SECTION V

Muscle Physiology

Section Editor: William O. Reece

27 Physiology of Skeletal Muscle

William O. Reece
Iowa State University, Ames, IA, USA

The most visible aspect of muscle function is that which is related to locomotion. Animals are able to stand and lie down, graze in pastures, run when threatened, or compete at racetracks. Other functions not so visible, but necessary for overall body function, include muscles for respiration, digestion, parturition, blood and lymph circulation, swallowing, and generation of body heat.

Overview of muscle physiology

1 What is the difference between the origin and the insertion of a skeletal muscle?
2 What is the difference between a flexor and an extensor skeletal muscle?
3 What is the difference between an adductor and an abductor skeletal muscle?

Muscle is a contractile tissue and accomplishes diverse functions by shortening and pulling on other structures. In addition to shortening, muscle has other properties that include **excitability**, the capacity to receive and respond to a stimulus, **extensibility**, the ability to be stretched, and **elasticity**, the ability to return to original shape after being stretched. There are three types of muscle fibers in the animal body: skeletal, smooth, and cardiac. Each is characterized not only by microscopic structural differences but also by their location, function, and innervation.

Arrangement and location

A primary consideration in determining what muscles accomplish is their fiber arrangement. Accordingly, the muscle fibers might be arranged in sheets, sheets rolled into tubes, bundles, rings (sphincters), or cones, or they might remain as discrete fibers or clusters for more precise or less forceful action. The emptying of visceral structures (e.g., urinary bladder, stomach, heart) or conveyance of intestinal contents or organ secretions, as provided by smooth and cardiac muscle, is accomplished because of their intimate association with the affected part. Apart from the skeletal muscle sphincters, the effects of skeletal muscle may be noted at a point some distance from their location. This means that their contraction must be transmitted somehow to the affected part, whereby one end of the muscle must be relatively fixed or anchored and the other end must be attached directly or by a tendon to the moveable part. Accordingly, the anatomic description of a skeletal muscle sometimes refers to its **origin** and **muscle insertion**, the origin being the least moveable end and the insertion the most moveable end. Contraction of skeletal muscle brings the origin and the insertion closer together and, when attachments involve two bones, one or both of the bones will move.

Types of movement

Skeletal muscles are often described according to the type of movement performed and are strategically located to best serve the structure they affect. They are **flexors** if they are located

Dukes' Physiology of Domestic Animals, Thirteenth Edition. Edited by William O. Reece, Howard H. Erickson, Jesse P. Goff and Etsuro E. Uemura.

Companion website: www.wiley.com/go/reece/physiology

on the side of the limb toward which the joint bends when decreasing the joint angle. They are **extensors** if they are located on the side of the limb toward which the joint bends when increasing the joint angle. **Adductors** are muscles that pull a limb toward the median plane, and **abductors** pull a limb away from the median plane. **Sphincters** are arranged circularly to constrict body openings. Lack of adduction occasionally occurs in the hindlimb of cows after parturition or calving. The adductor muscles are supplied by the obturator nerves (one to each leg), each of which passes through an opening (obturator foramen) in the birth canal. Injury of the nerves during the calving process can be followed by the inability to adduct one or both of the hindlegs and is identified as obturator paralysis.

Skeletal muscle

1 What is the explanation for the greater number of capillaries and mitochondria associated with red fibers?
2 Which fiber type is associated with sustained flight?
3 Which fiber type is associated with the pectoralis muscle of chickens and pheasants (rapid reaction, short duration)?

Fiber types

Individual skeletal muscles can be observed by gross anatomic inspection and by dissection and comprise the major portion of the muscle mass of the animal body. Skeletal muscle fibers can be classified into three types: (i) red or dark (type I; slow twitch); (ii) white or pale (type II; fast twitch); and (iii) intermediate with characteristics between those of red and white fibers (Figure 27.1). Most skeletal muscles are probably a mixture of these three types but in some animals the red, and in others the white, predominates. Multiple peripherally arranged nuclei are present in each fiber (Figure 27.2).

Red fibers

The crimson red pectoralis muscle (breast muscle) of pigeons contrasts sharply with the white color of the chicken pectoralis muscle. In birds, the amount of red pigmentation in the pectoralis muscle can be correlated directly with the ability to sustain flight. Geese, ducks, and pigeons are known for their sustained flight and have a predominance of red pectoralis muscle fibers. Red fibers are also known as **slow twitch fibers**. The reddish appearance is due to the large amounts of myoglobin, the transporter of oxygen. A large number of mitochondria and capillaries are present in red fibers (see Figure 27.1) and, coupled with the substantial amounts of

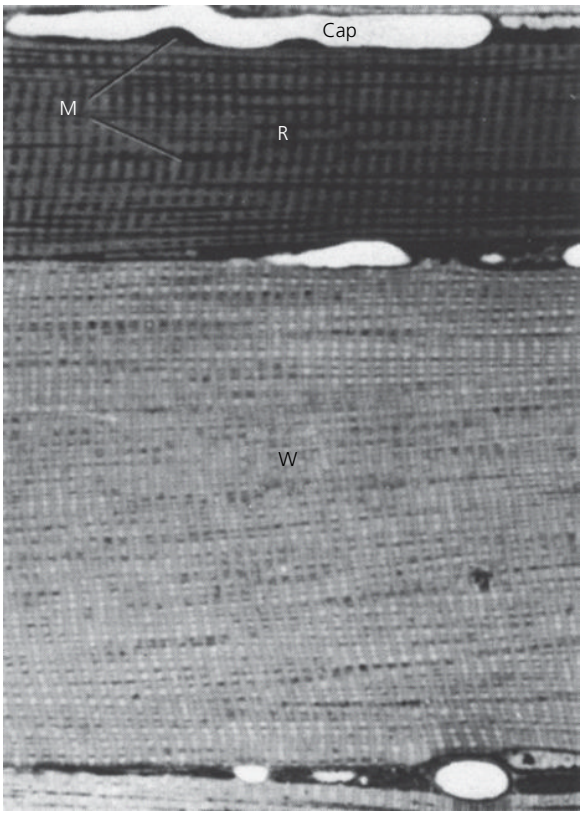

Figure 27.1 Photomicrograph of skeletal muscle showing red fibers (R) and white fibers (W). Red fibers have more mitochondria (M) packed between their myofibrils, especially in association with capillaries (cap). From Cormack, D.C. (1987) *Ham's Histology*, 9th edn. J.B. Lippincott, Philadelphia. With permission from Lippincott Williams & Wilkins.

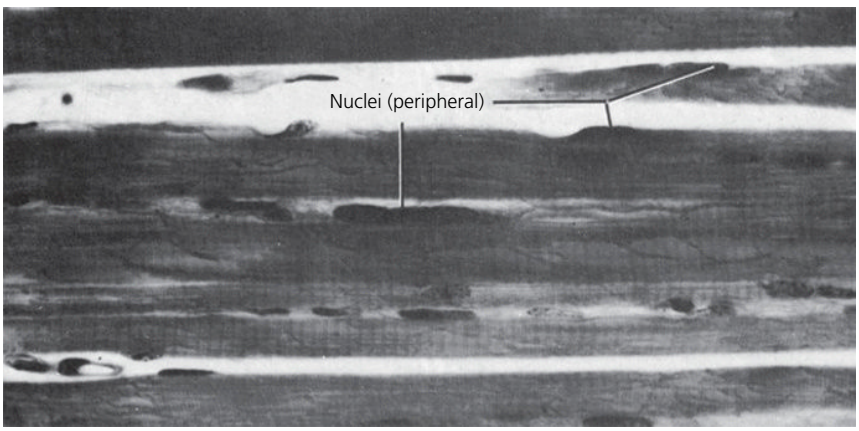

Figure 27.2 Photomicrograph of a longitudinal section of skeletal muscle fibers. Note the striations and the multiple peripherally located nuclei. From Cormack, D.C. (1987) *Ham's Histology*, 9th edn. J.B. Lippincott, Philadelphia. With permission from Lippincott Williams & Wilkins.

myoglobin, support the greater oxidative metabolism needed for sustained flight or other activities of this nature (e.g., horses in competition or sustained running to a destination).

White fibers

White fibers are also known as **fast twitch fibers** and are characteristic of the white pectoralis muscle of the chicken and pheasant. These are muscles that react rapidly and with short duration and consist of large fibers with great strength of contraction. They have an extensive sarcoplasmic reticulum for rapid release of energy via the glycolytic process. There is a less extensive blood supply and fewer mitochondria because oxidative metabolism is of secondary importance.

Skeletal muscle harnessing

1 What is the organization of the connective tissue components from within outward?
2 What is a muscle bundle?

Muscle tissue, in addition to muscle cells (muscle fibers), contains a connective tissue component that provides for harnessing. The whole muscle is wrapped in an outer connective tissue sheath known as the **epimysium**, and any given muscle is composed of muscle bundles, each containing a collection of muscle fibers (Figure 27.3). Connective tissue extensions from the epimysium, known as the **perimysium**, surround the muscle bundles. Extensions from the perimysium, known as the **endomysium**, surround each of the muscle fibers and are attached to the **sarcolemma** (muscle fiber membrane). The muscle fiber is the contractile unit that shortens, and the pull that it exerts is transmitted by endomysium, perimysium, and epimysium to the tendon or aponeurosis that is attached to a bone, thereby causing its movement.

Some muscles seem to arise directly from a bone, and their attachment could be considered a fleshy **attachment**. These muscle fibers, however, do have a short tendinous attachment to the periosteum of the bone.

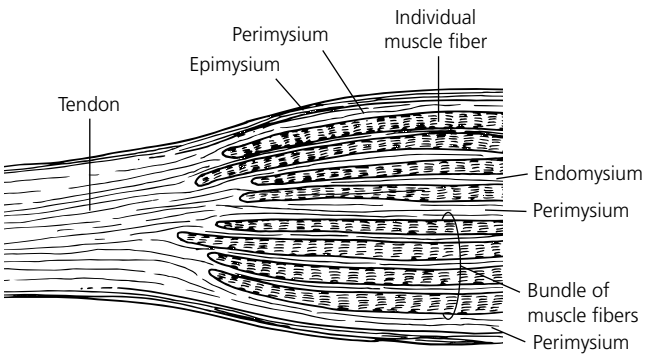

Figure 27.3 Longitudinal section of a muscle. The connective tissue elements of muscle are continuous with a tendon. Adapted from Ham, A.W. (1974) *Histology*, 7th edn. J.B. Lippincott, Philadelphia. Reproduced with permission from Lippincott Williams & Wilkins.

Microstructure of skeletal muscle

1 What is a muscle fiber?
2 Are the sarcomeres of a myofibril in alignment with the sarcomeres of all the myofibrils of the muscle fiber?
3 Which one of the myofilaments projects from the Z line into the sarcomere that it separates?
4 Which one of the myofilaments occupies the central location when viewing the spatial arrangement?
5 What is the ratio of actin to myosin?
6 Are the tubules of the sarcotubular system located within the myofibrils or outside the myofibrils?
7 How is the sarcoplasmic reticulum oriented relative to the T tubules?
8 Which one of the sarcotubular system tubules contains extracellular fluid?
9 Which one of the sarcotubular system components is a storage site for calcium ions?

Skeletal muscle cells are more commonly known as muscle fibers because of their elongated shape. Individual fibers generally range from 5 to 100 μm in diameter and 10 to 30 cm in length and may not extend the full length of a whole muscle. However, they may be attached end to end to form longer structures. Each has its own wrapping of endomysium that also contains an associated rich capillary network.

