Muscle

Anthony C Wareham

Abstract

Two important types of muscle are skeletal and smooth muscle. Their similarities and differences are described with regard to general morphology and ultrastructure (arrangement of filaments and t-tubules), linking structure to physiological functions. The sliding-filament theory of muscle contraction is explained. Finally, the processes by which nerves excite muscle contraction (excitation-contraction coupling) are outlined, again relating variations in these processes in the two types of muscle to differences between them in their role in the body.

Keywords Actin; calcium; contractile filaments; myosin; sarcolemma; sarcomere; sarcoplasm; t-tubules; tropomyosin

Learning objectives

After reading this article, you should be able to:

- outline the main functional differences between skeletal and smooth muscle
- describe the structure of both types of muscle, including (if present) the arrangement of actin and myosin filaments, troponin and tropomyosin, and the sarcoplasmic reticulum. Also, to describe the arrangement of T tubules (or their equivalent structure in smooth muscle)
- explain the 'sliding filament hypothesis', and illustrate its proposed mechanism of action by reference to the detailed structure of the skeletal muscle sarcomere. Also, to be able to outline the differences in the contraction process in smooth muscle
- explain how the processes of muscle activation and relaxation takes place in skeletal muscle and how these differ in smooth muscle

Morphology

Skeletal muscle

A skeletal muscle is composed of thousands of elongated muscle fibres running in parallel. Fibres are multinucleate cells, formed from the fusion of single nucleated myoblasts. In healthy fibres, the nuclei lie peripherally just under the cell membrane. In large limb muscles, fibres may reach a length of 30 cm with a diameter of 100 μm. The cell membrane (the sarcolemma) surrounds the cytoplasm (the sarcoplasm). The sarcoplasm contains several hundreds to thousands of contractile elements, the myofibrils, each of which is 1–2 μm in diameter. A myofibril is compartmentalized into as many as 10,000 repeating units called sarcomeres joined together by dense material at Z lines. These repeating units in myofibrils endow the muscle fibre with repeated cross-striations (easily seen under the light microscope), which leads to the alternative term striated muscle for skeletal muscle. The sarcolemma is invaginated at each sarcomere to form blind-ending transverse tubes (T tubules) that run into the centre of the fibre and have a crucial role in the activation of contraction. Running longitudinally between the repeating T tubules are blind-ending membrane tubes or sacs called the sarcoplasmic reticulum. The ends of the tubes of the sarcoplasmic reticulum, terminal cisternae, abut closely to the membranes of the T tubules, forming triads. A triad is part of a T tubule and the terminal cisternae on either side and is the site of excitation–contraction coupling.

Fibres are categorized by their speed of contraction, from slow to fast. Primarily, speed of contraction depends on the activity of myosin adenosine triphosphatase (ATPase). Slow fibres receive a plentiful blood supply and have oxidative metabolism whereas fast fibres can operate anaerobically and do not have such a rich blood supply. All human muscles are composed of a mix of slow and fast fibres, the ratio depending on their function and the amount and type of exercise.

Smooth muscle

Smooth muscle fibres are not striated. They are smaller than striated fibres (5–10 μm in diameter, 30–200 μm long) forming small cells, tapering at each end. They have only one, centrally located nucleus. Cells do not contain ordered sarcomeres, nor is the cell membrane invaginated into T tubules. The sarcoplasmic reticulum system is present but not as well developed as in striated fibres. The cell surface forms folds or pits called calveolae, which are thought to function in a similar way to T tubules, and which are associated with tubules of the sarcoplasmic reticulum.

The most common type of smooth muscle is visceral (single unit) muscle, which is composed of smooth muscle cells tightly bound together with gap junctions to form a continuous network. Gap junctions connect the cells together electrically so that an action potential generated in one cell is transmitted to all other cells in the network. Since any smooth muscle cell can be spontaneously active, a sheet of visceral muscle is normally partly contracted and has tone. It is found in the walls of small arteries and veins and lining the hollow viscera. Multi-unit smooth muscle is less common. It consists of individual fibres, each with their own motor nerve endings, and does not function as a network. Multi-unit fibres are found in the walls of large arteries and large airways, in erector pili muscles attached to hair follicles, and in the intrinsic eye muscles.

