Muscle

Introduction

Muscle is perhaps the most conspicuous part of our bodies, making up about half of our adult mass. The muscles we see as fleshing out the structure of our bodies are attached to our skeletons and represent only one of three types. Two of these, the skeletal and cardiac muscles, appear striped when viewed under the microscope because of the regular arrangements of the proteins (actin and myosin) which make up their contractile mechanisms. They are therefore referred to as striated muscle. The skeletal muscles which cause movement of our body about its joints are attached to the skeleton by tough connecting structures called tendons. Skeletal muscles are under our conscious control and are therefore sometimes alternatively referred to as voluntary muscle. This type of muscle, because in part it represents a large fraction of our mass, accounts for a quarter of our oxygen consumption at rest, this oxygen usage can increase 20 times during vigorous exercise. The cells which make up skeletal muscle are called fibres because of their extremely elongated shape. Muscle fibres have the power to shorten to an amazing degree. Shortening is brought about by the molecules of their cells sliding between each other. When a whole skeletal muscle shortens, not all its fibres necessarily participate. A whole skeletal

muscle is made up of groups of fibres called motor units, each commanded by a single motoneurone; as the demand for tension is increased, more and more of the members of this 'team' are recruited. It is common experience that our voluntary muscle can fatigue, although different muscle fibres have different abilities to resist fatigue.

Cardiac muscle on the other hand has built-in protection against fatigue, although even it can be worked beyond its considerable powers of endurance. Uniquely situated in the heart, it is important that all the cells of this muscle type act in unison. To ensure this synchronization, all cardiac muscle cells are in electrical contact with each other and contract spontaneously, independently of motor nerves, although nerves of the autonomic system influence the rhythm of this contraction.

The third type of muscle found in our bodies is smooth muscle, so called because its contractile structures, although the same as those found in skeletal and cardiac muscle, are not arranged in a regular way and so do not form striations. Smooth muscle is inconspicuous because it is largely restricted to internal organs but is important because these organs include arteries, veins, the urinary bladder and gut. Smooth muscle exhibits properties which make it well suited to form the walls of these hollow organs and its activity is in many cases spontaneous but modulated by hormonal and neural control.

Section overview

This section outlines:

- The three basic muscle types, their origins, development and differences
- The division of a voluntary muscle into its parts by connective tissue
- The structure of the myofilaments of actin and myosin which interdigitate to give striated muscle its striped appearance
- How Ca^{2+} controls contraction and how contraction is released
- Sliding filament theory and how this depends on crossbridge formation
- Details of crossbridge cycling powered by ATP
- Triggering of contraction by excitation–contraction coupling
- Elastic properties of muscle, which exist even when it is not contracting
- Isotonic and isometric contractions which can be pre- or afterloaded
- The energetics of contraction and how an O_2 debt develops
- Two major types of voluntary muscle slow-twitch and fast-twitch
- Training effects and heat production
- The consequences of less organized smooth muscle general structure on its microscopic appearance and contractile properties
- Differences in innervation of the two types of smooth muscle
- How excitation and inhibition of smooth muscle differs from that of voluntary muscle
- The contractile mechanisms and mechanical properties of smooth muscle.

Cardiac muscle is dealt with in detail in Section 6.

Origin and types

2.1

Introduction

Movement is a universal characteristic of living material and may have evolved from the changing shape shown by some enzyme and protein molecules when they are involved in energy exchanges, usually linked to ATP.

Movement of this type – at a cellular level – drives the slow migration of the elements of the mitotic spindle in cell division, and displays several characteristics of the more rapid movements of the structures within muscles.

Muscle is a tissue with a very ancient history. The anaerobic biochemical pathways used by our muscles when the energy demands on them exceed their oxygen supply are probably the same as those used by cells over 3500 million years ago, before oxygen became a constituent of the earth's atmosphere. The humble and ancient amoeba extended its pseudopodia through primeval seas using the same body chemicals and energy sources that activate your fingers to turn these pages. Even the primitive ciliated organisms of prehistory caused their cilia to beat by mechanisms which can claim lineage with the basic mechanism that slides one filament of our muscles over another, causing them to contract (the protein involved in the cilium, dynein, is slightly different from that in our muscles but the principle is the same).

Basic Science 2.1.1

Muscle forces

Muscles are involved in producing forces, and consequently produce stress and strain within themselves and their tendons.

Force (L. *fortis* – strong). Force is an ambiguous concept, the meaning of which everyone understands but few can define. We can do worse than use one of the Oxford English Dictionary's definitions: 'an agency or influence that produces or tends to produce a change in the motion of a moving body, or produces motion or stress in a stationary body'.

When an external force is applied to a body it either moves or, if it is standing on a surface, say, and the applied force cannot produce movement, a reactionary force is generated such that the body is distorted by the two forces. In this case, the body's molecules are displaced from their rest positions. They tend to return to their original position and this tendency accounts for the **elasticity** of a body.

Stress is a measure of the cause of a deformation, and is defined by:

$$\text{Stress} = \frac{\text{Force}}{\text{Area}}$$

The unit of stress is the pascal (Pa) or the newton per square metre (N/m^2): 1 Pa = 1 N/m^2.

Thus the stress on a muscle depends not only on the force it is producing but also on its cross-sectional area.

Strain is a measure of the extent of deformation, and is defined by:

$$\text{Strain} = \frac{\text{Change in dimension (length say)}}{\text{Original dimension}}$$

Muscles make up about half of the body mass and account for a large but extremely variable fraction of the body's metabolism (25% at rest). Skeletal muscle can alter its metabolic rate more than any other tissue, increasing its activity to more than 20 times its rest level. The demands for oxygen and nutrients and the need to remove metabolites and heat increase in step with this change in activity, and vigorous muscular activity is accompanied by increased activity in those organs which service the muscle's requirements.

Types of muscle

Muscle exists in three basic types:

- skeletal (voluntary) } striated
- cardiac (heart) } striated
- smooth (involuntary) unstriated.

Development

All three types show their common origin in the embryo where mesodermal cells called **myoblasts** form **somites**, the origins of **skeletal muscles** (except those of parts of the head and limbs), and cells which, early in development, migrate to form the smooth and cardiac muscles of the body.

From the fifth to the eighth week of human embryonic development, muscles differentiate into their mature shapes and positions in the body. The paired somites (Fig. 2.1.1), which develop into the majority of skeletal muscles, are made up of distinct layers which form very different parts of the embryo. The **dermatome** (Gr. skin slice) develops into connective tissue, including the dermis of the skin. The **sclerotome** (Gr. hard slice) migrates to spaces around the developing spinal cord where it forms connective tissue.

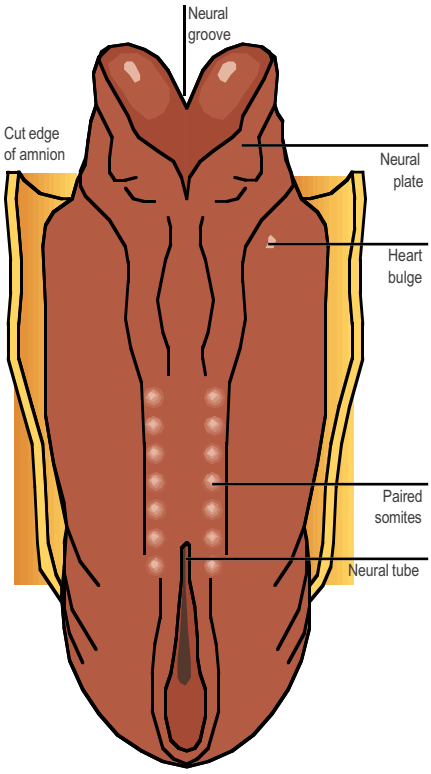


Fig. 2.1.1 **Dorsal view of 21-day-old embryo.** The paired somites are seen on either side of the neural tube.

The **myotome** (Gr. muscle slice) or middle layer of each somite is made up of cells which come to lie parallel with the long axis of the embryo and eventually differentiate into the majority of the skeletal muscles of the body. Some of the muscles of the anterior part of the body, however, are derived from branchial (gill) arch cells. Like the two other types of muscle, **smooth muscle** develops from the middle layer of the three-layered early embryo (the mesoderm).

Rather than forming paired somites like skeletal muscle, or developing at a single site like **cardiac muscle**, the primitive mesodermal cells of smooth muscle migrate to the linings of the developing digestive, vascular, respiratory, urinary and reproductive organs; and to the millions of individual sites in the skin where they will make up the arrector pili muscles associated with single hairs.

Cardiac muscle develops very early, probably because the embryonic circulatory system is called upon even before the third week after fertilization to fulfil the nutritional and respiratory needs of the embryo. A tube of endocardium becomes covered with muscular myocardium and twisted into an S shape which by the fourth week can be seen to be dividing into functional segments.

We can see that even at this early age the muscles of our body are set along very different paths from their common mesodermal origin toward their final varied functions. Nevertheless, the prime function of muscle of any type to contract, depends on a common 'sliding filament' mechanism, even though smooth muscle shows ingenious adaptations which enable it to be 'latched' or locked in a contracted state to save energy. This common sliding filament mechanism is built up in different ways to provide the varied structural basis of varied function. Thus in smooth muscle there is no practical limit to the distance the filaments can slide relative to each other and this gives smooth muscle its superior extensibility compared with skeletal or cardiac muscle. This difference is clearly seen in the way regularly repeated molecular structures of the sliding filaments give skeletal and cardiac muscle their striated appearance while smooth muscle structure has, until recently, eluded definition because, in part, of its irregular nature.

Innervation

The innervation of the types of muscle found in our bodies reflects the differences in the muscle fibres themselves. Skeletal muscle, utilized for immediate and rapid action or postural maintenance, is innervated by large-diameter motor nerves which can rapidly recruit more and more fibres to provide the force required. Smooth muscle on the other hand shows a degree of automatic contraction in response to stretch of

the hollow organs it surrounds, and can also respond to activity in both branches of the autonomic nervous system, hormones in the blood, and intrinsic slow waves of membrane depolarization and repolarization. Cardiac muscle shows the extreme case of this independence from innervation and sets its own rate of contraction and relaxation that makes up the cardiac rhythm, although this is modified extensively by autonomic nerves.

Subdivisions

The three major types of muscle can themselves be subdivided:

- skeletal muscle into white, fast-twitch muscles and red, slow-twitch muscles suitable for prolonged and steady contraction (although most human muscles are a mixture of both)
- smooth muscles into 'single-unit' (unitary), where large numbers of cells are united to form a sheet or mass, and 'multi-unit' where each fibre operates independently, usually in response to its individual innervation
- cardiac muscle into contractile cells that make up the atria and ventricles and those that conduct electrical impulses in the heart, have lost most of their contractile ability, but are muscle cells nevertheless.

A comparison of some of the properties of types of muscles is made in Table 2.1.1.

Table 2.1.1 Differences between muscle types

Alternative names	**Skeletal** **Voluntary** **Striated**	**Cardiac** **Heart**	**Smooth** **Visceral** **Unstriated**
General structure	Bundles of cells with some connective tissue	Syncytium with little connective tissue	Sheet of cells or individual cells in connective tissue
Connection	Both ends to bones	To itself to form cavity	To itself to form cavity or tube
Cell size	10–100 μm diameter Very long (cms)	10–20 μm diameter 50–100 μm long forming a syncytium	2–5 μm diameter 100 μm long
Nuclei	Many per cell	One	One
Intracellular filaments	Regularly organized parallel to long axis of cell	Regularly organized parallel to long axis of cell	Run in many directions
Filament attachment	Intracellular Z-disk	Intracellular Z-disk	Dense bodies and dense bands
Mechanical connection of cells	In parallel. Can function independently	Connected end to end and in parallel. Function as a unit	Mechanically linked, all bear same stress
Innervation	Motor fibres	Autonomic	Autonomic
Effect of innervation on contraction	Contraction totally dependent on innervation	Innervation modifies contraction	Innervation initiates or modifies contraction

Table 2.1.1 *(continued)*

Alternative names	Skeletal Voluntary Striated	Cardiac Heart	Smooth Visceral Unstriated
Neuromuscular junction	Motor endplate	Free nerve terminals	Free nerve terminals and varicosities
Electrical activity	Stereotype brief action potential	Stereotype sustained action potential	Slow changes in membrane potential and action potentials
Excitation–contraction coupling	Troponin	Troponin	Calmodulin
Source of Ca^{2+} for contraction	Sarcoplasmic reticulum	Sarcoplasmic reticulum and extracellular fluid	Mainly ECF
Speed of contraction	Voluntarily controlled, fast or slow	Autonomically controlled, fast or slow	Generally slow
Metabolic cost of contraction	High	High	Low

Summary

Differences and similarities between muscle types

- Muscle exists in three types – skeletal, cardiac (both striated) and smooth (unstriated).
- All types originate from the embryonic mesoderm.
- All muscular contraction depends on a common 'sliding filament' mechanism.
- The muscle types show clear differences in the way their cells are connected, their innervation, type of electrical activity and speed of contraction.
- The three major types can be further subdivided in terms of their metabolic, electrical and mechanical properties.

Striated muscle

2.2

Introduction

Skeletal and cardiac muscles are striated because the orderly arrangement of the contractile proteins **actin** and **myosin** which make up the majority of their bulk gives them a striped (striated) appearance of light and dark bands. We will first consider skeletal muscle (sometimes called voluntary muscle because it is usually consciously activated). Cardiac muscle is dealt with in detail in Section 6 in the context of the structure and function of the heart.

The parts of a muscle

A skeletal muscle is made up of very many individual multinucleate muscle cells or **fibres**, so called because of their elongated shape (Fig. 2.2.1). These are made up of the functional units of striated muscle the **myofibrils**, which in turn are made up of the contractile mechanisms of muscle, interacting myosin and actin filaments.

The individual muscle cells are held together by fibrous connective tissue, **fascia**.

The connective tissue which covers the whole skeletal muscle is **epimysium**. That which separates the muscle fibres into bundles (fasciculi) is **perimysium** and that which covers individual muscle fibres (single muscle cells) is **endomysium**. These connective tissues are continued beyond the body of the muscle, gradually blending into a **tendon** which attaches the

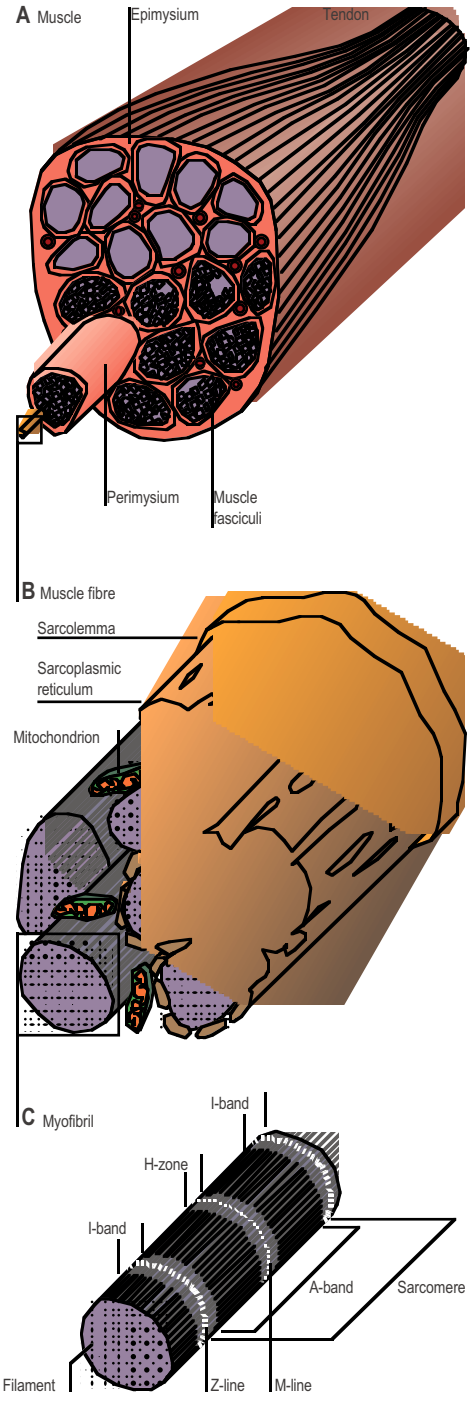


Fig. 2.2.1 The parts of a muscle. The component parts of a voluntary muscle, from the functional units (myofibrils) to the epimysium which contains the whole muscle and is continuous with the tendons of origin and insertion. **A.** Muscle. **B.** Muscle fibre (cell). **C.** Myofibril.

skeletal muscle to bone or cartilage. Tendons which are in the form of thin sheets are called **aponeuroses**. The tendon attaching a muscle to a stationary part of the body, the body trunk for example, is called the **origin**. The more mobile tendon is the **insertion** and is usually distal.