The division of muscles into smaller and smaller parts, ending in **myofibrils**, is shown in Figure 27.4. Depending on the diameter of the muscle fiber, there might be several hundred to several thousand myofibrils within one muscle fiber. Each myofibril has striations or banding. The further division of myofibrils into repetitive units (**sarcomeres**) and their components is shown in Figure 27.5. Sarcomeres contain protein **myofilaments** called **actin** and **myosin**, which by their arrangement give rise to striations (Figure 27.5B). Inasmuch as the striations are characteristic of the muscle fiber, it is apparent that the sarcomeres of a myofibril are in alignment with the sarcomeres of all the other myofibrils of the muscle fiber. The **Z line** is located at each end of a sarcomere and is common to both sarcomeres that it separates. Actin filaments project from the Z line into the sarcomeres that it separates (Figure 27.5B). Thus, each sarcomere has actin filaments projected toward its center from each end. The actin of two sarcomeres common to the same Z line compose an **I band**. The myosin filaments are centrally located within a sarcomere and, coupled with the overlay of actin filaments, provide the dark banding (**A band**) of the characteristic striations (Figure 27.6). The actin and myosin filaments have a regular spatial arrangement to each other, as shown in the cross-section of a myofibril (Figure 27.5C), which has a 2 : 1 ratio of actin to myosin. A longitudinal section of the spatially arranged

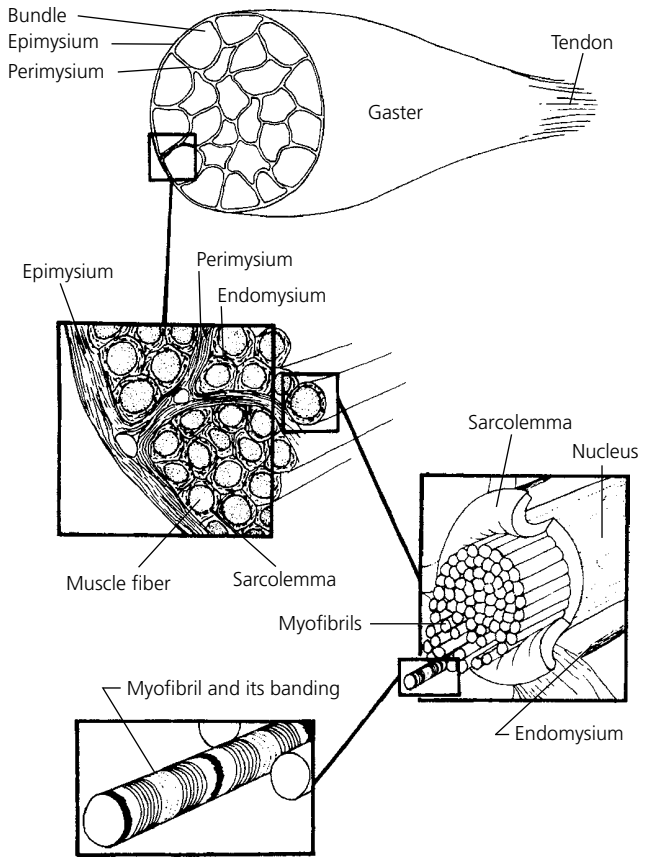

Figure 27.4 The division of muscles into smaller parts, ending in myofibrils. From Feduccia, A. and McCrady, E. (1991) *Torrey's Morphogenesis of the Vertebrates*, 5th edn. John Wiley & Sons, New York. Reproduced with permission from Wiley.

myofilaments shows cross-linkages extending from the myosin filaments toward the actin filaments (Figure 27.5D). During muscle-fiber shortening, the actin filaments appear to slide deeper into the myosin filaments.

Sarcotubular system

Skeletal muscle fibers contain a network of tubules known as the sarcotubular system. These tubules are located within the muscle fiber, but are outside the myofibrils. The sarcotubular system is composed of two separate tubule sets, with each set having a different arrangement among the myofibrils (Figure 27.7). The tubules arranged parallel to the myofibrils and which encircle them are known as the **sarcoplasmic reticulum**. The tubules arranged transversely (right angles) to the myofibrils are known as **T tubules**. T tubules extend transversely from one side of the fiber to the other. They open to the outside of the fiber (surface of the sarcolemma), and therefore their lumens contain extracellular fluid. The T-tubule openings are regularly spaced throughout the length of the muscle fiber because of their orientation to each sarcomere. Similarly, their openings are regularly spaced around the circumference of the fiber so that all myofibrils are intimately served by the sarcotubular system.

In reference to a sarcomere, the T tubules are located near the junction of the actin filaments with the myosin filaments. Therefore, each sarcomere is close to two T tubules (see Figure 27.7). The individual tubules (**sarcotubules**) of the sarcoplasmic reticulum are located regularly throughout the length of the muscle fiber between the T tubules, and they in turn contain intracellular fluid. The T tubules do not open into the sarcoplasmic reticulum; instead the bulbous ends of the

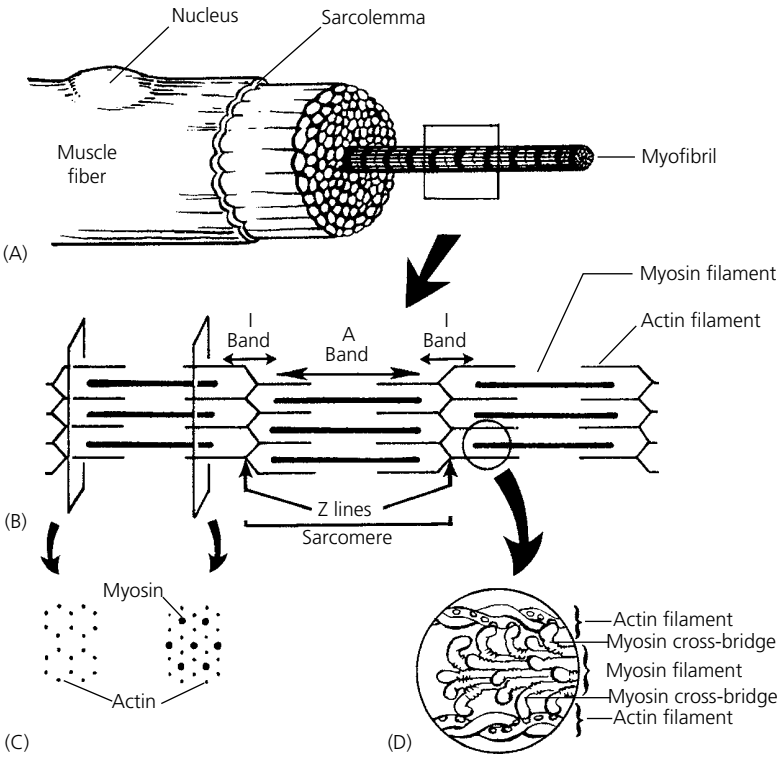

Figure 27.5 The division of myofibrils into sarcomeres. (A) Cross-section of a muscle fiber. (B) Longitudinal arrangement of myofilaments within sarcomeres. (C) Spatial arrangement of the myofilaments within a sarcomere. (D) Further details of the relationship between actin and myosin molecules. From Reece, W.O. (2009) *Functional Anatomy and Physiology of Domestic Animals*, 4th edn. Wiley-Blackwell, Ames, IA. Reproduced with permission from Wiley.

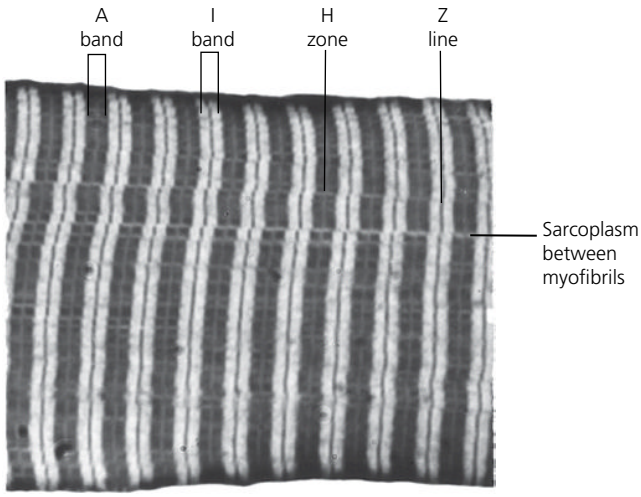

Figure 27.6 Photomicrograph of a longitudinal section of a skeletal muscle fiber showing the characteristic banding. From Cormack, D.C. (2001) *Essential Histology*, 2nd edn. Lippincott Williams & Wilkins, Baltimore. With permission from Lippincott Williams & Wilkins.

sarcoplasmic reticulum are closely associated with the T tubules (Figure 27.8). The point of closeness of a T tubule with the bulbous ends of two adjoining sarcoplasmic reticula is known as a **triad**. The principal function of the sarcotubular system is to provide a means for conduction of an impulse from the surface of the muscle fiber to its innermost aspects. The sarcoplasmic reticulum is an important storage site for calcium ions and has a prominent role in the initiation and termination of muscle contraction. It has an anastomosing channel-like structure that surrounds each myofibril (see Figure 27.7).

The neuromuscular junction

1. Where does the terminal branch of a motor neuron make contact with a skeletal muscle fiber?
2. What is the action of calcium ions when they enter the terminal bulb of an axon?
3. What is the neurotransmitter that is stored in the membrane-bound vesicles within the terminal branch of the axon?
4. What is the synaptic cleft?

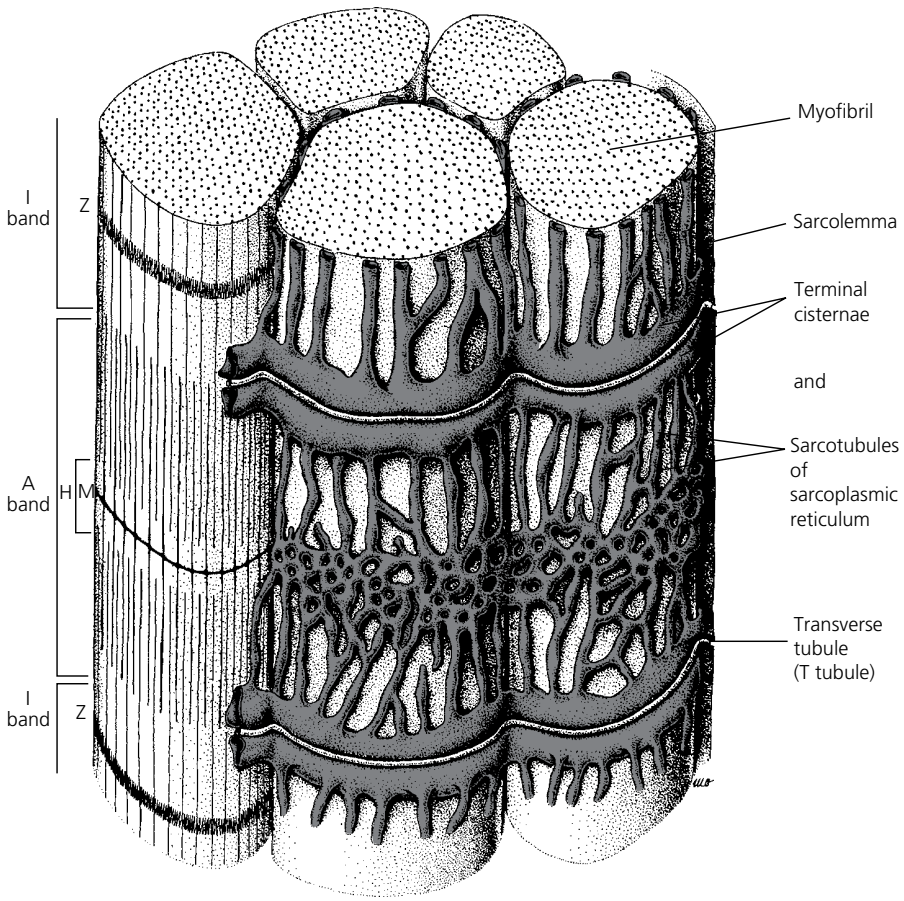

Figure 27.7 Diagram of part of a mammalian skeletal muscle fiber showing the sarcoplasmic reticulum that surrounds myofibrils. Two transverse (T) tubules supply a sarcomere and are in close association with the sarcoplasmic reticulum. The T tubules open to the surface of the sarcolemma. From Cormack, D.C. (2001) *Essential Histology*, 2nd edn. Lippincott Williams & Wilkins, Baltimore. With permission from Lippincott Williams & Wilkins.

