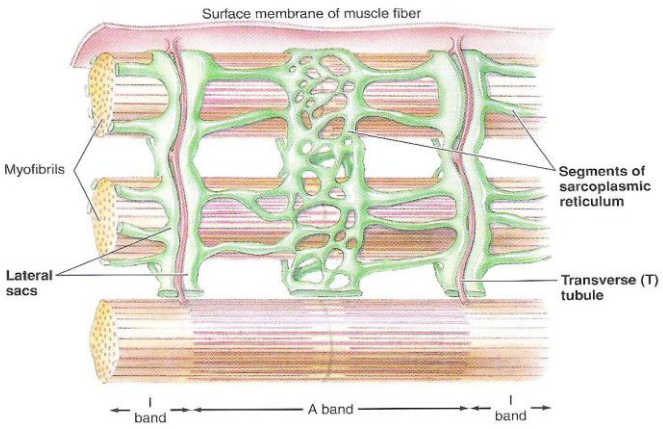


FIGURE 8-9

The T tubules and sarcoplasmic reticulum in relationship to the myofibrils. The transverse (T) tubules are membranous, perpendicular extensions of the surface membrane that dip deep into the muscle fiber at the junctions between the A and I bands of the myofibrils. The sarcoplasmic reticulum is a fine, membranous network that runs longitudinally and surrounds each myofibril, with separate segments encircling each A band and I band. The ends of each segment are expanded to form lateral sacs that lie next to the adjacent T tubules.

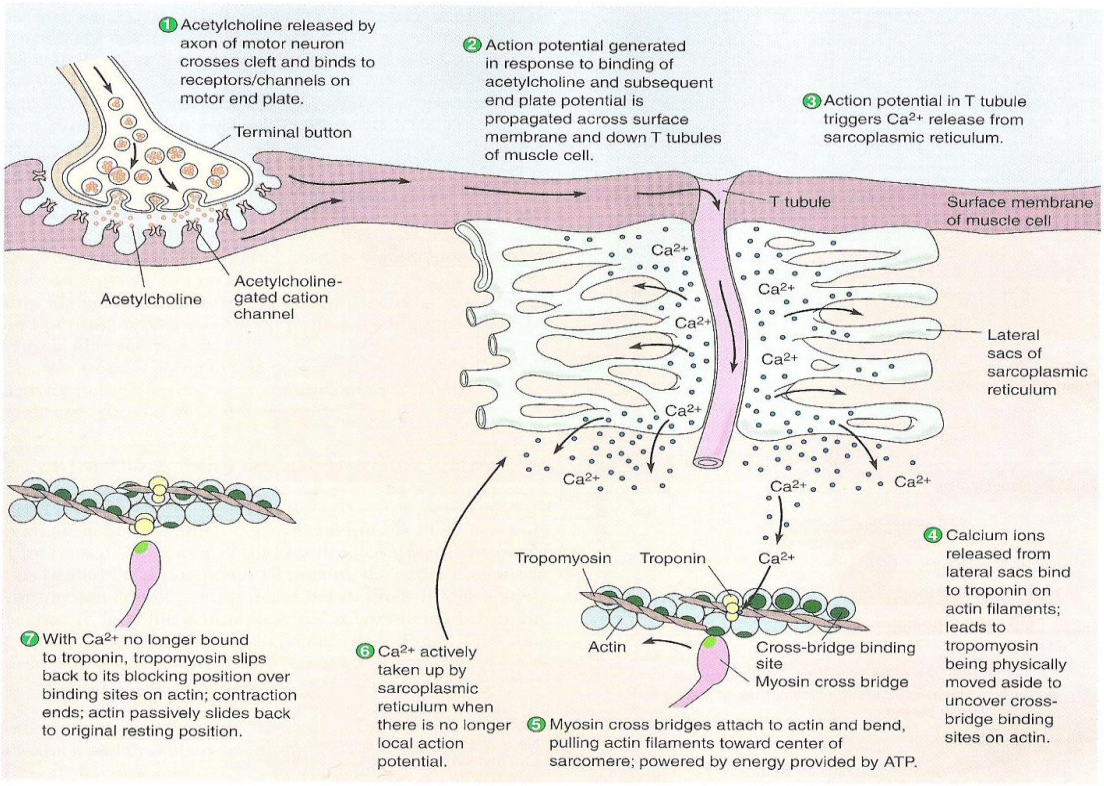


FIGURE 8-10

Calcium release in excitation–contraction coupling. Steps 1 through 5 show the events that couple neurotransmitter release and subsequent electrical excitation of the muscle cell with muscle contraction. Steps 6 and 7 show events associated with muscle relaxation.

