Contraction and Excitation of Smooth Muscle

Smooth muscle, which is present in the walls of many visceral organs, in blood vessels, and a number of other places in the body, has a similar contractile mechanism as skeletal muscle: interaction of actin and myosin fibers. However, there are also many differences, as will be described below.

Smooth muscle can be broadly divided into two types:

Multi-unit Smooth Muscle: This type of smooth muscle is in some ways analogous to skeletal muscle. Individual muscle fibers contract independently, and the contraction is mainly controlled by neural inputs.   Examples: smooth muscle that affects pupillary size and muscles that produce piloerection.

Unitary Smooth Muscle (Syncytial or Visceral Smooth Muscle): In unitary smooth muscle, individual fibers are mechanically linked together in a sheet. Furthermore, gap junctions provide electrotonic coupling between adjacent fibers to assure that they contract as a "unit." Unitary smooth muscle is the more common type, and is present in the walls of most visceral organs.

Physical and Chemical Basis of Smooth Muscle Contraction

The same interaction of actin and myosin mediates smooth muscle contraction as is responsible for skeletal muscle contraction. Furthermore, the process of contraction is similarly activated by calcium ions, and is "powered" by the conversion of ATP to ADP. However, there are also large differences in the biophysical basis of smooth and skeletal muscle contraction.

Perhaps the largest difference between smooth and skeletal muscle contraction is the fact that smooth muscle lacks troponin. Instead, smooth muscle contraction is activated when calcium ions bind with a regulatory protein called **_calmodulin._** Once calmodulin binds to calcium, it can join with and activate a phosphorylating enzyme, **_myosin kinase_**. In turn, myosin kinase phosphorylates a subunit of the myosin head, which is necessary to permit the interaction with actin. Once phosphorylated, myosin will interact with actin indefinitely until another enzyme, **_myosin phosphatase_**, severs the phosphate from the myosin head.

Another difference between smooth muscle and skeletal muscle is that ATPase activity is much lower in smooth muscle. Thus, myosin heads will remain in contact with actin for a relatively long period of time, and cross bridge cycling will be slow.

As a result of these differences, smooth muscle contraction is much slower than skeletal muscle contraction, and relaxation also occurs slower.   Because of the prolonged interactions between actin and myosin, sustained contraction requires less energy than in skeletal muscle. In addition, the force of muscle contraction is very strong.

Once smooth muscle is fully contracted, very little energy is required to sustain the contraction. This is called the ***latch mechanism***. It has been postulated that the latch mechanism is related to a deactivation of both myosin kinase and myosin phosphatase during prolonged contractions, so that myosin remains bound to actin without expenditure of energy. The process by which these enzymes are "turned off" is not fully appreciated.

Control of Smooth Muscle Contraction

Smooth muscle differs from skeletal muscle in that it lacks a T-tubule system and extensive sarcoplasmic reticulum, and a completely different mechanism is responsible for getting calcium ions into smooth muscle cells. Calcium mainly flows in from outside of the cell through specific channels, although depolarization of a smooth muscle cell does also evoke some calcium release from the rudimentary sarcoplasmic reticulum. Because calcium flows into smooth muscle cells through channels associated with a variety of receptor types, the control of contraction can be more complex than in skeletal muscle. A large variety of chemicals can affect calcium channel opening through binding to specific receptors. Furthermore, binding to other receptors can activate second messenger systems (cAMP or cGMP) that influence the enzyme that pumps calcium out of the smooth muscle cell, thereby affecting the length of muscle contraction.

