen and nutrients and removal of wastes.

In the next three lectures on the cardiovascular system we will consider the mechanical and electric properties of the heart as a pump and its regulation.

KEY CONCEPTS

- Smooth muscle is an involuntary, non-striated type associated with blood vessels and visceral organs. Cardiac muscle is the involuntary, striated type that forms the heart wall.
- Both smooth and cardiac muscle have two sets of overlapping protein myofilaments, actin and myosin, the relative sliding of which produces shortening and generates force. This process involves cross bridge formation between actin and myosin which is driven by ATP.
- In both smooth and cardiac muscle, coupling between the membrane action potentials and contraction is mediated by calcium ions. In cardiac muscle Ca++ regulates the thin filament (actin) to enable cross bridge formation. In smooth muscle, Ca++ regulates the thick filament (myosin) to enable cross bridge formation and contraction.
- Cardiac and smooth muscle is regulated by the autonomic nervous system. Some smooth muscle is regulated by stretch and hormones.
- Relaxation of cardiac and smooth muscle, like skeletal muscle, is by removal of Ca++.
- The force of contraction in cardiac muscle is increased by stretch (Frank-Starling law). This is in contrast to skeletal muscle which increases force either by recruiting more muscle fibers or by summing twitches (fused tetanus).
- Cardiac muscle comprises the walls of the heart. The heart consists of two separate pumps that move blood in a unidirectional manner through the pulmonary circulation for gas exchange and then to the systemic circulation for the delivery of O2 and nutrients and removal of waste products.