Through these open Ca^{2+} -release channels, calcium is released into the cytosol from the lateral sacs. By slightly repositioning the troponin and tropomyosin molecules, this released Ca^{2+} exposes the binding sites on the actin molecules so they can link with the myosin cross bridges at their complementary binding sites (Figure 8-10) .

ATP-POWERED CROSS-BRIDGE CYCLING

Recall that a myosin cross bridge has two special sites, an actin-binding site and an ATPase site. The latter is an enzymatic site that can bind the energy carrier *adenosine triphosphate (ATP)* and split it into *adenosine diphosphate (ADP)* and *inorganic phosphate (Pi),* yielding energy in the process. The breakdown of ATP occurs on the myosin cross bridge before the bridge ever links with an actin molecule (step 1 in Figure 8-11). The ADP and Pi remain tightly bound to the myosin, and the generated energy is stored within the cross bridge to produce a high-energy form of myosin. When the muscle fiber is excited, Ca^{2+} pulls the troponin-tropomyosin complex out of its blocking position so that the energized myosin cross bridge can bind with an actin molecule (step 2a). This contact between myosin and actin causing the cross-bridge bending that produces the power stroke (step 3).

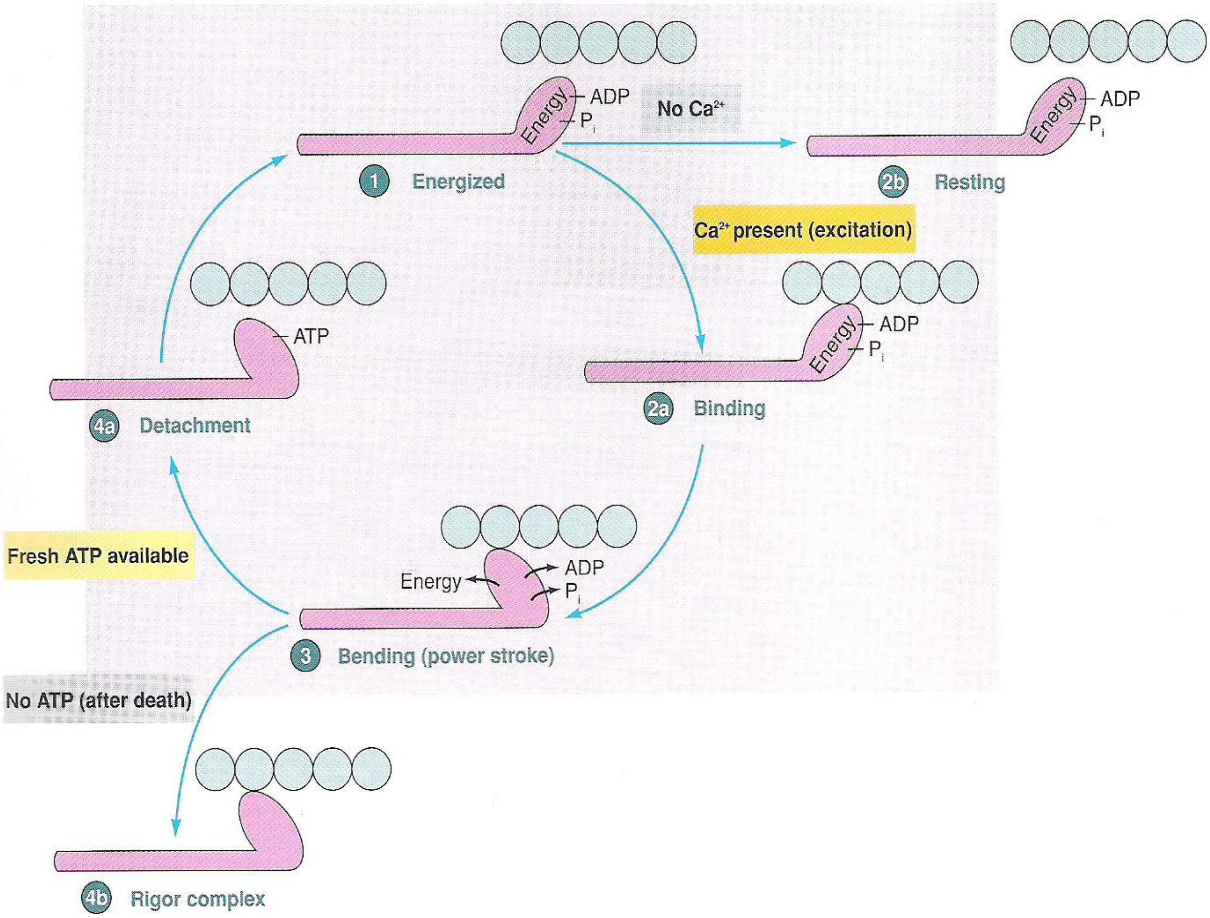
When the muscle is not excited and Ca^{2+} is not released, troponin and tropomyosin remain in their blocking position, so that actin and the myosin cross bridges do not bind and no power stroking takes place (step 2b). Attachment of the new ATP molecule permits detachment of the cross bridge, which returns to its unbent form, ready to start another cycle (step 4a). The newly attached ATP is then split by myosin ATPase, energizing the myosin cross bridge once again (step 1).