The arrangement of the cells in a skeletal muscle is ideally suited to producing a controlled, graded response to order. The cells are enormously long and all are parallel to each other. Each cell is part of a motor unit consisting of those cells activated by a single motoneurone. A muscle is made up of many motor units. Thus the force exerted by an individual muscle is determined by the number of motor units activated and the intensity of that activation.

Skeletal muscles almost invariably come in opposing pairs. A skeletal muscle cannot return to its rest length of its own accord after

Summary

Structure of striated muscle

- A striated muscle is made up of fasciculi made up of fibres made up of fibrils made up of filaments.
- Muscle fibres (muscle cells) are bound together by connective tissue endomysium, the fasciculus so formed is covered by perimysium and the bundle of fasciculi which makes up a muscle is covered by epimysium.
- A striated muscle cell contains many nuclei.
- The connective tissue covering the contractile elements of a muscle blend together to form the proximal tendon of origin and the more distal and mobile tendon of insertion.
- Skeletal muscles usually come in opposing pairs because a muscle cannot return to its rest length of its own accord and must therefore be stretched.

contracting, but must depend on an opposing muscle or gravity to stretch it. Similarly, smooth and cardiac muscle in the walls of hollow organs rely on internal pressure to stretch them back to their rest length after contracting.

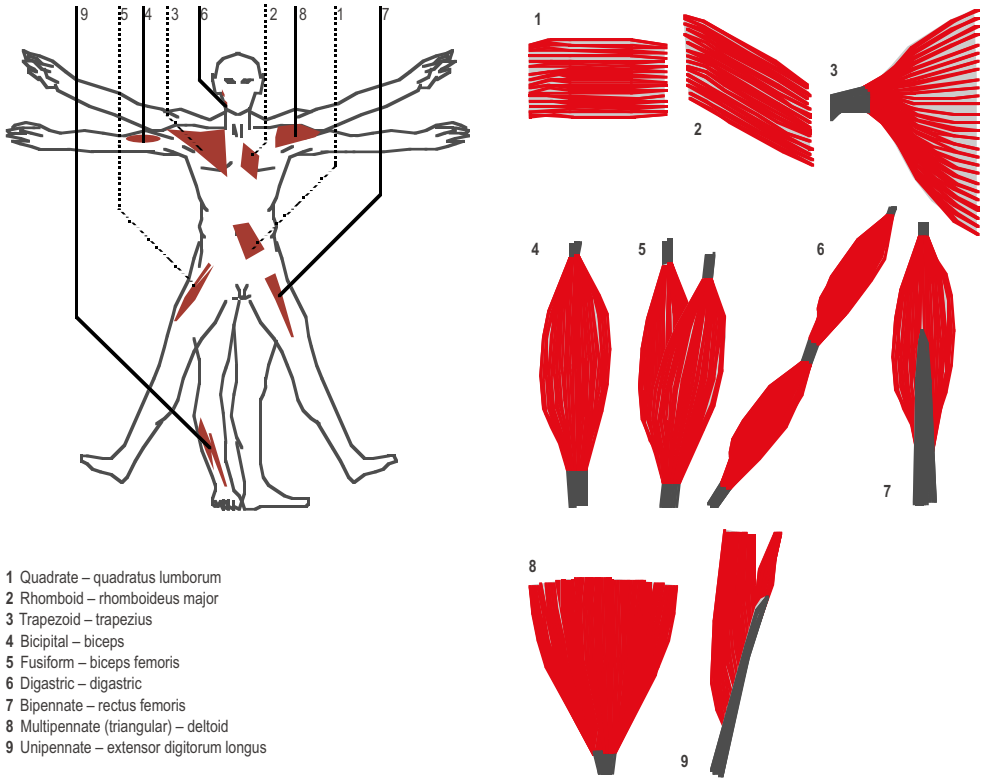
Skeletal muscles (Fig. 2.2.2) are often described, rather fancifully, in terms of their shape, as, for example, pennate (feather-like) or digastric (two stomachs).

Fine structure of a muscle

Functional units

The major characteristic of skeletal muscle is its ability to produce tension and shorten in a controlled fashion. This graded response results from activation of increasing numbers of functional units (motor units) within the whole muscle.

The cells of skeletal muscle are very long (see Fig. 2.2.1), often extending the whole length of the small muscles (although several end-to-end are required to extend the length of most muscles), and very thin, 10–100 µm in diameter. The muscle cell is multinucleated with sometimes as many as several hundred nuclei in a single fibre. Large muscles contain large-diameter fibres while small muscles contain small-diameter fibres. The diameters of all fibres in a particular muscle are about the same. All these cells lie parallel with the long axis of the muscle.



1 Quadrate – quadratus lumborum
2 Rhomboid – rhomboideus major
3 Trapezoid – trapezius
4 Bicipital – biceps
5 Fusiform – biceps femoris
6 Digastric – digastric
7 Bipennate – rectus femoris
8 Multipennate (triangular) – deltoid
9 Unipennate – extensor digitorum longus

Fig. 2.2.2 Muscle types. The architecture, and naming, of muscle types, is closely related to the function of the muscle. A strap muscle, for example, has all its fascicles running parallel to the long axis of the muscle. Pennate (feather-like) muscles have many short fascicles set at an angle to a tendon which extends the whole length of the muscle. Circular muscles, which do not attach to a tendon, are a rather rare form of voluntary muscle and include the orbicularis oris which encircles the mouth, the orbicularis oculi which surrounds the eye and the muscles of the external anal sphincter.

Clinical Example

Duchenne muscular dystrophy

The muscular dystrophies are a group of inherited diseases which usually affect skeletal but occasionally cardiac muscle. The Duchenne form affects only boys and the locus of the defect has been identified on the Xp21 region of the X chromosome. It occurs in 1 in 3000 boys, both as a result of inheritance and, in 1 out of 3 cases, as a result of spontaneous mutation. The sister of an affected individual has a 50% chance of carrying the defective gene and a 70% chance of having raised creatine phosphokinase levels in her blood. Accurate carrier and prenatal diagnosis can be made using cDNA probes that are co-inherited with the dystrophic locus on the gene.

The result of this defect is the absence of dystrophin, a rod-shaped protein that is part of the muscle cytoskeleton. Muscle biopsy shows disorder of the cytostructure of the cells with some fibres becoming hypertrophic and others atrophic. There is fibre necrosis and replacement of fibres by fat. The deposition of large amounts of fat and connective tissue gives this disease the alternative name of pseudohypertrophic muscular paralysis.

The condition is usually obvious by the age of 5 with the boy showing great weakness, so much so that he has to 'climb up his legs with his hands' to stand upright (Gower's sign). There is no cure. The boy is usually severely disabled by the age of 10 with the myocardium becoming affected and he seldom survives beyond his teens. Death commonly results from involvement of the respiratory muscles.

Within each cell are thick and thin **myofilaments** which are the physical basis of muscle contraction. The cytoplasm surrounding the myofilaments is the **sarcoplasm**. The muscle cell, and therefore the myofilaments within it, is divided at very regular intervals along its length into **sarcomeres**. The sarcomeres are separated by Z-disks which segment the muscle cell into compartments, somewhat like a tube train is divided into compartments. In histological sections, these disks are cut through and appear as **Z-lines**. To the Z-lines are attached thin actin myofilaments held in strict hexagonal array. The light **I-band** seen in a micrograph of striated muscle (Fig. 2.2.3) extends from either

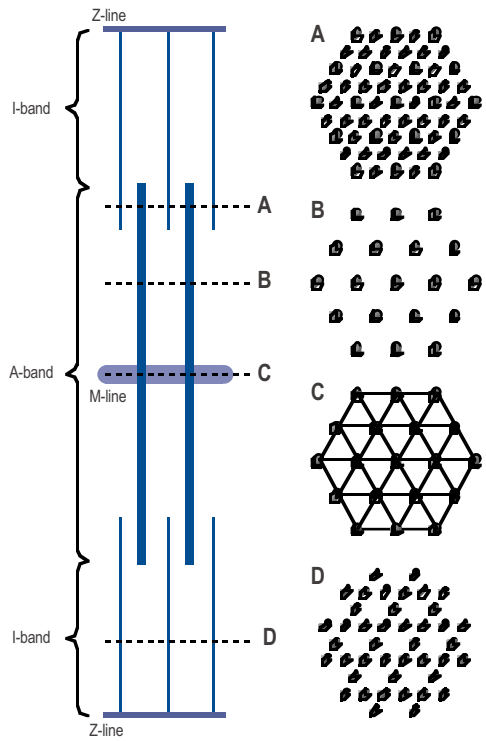


Fig. 2.2.3 **Structure of a sarcomere.** The light and dark bands of a sarcomere, extending between two Z-lines, are the result of the presence of:

- actin filaments only (I-band)
- actin and myosin filaments (A-band)
- myosin filaments only (H-zone).

side of the Z-line to the beginning of the thick myosin myofilaments which make up the **A-band**. The width of the I-band and the light **H-zone** in the centre of the sarcomere depend on the state of contraction of the muscle. A disk of delicate filaments, the **M-line**, in the middle of the H-zone holds the myosin myofilaments in position, each surrounded, outside the H-zone, by six actin filaments.

Structure of the myofilaments

The actin filaments which stretch from the Z-lines consist of two helical strands of **F-actin**, each made up of approximately 200 units of globular **G-actin**. The whole is like two strands of a bead necklace twined together (Fig. 2.2.4A). On each of the 'beads' is a site where myosin can bind during contraction. Laid along the

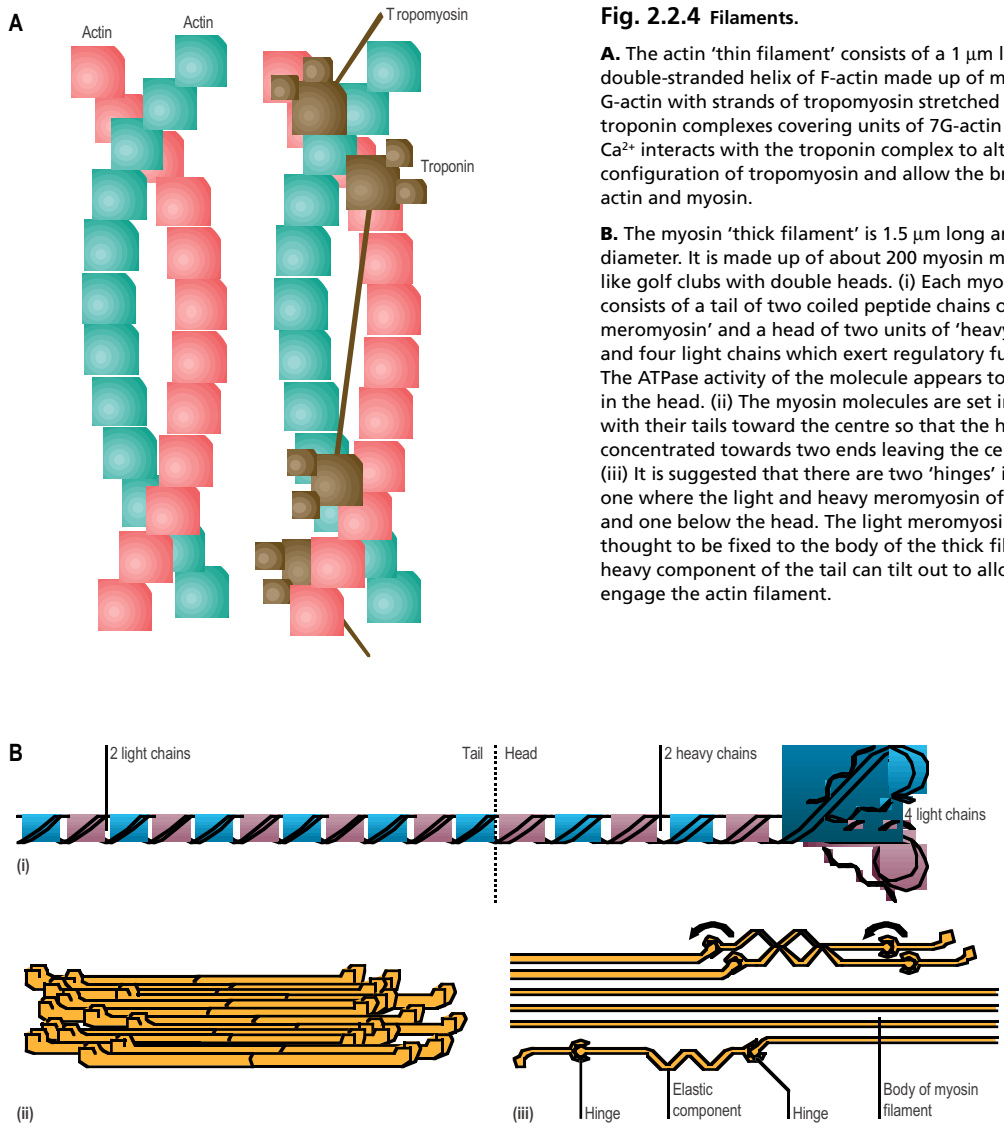


Fig. 2.2.4 **Filaments.**

A. The actin 'thin filament' consists of a 1 μm long double-stranded helix of F-actin made up of molecules of G-actin with strands of tropomyosin stretched between troponin complexes covering units of 7G-actin molecules. Ca^{2+} interacts with the troponin complex to alter the configuration of tropomyosin and allow the bridging of actin and myosin.

B. The myosin 'thick filament' is 1.5 μm long and 15 nm diameter. It is made up of about 200 myosin molecules shaped like golf clubs with double heads. (i) Each myosin molecule consists of a tail of two coiled peptide chains of 'light meromyosin' and a head of two units of 'heavy meromyosin' and four light chains which exert regulatory functions. The ATPase activity of the molecule appears to be concentrated in the head. (ii) The myosin molecules are set in the filament with their tails toward the centre so that the heads are concentrated towards two ends leaving the centre portion bare. (iii) It is suggested that there are two 'hinges' in the molecule, one where the light and heavy meromyosin of the tail meet and one below the head. The light meromyosin of the tail is thought to be fixed to the body of the thick filament and the heavy component of the tail can tilt out to allow the head to engage the actin filament.

grooves between the two actin strands and governing their binding to myosin are two strands made up of **tropomyosin**, a long molecule stretching along seven G-actin 'beads', and alternating with molecules of **troponin**, which has affinities for actin, tropomyosin, and calcium.