Ultrastructure

Striated muscle

The contractile proteins are myosin (molecular weight 450 kDa) and actin (molecular weight 43 kDa). Within a sarcomere, filaments of actin are attached to the Z line by actinin. Lying between the thin actin filaments are thick myosin filaments that are not firmly attached to anything. They are kept in place by huge elastic protein molecules of titin (the largest known protein with 25,000 amino acids) which stretch from one Z line to the next. The action of titin

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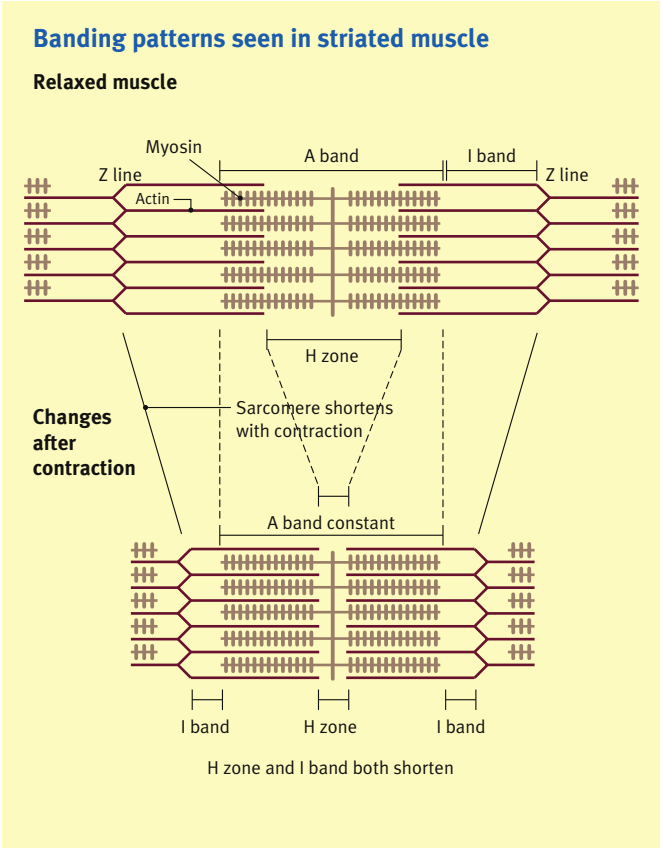

Figure 1

and nebulin (an inelastic giant protein lying alongside actin filaments and attached to one Z line of each sarcomere) ensures that actin and myosin are arranged in a very orderly way (Figure 1). Associated with actin filaments are two inhibitory proteins, troponin and tropomyosin, which prevent any uncontrolled reaction with myosin. The partial overlapping of actin and myosin results in distinct banding across each sarcomere (visible only under the electron microscope) of light areas (I band) where there is no overlap and dark areas (A band), where there is overlap. Actin filaments do not extend across the sarcomere, therefore the central region of the A band is lighter (H zone). The reaction between actin and myosin is responsible for the production of force and movement as the two types of filament are able to slide along each other, thus drawing the Z bands together and shortening each sarcomere and consequently the whole muscle fibre (Figure 1).

Smooth muscle

The contractile proteins, actin and myosin, are arranged in long bundles that extend diagonally around the cell, forming a lattice around the central nucleus. Owing to the oblique arrangement of filaments, smooth muscle cells become globular when they contract, rather than simply shortening. Actin filaments are not attached to Z lines but to dense bodies of protein in the cytoplasm at one end and to protein plaques in the cell membrane at the other end. Myosin filaments lie bundled within the long actin filaments. The ratio of actin to myosin filaments is 12:1 compared with 4:1 in skeletal muscle. Smooth muscle does not contain the inhibitory proteins troponin and tropomyosin.

Proteins involved in contraction

Myosin has at least 10 isoforms. Each myosin molecule consists of two heavy (2000 amino acids) alphahelical protein chains, wound together to form a rod-like tail, and two tadpole-like heads, S1, each connected to a flexible neck, S2. The S1 portion contains the active site that reacts with actin and the S2 portion allows movement of the head. Two lightweight protein chains are associated with each S1 head. Their function is unknown in striated muscle, but in smooth muscle they regulate contraction. One molecule of myosin is 150 nm long. About 250 molecules make up a thick filament in a sarcomere. The molecules are wound together in such a way that the S1 heads are clustered at each end of the thick filament, resulting in the central portion being just a bundle of myosin tails.