RIGOR MORTIS

Note that fresh ATP must attach to myosin to permit the crossbridge link between myosin and actin to break at the end of a cycle, even though the ATP is not split during this dissociation process. The need for ATP in separating myosin and actin is amply shown in **rigor mortis**. This "stiffness of death" is a generalized locking in place of the skeletal musc1es that begins 3 to 4 hours after death and completes in about 12 hours. Dead cells cannot produce any more ATP, so actin and myosin, once bound, cannot detach, because they lack fresh ATP. The thick and thin filaments thus stay linked together by the immobilized cross bridges, leaving dead muscles stiff (step 4b).

RELAXATION

The contractile process is turned off when Ca^{2+} is returned to the lateral sacs when local electrical activity stops. The sarcoplasmic reticulum has a Ca^{2+} -ATPase pump, which actively transports Ca^{2+} from the cytosol and concentrates it in the lateral sacs. When acetylcholinesterase removes acetylcholine from the neuromuscular junction, the muscle-fiber action potential stops. When a local action potential is no longer in the T tubules to trigger release of Ca^{2+}, the ongoing activity of the sarcoplasmic reticulum's Ca^{2+} pump returns released Ca^{2+} back into its lateral sacs. Removing cytosolic Ca^{2+} lets the troponin--tropomyosin complex slip back into its blocking position, so actin and myosin can no longer bind at the cross bridges. The thin filaments return passively to their resting position. The muscle fiber has relaxed.



1 ATP split by myosin ATPase; ADP and P_i remain attached to myosin; energy stored in cross bridge.

...or...

2b No excitation; no Ca^{2+} released; actin and myosin prevented from binding; no cross-bridge cycle; muscle fiber remains at rest.

2a Ca^{2+} released on excitation; removes inhibitory influence from actin, enabling it to bind with cross bridge.

3 Power stroke of cross bridge triggered on contact between myosin and actin; P_i released during and ADP released after power stroke.

...or...

4b If no fresh ATP available (after death), actin and myosin remain bound in rigor complex.

4a Linkage between actin and myosin broken as fresh molecule of ATP binds to myosin cross bridge; cross bridge assumes original conformation; ATP hydrolyzed (cycle starts again at step 1).

FIGURE 8-11

Cross-bridge cycle

SKELETAL MUSCLE MECHANICS

Whole muscles are groups of muscle fibers bundled together and attached to bones. Each muscle is sheathed by connective tissue that penetrates from the surface into the muscle to envelop each individual fiber and divide the muscle into columns or bundles. The connective tissue extends beyond the ends of the muscle to form tough, collagenous tendons that attach the muscle to bones.

Contractions of a whole muscle can be of varying strength: A single action potential in a muscle fiber produces a brief, weak contraction called a twitch, which is too short and too weak to be useful and normally does not take place in the body. Muscle fibers are arranged into whole muscles, where they function cooperatively to produce contractions of variable grades of strength stronger than a twitch. In other words, the force exerted by the same muscle can be made to vary, depending on whether the person is picking up a piece of paper, a book, or a 50-Kg weight. Two primary factors can be adjusted to accomplish gradation of whole-muscle tension: (1) *the Number of muscle fibers contracting within a muscle* and (2) *the tension developed by each contracting fiber*.

The number of fibers contracting within a muscle depends on the extent of motor unit recruitment: Each whole muscle is innervated by a number of different motor neurons. When a motor neuron enters a muscle, it branches, with each axon terminal supplying a single muscle fiber (Figure 8-13). One motor neuron innervates a number of muscle fibers, but each muscle fiber is supplied by only one motor neuron. When a motor neuron is activated, all the muscle fibers it supplies are stimulated to contract simultaneously. This team of concurrently activated components one motor neuron plus all the muscle fibers it innervates-is called a **motor unit**. The muscle fibers that compose a motor unit are dispersed throughout the whole muscle; thus their simultaneous contraction results in an evenly distributed, although weak, contraction of the whole muscle. Each muscle consists of a number of motor units. For a weak contraction of the whole muscle, only one or a few of its motor units are activated. For stronger and stronger contractions, more and more motor units are recruited, or stimulated to contract, a phenomenon known as **motor unit recruitment**.