The tropomyosin is like a cable slung between pylons of troponin, which govern the cable's position and are themselves, in turn, controlled by Ca^{2+} concentration.

The myosin filaments that make up the A-band of a sarcomere, and are each surrounded by six actin filaments, are of a very different structure. They consist of approximately 100 myosin molecules, each shaped like a golf club with a double head. About 50 molecules have their 'heads' pointing in one direction, and 50 point in the other (Fig. 2.2.4B(ii)). The 'head' of the molecule is hinged and the shaft is capable of shortening. ATPase in the heads can release energy from ATP and cause the head to bind to the active site on an actin molecule. This connection is called a **crossbridge**. Because the myosin heads are all concentrated at the two ends of the filament, the centre cannot form crossbridges and makes up the central part of the H-zone of the sarcomere.

Summary

Structure of striated cells

- The cytoplasm of a muscle cell is called sarcoplasm and contains long, thick and thin myofilaments parallel with the long axis of the cell.
- The overlapping of these filaments gives voluntary muscle its striped appearance.
- The structures between two Z-lines make up a sarcomere.
- Myofilaments are thick (myosin) or thin (actin).
- The interaction between thick and thin filaments which brings about contraction is the result of formation of crossbridges – a result of the interaction of tropomyosin and Ca^{2+}.

Cell membrane systems – the supply of Ca^{2+}

Packed between the myofibrils are numerous mitochondria and glycogen granules as might be found in many other types of active cell. However, muscle cells have a unique arrangement of regular invaginations of the sarcolemma which project into the fibre and wrap round the sarcomeres where the actin and myosin filaments overlap. Being continuous with the exterior of the cell, these **transverse** or **T-tubules** contain extracellular fluid. Near the T-tubules, the smooth endoplasmic reticulum, the **sarcoplasmic reticulum**, a specialized part of the intracellular network of tubules, is enlarged to form **terminal cisternae** which actively transport calcium ions from the sarcoplasm into their lumen. A T-tubule and its two adjacent cisternae are called a **triad** (Fig. 2.2.5).

The mechanism of contraction

Sliding filaments

When muscles shorten, the filaments of actin and myosin which make up a sarcomere do not shorten; rather they slide past each other like the fingers of two hands interdigitating. Actin and myosin molecules bind strongly to each other both in vitro and in vivo. In muscle this binding of myosin heads to the actin chain must be cyclical and involve many repeated shortenings of the myosin shaft to make up the substantial contraction of a whole active muscle.

The crossbridge cycle

This repeated binding, shortening, releasing and re-binding of crossbridges is something like a man climbing hand-over-hand up a rope

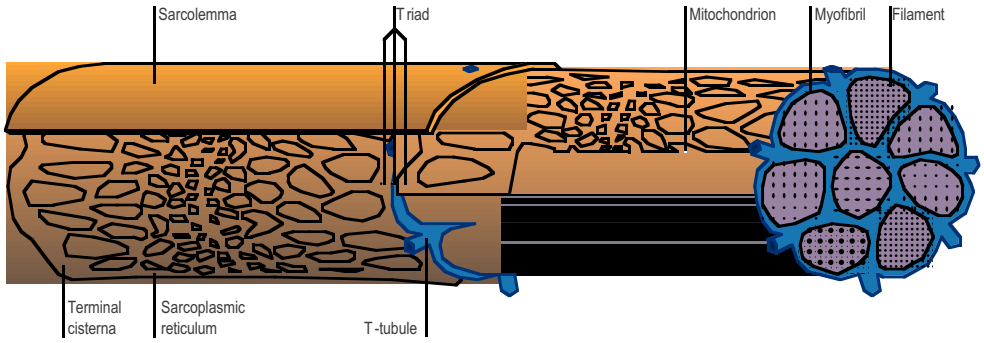


Fig. 2.2.5 **Triads.** The tubular system of a sarcomere consists of an intracellular sarcoplasmic reticulum which is made up of branching longitudinal tubes which enlarge into terminal cisternae where they abut the extracellular transverse, T-tubule system at the A-band–I-band junction. During contraction the junction moves in relation to the triads.

(Fig. 2.2.6). Recent research suggests that the myosin filaments rotate as they interact with the six actin filaments that surround them and bond with alternate myofilaments. So it may be more like a man climbing up six ropes but grasping only three.

In this **sliding filament theory** of muscle contraction, crossbridges are formed asynchronously so that some are 'gripping' while others are 'changing their grip'. This enables tension to be sustained. Myosin heads, which form crossbridges, only occur at the ends of the myosin filaments. This explains the fall off of tension with length on either side of a maximum value when a muscle is stimulated (Fig. 2.2.7).

Overstretching muscle does not allow the optimum number of crossbridges to make contact (Fig. 2.2.7(a)). Below the optimal length, crossbridges on the myosin are covered by actin filaments 'going the wrong way' (Fig. 2.2.7(b)), and eventually the myosin filament extends the whole length of the sarcomere (Fig. 2.2.7(c)), and can go no further.

The activity of the actomyosin crossbridges which bind actin filaments to myosin represents the fundamental process converting chemical energy into contraction by muscle. Each crossbridge has essential structural features which are involved in the contraction cycle. These

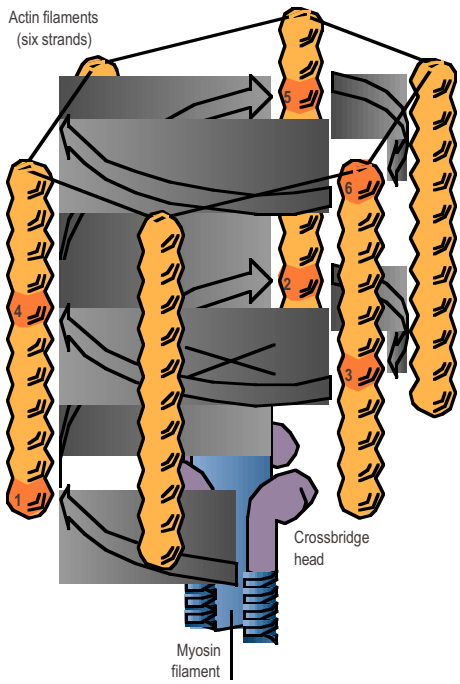


Fig. 2.2.6 **A myosin head 'climbing' its six actin filaments.** The myosin crossbridge binds with alternate actin filaments of the six that surround its myosin filament. The crossbridges on the myosin come in pairs at 180° to each other (like a nail driven right through a rod of wood), at 14.3-nm intervals along the filament, and with each pair turned through 120°. Therefore, in a straight line along the myosin filament, crossbridges occur directly underneath each other at every third interval ($3 \times 14.3 = 42.9$ μm).

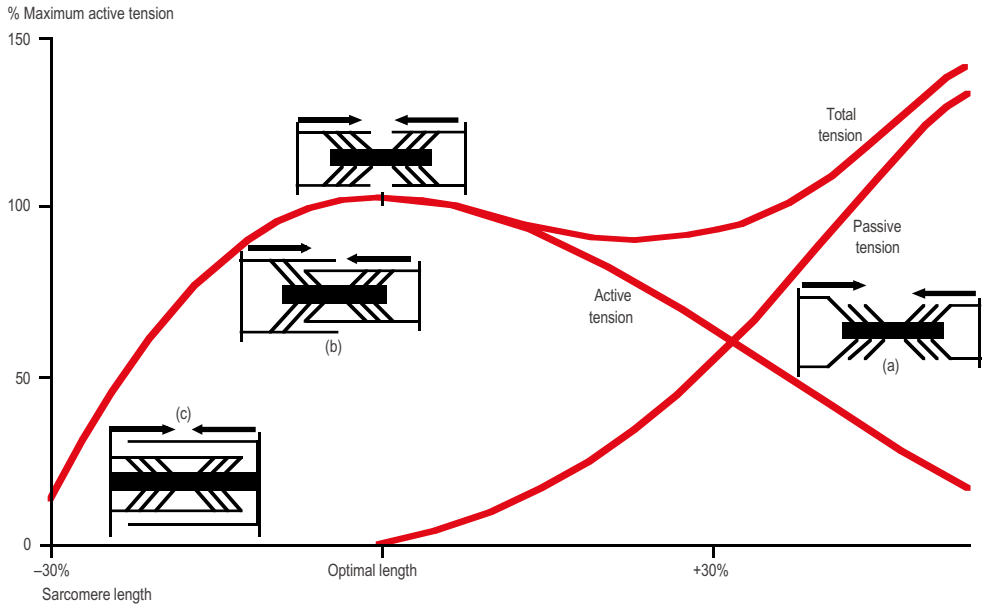


Fig. 2.2.7 **Length/tension of skeletal muscle.** The passive (due to stretching of elastic elements), active (due to contraction of sarcomeres alone) and total (sum of passive + active) tension in a skeletal muscle in relation to the optimal length for active tension production. The submaximal tension of the active curve on either side of the optimal length is due at (a) to the sarcomeres being so stretched that the filaments do not overlap and crossbridges cannot form, (b) the filaments overlapping to such a degree that crossbridges at the ends of the myosin filaments meet actin filaments 'coming in the wrong direction', (c) the myosin filament stretching from end to end of the sarcomere.

include a double head of myosin which contains the ATPase activity of the crossbridge and the potential to bind strongly to actin while at the same time rotating hinge-like relative to the crossbridge shaft (Fig. 2.2.8).

The shaft itself also has a 'hinge' where it joins the myosin filament, and elastic properties which can store energy when put under tension by rotation of the crossbridge head. X-ray diffraction studies demonstrate that the crossbridges form a spiral along the myosin filament with an interval of 14.3 nm between bridges. This interval is so tiny it will be clear that each bridge will have to 'pull itself along' the actin filament many times to produce any significant shortening of the whole muscle. The cyclic nature of this 'hand-over-hand' activity is probably as follows, and shown in Figure 2.2.8.

In resting muscle the crossbridge lies parallel to the myosin filament with its head perpendicular to it and not attached to the actin filament (1 in the cycle).

When contraction is triggered by release of Ca^{2+} from the sarcoplasmic reticulum (see below) the actin filament can accept the myosin head, which swings out to bind with it (2 in the cycle).

After attachment, the head tilts (3) using the energy stored in the myosin–ADP–P complex of the head. This is the power stroke of the crossbridge which stretches its elastic component to provide the energy to drag the actin filament along (4). ADP and P are released at this time which means that the head is primed to accept another ATP molecule which will cause it to detach (5).

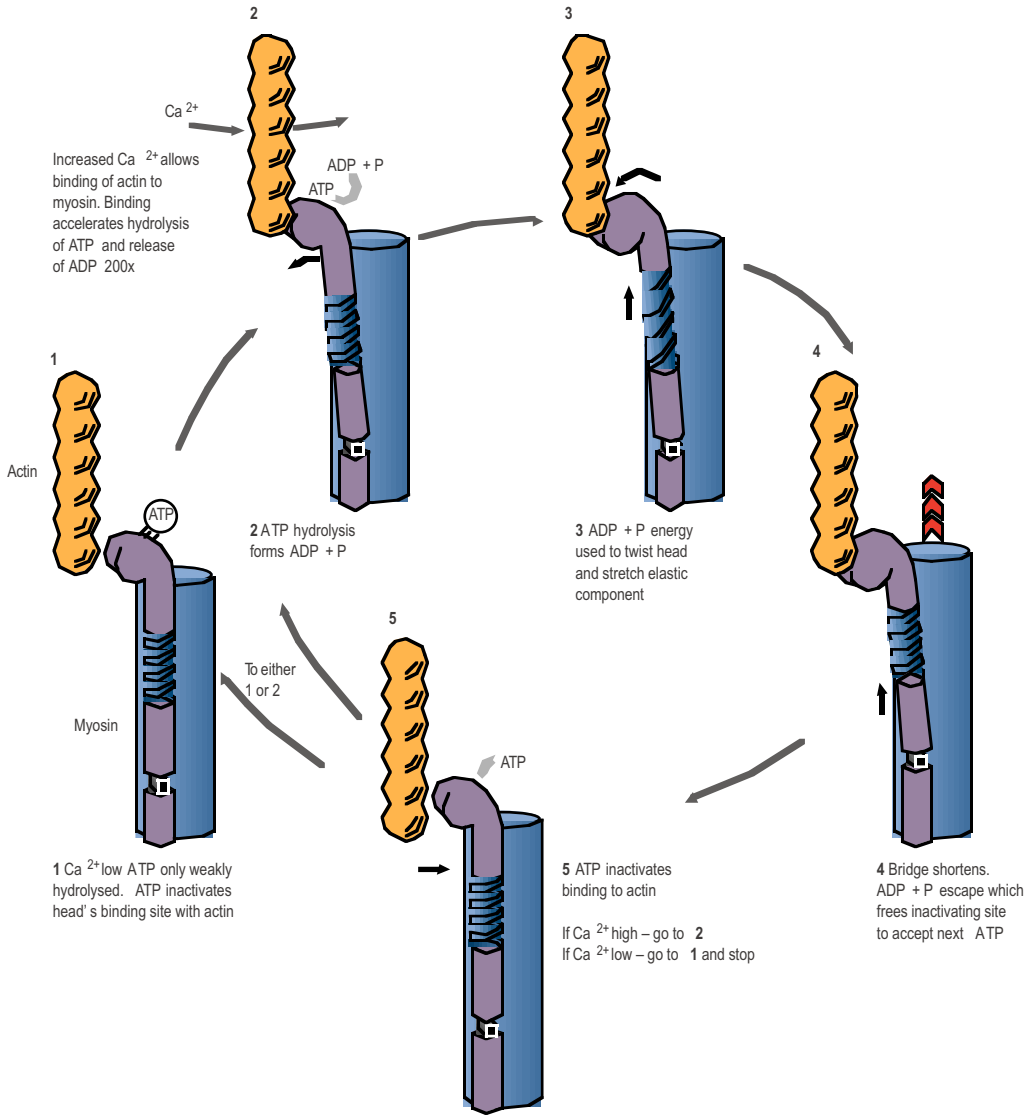


Fig. 2.2.8 **The crossbridge cycle and the reactions which provide its energy.**

Step 1. When Ca^{2+} concentration is low (less than 10^{-7} M), ATP in the crossbridge head is only weakly hydrolysed. The binding site on the actin filament is also blocked, so only weak, if any, crossbridges are formed.

Step 2. Elevated levels of Ca^{2+} allow the binding of the crossbridge head to the actin filament. Actin is a cofactor for myosin ATPase, increasing the rate-limiting step for hydrolysis and increasing by 200 times the release of ADP and P. Liberation of P binds the crossbridge more tightly.

Step 3. Energy from the hydrolysis of ATP causes the head of the crossbridge to twist, which stretches the elastic component of the shaft.

Step 4. The elastic component retracts drawing the actin filament along – this is the shortening step. ADP and P escape from the head, freeing the site for another molecule of ATP.

Step 5. The arrival of a new molecule of ATP in the crossbridge head releases its binding from the actin filament. Things can now go one of two ways. If Ca^{2+} is abundant, binding sites are still exposed on the actin and the cycle continues with attachment at a new binding site. If Ca^{2+} has been reabsorbed into the sarcoplasmic reticulum, the ATP is not fully hydrolysed and inhibits strong binding.