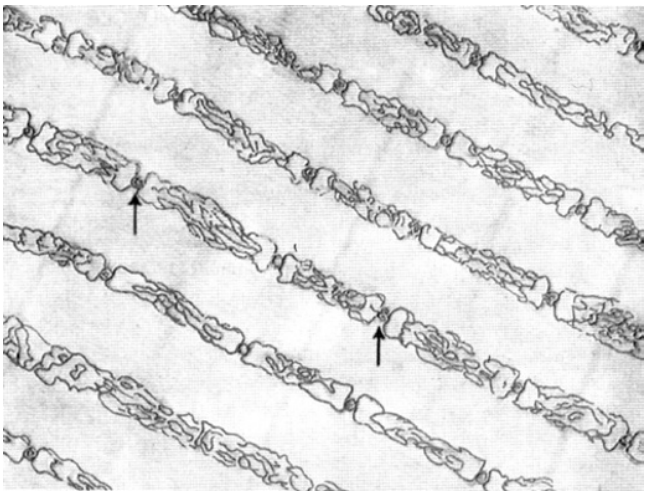

Figure 27.8 Sarcoplasmic reticulum in the extracellular spaces between the myofibrils, showing a longitudinal system paralleling the myofibrils. Also shown in cross-section are T tubules (arrows) that lead to the exterior of the fiber membrane and which are important for conducting the electrical signal into the center of the muscle fiber. From Fawcett, D.W. (1981) *The Cell*. W.B. Saunders, Philadelphia. With permission from Elsevier.

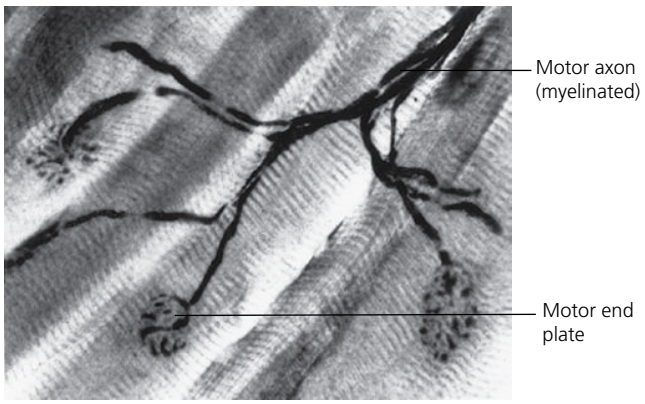

Figure 27.9 Photomicrograph showing the distribution of terminal branches from a nerve fiber to individual muscle fibers to compose a motor unit. A motor end plate is a small flattened mound on the muscle fiber surface formed by the axon terminal branch and its myelin covering. From Cormack, D.C. (2001) *Essential Histology*, 2nd edn. Lippincott Williams & Wilkins, Baltimore. With permission from Lippincott Williams & Wilkins.

A motor neuron can have a number of terminal branches, with each one ending on a separate muscle fiber (Figure 27.9). A **motor unit** consists of a motor neuron and the muscle fibers that it innervates. The largest motor units, in which one axon supplies many muscle fibers, are found in the limbs and postural muscles. The smallest motor units, in which one axon may supply only a few muscle fibers, are found in association with eye movements.

The end bulb of each terminal branch makes contact with an individual muscle fiber at a specialized area known as the **neuromuscular junction** (Figure 27.10) and occurs at the approximate midpoint of the muscle fiber. The terminal branch of the axon does not actually make contact with the muscle fiber

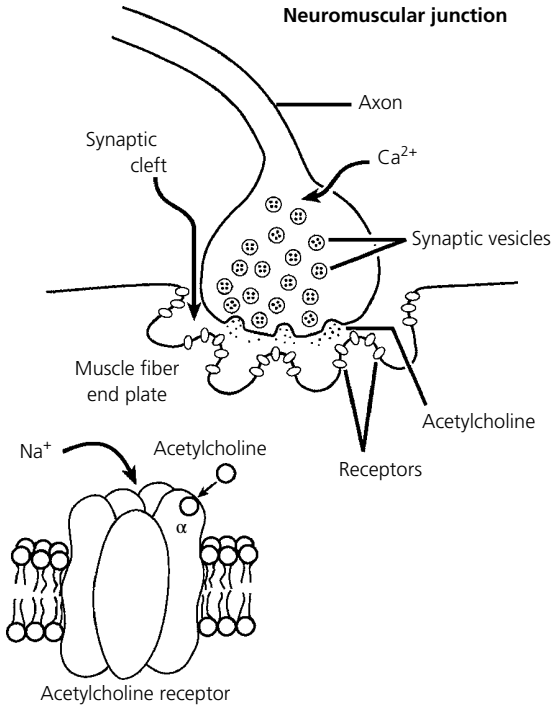

Figure 27.10 Schematic of the neuromuscular junction and the associated acetylcholine receptor channel. From Bailey, J.G. (2004) Muscle physiology. In: *Dukes' Physiology of Domestic Animals*, 12th edn (ed. W.O. Reece). Cornell University Press, Ithaca, NY. Reproduced with permission from Cornell University Press.

but is separated from it by a gap approximately 50 nm wide known as the **synaptic cleft**, a term derived from the word "synapse." A neurotransmitter, **acetylcholine (Ach)**, is stored in the membrane-bound vesicles within the terminal branch of the axon (see Figure 27.10). The neuromuscular junction functions as an amplifier for the spinal or cranial motor neuron action potential. Voltage-gated Ca^{2+} and Na^+ channels are opened when the action potential reaches the neuromuscular junction. An influx of calcium ions enters the terminal bulb of the axon, increasing the calcium ion concentration 10–100 times. Calcium ions trigger the binding of synaptic vesicles to the plasma membrane of the terminal bulb and the release of ACh into the synaptic cleft. ACh diffuses into invaginations of the muscle fiber sarcolemma located immediately below the synaptic cleft and is bound to ACh receptors at that site.

Depolarization of muscle fibers

1 What chemical begins depolarization of a muscle fiber and what is the direction of propagation from the neuromuscular junction?
2 Beginning with depolarization of the sarcolemma, what is the route of depolarization whereby it arrives at every sarcomere in the myofibril?
3 What enzyme hydrolyzes the neurotransmitter that initiated depolarization?
4 How does succinylcholine cause relaxation (prevents muscle contraction) of muscle?

Acetylcholine begins depolarization of muscle fibers by increasing the permeability of the sarcolemma for Na^+ ions, whereby the action potential is propagated by the opening and closing of Ca^{2+} and Na^+ channels and it proceeds in all directions from the neuromuscular junction, located centrally on the muscle fiber. The action potential is conducted into all parts of the muscle fiber beginning with the T tubules. The T tubules serve as communication links between the sarcolemma and the myofibrils within each muscle fiber. When a stimulus is received and depolarization of the sarcolemma begins, it continues in the T tubules and because of their close association with the sarcoplasmic reticulum, they also are depolarized and calcium ions (stored in the sarcoplasmic reticulum) are released into the cytosol of the muscle fiber, allowing contraction to begin. The signal which has caused depolarization has proceeded from the sarcolemma, into the T tubules, sarcoplasmic reticulum, myofibrils, and every sarcomere in the myofibril within milliseconds. Thus, all the myofibrils within a muscle fiber will contract at the same time and a more synchronized contraction results.

Almost immediately after its release, ACh is hydrolyzed by the enzyme **acetylcholinesterase (AChE)** into acetic acid and choline. The next action potential propagated to the muscle fiber must await a new action potential at the neuromuscular junction. AChE is present in large amounts in the synaptic cleft's small size and this, coupled with the limited diffusion distance of ACh in the synaptic cleft, accounts for the rapid hydrolysis of ACh.

Neuromuscular block

A low concentration of calcium in the extracellular fluid (hypocalcemia) is recognized clinically in dairy cows after calving (parturient paresis or milk fever) as a state of semiparalysis caused by partial neuromuscular block. This happens because fewer calcium ions are available to trigger the binding of synaptic vesicles to the axon end-bulb plasma membrane and release of ACh. Because ACh release begins depolarization of the sarcolemma, the lowered amount depresses the continuation of depolarization.

Hypocalcemia in the bitch may be recognized clinically after whelping as **eclampsia** or **puerperal tetany**. There appears to be a difference in function of the neuromuscular junction between the cow and the bitch, whereby it is blocked by hypocalcemia in cows leading to paresis, but not blocked in the bitch. In the bitch, there is a deficit of calcium ions, the voltage-gated Ca^{2+} and Na^+ channels become more permeable to sodium ions, and inward flow of sodium changes the membrane potential, thereby requiring a stimulus of lesser magnitude to depolarize. The nerve fiber becomes more excitable, discharging repetitively, rather than remaining in the resting state, causing tetanic muscle contractions.

Muscle relaxants

Induced relaxation of muscle is clinically useful for procedures requiring cessation of muscle contraction (e.g., surgical procedures, immobilization). **Muscle relaxants** commonly used for this purpose are **curare** and **succinylcholine**.

The active substance in curare, D-tubocurarine, blocks the effects of ACh by binding to ACh receptors. The conformational change of the ACh receptors that would have allowed opening of the Ca^{2+} and Na^+ channels and generation of postsynaptic action potentials are blocked, and skeletal muscle paralysis results. Curare has been used as a muscle relaxant for some surgical procedures. Another muscle relaxant that has been more useful clinically is succinylcholine. Because its structure is similar to ACh, it binds with ACh receptors but does not allow opening of the Ca^{2+} and Na^+ channels, and postsynaptic action potentials are blocked thereby preventing muscle contraction. Succinylcholine is not hydrolyzed by AChE but by nonspecific cholinesterases in plasma. The rate of hydrolysis is rather rapid although slow compared with hydrolysis by AChE. The amount of nonspecific cholinesterase varies among animal species, so that the length of induced relaxation will vary.

Skeletal muscle contraction

1. How is the natural attraction between actin and myosin inhibited during relaxation?
2. What are the three major components of the actin filament?
3. What causes the active sites on the actin and tropomyosin strands to be uncovered? How are calcium ions involved?
4. What "cocks" the myosin cross-bridge heads prior to their attachment to the active sites on actin?
5. What causes detachment of myosin cross-bridge heads from the actin myofilaments?
6. What provides for the rephosphorylation of ADP? Why is this referred to as oxidative phosphorylation?
7. What is the primary fuel for muscle contractions during prolonged endurance exercise?
8. What is the cause of physiologic contracture? Is this known as muscle cramping?
9. What is tetany?
10. What is the function of treppe?

Muscle activity involves repeated cycles of contraction and relaxation. Contraction, or shortening, occurs when calcium ions are released from the sarcoplasmic reticulum into the myofibrils. This is followed by relaxation after the calcium ions are rapidly returned by active transport to the sarcoplasmic reticulum. Another cycle begins when calcium ions are again released following the next depolarization of the sarcolemma. These cycles are referred to as **excitation–contraction coupling**.