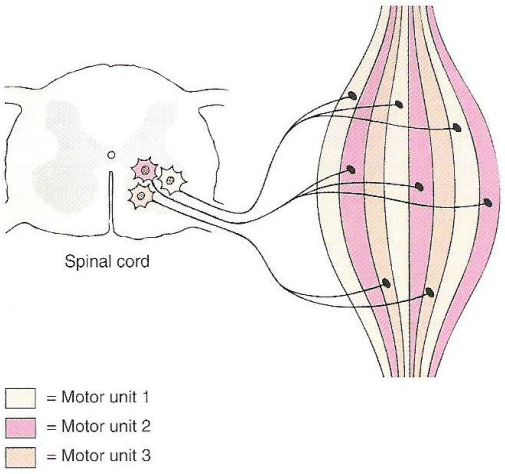
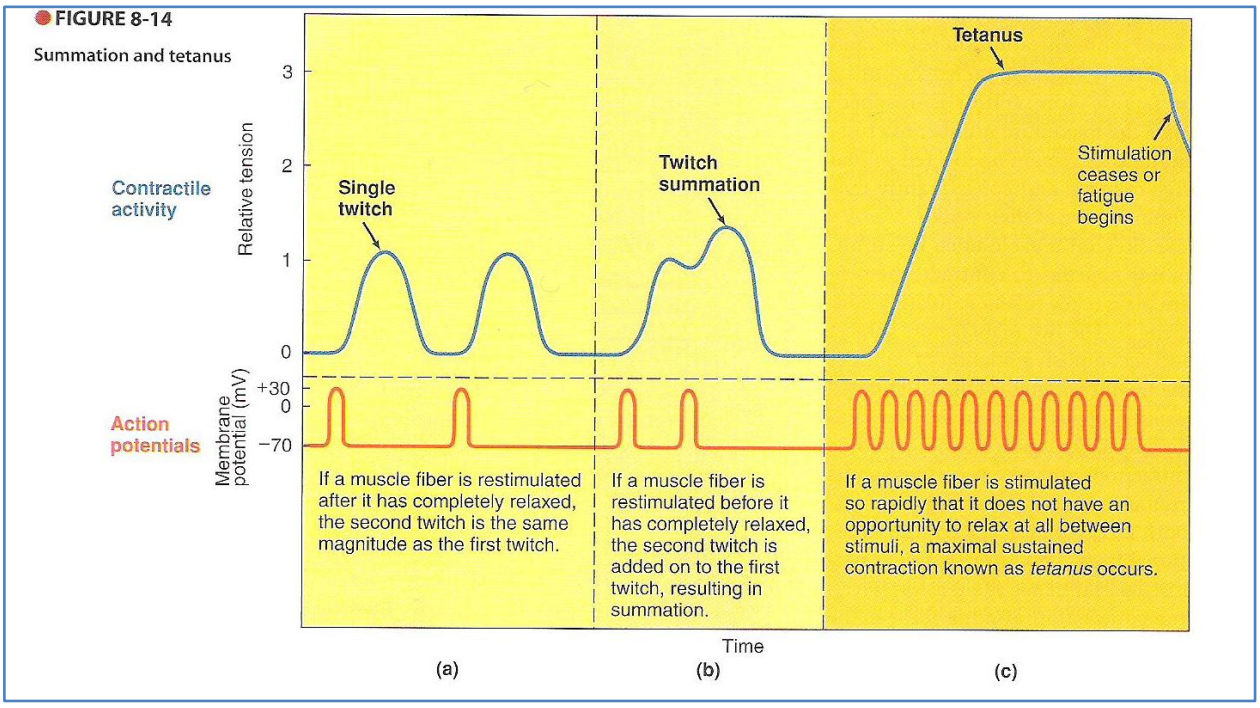


FIGURE 8-13
Schematic representation of motor units in a skeletal muscle

The frequency of stimulation can influence the tension developed by each muscle fiber: If the muscle fiber has completely relaxed before the next action potential takes place, a second twitch of the same magnitude as the first occurs (Figure 8-14a). The same excitation-contraction events take place each time, resulting in identical twitch responses. If, however, the muscle fiber is stimulated a second time before it has completely relaxed from the first twitch, a second action potential causes a second contractile response (Figure

8-14b). The two twitches from the two action potentials add together, or sum, to produce greater tension in the fiber than that produced by a single action potential. Twitch summation is possible only because the duration of the action potential (1 to 2 msec) is much shorter than the duration of the resulting twitch (100 msec). If the muscle fiber is stimulated so rapidly that it does not have a chance to relax at all between stimuli, a smooth, sustained contraction of maximal strength known as tetanus occurs (Figure 8-14c). A tetanic contraction is usually three to four times stronger than a single twitch. (Don't confuse this normal physiologic tetanus with the disease tetanus.