The cycle will continue until Ca^{2+} is removed by control systems which bring about relaxation or until ATP is exhausted and the muscle goes into **rigor**, as in **rigor mortis** of death when a large percentage of crossbridges remain attached to the actin filaments. ATP therefore acts at two points in the process of contraction:

1. it provides energy for contraction, and
2. it detaches the crossbridge from actin to allow the attachment–contraction–detachment cycle to be repeated. This is known as a plasticizing effect.

The energetics of a crossbridge cycling is outlined in Figure 2.2.8. The absolute permissive role of Ca^{2+} in allowing crossbridge formation is being questioned. It is now thought that up to 25% of the myosin heads maintain a weak binding even during relaxation and the block of crossbridge formation in the absence of Ca^{2+} is not as complete as was once supposed.

Summary

Initiation of striated muscle contraction

- Within a sarcomere, transverse T-tubules are sandwiched between terminal cisternae to form triads which control calcium levels in the sarcoplasm.
- Increased Ca^{2+} levels in the sarcoplasm initiate muscle contraction.
- Contraction is brought about by the sliding of actin and myosin filaments over each other.
- Sliding of filaments is brought about by the cyclic formation, shortening and release of crossbridges.
- Crossbridge formation is powered by the hydrolysis of ATP.

Triggering and types of contraction

Triggering contraction

The mechanism by which an action potential produced in the sarcolemma at the neuromuscular junction (see Section 3) triggers contraction of a muscle is called **excitation–contraction coupling**.

The interaction of Ca^{2+} with troponin, which holds tropomyosin in place, covering the binding sites for myosin crossbridges on actin, is central to this process.

When a muscle fibre is at rest, the sarcoplasmic reticulum pumps Ca^{2+} out of the sarcoplasm into the cisternae where most of it is stored by binding reversibly to a protein, **calsequestrin**. Ca^{2+} in the sarcoplasm is reduced to 0.1 µmol/l, which is below the level which influences troponin orientation. To initiate contraction, a muscle action potential initiated by a motor nerve spreads rapidly over the sarcolemma and into the transverse tubules, opening Ca^{2+} channels in the membrane.

Ca^{2+} floods out into the sarcoplasm, raising the concentration to more than 10 µmol/l, saturating binding sites on troponin. Activating these sites on troponin molecules causes them to allow the tropomyosin molecules strung between them to penetrate deeper into the groove between the two actin chains. This exposes sites which allow the myosin crossbridges to bond more strongly with the actin and begin the contraction cycle. The contraction will be maintained as long as the level of Ca^{2+} is high. The duration of a **twitch** (see Fig. 2.2.9) produced by a single action potential therefore depends on the rate at which the sarcoplasmic reticulum can pump Ca^{2+} back into the terminal cisternae. Fast-twitch fibres achieve this deactivation in 10 ms; slow-twitch fibres may take 50 ms. Human muscles are not made up exclusively of one or the other type of fibre but of different proportions of the two. The properties of the two major skeletal muscle types are listed in Table 2.2.1. Type II fibres can be further

divided into Types IIa and IIb, where IIa fibres are more similar to Type I fibres.

Resting tension

Even when the contractile elements of a muscle have not been activated, it still exerts tension when stretched. This means that it has passive elastic properties and these are thought to be both in **series** and in **parallel** with the contractile elements (Fig. 2.2.10). Although the tendons and connective tissue of a whole muscle form obvious sites of elasticity in series with the contractile elements, it has now been shown that

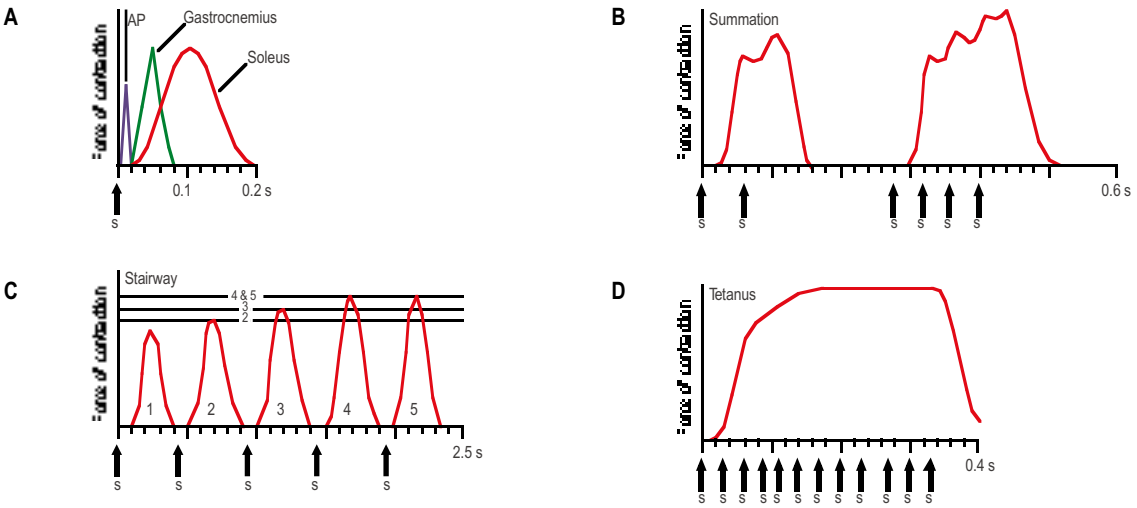


Fig. 2.2.9 **Muscle stimulation at different frequencies.** **A.** Single twitches of relatively fast (gastrocnemius) and slow muscles resulting from a stimulus (S) which produces a single action potential (AP). **B.** A stairway of increasing force of contraction resulting from repeated stimulation, at a frequency too low to produce summation, of a muscle which has been resting for some time. Eventually a plateau of force is reached (action potential is not shown). **C.** Summation of single twitches produced by stimuli applied at too great a rate to allow the muscles to completely relax between contractions. **D.** Tetanus where high rates of stimulation produce complete fusion of contractions.

Table 2.2.1 Comparison of skeletal muscle types

	Type I	Type IIa	Type IIb
Alternative names	Slow, oxidative (red)	Fast, oxidative (red)	Fast, glycolytic (white)
Fibre diameter (diffusion distance)	Intermediate	Small	Large
Oxidative capacity (capillary density, mitochondria, myoglobin)	High	Very high	Low
Twitch duration	Long	Short	Short
Motor unit size	Small	Intermediate	Large
Recruitment order	Early	Intermediate	Late
Resistance to fatigue	Best	Intermediate	Worse

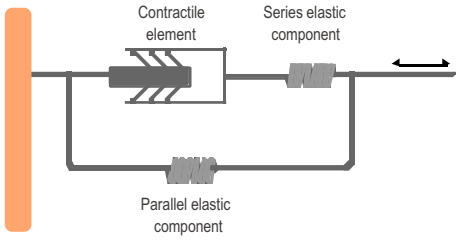


Fig. 2.2.10 A physical model of the components of skeletal muscle. The model shows the contractile element made up of actin and myosin and the elastic components which explain the behaviour of a whole muscle. Although the elastic components are shown outside the contractile element, a substantial proportion of both resides within the contractile mechanism.

even single skeletal muscle fibres have elasticity; which may reside in the 'hinges' or elastic components of the crossbridges themselves. The parallel component of muscle elasticity can, to a large extent, be attributed to the sarcolemma. There is, however, an additional intracellular contribution made by the highly elastic protein **titin** (tubulin), which forms a network around the actin and myosin filaments and probably contributes to the high resting tension at long sarcomere lengths when crossbridge formation is not possible (Fig. 2.2.7).

Isometric and isotonic contractions

Stimulation of a motoneurone results, after a **latent period** while excitation–contraction coupling is achieved, in contraction of a group of muscle fibres. The structure – motoneurone plus the muscle fibres it activates – is a **motor unit**.

Muscle fibres are only innervated by one motoneurone; so, while many (or few depending on the muscle) fibres can be innervated by one motoneurone, a muscle fibre can only have one motoneurone. Thus the total force developed by a skeletal muscle depends on:

- **Summation** of individual twitches which takes place when a second stimulus follows on a first stimulus before all the Ca^{2+} released has been resequestered and the sliding filaments have returned to their original position (Fig. 2.2.9).
- **Recruitment** when more and more motor units become active, recruiting more and more fibres. Those units associated with small numbers of fibres are recruited first. This means that we can apply a force with our muscles in a graded fashion, starting off gently and building up the tension. Also, muscles performing delicate precise movements are made up of motor units with small numbers of muscle fibres; muscles performing crude, powerful movements have motor units with many muscle fibres. The muscles of the eye have units of about 10 fibres. The muscles of the leg have units of several hundred.

Summation of twitches ultimately results in a **tetanus**, which is the normal type of contraction we use to lift and hold a weight (Fig. 2.2.9). To contract in this way a muscle must:

- respond to high levels of Ca^{2+} with sustained crossbridge formation
- have single twitches which last longer than a muscle action potential (so that action potentials can arrive at a rate that ensures that the Ca^{2+} concentration is maintained by repeated release).

When a muscle attempts to contract against an immovable load it is said to undergo an **isometric** (constant length) contraction in which **tension** in the muscle increases. If a muscle is already supporting a weight before it contracts, the weight, and therefore the tension in the muscle, does not increase with the contraction, which is **isotonic** (constant tension), but the muscle shortens.

If skeletal muscle which has been resting for some time is activated by a rapid but subtetanic series of stimulations, the successive contractions produced increase in amplitude until a steady-state is reached. In other words, the steady-state is not reached with the first stimulation. This is

Clinical Example

Contracture

This term is used clinically to describe sustained shortening of a muscle (or other tissue such as a burn or scar). In the context of muscle, the important difference between contract*ure* and a sustained (tetanic) contract*ion* is the absence of action potentials in the muscle sarcolemma.

In normal muscle contraction, a single suprathreshold stimulus of the motor nerve generates an action potential which is transmitted to the muscle and generates a muscle action potential. This spreads rapidly over the sarcolemma, initiating contraction, which follows at a much slower rate.

This excitation–contraction coupling depends on the release of Ca^{2+} and is terminated by the removal of Ca^{2+} back to its storage sites within the muscle. If this removal does not take place, a sustained contracture results.

The contracture is the result of some pathology short-circuiting the normal excitation–contraction mechanism. Muscle action potentials may be present or absent but they are irrelevant because the contraction mechanism is now being controlled further down the chain of command.

Contractures are seen in a variety of conditions including McArdle's disease (see below), muscular dystrophy and malignant hyperthermia. If the underlying pathology can be reversed they disappear.

called the '**staircase**' phenomenon. If the rate of stimulation is suddenly decreased, the amplitude of contraction decreases with successive stimulations until the second steady-state is reached. The staircase phenomenon is best, and was first, observed in cardiac muscle, and is thought to be due to the distribution of Ca^{2+} within the cell changing with changes in stimulus frequency.

High levels of Ca^{2+} persisting after tetanic stimulation of a muscle also explain the exaggerated single twitch displayed by fast muscles after a period of tetanus; and pharmacological agents which promote the release, or prevent the uptake, of Ca^{2+} can produce a state of prolonged contraction in the absence of action potentials, known as **contracture**.

Preload and afterload

When a muscle is stimulated directly or via its motor nerve, there is a delay or **latent period** before tension begins to develop. This is only in part due to the time taken up by excitation–contraction coupling. The rest of the time is taken in stretching elastic elements of the muscle in series with the contractile elements. By loading or stretching the muscle in different ways, the nature of the contractile process and the part played by elastic tissue have been investigated.

A **preloaded** muscle is stretched by the weight it supports even before it begins to contract (Fig. 2.2.11). The latent period before it begins to lift (or attempts to lift) the weight is largely due to the time taken by excitation–contraction coupling and is fairly constant. Because the overall time from stimulation to the end of contraction is constant, the duration of the mechanical process of contraction is also constant. The distance shortened by the muscle, however, depends on the load being lifted.

When a muscle is **afterloaded**, the elastic tissue in series with the contractile portion is

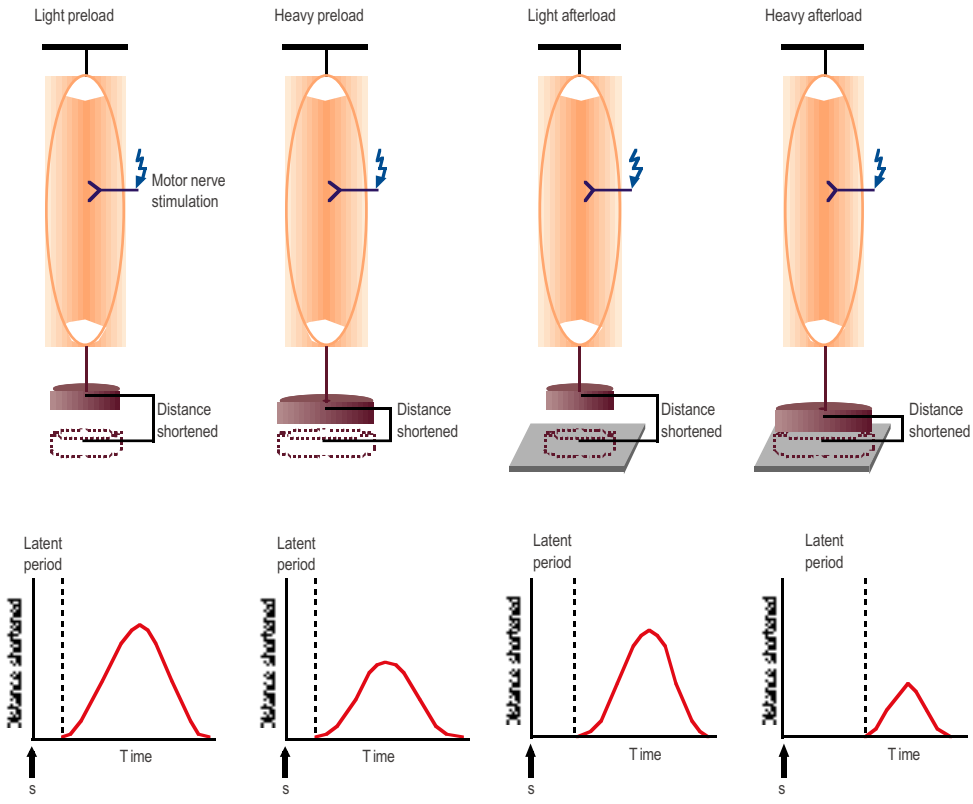


Fig. 2.2.11 **Preloading and afterloading: the effects on muscle shortening and latency in response to a single stimulation.** Increasing preload does not affect latent period and slightly reduces the distance shortened. Increasing afterload increases the latent period and reduces the distance shortened.

slack. (The load is supported in such a way as to be closer to the muscle than its resting length.) When an afterloaded muscle contracts it must first take up this slack and then put sufficient tension in the elastic element to lift the load before any shortening of the whole muscle is seen. Because the latent period now incorporates the time taken to stretch the elastic component to a tension that will lift the load, latent period is now proportional to the afterload. This encroaches on the total time for the twitch and so the duration of the mechanical shortening and the distance shortened both depend on the afterload on the muscle (Fig. 2.2.11).