The principal neural influences on smooth muscle are provided by the sympathetic and parasympathetic systems, which release acetylcholine or norepinephrine that bind to receptors on the smooth muscle membrane. Through these actions, norepinephrine and acetylcholine can either produce an increase or decrease in opening of calcium channels, thereby regulating smooth muscle contraction. Depending on the receptors on a particular smooth muscle cell and how they are linked to channels, norepinephrine and acetylcholine can have either excitatory or inhibitory effects. However, the actions of the two transmitters are typically antagonistic, so that if contraction is promoted by norepinephrine then it will usually be inhibited by acetylcholine (and vice-versa).
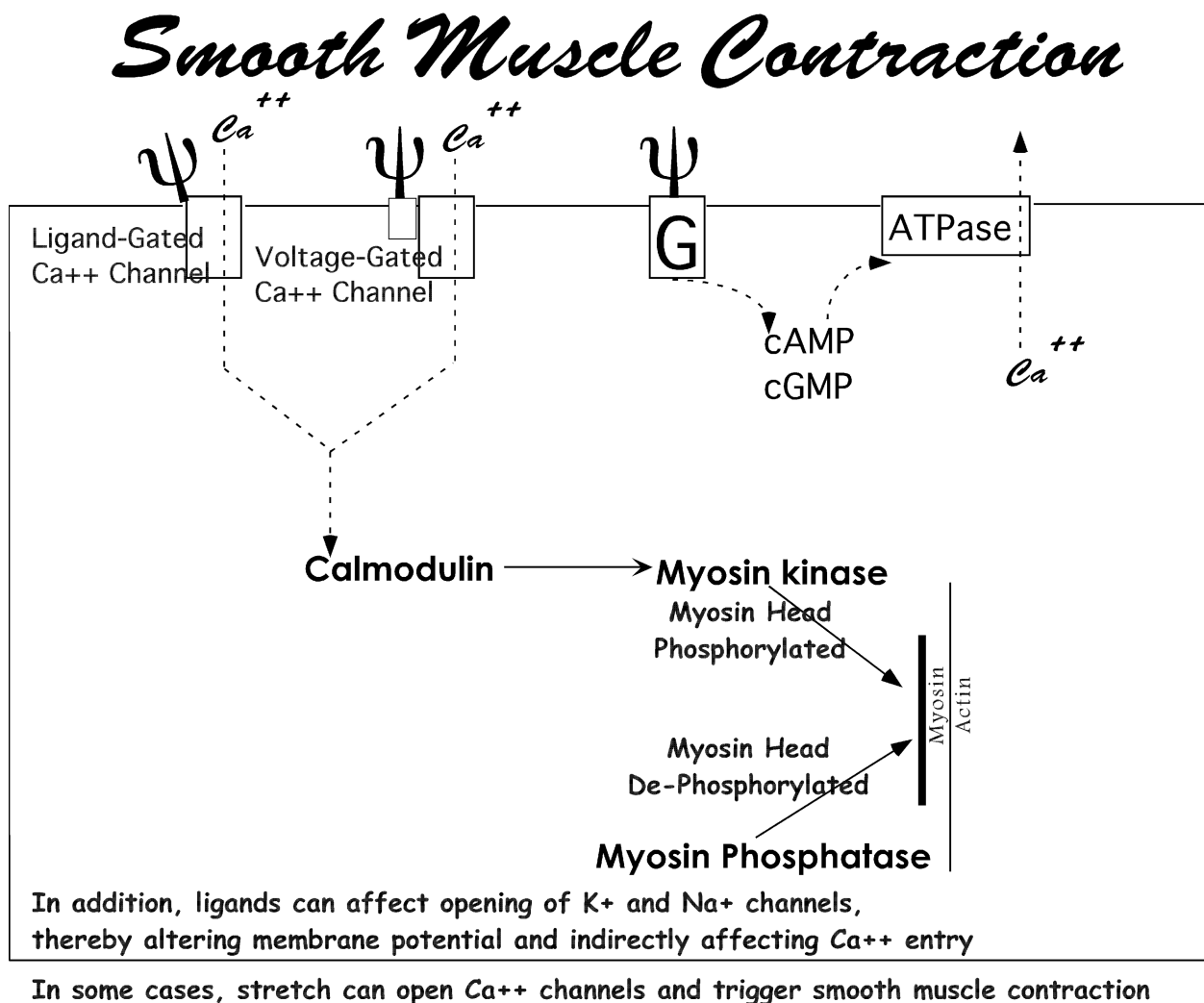
Smooth muscle possesses some voltage-gated channels, but these are more often calcium channels than sodium channels. Thus, opening of receptor-gated calcium channels can in turn lead to depolarization of the smooth muscle cell and an opening of voltage-gated calcium channels. Thus, calcium may play "two roles" in smooth muscle, serving both to activate contraction and to mediate channel opening. Opening of voltage-gated calcium channels typically leads to the production of action potentials in unitary smooth muscle, but not in multi-unit smooth muscle (which rarely exhibits spikes).

Sympathetic and parasympathetic fibers do not make synapses like the neuromuscular junction on smooth muscle cells. Instead, these fibers branch diffusely on the top of a sheet of smooth muscle, providing many varicosities that are separated from the smooth muscle cell membranes by distances of a few nanometers to a few micrometers.

Smooth muscle cells also have receptors for a variety of hormones that can affect contraction by opening or closing receptor-gated calcium channels, changing the sensitivity of voltage-gated calcium channels, activating second messengers, or opening or closing sodium or potassium channels to alter the resting membrane potential. Thus, hormones can have complex effects on smooth muscle excitability. Amongst the large number of hormones that affect smooth muscle contraction are epinephrine, acetylcholine, oxytocin, vasopressin, and histamine.

Other factors can also produce opening or closing of channels on smooth muscle cells, thereby affecting muscle contraction. These factors include muscle stretch, body temperature, and presence of lactic acid.

Summary

Smooth Muscle Contraction

Ca^{++} Ca^{++}

| Ligand-Gated Ca++ Channel | Voltage-Gated Ca++ Channel | G | ATPase |

cAMP
cGMP

Ca^{++}

Calmodulin → **Myosin kinase**

Myosin Head
Phosphorylated

Myosin
Actin

Myosin Head
De-Phosphorylated

Myosin Phosphatase

In addition, ligands can affect opening of K+ and Na+ channels,
thereby altering membrane potential and indirectly affecting Ca++ entry

In some cases, stretch can open Ca++ channels and trigger smooth muscle contraction

Skeletal Muscle	Smooth Muscle
Cells are large	Cells are small
Cells are independent	Cells are often connected by gap junctions
Striated	Actin/myosin bundles are aligned obliquely
Ca++ enters from sarcoplasmic reticulum	Ca++ enters mainly from outside
ATPase activity is high	ATPase activity is very low
Contraction terminated abruptly by removal of Ca++	Contraction terminated slowly by myosin phosphatase
Contraction is very rapid	Contraction is very slow
Specific Neural inputs	Nonspecific neural inputs; hormonal inputs
No Latch mechanism	Latch mechanism