SKELETAL MUSCLE METABOLISM AND FIBER TYPES

Three different steps in the contraction-relaxation process require ATP:

1. Splitting of ATP by myosin ATPase provides the energy for the power stroke of the cross bridge.
2. Binding (but not splitting) of a fresh molecule of ATP to myosin lets the bridge detach from the actin filament at the end of a power stroke so that the cycle can be repeated. This ATP is later split to provide energy for the next stroke of the cross bridge.
3. The active transport of Ca^{2+} back into the sarcoplasmic reticulum during relaxation depends on energy derived from the breakdown of ATP.

Muscle fibers have alternate pathways for forming ATP: Because ATP is the only energy source that can be directly used for these activities, for contractile activity to continue ATP must constantly be supplied. Only limited stores of ATP are immediately available in muscle tissue, but three pathways supply additional ATP as needed during muscle contraction: **(I)** transfer of a high-energy phosphate from creatine phosphate to ADP, (2) oxidative phosphorylation (the

citric acid cycle and electron transport system), and (3) glycolysis.

CREATINE PHOSPHATE

Creatine phosphate stores typically power the first minute or less of exercise.

OXIDATIVE PHOSPHORYLATION

Oxidative phosphorylation takes place within the muscle mitochondria if enough O_2 is present. Although it provides a rich yield of 36 ATP molecules for each glucose molecule processed, oxidative phosphorylation is relatively slow because of the number of steps involved. To sustain ongoing oxidative phosphorylation, the exercising muscles depend on delivery of adequate O_2 and nutrients to maintain their activity. Activity that can be supported in this way is aerobic ("with O_2") or endurance-type exercise.

GLYCOLYSIS

There are respiratory and cardiovascular limits to how much O_2 can be delivered to a muscle. That is, the lungs and heart can pick up and deliver just so much O_2 to exercising muscles. Furthermore, in near-maximal contractions, the powerful contraction compresses almost closed the blood vessels that course through the muscle, severely limiting the O_2 available to the muscle fibers. Even when O_2 is available, the relatively slow oxidative-phosphorylation system may not be able to produce ATP rapidly enough to meet the muscle's needs during intense activity.

When O_2 delivery or oxidative phosphorylation cannot keep pace with the demand for ATP formation as the intensity of exercise increases, the muscle fibers rely increasingly on glycolysis to generate ATP. The chemical reactions of glycolysis yield products for ultimate entry into the oxidative phosphorylation pathway, but glycolysis can also proceed alone in the absence of further processing of its products by oxidative phosphorylation. During glycolysis, a glucose molecule is broken down into two pyruvic acid molecules, yielding two ATP molecules in the process. Pyruvic acid can be further degraded by oxidative phosphorylation to extract more energy. However, glycolysis alone has two advantages over the oxidative phosphorylation pathway: (I) glycolysis can form ATP in the absence of O_2 (operating *anaerobically,* that is, ("without O_2"), and (2) it can proceed more rapidly than oxidative phosphorylation. Although glycolysis extracts considerably fewer ATP molecules from each nutrient molecule processed, it can proceed 50 much more rapidly that it can outproduce oxidative phosphorylation over a given period of time if enough glucose is present. Activity that can be supported in this way is anaerobic or high-intensity exercise.

There are three types of skeletal muscle fibers, based on differences in ATP hydrolysis and synthesis. Classified by their biochemical capacities, there are three major types of muscle fibers:

1. Slow-oxidative (type I) fibers
2. Fast-oxidative (type IIa) fibers
3. Fast-glycolytic (type IIb) fibers

As their names imply, the two main differences among these fiber types are their speed of contraction (slow or fast) and the type of enzymatic machinery they primarily use for ATP formation (oxidative or glycolytic).

FAST VERSUS SLOW FIBERS

Fast fibers have higher myosin ATPase (ATP-splitting) activity than do slow fibers. The higher the ATPase activity, the more rapidly ATP is split and the faster the rate at which energy is made available for cross-bridge cycling. The result is a fast twitch, compared to the slower twitches or those fibers that split ATP more slowly. Thus two factors determine the speed with which a muscle contracts: the load and the myosin ATPase activity of the contracting fibers.