Mechanical changes of actin and myosin

The contraction process involves an interaction between the actin and the myosin myofilaments. There is a natural attraction between actin and myosin for each other that involves active sites on the actin molecule. Attraction is inhibited during relaxation because the active sites are covered, but when calcium ions enter the myofibril the active sites are uncovered. The relative location of the actin and myosin myofilaments to each other

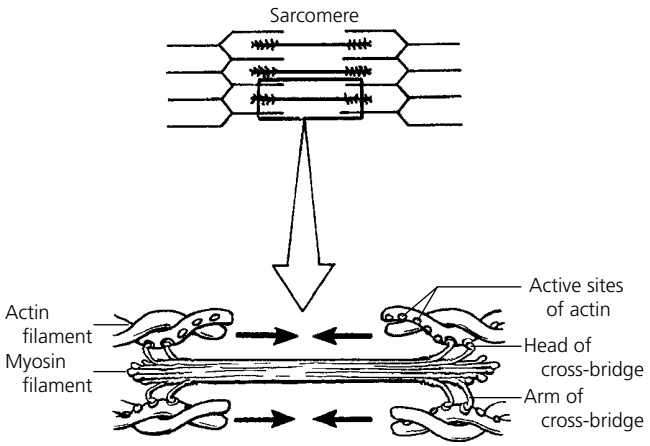

Figure 27.11 The components of the actin and myosin myofilaments associated with contraction of the sarcomere. Arrows indicate the direction of actin movement during contraction (shortening of myofibrils). From Reece, W.O. (2009) *Functional Anatomy and Physiology of Domestic Animals*, 4th edn. Wiley-Blackwell, Ames, IA. Reproduced with permission from Wiley.

within a sarcomere is shown in Figure 27.11. The projecting portions of the myosin molecules (**cross-bridges**) attach to the active sites during contraction and bend toward the center, causing the actin to slide toward the myosin molecule center.

The actin filament has three major components (all protein): **actin**, **tropomyosin**, and **troponin** (Figure 27.12A). Actin and tropomyosin are arranged in helical strands interwoven with each other. Troponin is located at regular intervals along the strands and contains three proteins, two of which bind actin and tropomyosin together and a third which has an affinity for calcium ions. Active sites (places where myosin cross-bridges attach) are located on the actin strands and are normally covered by the tropomyosin strands (Figure 27.12B). When calcium ions bind to the troponin complex, a conformational change occurs between the actin and tropomyosin strands that causes the active sites to be uncovered. The uncovered sites favor activation of the natural attraction that exists between actin and myosin and allows attachment of myosin cross-bridge heads (Figure 27.12C). The mechanics of contraction and relaxation are shown in Figure 27.13.

Energy changes

The energy changes that permit attachment and detachment of the myosin cross-bridge heads are synchronized with the mechanical changes of the actin molecule during contraction and relaxation. These are summarized as follows and illustrated in Figure 27.14.

1 **Adenosine triphosphatase (ATPase)** of the myosin cross-bridge heads hydrolyzes ATP to adenosine diphosphate (ADP) and inorganic phosphate (P_i), leaving the ADP and P_i bound to the heads. Energy from the hydrolysis of ATP "cocks" the heads so that they increase their angle of attachment to the cross-bridge arm and become perpendicular to the active sites of the actin myofilaments (Figure 27.14A).

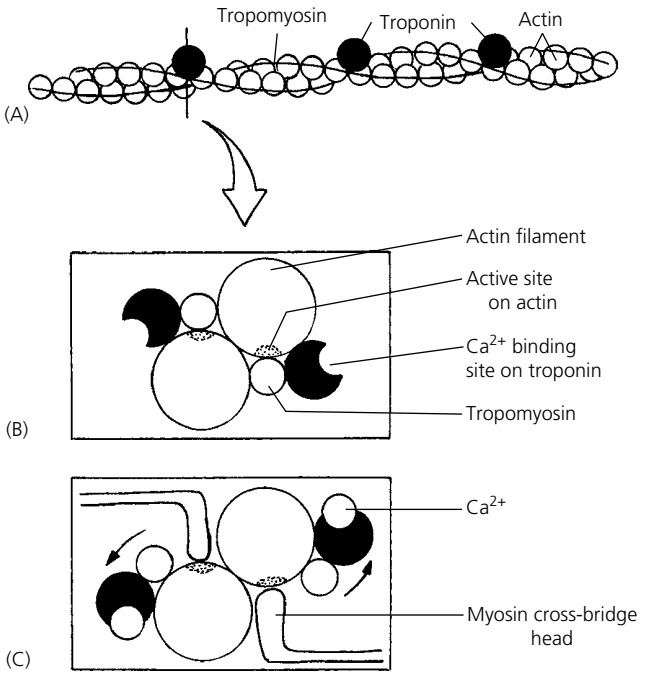

Figure 27.12 Conformational changes of the actin filament after calcium binding. (A) The actin filament with its three proteins, actin, troponin, and tropomyosin. The vertical line indicates the cross-section location for (B) and (C). (B) The active sites on actin are covered by tropomyosin. (C) Ca^{2+} binds to troponin, resulting in a conformational change that exposes the active sites on actin. Myosin cross-bridge heads attach to actin active sites, and myofibril contraction begins. From Reece, W.O. (2009) *Functional Anatomy and Physiology of Domestic Animals*, 4th edn. Wiley-Blackwell, Ames, IA. Reproduced with permission from Wiley.

2 After depolarization of the sarcotubular system, calcium ions diffuse from the sarcoplasmic reticulum into myofibrils and bind to the troponin complexes, whereby actin myofilaments are uncovered; calcium ions are returned rapidly to the sarcoplasmic reticulum once the shortening process begins (ATP is required for return). The natural attraction of myosin to actin is now permitted, and the "cocked" heads bind with active sites (Figure 27.14B).

3 Binding with actin causes conformational changes in the cross-bridge heads ("uncocking") and they bend (tilt) toward the cross-bridge arms (toward the center of the sarcomere), pulling actin with it. The energy is derived from previous ATP hydrolysis (Figure 27.14C).

4 Tilting of the cross-bridge heads causes release of ATP and P_i and sites on the heads are exposed for binding of new ATP. The binding of new ATP causes detachment of myosin cross-bridge heads from actin myofilaments (Figure 27.14D).

The ATPase of myosin cross-bridge heads then hydrolyzes ATP as before, cocking the heads; the process is repeated when the next neuromuscular transmission causes depolarization of the sarcotubular system. Repetition of the process causes the actin myofilaments to be pulled further into the center, thus shortening the sarcomere.

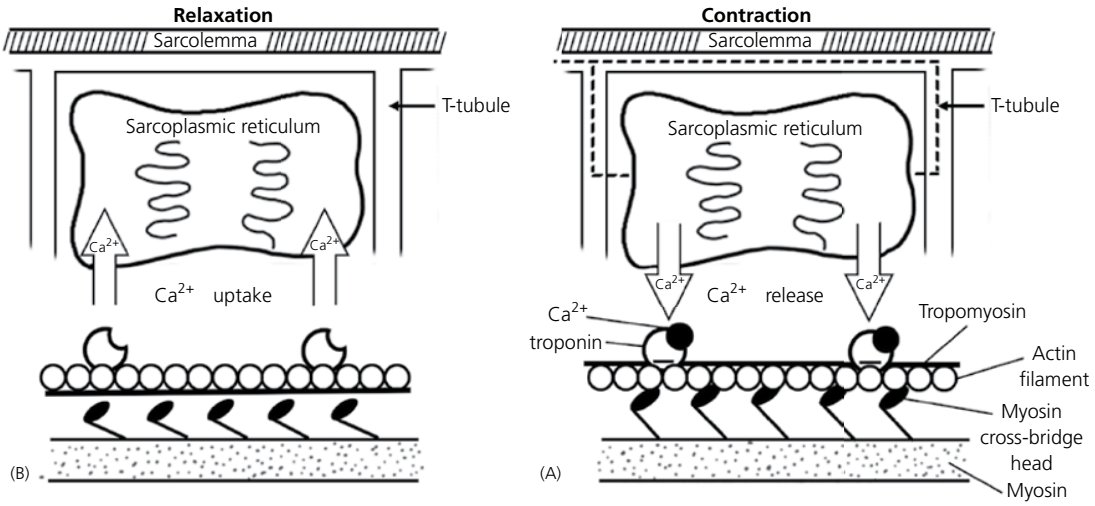

Figure 27.13 A cycle of contraction followed by relaxation. (A) The dashed line indicates transfer of depolarization from the sarcolemma and T tubules to the sarcoplasmic reticulum. Depolarization is followed by Ca^{2+} release from the sarcoplasmic reticulum with diffusion to the myofibrils. Ca^{2+} binds to troponin, removing blocking action of tropomyosin. Myosin cross-bridge heads attach to active sites on actin and bend toward center of myosin molecule. (B) ATP binds to myosin cross-bridge heads, causing their detachment from actin. Ca^{2+} is returned to the sarcoplasmic reticulum using energy supplied by ATP. Removal of Ca^{2+} from troponin restores blocking action of tropomyosin. From Reece, W.O. (2009) *Functional Anatomy and Physiology of Domestic Animals*, 4th edn. Wiley-Blackwell, Ames, IA. Reproduced with permission from Wiley.

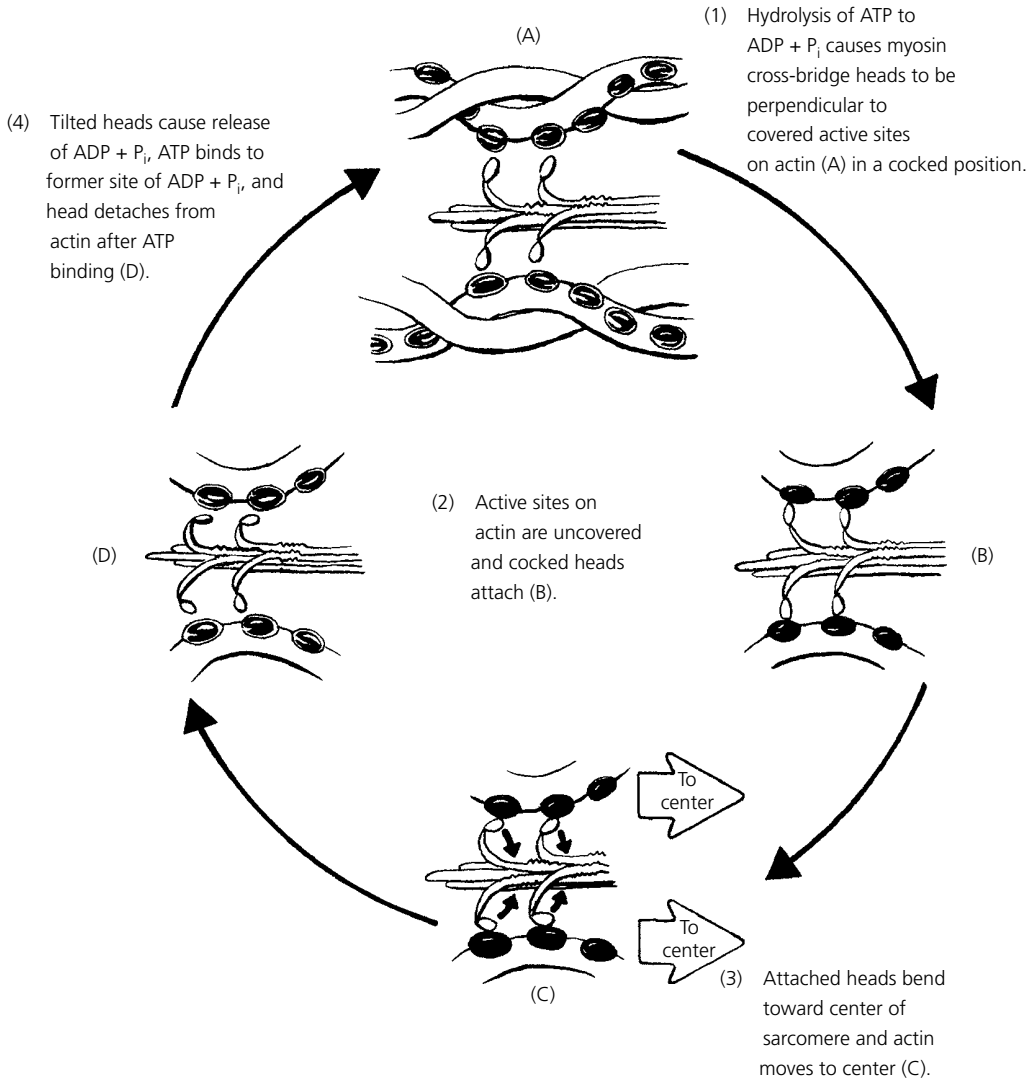

Figure 27.14 The sequence of actin and myosin interaction. This results in muscle shortening. ATP, adenosine triphosphate; ADP, adenosine diphosphate; P_i, inorganic phosphate. From Reece, W.O. (2009) *Functional Anatomy and Physiology of Domestic Animals*, 4th edn. Wiley-Blackwell, Ames, IA. Reproduced with permission from Wiley.