The relationship between passive, active and total tension of a muscle in relation to its length can, in part, be explained in terms of its active component and the elastic component in series with it (Fig. 2.2.7). It now seems that the interdigitation of the actin and myosin filaments is inadequate to explain the rising phase of the total tension curve, and that Ca^{2+} sensitivity of the actin filaments, which is influenced by muscle length, is involved.

Summary

The build-up of tension in a striated muscle

- Excitation–contraction coupling involves an action potential spreading from the neuromuscular junction releasing Ca^{2+} from the cisternae of the endoplasmic reticulum.
- Ca^{2+} in the sarcoplasm promotes the movement of tropomyosin to expose binding sites which form contractile crossbridges between the actin and the myosin.
- The duration of a single muscle twitch is largely determined by the rate at which Ca^{2+} can be removed from the sarcoplasm.
- Single twitches can summate, ultimately resulting in a tetanus.
- Muscles have elastic components in series and parallel with their contractile components. These produce a passive tension on stretching.
- The functional unit of a muscle is a motor unit. These are recruited sequentially as a muscle increases its tension.
- Attempted contraction against an immovable load is called isometric contraction. Contraction which produces constant tension by moving a constant load is called isotonic.
- A muscle is preloaded when its load produces tension even before it begins to contract.
- A muscle is afterloaded when it must contract before it begins to lift its load.

Muscle energetics and oxygen debt

The source of energy used for all the molecular activities of resting or active muscle is ATP. The majority of this is used to:

- drive the Na^+/K^+ pump which maintains ionic gradients across the sarcolemma
- resequester the Ca^{2+} into the cisternae
- power contraction.

Of course, in an active muscle, contraction is the major user of ATP. The production of ATP can be the result of **anaerobic** respiration (without oxygen), which breaks glucose down into ATP and lactic acid, or **aerobic** respiration (with oxygen) when ATP, carbon dioxide and water are formed. Aerobic respiration is much more efficient than anaerobic, producing 38 molecules of ATP from each glucose molecule, compared to anaerobic respiration's two. However, anaerobic respiration more rapidly supplies ATP, especially when oxygen, and therefore aerobic metabolism, is limited.

A major problem for muscles is the immediate demand for energy during the first few seconds of exercise, after which the normal resting levels of ATP would be exhausted. To help avoid this, a second immediate reserve of energy exists in the form of **creatine phosphate**, which can donate phosphate to ADP to form ATP, becoming itself creatine. When a muscle is at rest, the excess ATP present favours the formation of creatine phosphate. In a resting muscle, glucose is stored as **glycogen** and in such a muscle, or one undergoing sustained moderate exercise, aerobic respiration synthesizes ATP from glucose or more usually **fatty acids**. During intense exercise, anaerobic respiration and the breakdown of creatine phosphate provide energy for a brief period (10–20 s), limited by the depletion of creatine phosphate and glucose and the build-up of lactic acid, which diffuses out of the muscle cell to allow anaerobic respiration to proceed for a little longer. Some of the lactic acid that enters the blood is resynthesized to glucose by an energy-requiring pathway in the liver. This glucose can then be

Clinical Example

McArdle's disease

McArdle's is a rare autosomal recessive glycogen storage disease. Unlike most of these diseases which manifest themselves very early in life, McArdle's presents in adults.

Glycogen can be made to a limited extent by all cells but the major manufacturers and users are liver and muscle. Glycogen is broken down in normal muscle by muscle phosphorylase to provide energy after the short-term fuels, ATP and creatine phosphate, have been used up. The end-product of this energy source is lactic acid. Patients with McArdle's disease specifically lack the muscle phosphorylase enzyme and so the effects of losing this glycogen energy source are restricted to the skeletal muscle system.

These effects, as could be predicted, are fatigue and painful muscle cramps. The absence of phosphorylase means that lactic acid is not produced and the tests for this disease include demonstrated absence of lactic acid by nuclear magnetic resonance, absence of lactic acid in the venous blood after anaerobic exercise or absence of phosphorylase in a muscle biopsy. High glucose or fructose diets have been reported to produce some improvement but patients usually have to modify their lifestyles to avoid the symptoms.

reused by the muscles that produced the lactic acid. This is the **Cori cycle**.

It was once thought that the elevated oxygen consumption after exercise – used to repay what is called the **oxygen debt** – was the result of the activity of the Cori cycle after the end of exercise. It now appears that much of the oxygen consumption after exercise is due not to the lactic acid Cori cycle but to changes in circulation, body temperature and hormone levels persisting after the end of exercise (Fig. 2.2.12).

Fibre types and training

The capability of some muscles to contract quickly but become quickly fatigued and other muscles to resist fatigue but contract slowly depends on the fibre types that make them up.

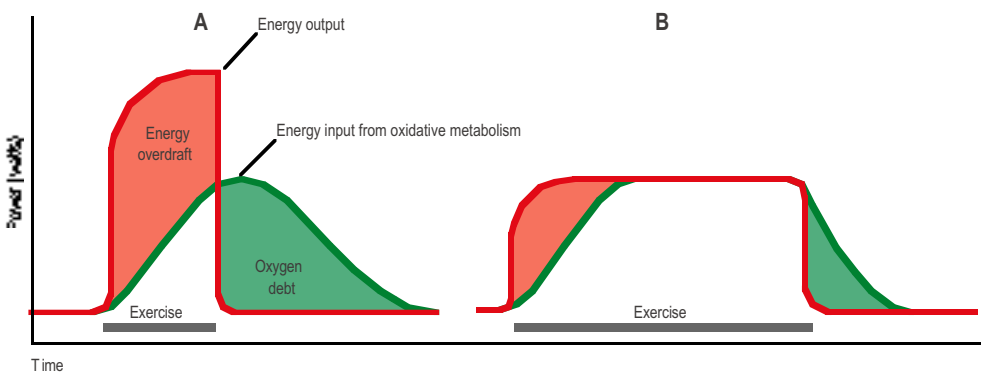


Fig. 2.2.12 **Oxygen debt. A.** The development of an 'oxygen debt' when fast glycolytic fibres generate a brief intense burst of energy which 'overdraws' on metabolic reserves. Oxygen consumption remains elevated until the debt is repaid. **B.** The timecourse of events when slow oxidative fibres alone are activated.

Muscle fibres are generally defined as being slow-twitch or fast-twitch.

Slow-twitch muscle fibres are relatively small in diameter, well-supplied with blood vessels and mitochondria and more resistant to fatigue than fast-twitch fibres. Aerobic metabolism provides their source of ATP and this form of metabolism is supported by **myoglobin** which acts as a small store of oxygen when the blood supply is cut off during muscle contraction. It is myoglobin that gives muscles in chicken legs their red colour. This muscle has a different function from that of the white muscle of the chicken's breast which is made up of fast-twitch fibres.

Fast-twitch muscle fibres are adapted for rapid contraction but this can only be sustained for a short time. Their speed of contraction is associated with the high speed at which their crossbridges can form, release and re-form. Fast-twitch fibres are less well supplied with blood vessels and mitochondria than are slow fibres but they contain large amounts of glycogen and rely heavily on anaerobic metabolism to provide ATP.

Slow- and fast-twitch fibres are sometimes called Type I and Type II respectively. Some people further divide Type II into Types IIb and IIa, the latter of which is intermediate between Type I and Type IIb (see Table 2.2.1).

Exercise and fatigue

Unlike the muscles of other animals, which can be made up exclusively of fast or slow fibres, human muscles usually contain fast and slow fibres in different proportions. For example, postural muscles contain mainly slow fibres while arm muscles are mainly fast. Exercise cannot change one type of fibre into the other, nor can it change the number of fibres in a muscle. Exercise increases the size of individual muscle fibres by increasing the number of myofibrils and sarcomeres within the fibre. Aerobic or anaerobic exercise preferentially trains those fibres that preferentially use one or other form of respiration, that is, slow or fast fibres respectively.

Training produces a greater improvement in muscular performance than might be expected from the increase produced in muscle size. This is due to an increase in the number of motor units that the nervous system can recruit simultaneously and an improvement in the number of capillaries perfusing the muscle.

Increase in bulk and strength of muscles has been the goal of many individuals. To increase strength by training, the most important factor appears to be to produce loads that are almost maximal for the muscle being trained. It does not seem to matter how you do this and a regimen of only 10 contractions per day, if strictly observed, will produce a significant increase in strength.

Not surprisingly, there is a highly significant difference in the percentage of muscle in the limbs of men and women. The forearms of young men contain 72% muscle while those of young women contain 60%. It is tempting to attribute this difference to the male sex hormone testosterone; and anabolic steroids which mimic its action can help to restore muscle mass to people who have become emaciated. However, it seems that the only advantage of such drugs in a healthy individual is to enable him or her to endure the damage of a punishing training schedule. Reviews of scientific studies of the effects of anabolic steroids suggest that benefits to healthy individuals are minimal, with the weight and muscle girth gains obtained probably being due to retention of water and salt. The dangerous side-effects of taking these drugs are clearly not worth the theoretical gains obtained (see Recent Advances box, p. 27).

Fatigue is a phenomenon that everyone has experienced. The discomfort or even pain associated with fatigue usually terminates exercise before the ability of muscles to contract is compromised. The basis of the discomfort of fatigue involves many factors including changes in pH and lowering of blood glucose. Although the output of neurotransmitter (acetylcholine) at

the neuromuscular junction may be reduced, the function of the central nervous system motor pathways is not impaired. Only highly trained or highly motivated (frightened?) individuals will endure the discomfort of exercise to the point where actual physiological motor unit fatigue takes place. Such fatigue results from the inability of metabolic and contractile processes of the muscle fibres to function. The limited reserves of a muscle, and its dependence on a blood supply, are demonstrated by the almost complete fatigue of a muscle within 60 s of its blood supply, and therefore nutrient and particularly oxygen supply, being cut off. Interruption of blood supply occurs completely during tetanic contraction of most muscles and to a lesser extent at lower tensions.

In experimental investigation of the development of fatigue, this circulatory component can be eliminated by exhausting the muscle by a series of brief tetani produced by electrical stimulation of its motor nerve. In the interval between contractions, perfusion returns to normal. In such an experiment involving a muscle made of a mixture of Type I and Type II fibres (most human muscles) tension falls rapidly with successive stimulation to a level that can be sustained for a long time.

This fatigue is due to rapid failure of the fast Type II fibres (Fig. 2.2.13) accompanied by glycogen and creatine phosphate depletion and accumulation of lactic acid.

Since the development of fatigue occurs before the ATP pool is much reduced, attention has been turned to other effects of acidosis on the energetics and mechanisms of contraction.

Intracellular pH in muscle falls from about 7.1 at rest to about 6.5 at fatigue with a parallel fall in maximum force production. The increase in H^+ causes an increase in $H_2PO_4^-$ and interferes directly with in vitro muscle contraction. The relevance of these changes to in vivo human fatigue is not clear since data from humans demonstrate that maximal muscle force is not necessarily reduced during increased $H_2PO_4^-$ and acidotic conditions.

During recovery from exercise, muscle blood flow and oxygen consumption are elevated for some time. There is an oxygen debt which is related to the amount of energy used in the exercise in excess of that provided by oxidative metabolism (Fig. 2.2.12). Oxygen debt occurs even at low levels of exercise because slow oxidative muscle fibres consume considerable ATP before oxidative metabolism can increase ATP production. The debt is, of course,

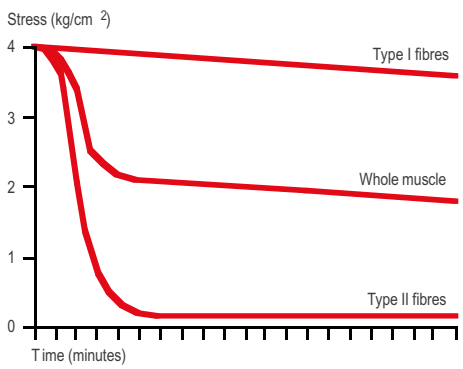


Fig. 2.2.13 **Fatigue of Type I and Type II fibres.** Development of fatigue in a skeletal muscle made up of Type I and Type II fibres as a result of brief tetanic stimulations at 1-second intervals. The Type I fibres maintain their normal response, the Type II fibres rapidly fatigue.

Summary

Exercise and fatigue in striated muscle

- Human muscle is generally a mixture of slow-twitch, fatigue-resistant aerobic and fast-twitch, easily fatigued anaerobic fibres.
- Fibres do not change type as a result of exercise.
- Exercising muscle builds up an 'oxygen debt' which is paid back after the exercise.
- The stages of activity in a muscle are reflected in its rate of heat production.

much greater in strenuous exercise when fast glycolytic fibres are in action.

Heat production

The metabolic activity involved in contraction recovery and the repayment of the oxygen debt is reflected by the rate of heat production by a muscle. Depriving a resting muscle of oxygen reduces its rate of heat production by about half, indicating that half its resting heat production is aerobic. When oxygen is resupplied there is additional heat production corresponding to the metabolism involved in repaying the 'oxygen debt'.

Isometric tetanic contraction is preceded by a burst of **initial heat** production and the sustained contraction is accompanied by the production of **maintenance heat**. After the contraction has ceased, heat production is elevated above resting level as **recovery heat**, which is related to the delayed oxidative metabolism of the oxygen debt. Part of the initial heat is related to the release of calcium from the sarcoplasmic reticulum to initiate contraction and is called **activation heat**. The production of heat by muscle contraction is necessary to maintain body temperature. During shivering, heat production from this source can increase up to five times.

Recent Advances

Anabolic steroids – bottled muscle

There is no doubt that for male and female athletes, anabolic steroids can increase muscle bulk and body weight. However, increases in strength are restricted to those who also undertake a regular training regimen. The long-term side-effects of steroid use are severe and can include early death from cardiovascular disease, sterility, masculinization in women and fetal effects. Perhaps the most sinister aspect of these effects is the delay of decades that occurs between the taking of large doses of steroids in youth and the full impact of the induced pathological changes in middle age.

Since time immemorial the waning of men's sexual and physical power has been associated with testicular failure, and many gruesome and unsuccessful remedies involving the testes of animals have been devised to reverse the process.

The active agent of the testes, testosterone, was first synthesized in 1935 and shown to have both androgenic actions, maintaining primary and secondary sexual characteristics, and anabolic actions which are mainly due to stimulation of protein synthesis, particularly in skeletal muscle.

Testosterone is a C-19 steroid hormone (Fig. RA2.2.1) derived from cholesterol. Men produce about 8 mg/day, 95% from the testes, 5% from the adrenal cortex. After puberty, plasma testosterone levels are approximately 60 μg/l in men and 3 μg/l in women, in whom the adrenal cortex and ovary are the major sources of production. Like most steroid hormones, testosterone acts on the nucleus of cells to activate the synthesis of proteins, which may be enzymes or structural proteins.

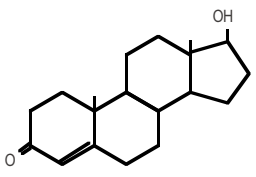


Fig. RA2.2.1 Structure of testosterone.

Recent Advances *(Continued)*

The clinical use of anabolic steroids is based on their mimicking the effects of testosterone.

They are used as replacement therapy in men and to stimulate sexual development. They combat breast tumours in postmenopausal women. The major clinical application with relevance to their use in sport is their use from the early 1940s to aid muscle regeneration after surgery, in debilitating disorders and in treating the emaciated victims from concentration camps. It is probably the publication of the results of such treatment that promoted the first use of anabolic steroids in attempts to increase muscle strength in athletes. It is clear from the results of these attempts that anabolic steroids alone will not increase strength, and that the increase in weight and muscle bulk in non-exercising healthy individuals is due to water and electrolyte retention. It is only in maximally exercising individuals that the positive, strength-enhancing effects of anabolic steroids are seen.