OXIDATIVE VERSUS GLYCOLYTIC FIBERS

Fiber types also differ in ATP-synthesizing ability. Those with a greater capacity to form ATP are more resistant to fatigue. Some fibers are better equipped for oxidative phosphorylation, whereas others rely primarily on anaerobic glycolysis for synthesizing ATP. Because oxidative phosphorylation yields considerably more ATP from each nutrient molecule processed, it does not readily deplete energy stores. Furthermore, it does not result in lactic acid accumulation. Oxidative types of muscle fibers are therefore more resistant to fatigue than glycolytic fibers are.

GENETICS OF MUSCLE FIBER TYPES

In humans, most muscles contain a mixture of all three fiber types; the percentage of each type is largely determined by the type of activity for which the muscle is specialized. Accordingly, a high proportion of slow-oxidative fibers are found in muscles specialized for maintaining low-intensity contractions for long periods of time without fatigue, such as the muscles of the back and legs that support the body's weight against the force of gravity. A prevalence of fast-glycolytic fibers are found in the arm muscles, which are adapted for performing rapid, forceful movements such as lifting heavy objects. The percentage of these various fibers not only differs between muscles within an individual but also varies considerably among individuals. Muscle fibers adapt considerably in response to the demands placed on them.

Different types of exercise produce different patterns or neuronal discharge to the muscle involved. Depending on the pattern of neural activity, long-term adaptive changes occur in the muscle fibers, enabling them to respond most efficiently to the types of demands placed on the muscle. Two types of changes can be induced in muscle fibers: changes in their ATP-synthesizing capacity and changes in their diameter.

IMPROVEMENT IN OXIDATIVE CAPACITY

Regular aerobic endurance exercise, such as long-distance jogging or swimming, induces metabolic changes within the oxidative fibers, which are the ones primarily recruited during aerobic exercise. These changes enable the muscles to use O_2 more efficiently. For example, mitochondria increase in number in the oxidative fibers. Muscles so adapted can better endure prolonged activity without fatiguing, but they do not change in size.

MUSCLE HYPERTROPHY

The actual size of the muscles can be increased by regular anaerobic, short-duration, high-intensity resistance training, such as "weight lifting". The resulting muscle enlargement comes primarily from an increase in diameter (**hypertrophy**) of the fast-glycolytic fibers that are called into play during such powerful contractions. Most of the fiber thickening results from increased synthesis of myosin and actin filaments, which permits a greater opportunity for cross-bridge interaction and consequently increases the muscle's contractile strength.

INFLUENCE OF TESTOSTERONE

Men's muscle fibers are thicker, and accordingly, their muscles are larger and stronger than those of women, even without weight training, because of the actions of testosterone. Testosterone promotes the synthesis and assembly of myosin and actin.

SMOOTH AND CARDIAC MUSCLE

The two other types of muscle-smooth muscle and cardiac muscle-share some basic properties with skeletal muscle, but each also displays unique characteristics. The three muscle types all have a specialized contractile apparatus made up or thin actin filaments that slide relative to stationary thick myosin filaments in response to a rise in cytosolic Ca^{2+} to accomplish contraction. Also, they all directly use ATP as the energy source for cross-bridge cycling. However, the structure and organization of fibers within these different muscle types vary, as do their mechanisms of excitation and the means by which excitation and contraction are coupled.

Smooth muscle cells are small and unstriated: Most smooth muscle cells are found in the walls of hollow organs and tubes. Their contraction exerts pressure on and regulates the forward movement of the contents of these structures. Both smooth and skeletal muscle cells are elongated, but in contrast to their large, cylindrical skeletal-muscle counterparts, smooth muscle cells are spindle shaped and much smaller. Also unlike skeletal muscle cells, a single smooth-muscle cell does not extend the full length of a muscle. Instead, groups of smooth-muscle cells are typically arranged in sheets.

A smooth muscle cell has three types of filaments: (1) thick myosin filaments, which are longer than those in skeletal muscle; (2) thin actin filaments, which contain tropomyosin but lack the regulatory protein troponin; and (3) filaments of intermediate size, which do not directly participate in contraction but are part of the cytoskeletal framework that supports the cell shape. Smooth muscle filaments do not form myofibrils and are not arranged in the sarcomere pattern found in skeletal muscle. Thus smooth muscle cells do not show the banding or striation of skeletal muscle, hence the term *smooth* for this muscle type. Lacking sarcomeres, smooth muscle does not have Z lines as such but has dense bodies containing the same protein constituent found in Z lines. The actin filaments are anchored to the dense bodies. The thick- and thin-filament contractile units are oriented slightly diagonally from side to side within the smooth muscle cell in an elongated, diamond-shaped lattice, rather than running parallel with the long axis as myofibrils do in skeletal muscle (Figure 8-22a).