Contraction of cardiac muscle

Cardiac muscle, like skeletal muscle, is striated. Furthermore, both types of muscle are similar in that contraction is initiated when Ca++ binds to troponin.   The sliding of cardiac and skeletal muscle actin and myosin filaments is also similar, and the rate limiting step is the breakdown of ATP by myosin ATPase. In other respects, the contraction process is similar to that of smooth muscle. Both cardiac and smooth muscle cells are joined electrically by gap junctions, and physically (in the case of cardiac muscle cells, by the interdigitation of membranes at sites called intercalated disks).   In some ways however, cardiac muscle differs completely from both smooth and striated muscle. Special cells in cardiac muscle are autorhythmic, in that they spontaneously generate action potentials without input from other sources. These so-called pacemaker cells set the rate of the heartbeat. Because of the existence of these specialized cells, the heart can contract in isolation, when removed from all neural and hormonal influences.
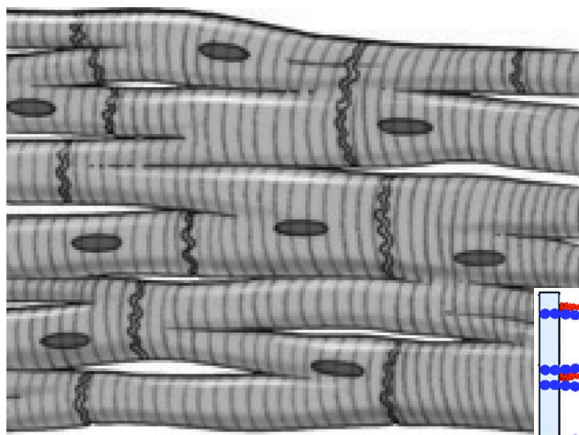
The intercalated disks hold the cardiac muscle cells into a latticework that maximizes pressure inside the heart chambers when the muscle cells contract. Cardiac muscle cells also contain an abundance of a protein called **titin**, which has springlike properties and plays a key role in generating tension within the cells during contraction.

SPRING

Titin
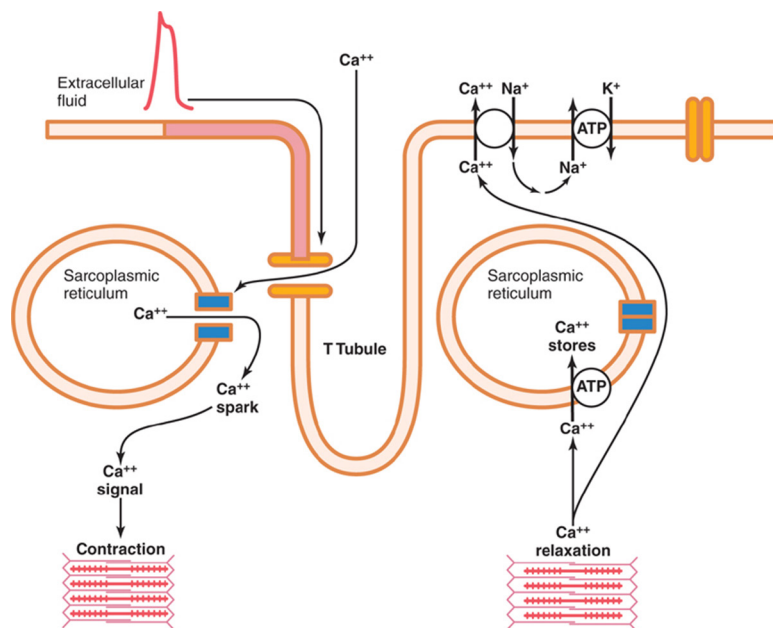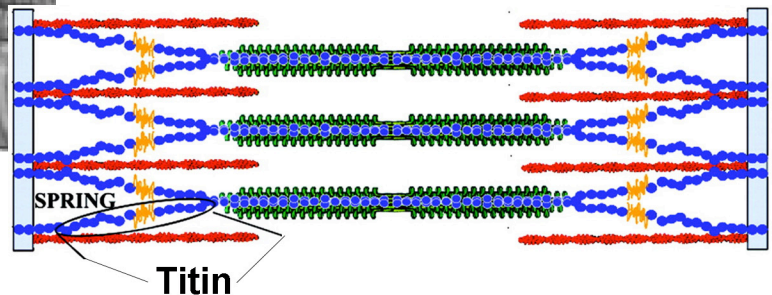
The initiation of contraction in a cardiac muscle cell begins when an action potential invades from an adjacent cell. This action potential includes a prominent Ca++ influx, as discussed below.

The Ca++ from the outside of the cell binds to a receptor on the sarcoplasmic reticulum called the **ryanodine receptor**. This binding causes an opening of a channel that permits Ca++ to flow out of the sarcoplasmic reticulum, in an event called the *calcium-induced calcium release.*

Like in skeletal muscle, the majority of Ca++ that binds to troponin is derived from the sarcoplasmic reticulum. As in skeletal muscle, contraction ends when Ca++ is pumped back into the sarcoplasmic reticulum by Ca++-ATPase. In addition, an indirect active transporter pumps Ca++ outside of the cell in exchange for Na+ ions (this is indirect active transport, because the movement of Ca++ against its concentration gradient is dependent on low intracellular Na+, established by the Na+-K+ ATPase). This mechanism is not very efficient, because the import of *three* sodium ions is needed to export *one* Ca++ ion.