If such improvements are restricted to continuous hard-training regimes, why is it that so many more general claims are made for steroids? It may be that steroids make athletes 'feel better' by making them more competitive and aggressive; also, anabolic steroids improve the reparative powers of muscles, allowing more intense exercise to take place, thus stimulating muscle growth.

This effect on muscle healing is not without considerable costs. Of these the most significant to athletes are cardiovascular – since exercise imposes particular strain on the cardiovascular system – and hepatic – since anabolic steroids are suspected hepatic carcinogens in the doses taken by athletes.

Steroids increase the rate of atherosclerosis in arteries and arterioles. It is thought to be the effects of testosterone that cause the greater incidence of coronary heart disease in men compared to women. Anabolic steroids decrease the concentration of high-density lipoproteins (HDL) which appear to protect against atherosclerosis. It has been suggested that a reduction of 10% in blood HDL increases the chance of coronary heart disease by 25%. In athletes taking anabolic steroids, HDL commonly falls by 20%.

The retention of salt and water by steroid users, which produces gains in body weight and muscle circumference but not in strength, also increases the blood volume and workload on the heart. This is a basis for potentially fatal hypertension in athletes on anabolic steroids.

Tumour formation, particularly in the liver and kidney of athletes taking steroids, has now been firmly established, together with significant changes in liver biochemistry in 80% of these otherwise healthy athletes. This may also be associated with a type of hepatitis in which hepatic tissue degenerates and is replaced by blood-filled spaces. Some of the most dramatic effects of anabolic steroids are, as one might expect, on the reproductive system. During administration, sperm counts fall by 73% with a 30% decrease in the number of mobile sperm. Much clinical data suggest that steroids produce irreversible atrophy of testicular tissue.

Because of their lower circulating levels of testosterone, the effects of a specific dose of anabolic steroids on women athletes is greater than in men, with concomitantly greater risks of side-effects including acne, facial hair, deepening of the voice and menstrual irregularities.

With more and more sophisticated methods of detecting steroid abuse becoming available, rogue athletes or their coaches are turning to other substances to improve performance. One of the most sinister of these is human growth hormone (hGH) and there is suspicion that unscrupulous individuals have been giving hGH to prepubertal children of athletic promise in the hope of producing a group of super-athletic giants.

Smooth muscle

2.3

Introduction

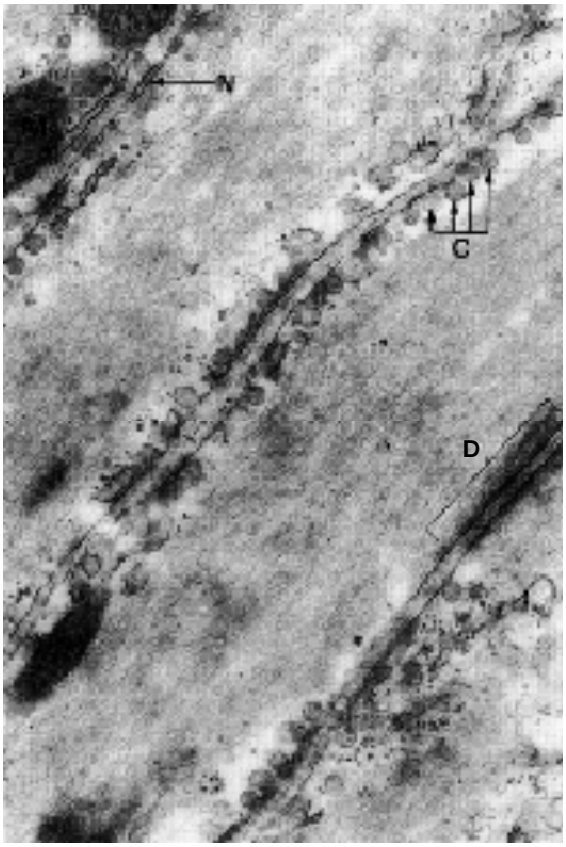
General structure and specific variations

Smooth muscle is widely distributed throughout the body and is particularly associated with hollow internal organs, the pupil of the eye, the skin (attached to hair), and glands. Unlike skeletal muscle, which develops from paired segmental somites in the embryo, smooth muscle develops from mesodermal cells which *migrate* to their final sites in the walls of hollow organs and even to the myriad of sites that finally make up the tiny arrector pili muscles associated with individual hairs.

The wide variety of structures containing smooth muscle reflects the more varied functions of this type compared with striated or cardiac muscle. Although many organs contain smooth muscle with properties appropriate to its function, it is a universal fact that smooth muscle cells are smaller (1/20th the diameter) than striated muscle cells, being from 20–200 μm long and 5–10 μm in diameter.

The absence of striations within the cells and the less organized arrangement of the fibres give this type of muscle its 'smooth' appearance under the microscope. That these fibres differ from striated muscle is demonstrated by their slower, more energy-efficient contraction. Unlike striated muscle, each cell of smooth muscle contains only one nucleus situated near the centre

Fig. 2.3.1 **The microscopic structure of a smooth muscle fibre.**

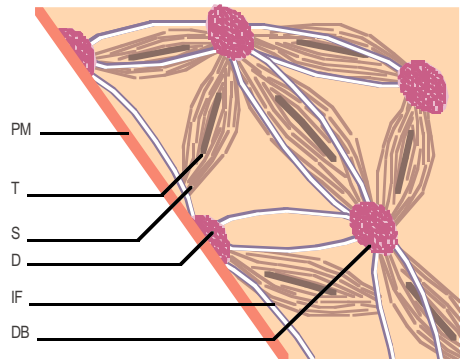


A

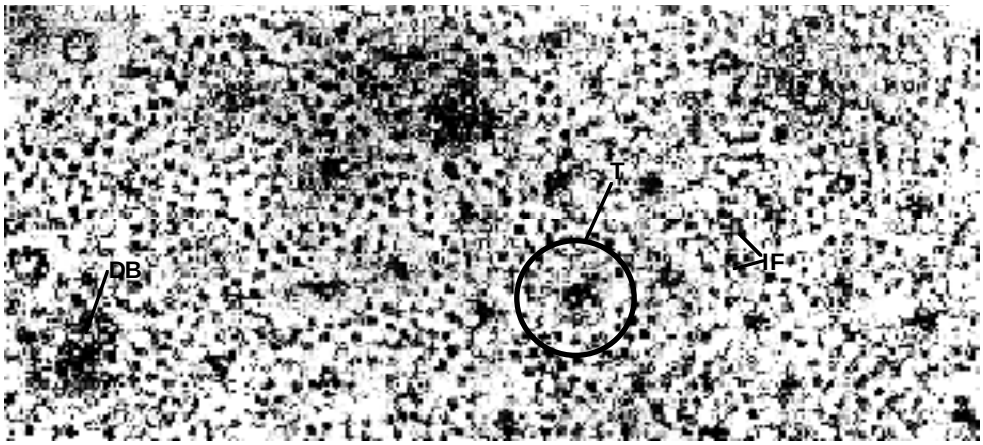
A. Longitudinal section of the plasma membrane of a smooth muscle cell showing caveolae (C), counterparts of the T-tubules in striated muscle involved in Ca^{2+} release into the cell. Specialized region of the membrane form nexus-like junctions (N) which facilitate the spread of excitation from cell to cell, while others (D) form desmosome-like connections between cells to transmit tension.

B. High-power transverse section showing: (T) a halo of thin filaments (7 nm diameter) surrounding a thick (15 nm diameter) filament. Intermediate thickness filaments (IF; 10 nm diameter) join the dense bodies (DB).

C. The probable arrangement of fibres and dense bodies in a smooth muscle cell. The dense bodies (DB) provide anchor points for the thin filaments (S) and intermediate filaments (IF), somewhat like the Z-lines in striated muscle. When these bodies are attached to the plasma membrane (PM), they are known as dense bands (D) and may form physical links between cells. The intermediate filaments may assist in transmitting the force produced by the interaction between the thick (T) and thin filaments to the dense regions of the cell.



C



B

of the fibre, its widest point. Although the contents of the fibres are similar to those of striated muscle, actin, myosin, tropomyosin (troponin is absent), the actin and myosin myofilaments within the myofibrils are very thin and there are slight differences in chemical composition compared to striated muscle. The internal structures of a sarcoplasmic reticulum are sometimes poorly developed, and the T-tube system is absent.

Unique structures found in smooth muscle fibres are the **dense bodies** (Fig. 2.3.1) or, where they are fixed to the plasma membrane, dense bands (so called because they are electron dense to the beam of the electron microscope). These are made of α-actinin and represent condensations of actinin on the actin filaments in the fibre. The dense bodies are made up of the same material as the Z-disks in striated muscle and may serve the same function of providing an anchor against which the actin–myosin mechanism can pull. The dense bands on the membrane are attached to microfibrils which extend out of the cell and anchor on collagen fibres in the surrounding connective tissue, thus binding together all the individual cells in the sheet of muscle.

Scattered among the actin filaments with their dense bodies are thick myosin filaments, 2.5 times the diameter of the thin actin filaments but only about 1/12th in number. Although it contains less myosin, a smooth muscle can generate as much tension as a striated muscle of the same cross-sectional area.

Although the sarcoplasmic reticulum in many smooth muscle fibres consists only of tubules restricted to the periphery of the cells, where their membrane is invaginated into many dimples called **caveolae** (Fig. 2.3.2), the sarcoplasmic reticulum in others is as extensive as in striated muscle. The responses of smooth muscle depend on the influx of Ca^{2+}. Because smooth muscle cells are small, diffusion distances are short, and this coupled with the relatively slow speed of events in their contraction and relaxation allows the sarcolemma and the extracellular space to play the roles of endoplasmic reticulum and cisternae found in striated muscle in regulating intracellular Ca^{2+}.

Because smooth muscle is arranged in sheets in the walls of a variety of hollow organs, rather than being connected to two bones, there is a greater variety of orientation of the fibres. For example, the sheets of fibres in the small intestine are arranged at right angles to each other so that segmentation and shortening of the gut are brought about by the circular and longitudinal layers respectively.

Hollow organs in which regulation of pressure or expulsion of contents is their function have smooth muscles arranged in their walls in a more random fashion. This is the case for the bladder and uterus. The diameter of conducting channels such as the bronchi and arteries is effectively controlled by smooth muscle arranged in circular layers.

Fig. 2.3.2 **The plasma membrane and endomembrane system of smooth muscle.** The caveolae (C) are thought to be analogous to the T-tubule system of voluntary muscle.

Smooth muscle types

The arrangement of smooth muscle within an organ is largely determined by the function it serves, and, on the basis of its arrangement into single bodies or bundles, it is often classified as single-unit or multi-unit type.

Single-unit smooth muscle

This is sometimes called visceral smooth muscle because it surrounds the hollow organs of the body – the stomach, intestines, urinary bladder, uterus and some blood vessels. This type of muscle is arranged in large sheets of fibres (Fig. 2.3.3A).

Visceral smooth muscle exhibits many **gap junctions** (Fig. 2.3.4) between the cells which allow action potentials to pass from cell to cell producing a steady wave of contraction that travels through the whole sheet of muscle as if it were a single unit. The smooth muscle fibre that receives the stimulus from a nerve that initiates the contraction that is then passed on to adjacent fibres is called the **pacemaker**. In addition to this stimulated form of contraction, which is found for example in the bladder, visceral smooth muscle often shows two types of automatic activity:

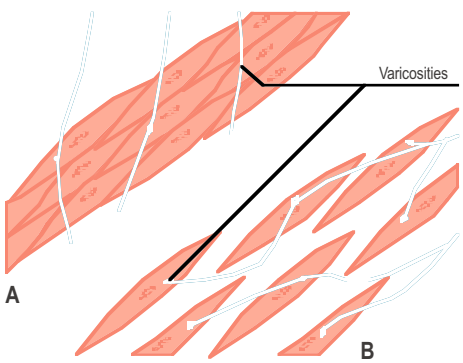


Fig. 2.3.3 **Types of smooth muscle. A.** Single-unit or visceral in which few fibres are innervated and impulses for contraction pass from cell to cell via gap junctions. **B.** Multi-unit in which every fibre is individually innervated.

- **Autorhythmic activity** is found in the digestive tract, and the rhythmicity is modulated by nervous activity.
- **Tonic activity** causes the muscle to remain in a constant state of tonus or partial contraction until deliberately relaxed. This tonus is found in the sphincters which regulate the movement of food through the digestive tract. Tonus relaxation also prevents a permanent stretching of organs such as the stomach and bladder, which regularly undergo large changes in volume. In such organs, passive increase or decrease of volume produces only transitory changes in tension of their walls, which is restored to normal by changes in tonus of the single-unit smooth muscle they contain.

Summary

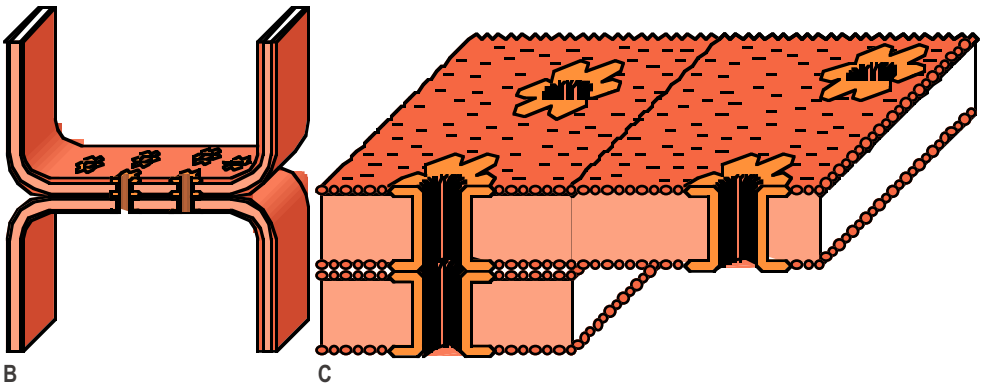
Smooth muscle structure and types

- Smooth muscle cells are smaller (20–200 μm by 5–10 μm) than striated muscle cells.
- They only have one nucleus per cell.
- They appear 'smooth' because there is no regular arrangement of their fibres as in striated muscle.
- Dense bodies may serve the same anchoring function as Z-disks in striated muscle.
- Caveolae on smooth muscle cell membrane regulate the influx of Ca^{2+} which initiates contraction.
- Single-unit (visceral) smooth muscle has gap junctions in its cell membrane which are involved in passing the signal for contraction from cell to cell, promoting autorhythmicity and tonic contraction.
- Multi-unit smooth muscle lacks gap junctions, is less autorhythmic than single-unit muscle and mainly contracts in response to nerves or hormones.

Multi-unit smooth muscle (Fig. 2.3.3B)

This is made up of individual fibres not connected by gap junctions, which can be stimulated by separate autonomic motor nerves. Multi-unit muscle is much less autorhythmic than single-unit and generally only contracts when stimulated by nerves or hormones. It is found in the ciliary muscles of the eye, and in its iris where rapid adjustments are necessary. This type of smooth muscle is found in sheets in the walls of blood vessels or as small bundles or single cells as in the capsule of the spleen.