Source of energy

The immediate energy for muscle contraction is thus derived from ATP, forming ADP and P_i. The amount of ATP in muscle fibers is limited, and rephosphorylation of ADP must occur so that contraction can continue. This is accomplished by the transfer from **creatine phosphate (CP)**, which is about five times more plentiful than ATP, according to the following reaction:

$$CP + ADP \xrightarrow{\text{kinase}} C + ATP$$

Because the amount of CP is also limited, the necessary rephosphorylation of creatine (C) to CP and ADP is ultimately derived from intermediary metabolism within the muscle fiber and from the associated reoxidation of reduced cofactors that occurs in the electron transfer chain of the mitochondria. This process is an aerobic system known as **oxidative phosphorylation**.

Aerobic metabolism is important as an energy source for muscle contractions of animal athletes and for endurance exercise required of migrating animals, where repetitive skeletal muscle contractions continue for hours or days. The primary fuel for muscle contractions during prolonged endurance exercise is fatty acids rather than glucose. The fatty acids are broken down to acetyl-CoA and enter the citric acid cycle resulting in the formation of ATP.

Muscle contraction is 50–70% efficient in regard to accomplishment of work. The nonwork portion is dissipated as heat. This heat source is important to the body for the maintenance of body temperature. When at rest, body cooling may result in shivering, which is an attempt to generate heat by muscle contraction.

Contraction versus contracture

Muscle shortening can occur in the absence of action potentials. This type of shortening is referred to as **rigor** or **physiologic contracture**, as opposed to contraction. The actin and myosin filaments remain in a continuous contracted state because sufficient ATP is not available to bring about relaxation (see previous section). Contracture that occurs after death is referred to as **rigor mortis**. However, in this case lack of ATP for relaxation endures, and relaxation only occurs as a result of postmortem autolysis caused by lysosomes 12–24 hours after death. Those muscles that were most active just before death are those that develop rigor mortis first (i.e., greater exhaustion of ATP and CP associated with greater muscle activity). The generation of new ATP via intermediary metabolism is no longer available.

Contraction strength

Contraction strength varies and is achieved by motor unit summation or by wave summation. The stimulation of one motor unit causes a weak contraction, whereas the stimulation of a large number of motor units develops a strong contraction. This is known as **motor unit summation**. All gradations of contraction strength are possible, depending on the number of motor units stimulated. Increasing the strength of contraction by **wave summation** occurs when the frequency of contraction is increased. When a muscle is stimulated to contract before the muscle has relaxed, the strength of the subsequent contraction, as measured by the height of a lifted load, is increased. When the frequency is sufficient such that the individual muscle twitches become fused into a single prolonged contraction, the strength is at a maximum; this condition is known as **tetany** (Figure 27.15).

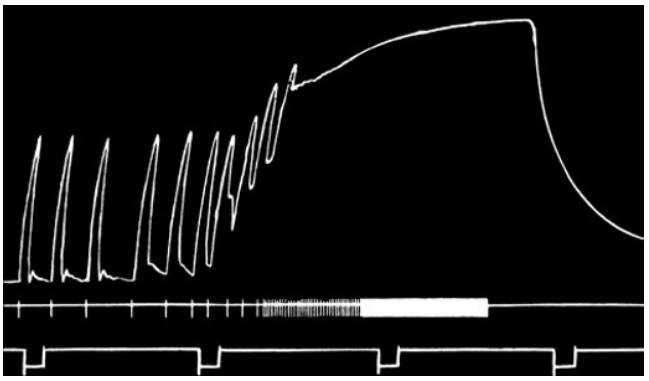

Figure 27.15 Increasing muscle strength by increasing the frequency of contraction. This is known as wave summation. Tetany occurs when individual contractions are fused and cannot be distinguished from each other. From Carlson, A.J. and Johnson, V. (1953) *The Machinery of the Body*, 4th edn. University of Chicago Press, Chicago. Reproduced with permission from University of Chicago Press.

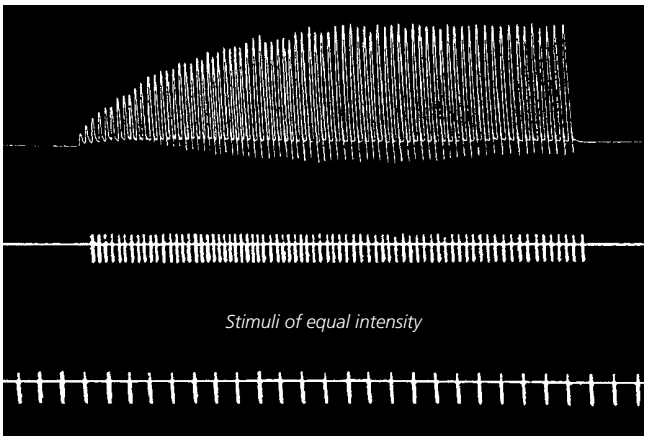

Figure 27.16 The staircase phenomenon of skeletal muscle. This is also known as treppe. Successive stimuli of the same intensity produce contractions of increasing strength. From Carlson, A.J. and Johnson, V. (1953) *The Machinery of the Body*, 4th edn. University of Chicago Press, Chicago. Reproduced with permission from University of Chicago Press.

Muscles seem to "warm up" to a maximum contraction state. This can be shown by applying stimuli of equal intensity a few seconds apart to a muscle. Each successive muscle twitch has slightly more strength than the preceding one, until optimal contraction strength is reached (Figure 27.16). This phenomenon is referred to as **treppe**, or the **staircase phenomenon**. Successive stimulations are believed to provide an increasing concentration of calcium ions in the sarcoplasm during the initial contractions of rested muscles.

Self-evaluation

Answers can be found at the end of the chapter.

1 Cardiac muscle cells have separations between adjacent cells known as intercalated disks. Their function is to:
- **A** Regenerate new cells
- **B** Provide a location for neuromuscular junctions
- **C** Provide low electrical resistance and thus facilitate depolarization from one cell to the next
- **D** Release Ca^{2+} for initiation of muscle contraction

2 Pelvic delivery of an unusually large calf has caused a cow to be down and unable to bring her hindlegs together. Obturator nerve paralysis is suspected, and the affected muscles are classified as:
- **A** Abductors
- **B** Adductors
- **C** Extensors
- **D** Flexors

3 Which one of the following is the smallest component of a skeletal muscle?
- **A** Sarcomere
- **B** Myosin
- **C** Myofibril
- **D** Muscle fiber

4 The sarcotubular system:
- **A** Is located within muscle fibers but outside of myofibrils
- **B** Is a system within each of the myofibrils
- **C** Has no direct communication (openings) with extracellular fluid
- **D** Consists of a nerve fiber and the muscle fibers that it innervates

5 Conduction of depolarization from the surface of a muscle fiber to its inner aspects is accomplished by the:
- **A** Neuromuscular junction
- **B** Actin filaments
- **C** Endomysium
- **D** Sarcotubular system

6 Which tubule set of the sarcotubular system releases Ca^{2+} when depolarized for its diffusion to the myofibrils?
- **A** Transverse tubules
- **B** Sarcoplasmic reticulum

7 What chemical begins the depolarization of skeletal muscle fibers after a nerve impulse initiates its release?
- **A** Ca^{2+}
- **B** Acetylcholine
- **C** Succinylcholine
- **D** Acetylcholinesterase

8 The Ca^{2+} released from the sarcoplasmic reticulum begins the contraction process by:
- **A** "Cocking" the myosin filament cross-bridge heads
- **B** Rephosphorylating ADP
- **C** Exposing actin filament cross-bridge binding sites
- **D** Facilitating ACh release from the neuromuscular junction

9 Myosin cross-bridge heads detach from actin active sites when the cross-bridge heads bind:
- **A** Ca^{2+}
- **B** ATP
- **C** Creatine phosphate
- **D** ADP + P_i

10 Rigor mortis is an example of _____, which results from a depletion of _____ and a failure of cross-bridge heads to _____ to/from actin. (Select appropriate combination below.)
- **A** Contraction; Ca^{2+}; attach
- **B** Relaxation; Ca^{2+}; attach
- **C** Contracture; ATP; detach
- **D** Contraction; ATP; detach

Suggested reading

Bailey, J.G. (2004) Muscle physiology. In: *Dukes' Physiology of Domestic Animals*, 12th edn (ed. W.O. Reece), pp. 871–885. Cornell University Press, Ithaca, NY.

Hall, J.E. (2011) Excitation of skeletal muscle: neuromuscular transmission and excitation–contraction coupling. In: *Guyton and Hall Textbook of Medical Physiology*, 12th edn, pp. 83–88. Saunders Elsevier, Philadelphia.

Reece, W. (2009) Muscle. In: *Functional Anatomy and Physiology of Domestic Animals*, 4th edn, pp. 206–229. Wiley-Blackwell, Ames, IA.

Answers

1 C
2 B
3 B
4 A
5 D
6 B
7 B
8 C
9 B
10 C

28 Physiology of Smooth Muscle

William O. Reece
Iowa State University, Ames, IA, USA

Smooth muscle is so named because it has no visible striations. **Myofilaments** are present and are composed of the contractile proteins **actin** and **myosin**, as in skeletal muscle. However, the filaments are more loosely organized than those in skeletal muscle, which accounts for the lack of visible striations. Smooth muscle is an important functional part of many organs, including the contractile aspect of the intestines, urinary bladder, ureter, blood vessels, uterus, the iris and ciliary muscles of the eye, and the arrector pili muscles that cause hair on the skin to erect. These structures receive innervation from the autonomic nervous system but some may also respond, directly or indirectly, to stretch or extracellular fluid change (e.g., acidosis or alkalosis).

Smooth muscle functions in some sites by performing active contractions (e.g., **peristalsis**) and in other sites with states of sustained contraction called **tone**. In the intestine, tone is maintained constantly and peristalsis inconstantly. The size of arterioles depends on tone of the encircling smooth muscle, which assists in regulating blood pressure.

Smooth muscle types

1 What is the difference between multiunit smooth muscle and single-unit smooth muscle?
2 Which smooth muscle type would be associated with peristaltic waves?
3 What is the purpose of gap junctions between cell membranes of single-unit smooth muscle?

There are two general types of smooth muscle that vary according to their location, function, organization into sheets or bundles, and characteristics of innervation. These general types are (i) **multiunit smooth muscle** and (ii) **single-unit smooth muscle** (also known as unitary and visceral) (Figure 28.1).

Multiunit smooth muscle

This type of muscle is found in the ciliary body and iris of the eye, the arrector pili muscle of skin hair, and the walls of large arteries. It is composed of discrete smooth muscle fibers. Each muscle fiber is innervated separately and contracts only when it receives synaptic stimuli. Therefore, each fiber can contract independent of the others. Conduction of impulses from one cell to the next does not exist. The individual cells may exist in bundles, but not in sheets.