1
K⁺ Out

2
Ca²⁺ In
K⁺ Out

+52 mV

0
Na⁺ In

3
K⁺ Out

Total Duration = 200-300 msec

4

-96 mV

4
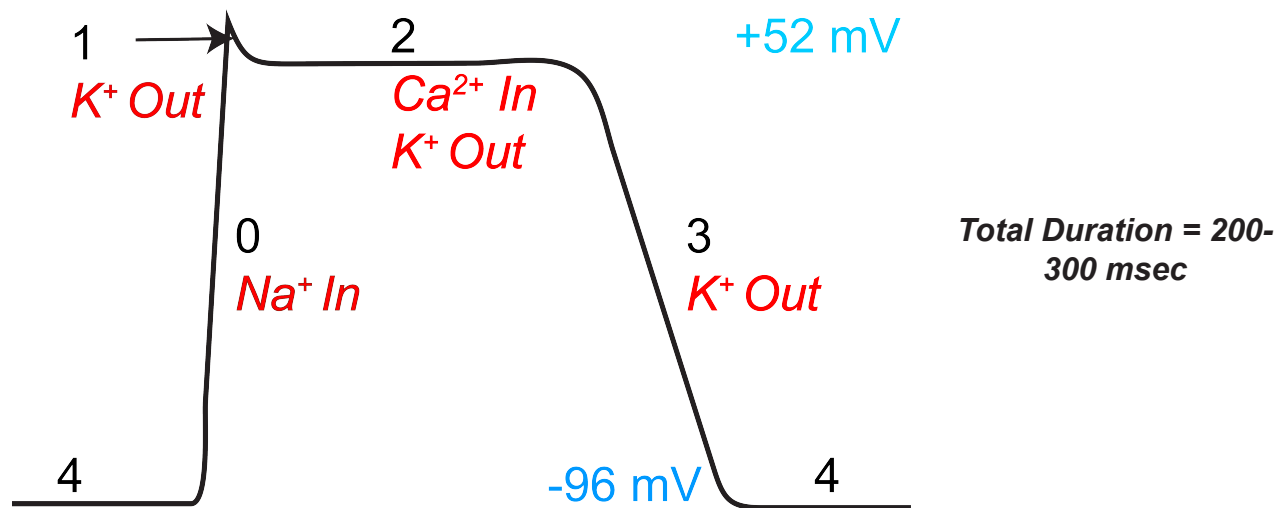
The action potential in cardiac muscle is much longer in duration than that in skeletal muscle.

Phase 4 is the resting membrane potential, which is near -96 mV.

In _Phase 0_, fast sodium channels open, rapidly depolarizing the myocyte. This component of the cardiac action potential is similar to that of the skeletal muscle or nerve action potential.

In _Phase 1_, the fast sodium channels inactivate, and the *cardiac transient outward potassium current (I_{TO})* is initiated.

Phase 2 is the long plateau phase of the cardiac action potential. This long period of constant depolarization is sustained by a balance between inward movement of Ca^{2+} through L-type calcium channels and outward movement of K^+ through the slow delayed rectifier potassium channels (I_{Ks}). The balance of Ca^{2+} in and K^+ out allow sustained ionic fluxes without a change in membrane potential. **The calcium entry into the cardiac muscle cell during Phase 2 triggers the calcium-induced calcium release from the sarcoplasmic reticulum, which initiates contraction.**

Phase 3 is the repolarization phase of the cardiac action potential. The L-type calcium channels close, while the I_{Ks} channels remain open. As a result, the membrane potential moves towards 0 mV. This causes two other types of potassium channels to open: the rapid delayed rectifier K^+ channels and the inward-rectifier K^+ channels. With these channels open, the membrane hyperpolarizes to a potential of ~-90mV. These potassium channels then mainly close, although some inward-rectifier potassium channels remain open to sustain the hyperpolarization.

Hence, the cardiac action potential involves many more types of channels than the action potentials in skeletal muscle or nerve, which generates its unique properties.

A net result of this long-duration action potential in cardiac muscle is the fact that the action potential duration almost exactly matches the duration of contraction. Of course, during the period when the action potential is occurring, the membrane is refractory to the generation of new action potentials. As a result, tetanic contractions cannot occur in cardiac muscle as they do in skeletal muscle.
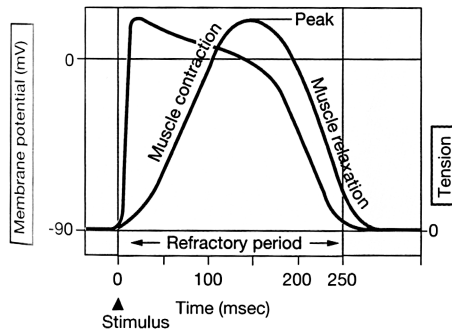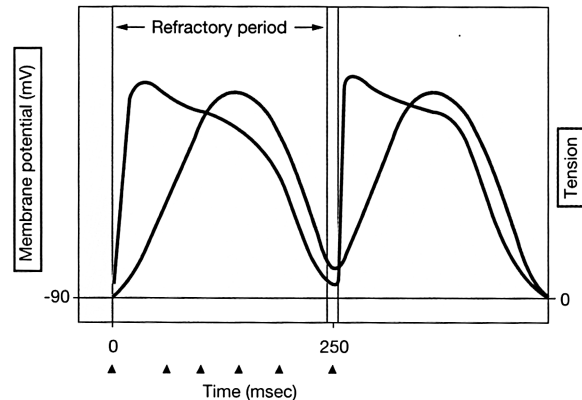
(a) Skeletal muscle fast-twitch fiber
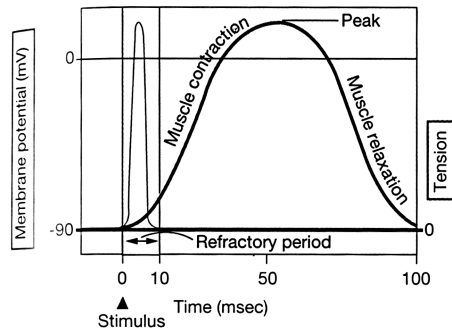
(b) Tetanus in a skeletal muscle fiber. Action potentials not shown.