Actin the actin molecule is a globular protein (G-actin). The actin of the thin filament in a sarcomere is a polymerized form called F-actin. The thin filament is composed of two F-actin filaments wound together like two strands of beads. Each 'bead' of G-actin in the filament has a binding site for a myosin S1 head.

Tropomyosin(molecular weight 70 kDa) is an elongated protein polymer that is wrapped around the actin filament and partly obscures the binding sites. In such a position, myosin S1 heads bind only weakly and cannot create a power stroke.

Troponin is a complex of three proteins associated with tropomyosin. Troponin I is inhibitory, troponin T binds to tropomyosin

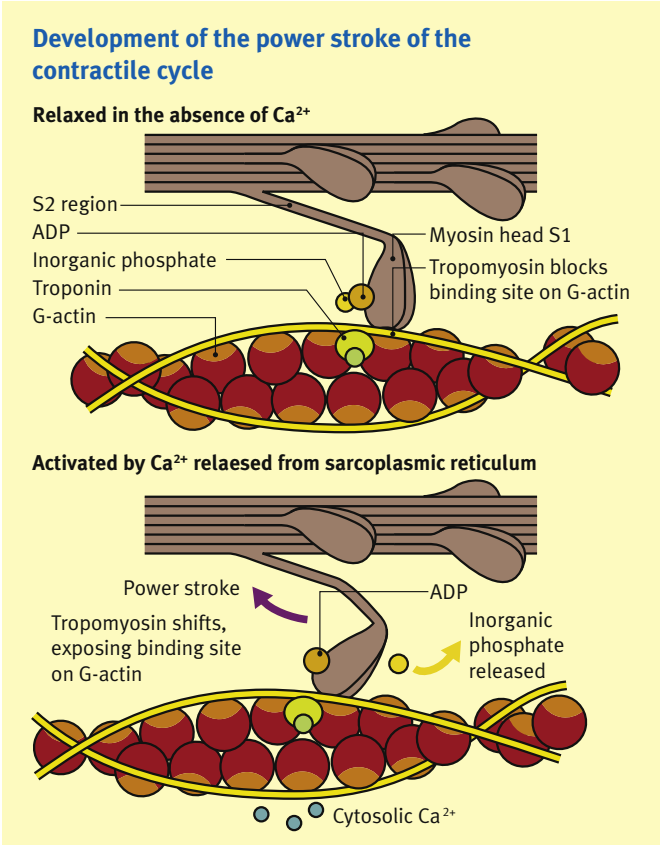

Figure 2

Excitation–contraction coupling

Excitation–contraction coupling is caused by the release of Ca^{2+} from the terminal cisternae of the sarcoplasmic reticulum

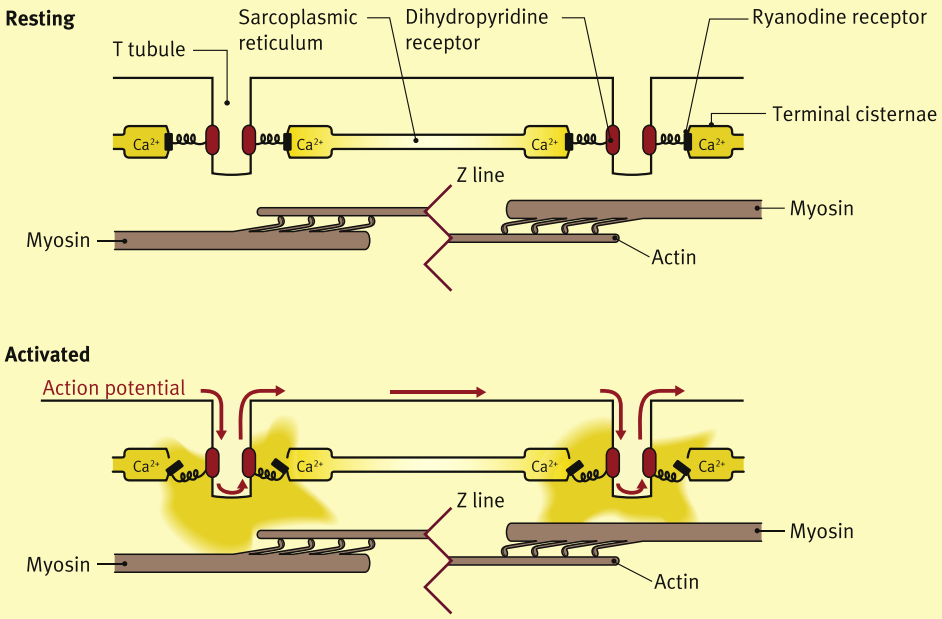

Figure 3

and troponin C binds reversibly to Ca_2^+. Ca_2^+ binding pulls tropomyosin away from the myosin-binding sites. In such a position, myosin S1 heads can bind and carry out their power stroke. Troponin and tropomyosin are absent from smooth muscle.