Single-unit (visceral) smooth muscle

The term "single-unit" does not mean single muscle fibers but rather a large mass of muscle fibers. In this type of smooth muscle, large areas of muscle tissue contract simultaneously and are responsible for **peristaltic waves** of contraction that move intestinal contents from one end of the digestive tract to the other. These waves also occur in the uterus and ureters. Harnessing of single-unit smooth muscle occurs in the following manner.

1 Cell membranes of the fibers within a sheet of fibers are adherent to each other at multiple points, whereby the force generated by one muscle fiber can be transmitted to the next.
2 There are also **gap junctions** between cell membranes that allow ions to flow freely from one muscle fiber to the next. This allows actions potentials to travel from one fiber to the next causing the muscle fibers to contract together.

Dukes' Physiology of Domestic Animals, Thirteenth Edition. Edited by William O. Reece, Howard H. Erickson, Jesse P. Goff and Etsuro E. Uemura.

Companion website: www.wiley.com/go/reece/physiology

Microstructure of smooth muscle

1 What are dense bodies that are associated with smooth muscle fibers?
2 What is the ratio of actin to myosin in smooth muscle?
3 What is the counterpart of skeletal muscle T tubules in smooth muscle?

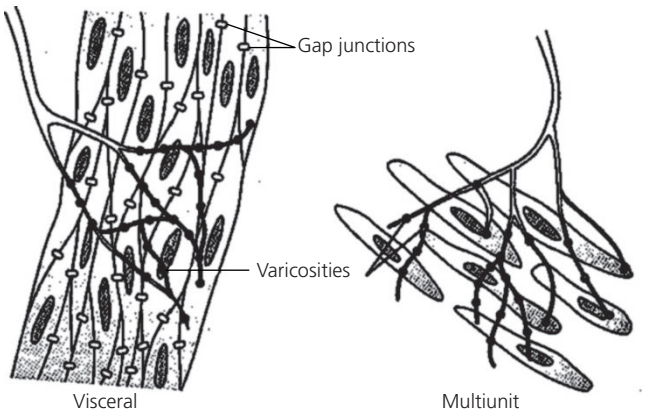

Figure 28.1 Multiunit and visceral smooth muscle types. Autonomic motor neurons synapse with individual multiunit smooth muscle fibers and with several single-unit smooth muscle fibers. Varicosities distributed along the terminal axons of both fiber types contain transmitter substance within their vesicles. Gap junctions between visceral smooth muscle fibers allow free ion flow from one muscle fiber to the next. From Hall, J.E. (2011) *Guyton and Hall Textbook of Medical Physiology*, 12th edn. Saunders Elsevier, Philadelphia. With permission from Elsevier.

The individual cells are spindle-shaped and have a centrally located nucleus (Figure 28.2), in contrast to skeletal muscle fibers that have multiple, peripherally located nuclei. Smooth muscle fibers are referred to as **fusiform** or **spindle-shaped** because they tend to be wide along the middle portion of the fiber and tapered at the ends. The tapered portion of each fiber lies adjacent to the wide portion of the neighboring fibers (see Figure 28.2). This arrangement permits adjacent fibers to be packed closely together, which is most favorable for contractile function.

The arrangement of the myofilaments within a single muscle fiber is shown in Figure 28.3. Note the presence of **dense bodies** that are points of attachment for actin thin filaments. Some dense bodies are scattered throughout the cytoplasm attached to an intermediate filament that links several dense bodies together, while others are attached to the sarcolemma. The dense bodies are rigid stable structures that retain their original shape and attachment during contraction. In this manner, the dense bodies correspond to the **Z lines** of skeletal muscle. Because actin attaches to the fiber sarcolemma-associated dense bodies, smooth muscle fibers develop a wrinkled appearance along their borders when contracted (see Figure 28.3).

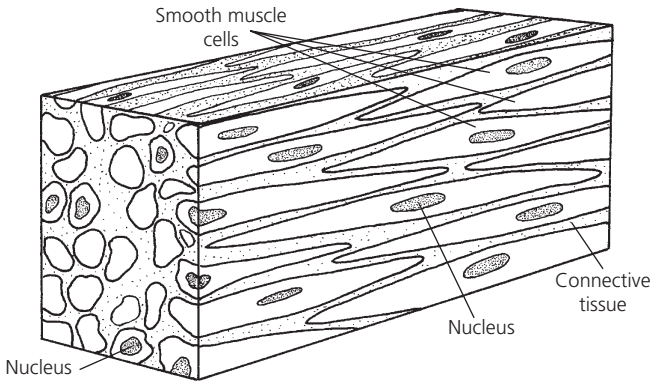

Figure 28.2 Smooth muscle cells exposed in longitudinal and cross-sectional planes. The cells are characteristically spindle-shaped and have a centrally located nucleus. From Reece, W.O. (2009) *Functional Anatomy and Physiology of Domestic Animals*, 4th edn. Wiley-Blackwell, Ames, IA. Reproduced with permission from Wiley.

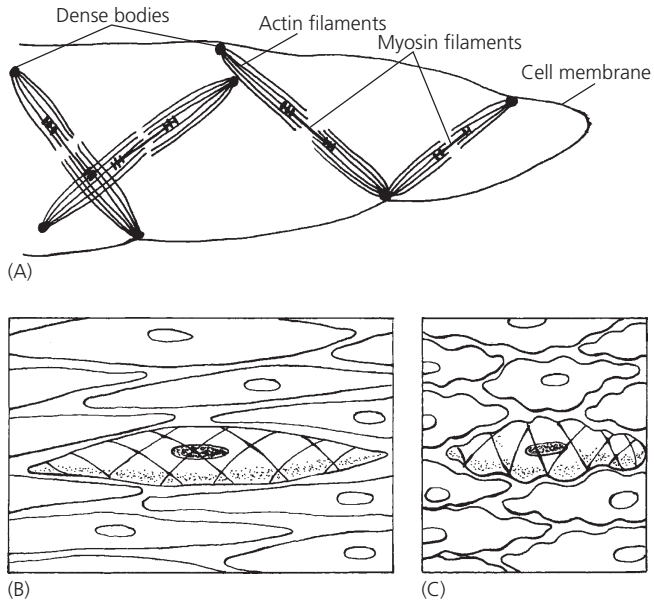

Figure 28.3 Contraction of smooth muscle. (A) Physical structure of smooth muscle. Dense bodies attach either to the cell membrane or to an intracellular structural protein that links several dense bodies together. The dense bodies are functionally similar to Z lines. (B) A translucent view of a relaxed smooth muscle cell. (C) A translucent view of a contracted smooth muscle cell. Dense bodies not shown in (B) and (C). From Reece, W.O. (2009) *Functional Anatomy and Physiology of Domestic Animals*, 4th edn. Wiley-Blackwell, Ames, IA. Reproduced with permission from Wiley.

Interspersed among the actin filaments in the muscle fiber are myosin thick filaments. The myosin filaments have a diameter more than twice that of the actin filaments and the ratio of actin to myosin is 15 : 1 instead of 2 : 1 as in skeletal muscle. The actin filaments from two separate dense bodies extend toward each other and surround a myosin filament (see Figure 28.3), thereby providing a contractile unit that is similar to a contractile unit of skeletal muscle (i.e., the sarcomere).

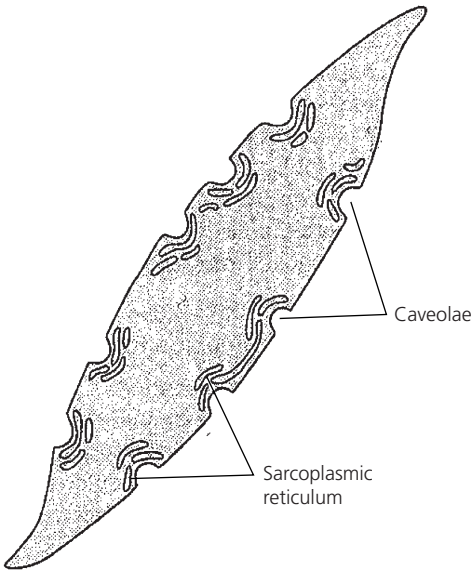

Figure 28.4 Sarcoplasmic tubules in a large smooth muscle fiber showing their relation to invaginations in the cell membrane called calveolae. From Hall, J.E. (2011) *Guyton and Hall Textbook of Medical Physiology*, 12th edn. Saunders Elsevier, Philadelphia. With permission from Elsevier.

T tubules are absent in smooth muscle fibers, but there are numerous invaginations in the fiber membrane called **calveoli** (Figure 28.4). It is believed that they may have a function similar to T tubules in that they are in close proximity to portions of rudimentary sarcoplasmic reticuli found in smooth muscle fibers.

Smooth muscle contraction

1 What is calmodulin?
2 What is the action of myosin kinase?
3 What "cocks" the myosin cross-bridge heads?
4 What is accomplished by the regulatory chain of myosin cross-bridge heads after they are "cocked" and repetitive binding with uncovered active sites of actin?
5 What is the action of myosin phosphatase that causes repetitive binding to stop?

A big difference between skeletal muscle and smooth muscle is that skeletal muscle contracts and relaxes rapidly and smooth muscle contraction is prolonged and often of a tonic nature.

Excitation–contraction coupling in smooth muscle

Smooth muscle does not have the tropomyosin–troponin complex, the protein that covers active sites on the actin filament in skeletal muscle. Further, the active sites are uncovered when troponin combines with calcium ions. Instead of the tropomyosin–troponin complex, smooth muscle contains another protein known as **calmodulin**, a regulatory protein similar to the tropomyosin–troponin complex, but which differs in the manner in which contraction is initiated. The sequence in smooth muscle whereby activation of the myosin cross-bridge heads supports contraction is as follows.

1 After the influx of calcium ions following depolarization of the fiber membrane, the calcium ions bind with calmodulin.
2 The **calcium–calmodulin** combination binds with and activates **myosin kinase** (phosphocreatine kinase in skeletal muscle), a phosphorylating enzyme.
3 Each of the **myosin cross-bridge heads** has what is called a **regulatory chain** that becomes phosphorylated in response to myosin kinase.
4 When the regulatory chain is phosphorylated ($ADP + P_i \rightarrow ATP$), the head is "cocked" and has the ability to bind repetitively with the uncovered active sites on the actin filament.
5 Repetitive binding with the actin active sites continues through the entire cycling process, with each binding adding to the muscle fiber contraction and development of tension.
6 Relaxation of contracted smooth muscle fibers requires the presence of the enzyme **myosin phosphatase** located in the intracellular fluid of the smooth muscle fiber. Myosin phosphatase splits the phosphate from the regulatory chain on the cross-bridge heads, the heads detach, whereby repetitive binding stops and contraction ceases.
7 Variations in the amount of time for contraction and maintenance of tension are probably determined by the amount of myosin phosphatase in the fibers.

Contrasts between smooth and skeletal muscle contraction

1 What are the reasons for the slower cycling of myosin cross-bridge head attachment and detachment?
2 How is ATPase activity related to attachment of myosin cross-bridge heads to actin?
3 Why is less energy required to sustain contraction tension in smooth muscle?
4 What are some reasons why the maximum force of contraction attained by smooth muscle can be greater than that of a skeletal muscle?

Aside from the structural differences, there are functional differences relating to the characteristics of contraction between smooth muscle and skeletal muscle.

1 The cycling of cross-bridge head attachment and detachment to actin sites is much slower in smooth muscle. The sarcoplasmic reticulum is rudimentary in smooth muscle fibers and calcium ions must enter the fiber from the extracellular fluid. Also, the Ca^{2+} pumps are in the fiber membrane and are much slower than those in the sarcoplasmic reticulum of skeletal muscles.