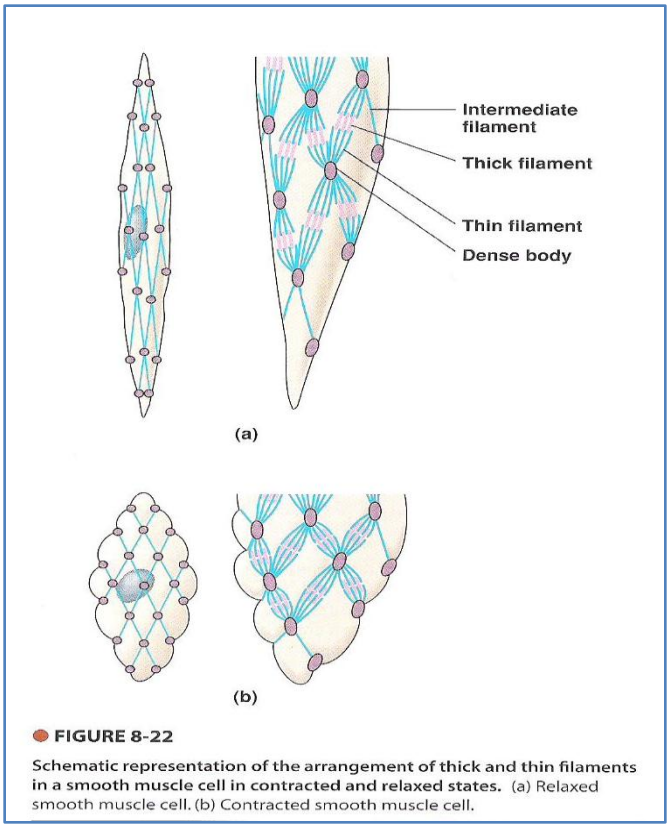


FIGURE 8-22

Schematic representation of the arrangement of thick and thin filaments in a smooth muscle cell in contracted and relaxed states. (a) Relaxed smooth muscle cell. (b) Contracted smooth muscle cell.

Smooth muscle cells are turned on by Ca^{2+} -dependent phosphorylation of myosin: The thin filaments of smooth muscle cells do not contain troponin, and tropomyosin does not block actin's cross-bridge binding sites. Then what prevents actin and myosin from binding at the cross bridges in the resting state, and how is cross-bridge activity switched on in the excited state? Smooth muscle myosin can interact with actin only when the myosin is *phosphorylated* (that is, has a phosphate group attached to it). During excitation, the increased cytosolic Ca^{2+} acts as an intracellular messenger, initiating a chain of biochemical events that results in phosphorylation of myosin. Phosphorylated myosin then binds with actin so that cross-bridge cycling can begin.

The increased cytosolic Ca^{2+} that triggers the contractile response comes from two sources. Most Ca^{2+} enters down its concentration gradient from the ECF on opening of surface-membrane Ca^{2+} channels. The entering Ca^{2+} triggers the opening of Ca^{2+} channels in the sarcoplasmic reticulum. Relaxation is accomplished by removal of Ca^{2+} as it is actively transported out across the plasma membrane and back into the sarcoplasmic reticulum. When Ca^{2+} is removed, myosin is dephosphorylated (the phosphate is removed) and can no longer interact with actin, so the muscle relaxes.