▲ = Stimulus for action potential
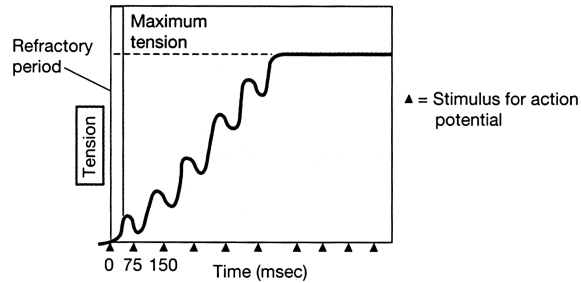
(c) Cardiac muscle fiber

(d) Long refractory period in a cardiac muscle prevents tetanus.

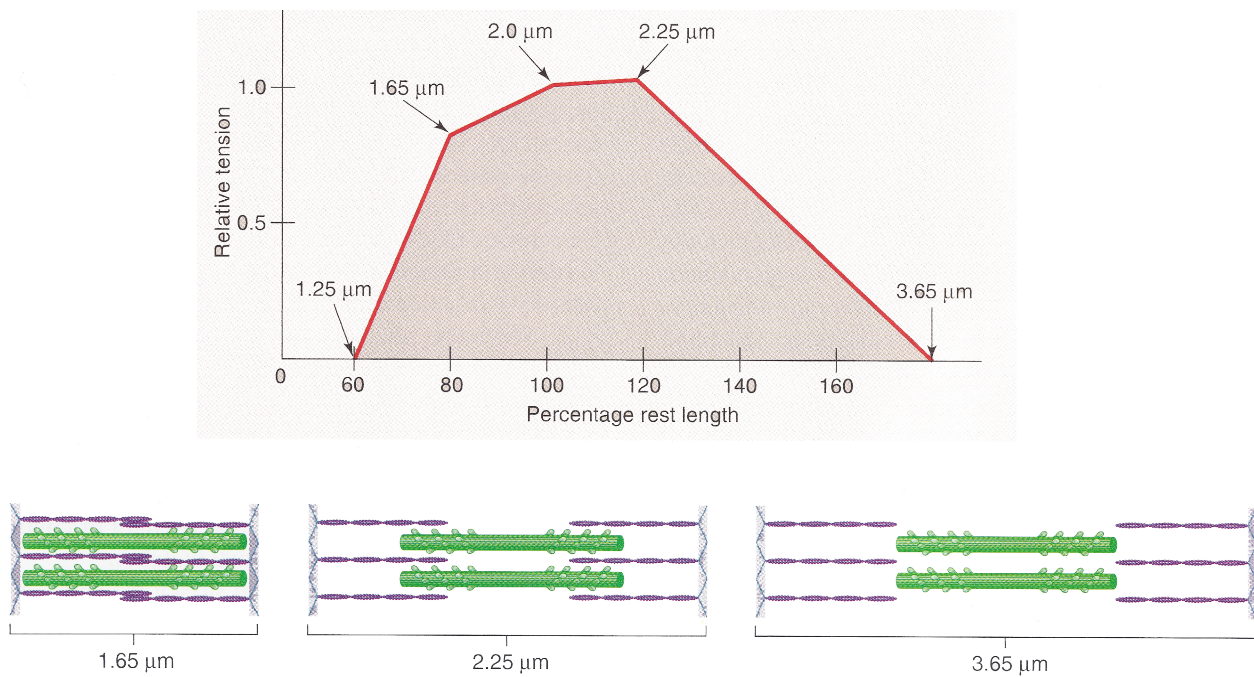> ***Discussion point:*** What is the practical significance of this adaptation?

As we discussed earlier, skeletal muscle contracts most efficiently when the overlap between actin and myosin is maximal. If the muscle is stretched or compressed substantially, then the tension produced by contraction is reduced.

Unlike skeletal muscle, resting cardiac muscle is shortened well below its optimal length. As a result, cardiac muscle cells have a tendency to contract very weakly. When blood fills a heart chamber, however, the cardiac muscle is stretched and brought closer to its optimal length. As a result, the tension of contraction increases.
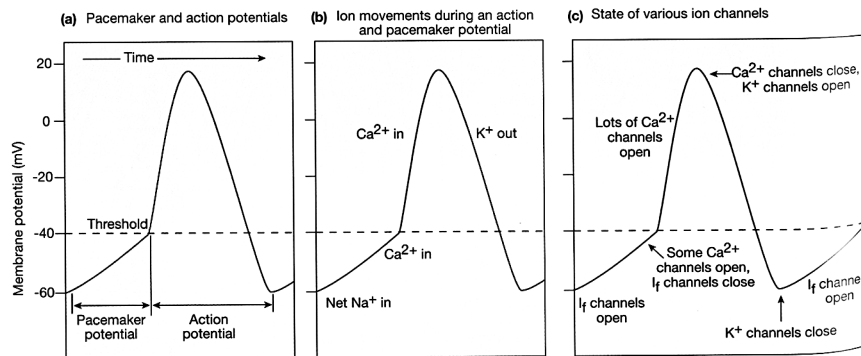
This principle is the fundamental basis for the **Frank-Starling Law of the Heart** (named after Otto Frank and Ernest Starling). This law states that within biological limits, as the volume of blood returning to a heart chamber increases (thereby stretching myocardial cells in that chamber to a more efficient resting length), then the force produced by contraction (and thus stroke volume) also increases. As a result, the heart will always pump out as much blood as is returned.