2 Cross-bridge heads have less ATPase activity (provides energy for attachment of cross-bridge heads to actin) in smooth muscle, thereby reducing movements of the cross-bridge heads and slowing the rate of cycling.
3 Much less energy is required to sustain contraction tension in smooth muscle because slow attachment and detachment cycling requires only one molecule of ATP for each cycle, regardless of its duration. Maintenance of tonic contractions (e.g., intestines, urinary bladder) without cycling provides energy economy for the body.
4 The maximum force of contraction attained by smooth muscle can be greater than that of skeletal muscle because of the prolonged attachment of myosin cross-bridge heads to the actin filaments. Also, smooth muscle tissue has much more **extracellular material** (i.e., collagen, elastin) than skeletal muscle. Each smooth muscle fiber is surrounded by a **basal lamina** and **reticular fibers** that when coupled with the extracellular material helps to organize the force produced by individual smooth muscle fibers into a combined effort, as in peristalsis of the gut and contractions of the uterus. In this regard, smooth muscle has the ability to produce a contractile force comparable to that of skeletal muscle.

Smooth muscle contraction stimuli

1 How does the innervation by autonomic nerve fibers to single-unit smooth muscle differ from that of skeletal muscle?
2 Are acetylcholine (parasympathetic) and norepinephrine (sympathetic) secreted by the same fiber?
3 What contributes to the simultaneous contraction of large areas of single-unit smooth muscle fibers?
4 Are multiunit smooth muscle fibers stimulated by stretch?

Autonomic nervous system

Neuromuscular junctions found in skeletal muscle fibers do not occur in smooth muscle. The autonomic nerve fibers innervating single-unit smooth muscle branch diffusely on top of a sheet of muscle fibers. Instead of making direct contact, there are multiple **varicosities** (similar to a terminal bulb of presynaptic neurons) distributed along the nerve fiber with vesicles containing the transmitter substance, either **acetylcholine** or **norepinephrine**. They are never secreted by the same fiber. Smooth muscle fibers are usually innervated by both sympathetic and parasympathetic nerve fibers, each having opposite effects on the muscle fibers. Some smooth muscle fibers may be innervated by only one division of the autonomic nervous system (e.g., blood vessels).

Smooth muscle cells normally have a certain level of **tone**, and the amount of released neurotransmitter determines whether the muscle fibers will contract further or relax. The neurotransmitter released by the varicosities diffuses over a large area and affects numerous single-unit smooth muscle fibers. In this way, large areas of smooth muscle contract simultaneously, with electrical stimuli being transmitted repeatedly among neighboring fibers by way of **gap junctions**. These allow action potentials to travel from one fiber to the next, causing muscle fibers that are not otherwise directly affected by the diffused neurotransmitter to contract together. This kind of activity is common in the large peristaltic waves of contraction that move intestinal contents from one end of the digestive tract to the other and similar peristaltic waves that occur in the uterus and the ureters.

Stimuli other than autonomic

The membrane of single-unit smooth muscle fibers is sensitive to mechanical stimuli. Stretching the membrane of these fibers leads to depolarization and consequently contraction, whereby contractile tension can be propagated or maintained over a large area of muscle tissue. With autoregulation of blood flow in arterioles, a rise in blood pressure causes stretch of the encircling smooth muscle that stimulates contraction. This maintains a fairly constant blood flow in the tissue they supply.

Multiunit smooth muscle is found in the ciliary body and the iris of the eye, in the ductus deferens, and the walls of large arteries. In these units of smooth muscle, each muscle fiber is innervated separately and contracts only when it receives synaptic stimuli.

In addition to the above stimuli, smooth muscle may be affected directly or indirectly by changes in oxygen concentration, pH, or ion concentrations in the extracellular fluid.

Self-evaluation

Answers can be found at the end of the chapter.

1 Smooth muscle is innervated by somatic nerves (spinal and cranial nerves) instead of autonomic nerves.
A True
B False

2 Single-unit (visceral) smooth muscle refers to a large mass of muscle fibers whereas multiunit smooth muscle refers to single muscle fibers.
A True
B False

3 Dense bodies in smooth muscle fibers are points of attachment for myosin (thick) filaments.
A True
B False

4 T tubules are absent in smooth muscle fibers but a similar function is associated with structures known as calveoli.
A True
B False

5 Smooth muscle is characterized by rapid contraction and relaxation rather than prolonged contraction that is often of a tonic nature.
A True
B False

6 Smooth muscle does not have the tropomyosin–troponin complex found in skeletal muscle but contains another protein known as calmodulin that initiates contraction in the same manner as the tropomyosin–troponin complex.
A True
B False

7 Each myosin cross-bridge head composes a regulatory chain that is phosphorylated in response to myosin kinase and "cocks" the myosin cross-bridge heads.
A True
B False

8 The cycling of cross-bridge attachment and detachment to actin sites is much slower in smooth muscle than in skeletal muscle.
A True
B False

9 Neuromuscular junctions found in skeletal muscle fibers are also associated with smooth muscle fibers.
A True
B False

10 The autoregulation of blood flow in arterioles is an example of the sensitivity of single-unit smooth muscle fibers to mechanical stimuli, whereby a rise in blood pressure causes stretch of encircling smooth muscle that stimulates contraction.
A True
B False

Suggested reading

Bailey, J.G. (2004) Muscle physiology. In: *Dukes' Physiology of Domestic Animals*, 12th edn (ed. W.O. Reece), pp. 887–889. Cornell University Press, Ithaca, NY.

Hall, J.E. (2011) Excitation and contraction of smooth muscle. In: *Guyton and Hall Textbook of Medical Physiology*, 12th edn, pp. 91–98. Saunders Elsevier, Philadelphia.

Reece, W. (2009) Muscle. In: *Functional Anatomy and Physiology of Domestic Animals*, 4th edn, pp. 222–223. Wiley-Blackwell, Ames, IA.

Answers

1 B
2 A
3 B
4 A
5 B
6 B
7 A
8 A
9 B
10 A

29 Physiology of Cardiac Muscle, Muscle Adaptations, and Muscle Disorders

William O. Reece
Iowa State University, Ames, IA, USA

Cardiac muscle

1 Why are cardiac muscle fibers considered a functional syncytium rather than a morphological syncytium?
2 What is the predominant source of energy when engaged in aerobic metabolism?
3 What is the function of gap junctions?

Cardiac muscle is found only in the heart and over the lifetime of a domestic animal contracts millions of times, demonstrating its properties of endurance. Cardiac muscle, like skeletal muscle, is striated, and has a similar organization of sarcomeres with actin and myosin filaments. There are differences, however, in how the fibers are organized and innervated that allow their coordinated function. Greater detail of heart function is described in Section VI. However, in order to compare the three types of muscle, a description of the fundamental properties of cardiac muscle is included herein.

Morphological differences

In contrast to skeletal muscle, cardiac muscle fibers do not fuse into a single multinucleated fiber during embryonic development. Cardiac muscle fibers are typically uninucleated, with the nucleus centrally placed within each fiber rather than peripherally as in skeletal muscle (Figure 29.1). Cardiac myocytes branch or bifurcate during embryonic development and bind to myocytes in adjacent chains. However, the fibers do not fuse and remain separated as distinct fibers with their respective sarcolemma throughout development.

Because the fibers do not fuse with each other they do not form a morphological syncytium, but because of their branching and bifurcations they form a **functional syncytium** that will allow coordinated contraction. The dark, dense cross-bands found on the ends of cardiac muscle fibers are called **intercalated disks** (see Figure 29.1), which are continuous with the sarcolemma and are intercellular junctions.

The diameter and length of mature cardiac muscle fibers are approximately 15 µm and 85–100 µm, respectively. Mature skeletal muscles have a larger diameter (0.1–0.5 mm) and a longer length (10–30 cm).

Energy sources

Mitochondria make up about 40% of the cytoplasmic volume compared with only about 2% in skeletal muscle. This reflects the reliance of cardiac muscle on aerobic metabolism. Cardiac muscle cells stop contracting after about 30 s of oxygen deprivation. There are numerous lipid droplets in cardiac muscle fibers that contain triglycerides, the storage form of fatty acids, which are the predominant energy source when engaged in aerobic metabolism.

Gap junctions and action potentials

Gap junctions present within the intercalated disks allow communication between the cytoplasm of adjacent end-to-end fibers, and permit the free diffusion of ions and action potentials. As a result of their end-to-end location, action potentials are conducted rapidly in a direction parallel to the longitudinal axis. Thus because of the gap junctions and intercalated disks all cardiac muscle fibers are electrically connected, whereas skeletal

Dukes' Physiology of Domestic Animals, Thirteenth Edition. Edited by William O. Reece, Howard H. Erickson, Jesse P. Goff and Etsuro E. Uemura.

Companion website: www.wiley.com/go/reece/physiology

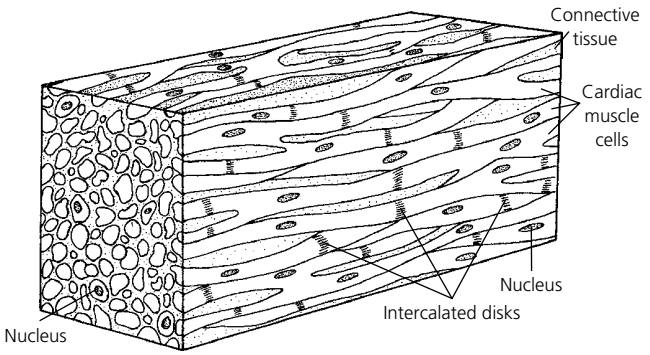

Figure 29.1 Cardiac muscle fibers exposed in longitudinal and cross-sectional planes. Note elongated branching fibers with irregular contours at their junctions with other fibers. From Reece, W.O. (2009) *Functional Anatomy and Physiology of Domestic Animals*, 4th edn. Wiley-Blackwell, Ames, IA. Reproduced with permission from Wiley.

muscle fibers must be separately stimulated by a motor neuron to form an action potential.

Action potentials in cardiac muscle tissue spread from fiber to fiber, which allows depolarization to spread through the entire heart, leading to coordinated virtually simultaneous contraction of all the cardiac muscle fibers in a heart chamber and permitting the movement of large volumes of blood through the cardiovascular system. This is why cardiac muscle tissue is considered to be a functional syncytium.

Excitation–contraction coupling

1 How does the source of calcium ions for muscle contraction in cardiac muscle differ from that in skeletal muscle?
2 Can a very high concentration of calcium ions in the extracellular fluid be detrimental?
3 How do the catecholamines affect cardiac muscle?

Recall that **excitation–contraction coupling** is the mechanism by which the action potential causes the myofibrils of muscle to contract. In cardiac muscle, as in skeletal muscle, the action potential spreads to the interior of the cardiac muscle fiber via the T tubules to the membranes of the sarcoplasmic reticulum (SR), followed by release of Ca^{2+} into the sarcoplasm of the sarcoplasmic reticulum. This is followed by muscle contraction. Differences exist in cardiac muscles that are related to Ca^{2+} release. In skeletal muscle, the SR provided all the Ca^{2+} to provide full contraction strength. However, the T tubules of cardiac muscle have a diameter much greater than that of the T tubules in skeletal muscle; therefore, in addition to the Ca^{2+} released into the sarcoplasm by the SR, a large quantity of extra Ca^{2+} also diffuses into the sarcoplasm from the T tubules at the time of the action potential. In addition, the inner aspect of the T tubules contains a large quantity of mucopolysaccharides that are electronegatively charged and which bind an abundant store of Ca^{2+} derived from extracelluar fluid (ECF). This is facilitated because the openings of the T tubules directly communicate with ECF surrounding the fibers. Therefore, the strength of contraction of cardiac muscle is dependent on the concentration of Ca^{2+} in the ECF, which is not the case for skeletal muscle because all the Ca^{2+} is released from the SR inside the fiber and the strength of contraction is affected very little by the ECF Ca^{2+} concentration.

An increase in the ECF concentration of Ca^{2+} increases contractile force, but a very high concentration leads to cardiac arrest during systole (contraction) due to **rigor** (contraction without action potentials) of cardiac muscle fibers.