A



B C

Fig. 2.3.4 **The gap junction. A.** The gap junction (also called a nexus junction) seen as a 'pepper-pot-like' structure at the top of an electron micrograph of cardiac muscle. **B.** Channels exist between the cytoplasm of the two cells involved. **C.** These channels are made up of an hexagonal array of six polypeptide molecules.

Activation of smooth muscle

Innervation

One of the most important characteristics of many groups of smooth muscle is their property of autorhythmic contractions in the absence of direct neural stimulation. This property is modified by sympathetic and parasympathetic nerves. Unlike striated muscle, smooth muscle cells are not organized into motor units. The autonomic nerves which initiate or modify their activity pass from fibre to fibre forming swellings, varicosities, on the cell surface. These varicosities show little specialization of either their pre- or postjunctional membranes. The gap between nerve and muscle can be from 20–200 nm and the density of innervation varies from a junction on almost every muscle cell in the vas deferens to a sparse innervation in the uterus where excitation spreads from cell to cell via intercellular connections. The dual innervation of smooth muscle by the sympathetic and parasympathetic autonomic systems allows for an increase or decrease in the largely intrinsic activity of the muscle. Thus parasympathetic activity generally increases strength of contraction whereas sympathetic activity, which can have what are known as α- or β-type effects, generally excites or inhibits respectively.

The ability to modify the activity of smooth muscle by interfering pharmacologically with these α- and β-type effects is of considerable importance in the treatment of diseases such as hypertension, where the object of treatment is to reduce arterial blood pressure by relaxing smooth muscle in the walls of arteries and arterioles. Although smooth muscle can function in the absence of extrinsic innervation, it shows supersensitivity to normal neurotransmitters after a period of denervation.

Electrical activity

The electrical properties of smooth muscle are much less uniform than those of striated muscle, reflecting its more diverse properties and functions. Its resting membrane potential can range from –50 to –60 mV compared to –85 mV in striated muscle, although both are probably generated by the same mechanisms. Unlike striated muscle, smooth muscle contracts in response to both action potentials and slow changes in resting membrane potential. The sensitivity to each type of stimulus depends on the type of smooth muscle. **Single-unit smooth muscle** (found in many viscera) generates action potentials (Fig. 2.3.5A) which spread through the muscle via gap junctions. The response is not all-or-none as in skeletal muscle; a series of action potentials usually results in a slow sustained contraction. Slow changes in the resting membrane potential due to spontaneous changes in the muscle membrane permeability to, or pumping of, Na^+ and Ca^{2+} also cause bursts of action potentials which in turn cause contraction (Fig. 2.3.5B).

The slow waves themselves do not cause contraction in this type of smooth muscle. However, a type of depolarization intermediate between slow waves and action potential, and very similar to cardiac action potential, does occur – **action potential with plateau** (Fig. 2.3.5C). This plateau, which can last for up to 1 second, accounts for the prolonged contraction seen in smooth muscles of the uterus and certain blood vessels.

The cell membrane of a single-unit smooth muscle is depolarized by stretching. This, combined with the normal slow waves of depolarization, sets up a series of action potentials causing the muscle to contract. This kind of activity is most clearly seen in the gut in response to distension by food.

In **multi-unit smooth muscle** (found in many blood vessels) electrical activity is not propagated from cell to cell and the characteristic of this type of muscle is to develop tension which is proportional to the degree of membrane depolarization even in the absence of action potentials (Fig. 2.3.5D).

The absence of action potentials in multi-unit smooth muscle may be related to the small size

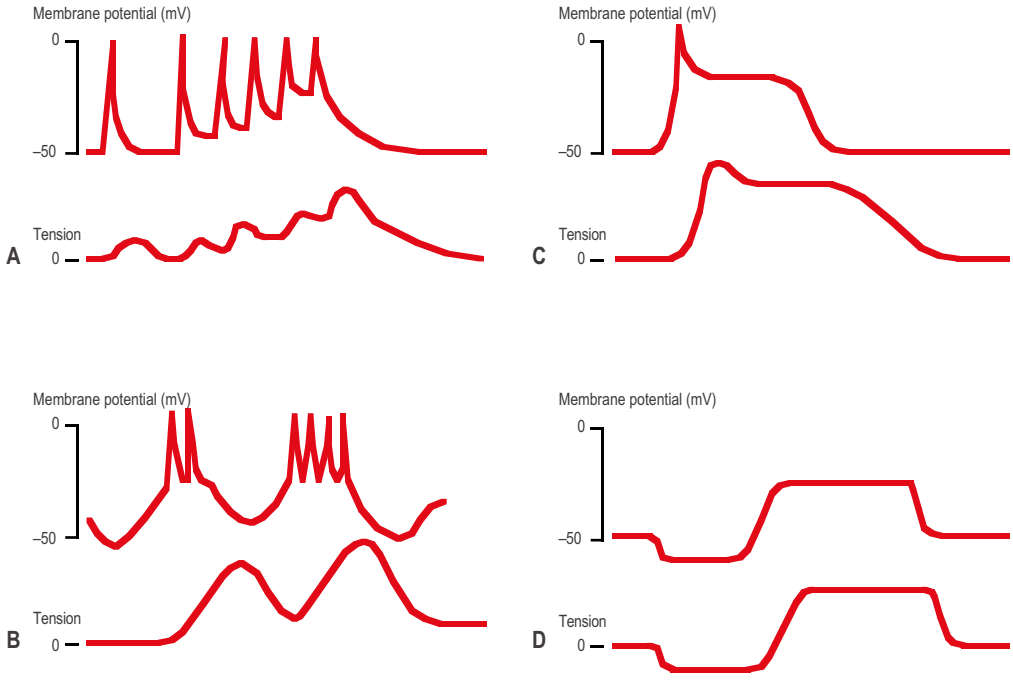


Fig. 2.3.5 **The relationship between membrane potential and tension in types of smooth muscle. A.** Action potentials characteristic of single-unit smooth muscles produce single or summated twitches. **B.** Slow changes in the resting membrane potential can trigger action potentials which produce changes in tension. This behaviour is typical of self-excitatory smooth muscle of the gut. **C.** Action potentials with plateaux occur in the smooth muscle of the uterus and some vascular smooth muscle and result in prolonged contractions. **D.** Depolarization without action potentials takes place in smooth muscle fibres too small to generate action potentials – such as are found in the iris of the eye. These waves of depolarization cause muscle contraction even in the absence of action potentials.

of its cells, 50 or more need to be depolarizing simultaneously before a self-propagating action potential can be recorded. This absence of action potentials does not prevent the muscle from functioning, usually in response to acetylcholine or noradrenaline secreted by nerves of the autonomic nervous system. These transmitters cause a local depolarization on the cell membrane which spreads 'electrotonically' over the whole fibre, bringing about a contraction. It might seem surprising that multi-unit smooth muscle, with its absence of conventional brief action potentials is generally found where a rapid contraction is required, the iris and ciliary muscles of the eye for example, sites where the properties of ubiquitous smooth muscle approach those of its striated relative.

Summary

Innervation and electrical activity in smooth muscle

- Smooth muscle can be autorhythmic and is not organized into motor units.
- Activity can be initiated and/or modulated by autonomic nerves passing from muscle fibre to fibre.
- Unlike single-unit smooth muscle, multi-unit muscle activity is not propagated via junctions, and tension is proportional to membrane potential.

The smooth muscle neuromuscular junction

The connection between the two previous topics, 'Innervation' and 'Electrical activity' in smooth muscles, is at the neuromuscular junction. Here chemicals released by nerves alter the electrical properties of the muscle cells to initiate, increase or decrease the likelihood of, or inhibit contraction. This is an altogether more varied response than that found in striated muscle where the activity of the neuromuscular junction is directed towards one end – a muscle action potential producing muscle contraction.

Factors which influence the neural control of smooth muscle include:

- the types of innervation and the transmitters released
- the receptors of the neurotransmitters on the muscle cell membrane
- the anatomical arrangement of the nerves in relation to the muscle fibres.

We have already seen that the innervation of smooth muscle by the autonomic nervous system can be divided into visceral (single-unit) or multi-unit types. These two main types can be supplied by three categories of nerve:

- extrinsic innervation – from the autonomic nervous system, which in turn can be mainly sympathetic (arteries), parasympathetic (ciliary muscles) or both (gut)
- intrinsic innervation – in self-contained plexuses within the smooth muscle itself (particularly in the gut)
- afferent sensory neurones – which, while not strictly having a direct effect on smooth muscle cells, set up reflex activation of motoneurones that do.

The importance of the innervation of smooth muscle is illustrated by the fact that the innervation of gut smooth muscle alone contains more nerve cells than the skeletal motor system. That much of this innervation is intrinsic is demonstrated by the continued peristalsis of gut taken out of the body, whereas a skeletal muscle with its nerve supply interrupted is flaccid.

The autonomic nerve fibres that innervate smooth muscle are usually restricted to the surface of the muscle sheet. The neurones do not have branching ends with motor endplates typical of skeletal muscle motor nerves but rather there are bulges, **varicosities**, at intervals along the nerve. At these points the covering layer of Schwann cells is absent to allow the free diffusion of transmitter substances released from vesicles within the varicosities. The process of release of the transmitter is similar to that in skeletal muscle and in some cases, called **contact junctions**, in multi-unit smooth muscle, the gap between nerve and muscle is as small (20–30 μm). This proximity reduces the latent period of smooth muscles innervated in this fashion to that of skeletal muscle. Where the distance for diffusion is greater, in **diffuse junctions**, the delay is, of course, longer, producing an average total contraction time of about 2 seconds, 30 times that of the average striated muscle, but with a range of 0.2–30 seconds.

The transmitter substances released by the autonomic nerves serving smooth muscle are also more varied than the ubiquitous acetylcholine released by motor nerves of skeletal muscle. Acetylcholine and noradrenaline are the transmitters released to smooth muscle; they are *never* both manufactured by the same nerve (Dale's principle), although some autonomic nerves release more than one transmitter. Both these transmitters can have either excitatory or inhibitory effects on smooth muscle, and which effect dominates is determined by the type of receptor present in a particular muscle. Some examples of this diversity of response of different smooth muscle sites to the same substances are given in Table 2.3.1.

This diversity is due to the variety of excitatory and inhibitory receptors found on the cell membrane of smooth muscle. These receptors also respond to substances circulating in the blood or released locally in the tissues to open channels in the cell membrane.

Table 2.3.1 The effect of sympathetic and parasympathetic nerve stimulation on smooth muscle in various tissues (reproduced from Rang H P, Dale M M 1991 *Pharmacology* 2nd edn. Churchill Livingstone, Edinburgh)

Organ	Receptor type	Sympathetic	Parasympathetic
Heart			
SA node	β_1	Rate ↑	Rate ↓
Atrial muscle	β_1	Force ↑	Force ↓
AV node	β_1	Automaticity ↑	Conduction velocity ↓ AV block
Ventricular muscle	β_1	Automaticity ↑ Force ↑	No effect
Blood vessels			
Arterioles			
Coronary	α	Constriction	
Muscle	β_2	Dilatation	No effect
Viscera, Skin, Brain	α	Constriction	No effect
Erectile tissue, Salivary gland	α	Constriction	Dilatation
Veins	α β_2	Constriction Dilatation	No effect
Viscera			
Bronchi			
Smooth muscle	β_2	No sympathetic innervation, but dilated by circulating adrenaline	Constriction
Glands		No effect	Secretion
GI tract			
Smooth muscle	α_2, β_2	Motility ↓	Motility ↑
Sphincters	α_2, β_2	Constriction	Dilatation
Glands		No effect	Secretion
Uterus			
pregnant	α	Contraction	Variable
non-pregnant	β_2	Relaxation	
Male sex organs	α	Ejaculation	Erection
Eye			
Pupil	α	Dilatation	Constriction
Ciliary muscle	β	Relaxation (slight)	Contraction
Skin			
Sweat glands	α	Secretion (mainly cholinergic)	No effect
Pilomotor	α	Piloerection	No effect
Salivary glands	α, β	Secretion	Secretion
Lacrimal glands		No effect	Secretion
Kidney	β_2	Renin secretion	No effect
Liver	α, β_2	Glycogenolysis Gluconeogenesis	No effect

Summary

Smooth muscle junctions and hormones

- The smooth muscle neuromuscular junction is more varied in structure than that found in striated muscle.
- Varicosities on the autonomic nerves serving smooth muscles act as the junction, releasing a variety of neurotransmitters.
- Excitatory or inhibitory receptors on the muscle cell membrane respond to neurotransmitters and substances in the extracellular fluid.

Local tissue factors and hormones

Smooth muscle responds rapidly to changes in the interstitial fluid surrounding it. This provides an efficient local homeostatic mechanism responding to changes in the respiratory gases, pH, ions and temperature. Many hormones, carried by the circulation, affect smooth muscle contraction. These include adrenaline, angiotensin, oxytocin, antidiuretic hormone (vasopressin), histamine and 5-hydroxytryptamine. As with the neurotransmitters noradrenaline and acetylcholine, the effects of these hormones may be excitatory or inhibitory. The mechanism of excitation can be dealt with separately from that of contraction.

Excitation of contractile mechanisms and their properties

Mechanisms of excitation or inhibition of smooth muscles

The final common pathway which leads to contraction of smooth muscle (or other muscle) cells is a rise in intracellular calcium concentration. Depolarization of the cell membrane, with or without action potentials, can be caused by the opening of Na^+ and Ca^{2+} channels; the influx of Ca^{2+} causes depolarization and increases intracellular [Ca^{2+}] as a primary effect (Fig. 2.3.6). Many of these types of channels respond to membrane receptor activation and are called '**receptor-operated**'. Calcium channels which open in response to depolarization of the membrane are said to be **voltage gated**; others are independent of depolarization; and yet other receptors activate **phospholipase C**, which, by a series of steps, releases Ca^{2+} from the sarcoplasmic reticulum, which increases intracellular Ca^{2+} without any flux across the cell membrane.

However, most of the Ca^{2+} involved in contraction of most smooth muscle comes from the extracellular fluid and so, when extracellular [Ca^{2+}] is reduced, so is smooth muscle contraction (like cardiac muscle but unlike skeletal muscle). Removal of this influx of Ca^{2+} is necessary for relaxation and most of this is done by membrane pumps. Like many other things about smooth muscle, these are slower than the pumps of striated muscle sarcoplasmic reticulum.

Recapture of Ca^{2+} by the smooth muscle sarcoplasmic reticulum is an active process driven by ATP and modulated by receptor activity. The fall in [Ca^{2+}] that results brings about relaxation. Relaxation of smooth muscle can also be brought about by the inactivation of an enzyme MLCK (myosin light-chain kinase), an essential component in the contraction process. The β effects of the sympathetic system largely act in this way (Fig. 2.3.6B).