In addition to mechanically affecting contraction strength by altering the relationship between the contractile proteins actin and myosin in cardiac muscle cells, stretch of a ventricle affects the sensitivity of the calcium-binding protein troponin for calcium. This heightened sensitivity increases the rate of cross-bridge attachment and detachment, and the amount of tension developed by the muscle fiber.

We will return to Starling's Law when we discuss cardiac return.

Action Potential Generation in Pacemaker Cells

(a) Pacemaker and action potentials

(b) Ion movements during an action and pacemaker potential

(c) State of various ion channels

■ Figure 14-16 **Action potentials in cardiac autorhythmic cells**

Myocardial autorhythmic cells have the ability to generate action potentials spontaneously without any inputs, and are important in regulating the cardiac cycle. These cells do not have a stable resting membrane potential. This is predominantly due to the fact that they possess a special group of channels, called **I_f channels** (the f stands for "funny"). I_f channels open when the membrane potential is depolarized to about -60 mV. The I_f channels allow both Na+ and K+ channels to flux, but at negative membrane voltages inward Na+ influx exceeds K+ efflux. As a result, the membrane slowly depolarizes. The depolarization causes a few voltage-gated Ca++ channels to open, and this depolarization eventually promotes more Ca++ channels to open, producing a full-blown action potential. The Ca++ channels then close, repolarization begins due to opening of K+ channels, the membrane returns to a negative potential, and the process begins again.

How do the sympathetic and parasympathetic systems affect heart contraction?
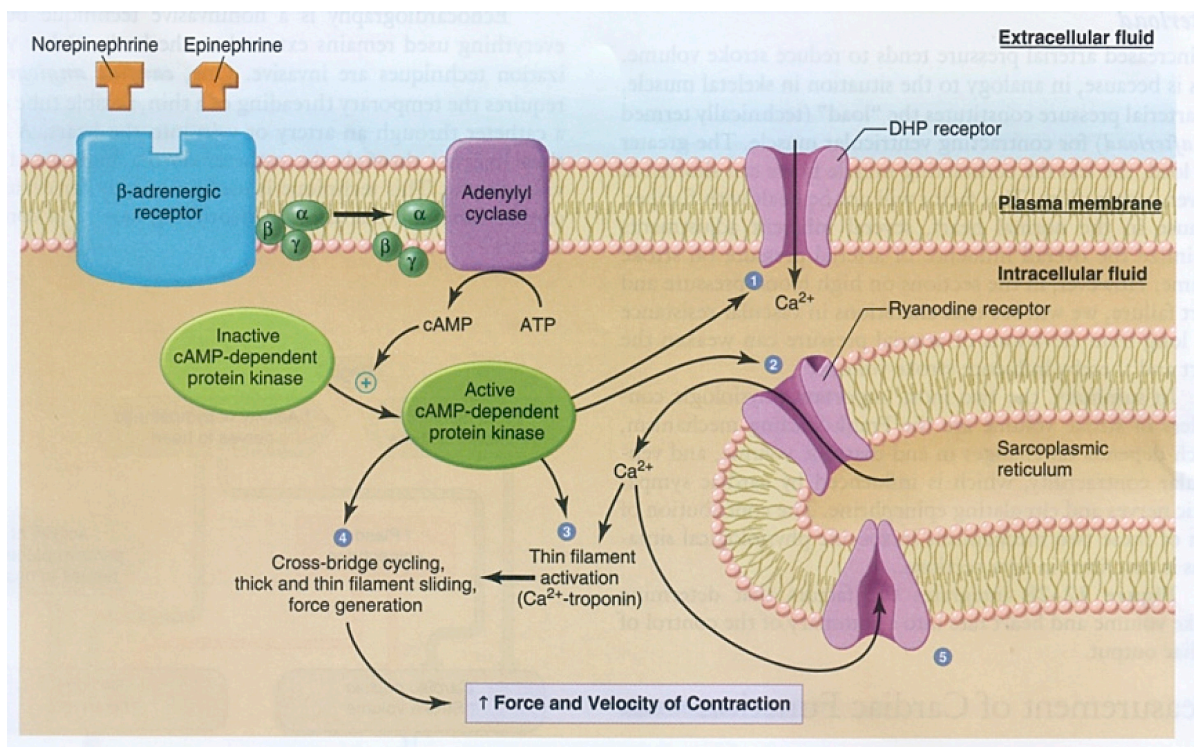
Release of ACH from vagal efferents acts to slow heart rate. The transmitter binds to muscarinic receptors on autorhythmic cells that influence both K+ and Ca++ channels. Potassium permeability increases, so the membrane potential becomes more negative after each action potential. At the same time, Ca++ permeability decreases. Thus, it takes more time for the cell to reach threshold for generating the Ca++-mediated action potential.