Catecholamines (i.e., epinephrine and norepinephrine) increase the movement of calcium ions into cardiac muscle fibers as well as increase the sensitivity of the contractile mechanism to the presence of calcium ions.

Muscle adaptations

1 Is regeneration of cardiac muscle fibers possible? What happens if they die?
2 How does hypertrophy differ from hyperplasia?
3 Does increase in cardiac muscle size involve hypertrophy or hyperplasia?
4 What is denervation atrophy?

Muscle is the most adaptive tissue in the animal body. Individual muscle fibers of skeletal, cardiac, and smooth muscle increase in size as a normal response to chronic mechanical stress, as with regular exercise. Similar stress in skeletal and smooth muscle causes division of muscle fibers through mitosis to produce new fibers. A decrease in size can occur in all three muscle types in response to disuse or disease.

Hypertrophy and hyperplasia

An increase in individual muscle-fiber size is referred to as **hypertrophy**. It is common in skeletal, cardiac, and smooth muscle fibers. Postnatal growth of skeletal muscle fibers is not accomplished by an increase in the number of muscle fibers but rather by the addition of myofibrils to the periphery and addition of sarcomeres to the tendinous ends.

An increase in the number of muscle fibers is called **hyperplasia**. Regeneration of skeletal-muscle fibers is possible from so-called **satellite fibers**, but this requires an intact endomysium for successful repair. Cardiac muscle fibers can increase in size in the same way as in skeletal muscle, in that it involves hypertrophy and not hyperplasia.

Regeneration of cardiac-muscle fibers does not occur, because there is no counterpart to the satellite cells of skeletal muscle. If myocardial fibers die, they are replaced by fibrous noncontractile scar tissue. Smooth-muscle organs can increase their size not only by hypertrophy but also by hyperplasia, which accounts for considerable regenerative ability.

Atrophy

A decrease in the size of a muscle is referred to as **atrophy**. When a body part has been immobilized for a period of time, the muscles become smaller (referred to as **disuse atrophy**). Loss of the nerve supply to a muscle results in **denervation atrophy**. This was formerly a common condition in harnessed draft horses. The presence of the collar presses on the suprascapular nerve that supplies the two major muscle masses of the shoulder blade. The resulting denervation causes the muscle of the shoulder to atrophy, resulting in a condition known as **sweeney** (also called **shoulder slip**).

Muscle disorders

1. What is the general mechanism whereby tetanus neurotoxin produces muscular spasm?
2. Is the expression of tetanus similar in all animal species?
3. What is the predisposing condition causing exertional rhabdomyolysis?
4. Does the acute form of exertional rhabdomyolysis occur in working dogs and racing greyhounds?
5. What are the dominant clinical signs of bovine parturient paresis? What is its cause?
6. Milk fever in the cow and eclampsia in the bitch are caused by hypocalcemia. Why are the clinical signs different?
7. What stress factors contribute to dark cutting beef?

The overview of muscle physiology at the beginning of Chapter 27 alluded to the multitude of body functions associated with muscles. Accordingly, it is not surprising that there are a large number of infectious, nutritional, and metabolic diseases that are manifested by muscle disorders. Only a few will be briefly considered in which muscle disorders are a distinguishing feature.

Tetanus

Tetanus is a bacterial disease caused by a potent neurotoxin elaborated by the organism *Clostridium tetani*. The neurotoxin reaches the central nervous system and prevents release of an inhibitory transmitter (glycine). The resulting sensitivity to the excitatory impulses, unchecked by inhibitory impulses, produces generalized muscular spasm (**tetany**). Tetanus in humans has been called lockjaw because the masseter muscles that close the mouth are stronger than the muscles that open the mouth and the jaws remain in a closed position. Expression of tetanus in animals varies somewhat among species. In the horse, tonic spasms of skeletal muscles are extensive. Beginning first at the head or in muscles of the hindlimbs, they extend either slowly or rapidly until the condition becomes generalized. Spasms may be limited to a definite group of muscles, such as muscles of the jaw, causing difficulty in prehension and mastication and drooling of saliva because of difficulty in swallowing. The clinical signs described for the horse are somewhat similar in other species but more distinctive in cattle, with extension of the head and neck, tucked-up abdomen, and extended tail.

Exertional rhabdomyolysis

Exertional rhabdomyolysis (ER) is a specific disease of horses characterized by a suddenly developing muscle pain or cramping of the hindlimbs. At one time, ER was considered a single entity, described as azoturia, tying up, or Monday morning disease. Several different myopathies are now recognized that have similarities in clinical presentation.

The disease occurs only in well-nourished animals and appears during exercise after a period of idleness, typically when individuals at regular work are kept idle with no exercise and no reduction in diet for 2–5 days, whereby an attack may develop in 15 min to 1 hour after exercise is resumed. This predisposing condition is the most essential causative influence. The intensity of exercise or work is of little significance when it occurs.

Clinical signs generally occur within 30 min after leaving the stable: sweating begins, the gait becomes stiff, and the animal is reluctant to move. Signs of distress include recumbency, pawing, and stretching. Firm, painful, lumbar and gluteal musculature are common signs. Urine is red/brown and often described as coffee-colored. The exercise induces muscle necrosis that results in the release of creatine kinase (CK) and myoglobin into the circulation. Excessive myoglobinuria may cause renal tubular damage and acute renal failure.

Acute ER may be sporadic and occur on a single occasion, or chronic where recurrent episodes occur repeatedly in susceptible horses. The acute episodes are identical regardless of their being sporadic or recurrent. Recurrent ER is seen frequently in thoroughbreds, standardbreds, and Arabian horses. It is likely due to abnormal regulation of intracellular calcium in skeletal muscle.

Acute ER occurs in racing greyhounds and working dogs where severe cases are characterized by muscle ischemia after exercise or excitement. The avascularity and lactic acidosis bring forth clinical signs and outcomes similar to equine ER.

Some nonexercise-associated rhabdomyopathies are nutritional myopathies, associated with vitamin E and selenium deficiency, and a genetic myopathy known as polysaccharide storage myopathy (PSSM).

Bovine parturient paresis (milk fever)

Parturient paresis is a paralysis and loss of consciousness leading to coma in dairy cows that have recently calved. The onset may be marked by tonic muscular spasms and twitching that are soon replaced by the dominant clinical signs of paresis and depressed consciousness, which are seen in the majority of cases. It is caused by a sudden drop in blood calcium (hypocalcemia) associated with the onset of lactation, and is most common in high-producing dairy cows.

Canine puerpenal tetany (eclampsia)

Puerpenal tetany is an acute condition usually seen at peak lactation 2–3 weeks after whelping and, like parturient paresis, is associated with hypocalcemia. Small-breed bitches with large litters are most often affected. Early clinical signs are restlessness. Subsequent changes include mild tremors, twitching, muscle spasms, stiffness, and ataxia. Severe tremors, tetany, and generalized seizure activity may be seen. The functional disturbances associated with hypocalcemia in the bitch are primarily the result of neuromuscular tetany, whereas in cows the clinical signs are related to paresis. The contrast is related to differences in function of the neuromuscular junction between the cow and the bitch. In cows, release of acetylcholine and transmission of nerve impulses across the neuromuscular junction is blocked by hypocalcemia, leading to muscle paresis. In the bitch, excitation–contraction coupling is maintained at the neuromuscular junction. The low concentration of calcium in the extracellular fluid has an excitatory effect on nerve and muscle cells, because it lowers the threshold potential and requires a stimulus of lesser magnitude to depolarize. Tetany occurs as a result of spontaneous repetitive firing of motor nerve fibers.

Dark cutting beef (dark cutters)

Dark cutting beef is a description for cuts of beef that do not "bloom" or brighten when they are exposed to air when marketed in a display case. Accordingly, it represents a financial loss to the meat industry. The retail products are referred to as "dark cutters."

The causes are linked to pre-harvest stress of live animals prior to slaughter and the depletion of muscle glycogen. The loss of muscle glycogen causes the pH to become more alkaline because glycogen content would ordinarily determine the concentration of lactic acid and acidity. Bacterial growth in meat is inhibited by low pH, and the higher pH of meat from glycogen-depleted animals spoils more easily. The meat has a firm texture and a dark appearance. Stress factors identified as contributing to dark cutting beef and that decrease the levels of muscle glycogen in the live animal include low energy intake by livestock, poor livestock handling, mixing groups of animals, and severe weather conditions during transport.

Self-evaluation

Answers can be found at the end of the chapter.

1 As compared to skeletal muscle fibers, the diameter and length of cardiac muscle fibers are:
- **A** Smaller
- **B** About the same
- **C** Larger
- **D** Larger in diameter but shorter in length

2 As compared to skeletal muscle fibers, the duration of action potentials in cardiac muscle fibers is:
- **A** Shorter
- **B** About the same
- **C** Longer
- **D** Too close to call

3 The predominant energy source for cardiac muscle fibers when engaged in aerobic metabolism is:
- **A** Glucose
- **B** Fatty acids
- **C** Amino acids
- **D** Triglycerides

4 Full contraction strength in cardiac muscle is related to release of Ca^{2+} into the sarcoplasm from:
- **A** Sarcoplasmic reticulum only
- **B** Sarcoplasmic reticulum and the T tubules
- **C** Sarcoplasmic reticulum, T tubules, and the extracellular fluid
- **D** Gap junctions

5 An increase in cardiac muscle size is associated with:
- **A** Atrophy
- **B** Hypertrophy and hyperplasia
- **C** Satellite cells
- **D** Hypertrophy

6 If myocardial fibers die:
- **A** Regeneration occurs from satellite cells
- **B** They are replaced by fibrous noncontractile scar tissue
- **C** There is replacement of cells followed by hypertrophy and hyperplasia
- **D** There is replacement of cells followed only by hypertrophy

7 Could the inability to swallow, causing difficulty in prehension and mastication and drooling of saliva, be the only clinical sign of tetanus (caused by a bacterial neurotoxin) in horses and/or cattle?
- **A** True
- **B** False

8 Which of the following clinical signs or characteristics are associated with exertional rhabdomyolysis in horses?
- **A** A suddenly developing muscle pain or cramping of the hindlimbs
- **B** Occurs in well-nourished animals and appears during exercise after a period of idleness
- **C** Exercise-induced muscle necrosis and release of myoglobin into the circulation
- **D** Acute episodes may be sporadic or recurring
- **E** All of the above

9 As compared to bovine parturient paresis, which of the following is not characteristic of canine puerperal tetany?
- **A** Both are associated with hypocalcemia
- **B** Both are associated with the onset of lactation
- **C** The transmission of nerve impulses across the neuromuscular junction is blocked

D The hypocalcemia lowers the threshold potential at the neuromuscular junction that results in spontaneous repetitive firing of motor nerve fibers
E Both **B** and **C**

10 Which one of the following statements relates to retail products known as "dark cutters"?
A They give a nice brightness when displayed at the meat counter
B Pre-harvest stress is not a factor because muscle glycogen is normal at the time of slaughter
C The causes are linked to pre-harvest stress (e.g., low energy intake, poor livestock handling) that decrease the levels of muscle glycogen in the live animal
D It is a preferred cut of beef by the meat industry

Suggested reading

Bailey, J.G. (2004) Muscle physiology. In: *Dukes' Physiology of Domestic Animals*, 12th edn (ed. W.O. Reece), pp. 885–887. Cornell University Press, Ithaca, NY.

Hall, J.E. (2011) Cardiac muscle: the heart as a pump and function of the heart valves. In: *Guyton and Hall Textbook of Medical Physiology*, 12th edn, pp. 101–104. Saunders Elsevier, Philadelphia.

Reece, W.O. (2009) Muscle. In: *Functional Anatomy and Physiology of Domestic Animals*, 4th edn, pp. 222–224. Wiley-Blackwell, Ames, IA.

Answers

1 A
2 C
3 B
4 C
5 D
6 B
7 A
8 E
9 E
10 C