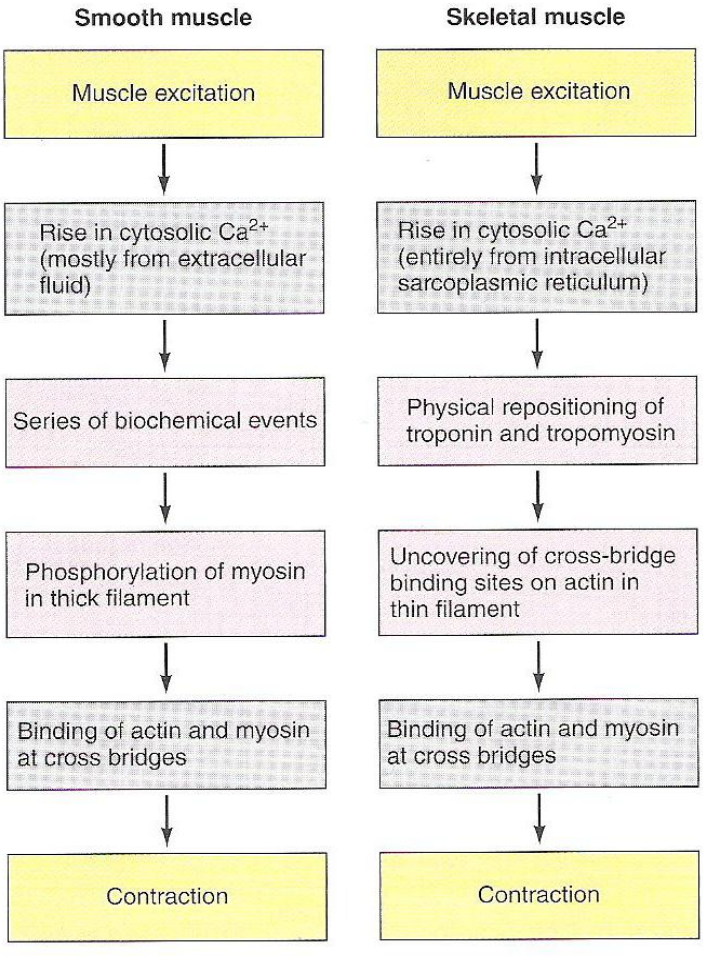


FIGURE 8-23

Comparison of the role of calcium in bringing about contraction in smooth muscle and skeletal muscle

Multiunit smooth muscle is neurogenic: a **multiunit smooth muscle** consists of multiple discrete units that function independently of each other and must be separately stimulated by nerves to contract, similar to skeletal-muscle motor units. Thus contractile activity in both skeletal muscle and multiunit

smooth muscle is neurogenic ("nerve produced"). That is, contraction in these muscle types is initiated only in response to stimulation by the nerves supplying the muscle. Whereas skeletal muscle is innervated by the voluntary somatic nervous system (motor neurons), multiunit (as well as single-unit) smooth muscle is supplied by the involuntary autonomic nervous system. Multiunit smooth muscle is found (1) in the walls of large blood vessels; (2) in large airways to the lungs; (3) in the muscle of the eye that adjusts the lens for near or far vision; (4) in the iris of the eye, which alters the pupil size to adjust the amount of light entering the eye; and (5) at the base of hair follicles, contraction of which causes "goose bumps."

Single-unit smooth muscle cells form functional syncytia: Most smooth muscle is **single-unit smooth muscle**, alternately called **visceral smooth muscle**, because it is found in the walls of the hollow organs or viscera (for example, the digestive, reproductive, and urinary tracts and small blood vessels). The term "single-unit smooth muscle" derives from the fact that the muscle fibers that make up this type of muscle become excited and contract as a single unit. The muscle fibers in single-unit smooth muscle are electrically linked by gap junctions. When an action potential occurs anywhere within a sheet of single-unit smooth muscle, it is quickly propagated via these special points of electrical contact throughout the entire group of interconnected cells, which then contract as a single, coordinated unit. Such a group of interconnected muscle cells that function as a unit is known as a **functional syncytium** (plural, *syncytia; syn* means "together"; *cyt* means "cell"). Muscle cells of the uterine wall act as a functional syncytium.

Single-unit smooth muscle is myogenic: Single-unit smooth muscle is self-excitable rather than requiring nervous stimulation for contraction. Clusters of specialized smooth muscle cells within a functional syncytium display spontaneous electrical activity; that is, they can undergo action potentials without any external stimulation. their membrane potential inherently fluctuates without any influence by factors external to the cell. Two major types of spontaneous depolarizations displayed by self-excitable cells are *pacemaker potentials* and *slow-wave potentials.*

PACEMAKER POTENTIALS

With pacemaker potentials, the membrane potential gradually depolarizes on its own because of shifts in passive ionic fluxes accompanying automatic changes in channel permeability (Figure 8-24a). When the membrane has depolarized to threshold, an action potential is initiated. After repolarizing, the membrane potential once again depolarizes to threshold, cyclically continuing in this manner to repetitively self-generate action potentials.

MODIFICATION OF SMOOTH MUSCLE ACTIVITY BY THE AUTONOMIC NERVOUS SYSTEM

Smooth muscle is typically innervated by both branches of the autonomic nervous system. In single-unit smooth muscle, this nerve supply does not *initiate* contraction, but it can *modify* the rate and strength of contraction, either enhancing or retarding the inherent contractile activity of a given organ.