The binding of epinephrine or norepinephrine to β-receptors on autorhythmic cells results in the activation of a second-messenger system (c-AMP), whose effect is to cause phosphorylation of I_f and Ca++ channels. The net result is that cation entry speeds up, which decreases the time required for the voltage-gated Ca++ channels to become activated during each action potential cycle. As a result, the time between action potentials decreases.
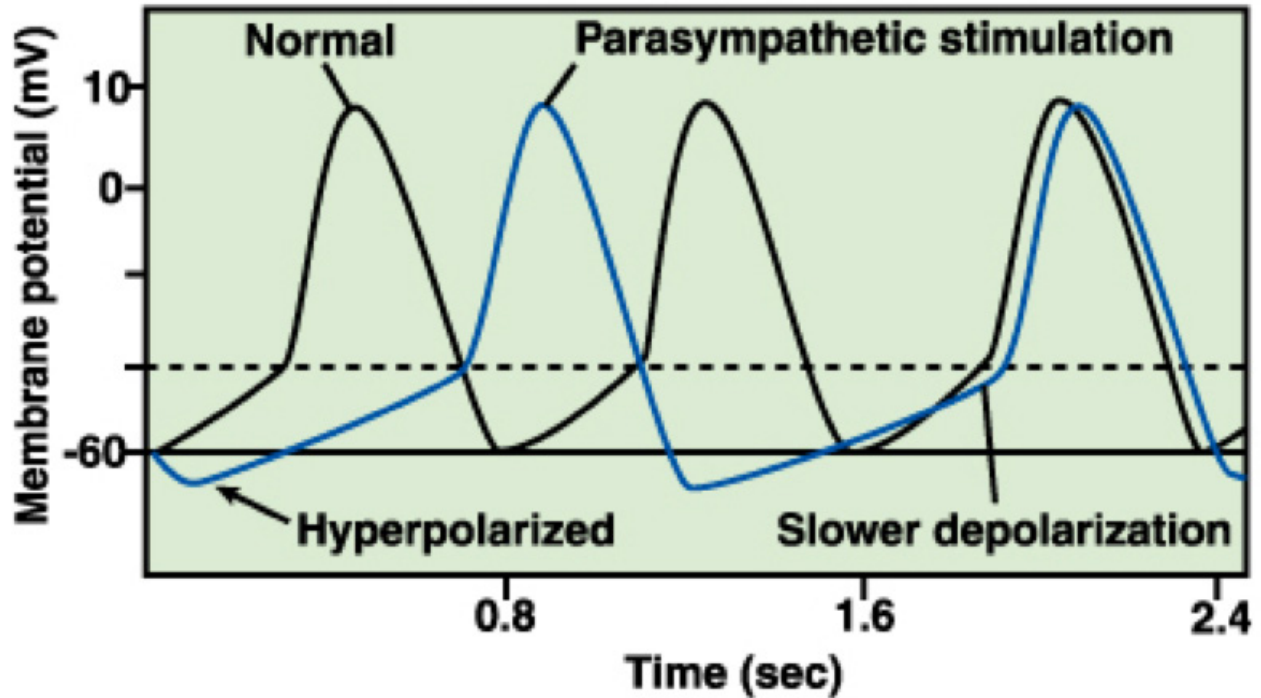
Typical myocardial cells are also affected by binding to β-receptors, which induces the production of cAMP. The phosphorylation of voltage-gated Ca++ channels increases the likelihood that they will open. In addition, phosphorylation of a regulatory protein, **phospholamban**, enhances Ca++—ATPase activity in the sarcoplasmic reticulum, so that more Ca++ is sequestered in the sarcoplasmic reticulum, and thus more Ca++ can be released during the calcium-induced calcium release. As a result, the actin filaments slide further along myosin, and contraction tension is increased.

In addition to activating phospholamban, catecholamines have a number of effects on myo-cardial cells that enhance contraction tension:
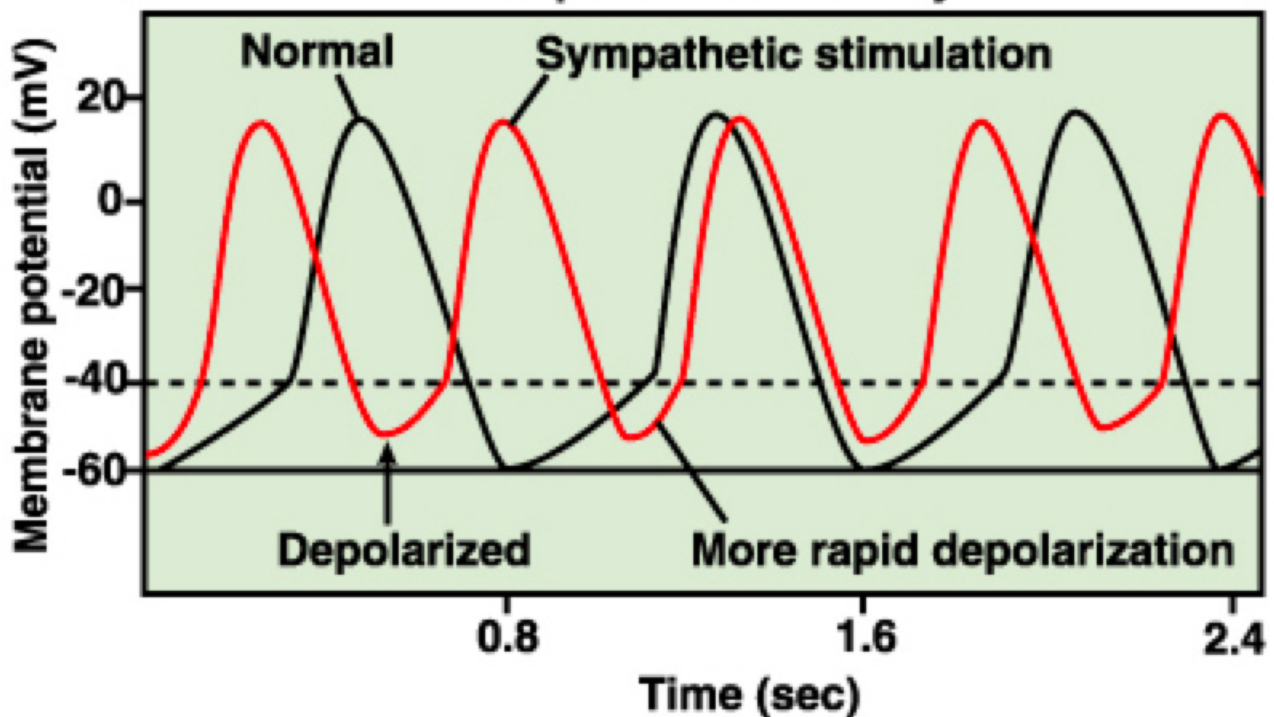
- The Ca2+ channels on the myocardial cell membrane open faster.
- The Ca2+ channels in the sarcoplasmic reticulum (ryanodine receptor) open faster.
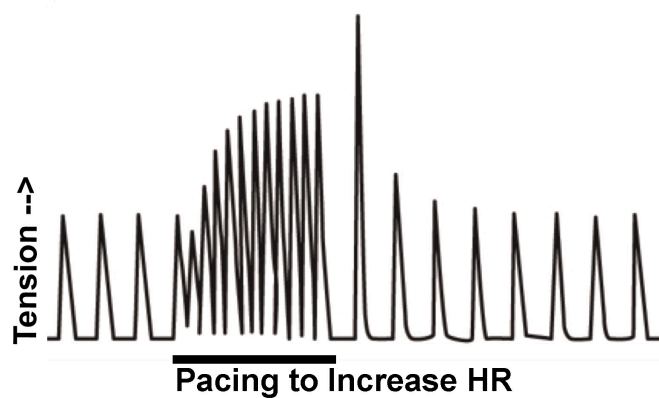- Cross bridge cycling occurs faster.