Sliding filament theory of contraction

When muscle is relaxed, the ends of the thin and thick filaments overlap slightly. As the muscle contracts, the thick and thin filaments slide past each other, moving the Z lines of the sarcomere closer together. The thick myosin filaments, seen as the A band, stay at a fixed length but the I band shortens as the actin slides into the myosin (Figure 1). The formation of cross-bridges between actin and myosin provides the power for this sliding movement. In the absence of ATP, the myosin S1 head is tightly bound to actin, called the rigour state. ATP, normally present in abundance in resting muscle, binds with the S1 head and releases it from actin (Figure 2). The nucleotide binding site on the S1 head hydrolyses ATP to adenosine diphosphate (ADP) and inorganic phosphate; both are retained at the site. The energy released rotates the S1 head on the flexible S2 region and it binds to a new site on the actin, one or two positions away from the G-actin where it started. At this point the S2 region is like a stretched spring ready to shorten. The power stroke begins when inorganic phosphate is released and the S2 region pulls the actin filament towards the centre of the sarcomere (Figure 2). To end the contractile cycle, myosin releases ADP and the myosin head is firmly bound to actin. The cycle continues to operate as long as the binding sites for cross-bridge formation are exposed. Therefore, control of contraction is linked to the regulation of troponin and tropomyosin. The contraction cycle is similar in smooth muscle even though it does not have sarcomeres, but the regulation of the cycle is different.

Excitation—contraction coupling

Skeletal muscle

The sarcoplasmic reticulum contains a high concentration of calcium owing to the activity of an inwardly directed calcium pump. The release of this calcium is the link between a muscle action potential and contraction. The sarcolemmal action potential travels into the centre of a muscle fibre along T tubules. At each triad, the depolarization activates voltage-sensitive dihydropyridine (DHP)-binding calcium channels. These activate ryanodine-binding calcium channels on the sarcoplasmic reticulum membrane. This activation, caused by either a physical link between the two types of calcium channel or calcium entering via the activated DHP channel, opens the ryanodine calcium channels and releases calcium from the sarcoplasmic reticulum (Figure 3). The calcium binds to troponin C, which moves tropomyosin on actin, exposes the actin binding sites and starts the contraction cycle. Provided the sarcoplasmic calcium concentration is kept high, by the repeated arrival of action potentials in the T tubules, the contraction cycle continues. However, as soon as the action potentials cease, calcium is rapidly sequestered back into the sarcoplasmic reticulum system, tropomyosin returns to cover the actin binding sites and the muscle relaxes.

Smooth muscle

In smooth muscle, initiation of the contraction cycle is different from that of skeletal muscle because it may take up to 500 ms after a smooth muscle action potential to produce the peak of tension. There are several reasons. Some of the calcium required to initiate the contraction cycle comes from the extracellular medium and some from the sarcoplasmic system, therefore the diffusion path is greater. A major cause of delay is that myosin in smooth muscle must be phosphorylated for the

activation of myosin ATPase. The pairs of myosin lightweight chains that appear to have no function in striated muscle regulate this process in smooth muscle. Calcium binds to calmodulin, which activates calmodulin-dependent myosin light chain kinase. This catalyses phosphorylation of the myosin S1 site, allowing myosin ATPase to be activated, and starts the contraction cycle between actin and myosin. Myosin is dephosphorylated by phosphatases in the cell but this does not necessarily lead to relaxation. There appears to be a latch bridge mechanism by which dephosphorylated myosin cross-bridges remain attached for some time after the cell calcium concentration has fallen, producing sustained contractions with little energy expenditure. Smooth muscle is unique in other ways because it is activated by stretch in the absence of external innervation and can adapt its tone to remain constant in the face of different amounts of stretch. ◆