Parasympathetic stimulation with SA node pacemaker activity

Normal — Parasympathetic stimulation — Hyperpolarized — Slower depolarization

Membrane potential (mV): 10, 0, -60

Time (sec): 0.8, 1.6, 2.4

Sympathetic stimulation with SA node pacemaker activity

Normal — Sympathetic stimulation — Depolarized — More rapid depolarization

Membrane potential (mV): 20, 0, -20, -40, -60

Time (sec): 0.8, 1.6, 2.4

The Staircase or Bowditch Effect


Tension -->

Pacing to Increase HR

It has been known since the late 1800s that pacing the heart (electrical stimulation to increase heart rate) results in an automatic increase in contractile tension, even if the heart muscle is removed from the body and thus is free of any influences of hormones or neural actions. This phenomenon is called the **Bowditch effect** or the **staircase effect**, as illustrated in the figure to the left.
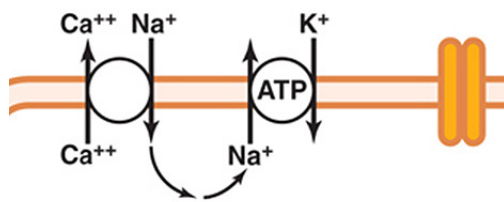
The physiological basis of the Bowditch effect is still debated, but most think it is due to the impaired ability to remove Ca++ from the sarcoplasm. As we have discussed, most of the Ca++ is transported into the sarcoplasmic reticulum via the Ca++—ATPase, although some is removed at the cell surface by indirect active transport (1 Ca++ ion is exchanged for 3 Na+ ions; Na+ is normally low inside the cytoplasm due the actions of Na+/K+ ATPase). When contraction rates are high, the Na+/K+ ATPase is overwhelmed, and levels of Na+ climb in the cell near the plasma membrane. Thus, there is less driving force for indirect active transport, so intracellular Ca++ levels increase, but not to the point where contraction is induced. However, this additional Ca++ facilitates the contraction once an action potential occurs.
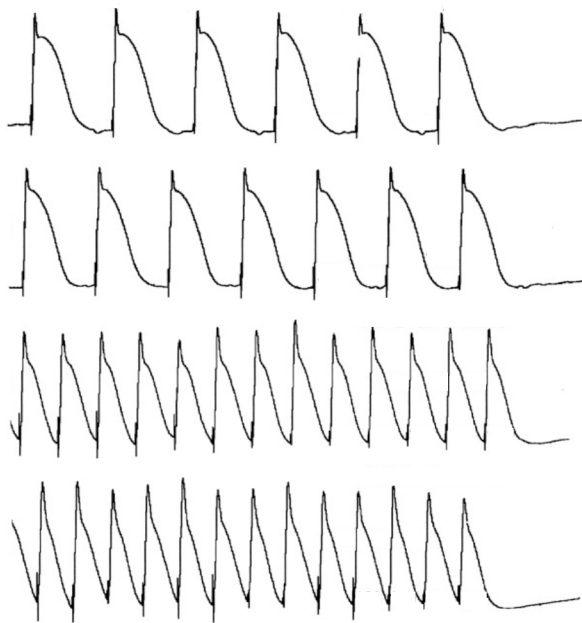
A related phenomenon is the relationship between heart rate and the length of the cardiac action potential. As heart rate increases, there is an automatic shortening in the length of the cardiac action potential, as illustrated to the left. The plateau phase of the action potential is the component that is reduced in duration. Since this component is due to a Ca++ influx, this influx must be attenuated during high heart rates.

This occurs for several reasons, but there seems to be one primary cause. The L-type Ca++ channel inactivates as a function of intracellular free Ca++ and membrane potential. Since the myocyte does a poorer job in eliminating Ca++ when heart rate is high, the persistent higher levels of calcium cause the channel to inactivate sooner.