The contractile mechanism of smooth muscle

Perhaps because of its more leisurely rate of contraction than striated muscle and less dramatic action than cardiac muscle, smooth muscle is often accorded a more primitive status. Quite the opposite is true; there is no equivalent

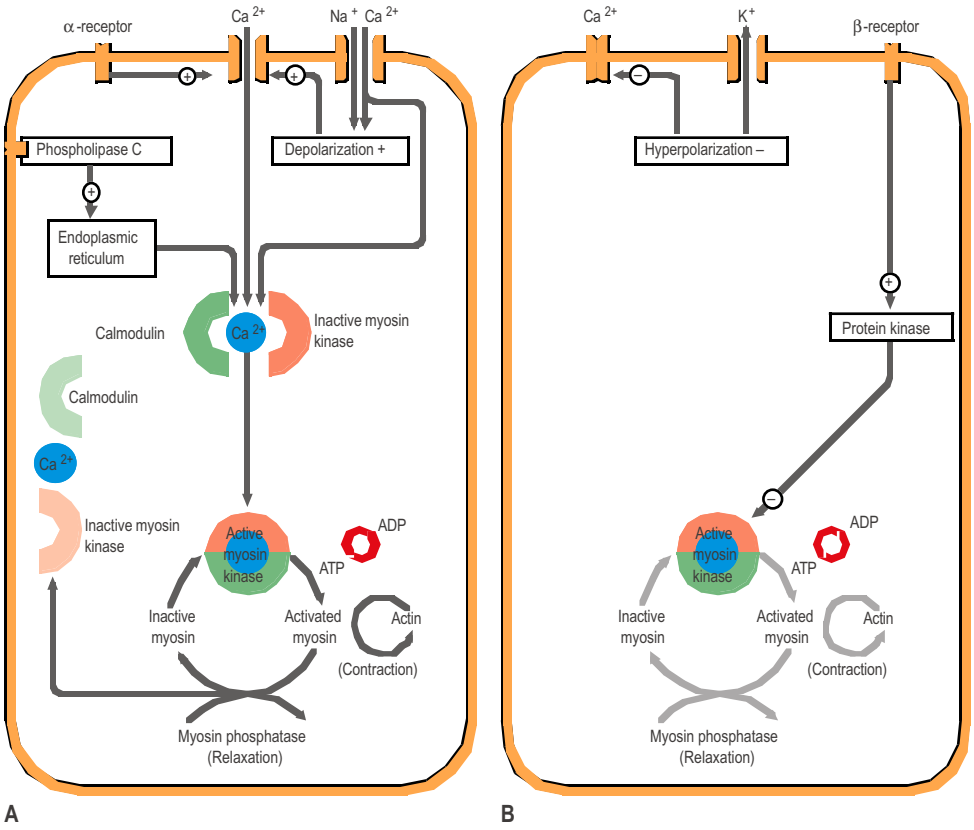


Fig. 2.3.6 **Receptor activation on smooth muscle. A.** Initiation and **B.** inhibition of smooth muscle contraction by receptor activation. Only a few of the routes by which receptor activation can increase intracellular Ca^{2+} (the final common pathway to active myosin kinase) are shown. There are also many forms of protein kinase which inhibit the formation of myosin kinase, sometimes called myosin light-chain kinase.

of vertebrate smooth muscle in the primitive phyla. Nevertheless, this inferior status is reflected in the lack of information available about the contractile apparatus of smooth muscle. The functional equivalent of the sarcomere in striated muscle is not yet defined and may be the thick and thin filaments stretching between two dense bodies (see Fig. 2.3.1).

The proportions of the components of the contractile mechanism of striated muscle are different in smooth muscle. The regulatory protein troponin is absent and there is twice as much actin and tropomyosin. Myosin, on the other hand, is only one-quarter as plentiful as in striated muscle, which is explained by the paucity of thick filaments.

The actin and myosin from smooth or striated muscle interact in the same way when extracted from the body and mixed in vitro. The initiation of this interaction is an increase in the concentration of Ca^{2+}. We have seen that in smooth muscle this can result from changes in membrane permeability produced by stretching, spontaneous electrical activity, neurotransmitters, hormones and changes in the extracellular fluid composition. In striated muscle, contraction is regulated by the interaction of Ca^{2+} with the protein troponin which

regulates actin–myosin crossbridge formation. This regulatory role is taken over in smooth muscle by an entirely different protein, **calmodulin**. This protein binds with Ca^{2+} to form a complex which, in turn, binds with an enzyme **myosin (light-chain) kinase** (Fig. 2.3.6) and, by phosphorylation, activates the myosin heads which form the crossbridges between actin and myosin. The energy for this phosphorylation comes from ATP, which is degraded to ADP.

You will remember from the section on striated muscle that the myosin molecule 'head' which forms a crossbridge has four light chains attached to it as well as the two heavy chains which attach it to the myosin filament. One of the light chains is a **regulatory chain** and, when phosphorylated by the myosin kinase–Ca^{2+}–calmodulin complex, the bridge goes through the attachment–shortening–release cycle described for striated muscle, which brings about contraction of the filament.

These final steps of attachment and shortening of the crossbridges are identical to those found in striated muscle in which the process of contraction is brought to an end by the removal of Ca^{2+}, allowing troponin to resume its inhibitory role. In smooth muscle there is no troponin and so while removal of Ca^{2+} reverses most of the process of contraction, it does not detach phosphate from the myosin molecule head, which consequently remains attached to the actin filament.

To bring about this removal, and relaxation of the muscle, requires a further enzyme, **myosin phosphatase**, and the rate of smooth muscle relaxation depends on the concentration of this enzyme.

This tendency of the filaments of smooth muscle to 'hang on' even when activating Ca^{2+} levels have fallen is quite different from the behaviour of striated muscle, which quickly 'lets go' once the motor nerve activity has ceased and Ca^{2+} has been rapidly reabsorbed into the extensive sarcoplasmic reticulum. This property of smooth muscle is sometimes called a 'latch' mechanism. Because of this, the activation of smooth muscle, by nerves for example, can be reduced and yet the muscle will maintain its force of contraction. The energy to sustain this latched contraction is only 1/100th of that required to sustain a similar effort in striated muscle in which only a very slight latch effect can be seen. By this mechanism, smooth muscle can sustain a contraction for hours with little expenditure of energy or stimulation from nerves.

Even the rate at which crossbridges are formed and released is different in smooth muscle, being up to 300 times slower than in striated muscle. As part of this effect, the time a crossbridge spends joining the actin and myosin filament together is increased; and as it is this which determines the force of contraction we can see why the maximum force of contraction per cm^2 cross-section for smooth muscle is of the order of 6 kg and that for striated muscle 4 kg.

Only one molecule of ATP is used to form and release one crossbridge. This slow rate of cycle in smooth muscle brings with it economies of energy usage (without loss of power, as seen above). This is very important in terms of those organs of the body that must maintain contraction at all times.

The immediate energy supply for contraction in smooth muscle comes from ATP, as is the case with striated muscle. Unlike striated muscle, there is no energy reserve in the form of creatine phosphate. The characteristically slower speed of shortening of smooth muscle offsets this to some extent by spreading out the demand for ATP. Smooth muscle also uses a wider variety of fats and carbohydrates as substrates for the production of ATP. However, smooth muscles are poorly adapted to anaerobic metabolism; they do not develop an oxygen debt and, in the absence of an adequate supply, quickly fatigue.

Summary

Excitation, inhibition and contraction

- Smooth muscle (like striated) contracts in response to an increase in intracellular Ca^{2+}.
- Depolarization of the cell membrane is caused by opening of Na^{+} and Ca^{2+} channels.
- Channels can be receptor gated or voltage gated.
- Receptors can activate phospholipase C to release Ca^{2+} from the endoplasmic reticulum.
- Smooth muscle cells contain twice as much actin and tropomyosin and only a quarter as much myosin as striated muscle.
- Troponin is absent and its regulatory role is taken over by calmodulin.
- Smooth muscle myosin tends to 'hang on' to actin even when Ca^{2+} levels fall.
- Myosin phosphatase brings about the release, and the rate of relaxation of smooth muscle depends on its concentration.
- Crossbridges form more slowly and efficiently in smooth than in striated muscle.
- Smooth muscles have poor energy reserves and under anaerobic conditions fatigue quickly.

Mechanical properties of smooth muscles

A variety of innervation, sensitivity, biochemistry and arrangement within a connective tissue matrix of variable composition endows smooth muscle with a much greater variety of mechanical properties than the more stereotyped striated and cardiac muscles. These properties have, of course, evolved to fit the role carried out by the particular muscle. The smooth muscles of the iris of the eye do not have properties that would be useful in the stomach, and vice versa. The diversity of properties found in smooth muscle is not even restricted to its properties of contraction. Its relationship with its surrounding connective tissue is more intimate than previously supposed. If smooth muscle cells, with all the characteristics of normal contractile muscle, are isolated and placed in tissue culture, they lose their contractile characteristics of myosin and actin filaments and develop an extensive endoplasmic reticulum and Golgi apparatus. These structures then proceed to make collagen and elastin (constituents of the whole muscle matrix) and lay them down outside the cells. It is almost as if the isolated cells are building a complete new muscle. This idea is reinforced by the observation that after laying down a certain amount of matrix, the cells regain their actin and myosin filaments, as if preparing to take up their contractile activity once more.

Smooth muscle can shorten to a much smaller fraction of its relaxed length than striated muscle (to one-third and two-thirds of their rest lengths respectively). This is a very useful property when smooth muscle has to reduce the lumen of a tube to zero, as in the case of sphincters in the gut or bladder, or in precapillary sphincters in the circulation. An important adjunct to the significant contraction of sphincter muscle in providing a 'watertight' seal is that the tissue underlying the muscle is incompressible and forms a 'bung' in the lumen of the tube of smooth muscle (Fig. 2.3.7).

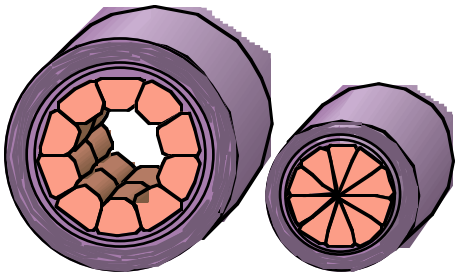


Fig. 2.3.7 **Smooth muscle 'plugging' of sphincters.** Smooth muscle can contract to a much smaller percentage of its rest length than can skeletal muscle. This is a useful property in the formation of sphincters where compression of tissue beneath a ring of smooth muscle in sustained contraction forms a watertight 'plug'.

This ability to contract to a smaller fraction of its rest length than can striated muscle is probably due to smooth muscle having longer actin filaments over which the myosin filaments can move.

It is common knowledge that exercise increases the size of skeletal muscle. This increase is almost exclusively due to an increase in the size of the individual cells, with only a fraction of a per cent of the increase due to increase in cell number. Smooth muscle cells, on the other hand, retain the ability to proliferate as well as increase in size in response to exercise.

Summary

Mechanical properties of smooth muscle

- Smooth muscle types show a greater variety of mechanical properties than striated muscles.
- Smooth muscles shorten to a much smaller fraction of their relaxed length than striated muscle.
- Unlike striated muscle, smooth muscle can proliferate as a result of training.

Applied physiology

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Exercise

Introduction

It seems to be generally agreed that this is the most sedentary age in history for most people in the western world. We are constantly chided by the media (usually at the prompting of manufacturers of sports equipment or sporting organizations) to take more exercise for our own good. The power used in carrying out a number of different activities is shown in Table 2.4.1. Like most campaigns by some to change the behaviour of others, these exhortations deserve closer examination before being swallowed whole.

Table 2.4.1 Power used by activities

Activity	Energy expenditure (watts)
Sleeping	86
Sitting	120
Housework	175
Walking	350
Marathon running	1000
Sprinting	4000

Most comparisons of the working lives of today seem to be made with those which are within oral history; grandparents and great-grandparents tell how they endured the excesses of the late Industrial Revolution when many types of work were not only long and physically demanding but took place under conditions which were harmful, uncomfortable, or often frankly dangerous. Undoubtedly conditions of work have become less physically arduous, but the Industrial Revolution in the late 18th and early 19th century was a very brief, if cataclysmic, period in social evolution. Taking even a slightly longer view, we see that the medieval peasant, with his working day circumscribed by the hours of daylight and a calendar punctuated by many feast and 'holy-days', may have worked fewer hours a year and under less stressful conditions than his modern counterpart who wishes to sustain the lifestyle the advertising agencies advise him is appropriate. Women, liberated from domestic drudgery, are now expected to find gainful employment outside the home. And, of course, peer pressure to conform with what is an acceptable appearance is as important in determining our activities as any wish to improve our health.

Victorians aspiring to be gentlefolk protected their skin from the tanning effects of sunlight to show that they did not labour in the open air. Today, their equivalents risk the most virulent types of skin cancer under ultraviolet lamps to give the impression that they can afford winter holidays in the High-Alps.

Rubens' voluptuous models, who demonstrated a clear ability to be well fed in a time in which people starved, would be considered pathologically obese in these days when a thin body flaunts the financial resources to provide an ideal diet and plenty of free time to spend at the exercise machines (*O tempora, O mores!*).

The effects of exercise on the body

Exercise is perhaps the best example of integration of the systems of the body, because few, if any, are not involved when one exercises. Of all the systems of the body that are changed by exercise, the musculoskeletal system is perhaps the most obvious and the one most usually intended to be changed. It may be that the participant in exercise wishes to lose fat (frequently euphemistically referred to as 'weight'), but it is the musculoskeletal system that is frequently used, in part, to achieve that end.

What does exercise do to skeletal muscle?

The effects on skeletal muscle depend on the type of exercise undertaken. There are as many exercise regimens as there are coaches willing to teach them, but they all fall somewhere between two extremes aimed at improving strength or endurance.

- In exercise to improve *endurance*, light loads are moved continuously for long periods of time, as in long-distance running.
- In exercise to improve *strength*, heavy loads, even straining against immovable objects, are briefly applied a small number of times.

The effects on the skeletal muscles and the other systems of the body of these two types of regimen are very different, but before we can describe the different *types* of exercise we need a measure of *how much* exercise an individual is doing. At rest, we metabolically 'burn' the substrate of foodstuff to provide the energy to sustain us at a fairly low rate. When we exercise we consume substrate and oxygen at increasing rates with increasing levels of exercise up to the maximum level we can sustain for just a few seconds. We are then using oxygen at our maximum rate. This is called our $V\mathrm{O}_{2\mathrm{max}}$ and against this we usually measure the level at which we are working.

Endurance training

This type of training is frequently undertaken to improve general 'fitness' and its global effect on all the systems of the body makes it ideal for that purpose.

During endurance training, the workload must be sufficiently light (and usually isotonic; see p. 100) to enable it to be sustained for the long periods necessary to improve endurance. A subject might start at a work rate which produces an oxygen consumption of less than 50% $V\text{O}_{2max}$ working up slowly to 80% $V\text{O}_{2max}$ or higher.

Metabolism of the exercising muscles during endurance training must be mainly aerobic (p. 100) or it could not be sustained. The changes that take place in the other systems of the body as a result of this type of exercise are necessary to support this increased metabolism. The slow muscle fibres (p. 100) are mainly affected by endurance training, although there is little obvious change in the muscle mass or appearance of the fibres under the microscope. The changes which take place within the muscle itself are mainly an increase in the number of mitochondria, which generate ATP (p. 100), and an increase in the density of capillaries that provide oxygen to enable the mitochondria to do this. This increase in mitochondria and capillaries results from low oxygen partial pressure (it also occurs at altitude), an increase in blood flow and a build-up of metabolites. The decrease in partial pressure of oxygen is of course a result of increased oxygen consumption. Endurance training improves performance in activities such as walking, cycling, running and swimming over appreciable distances.

Strength training

Unlike endurance training, strength training is specific to the muscles being trained, and the general effects on the other systems of the body, although present, are less marked. Anyone who has suffered a broken limb which is immobilized by a cast may have experienced the results of abstaining from strength training, which manifests itself as weakness and atrophy of the immobilized muscles. These deleterious effects can very simply be counteracted by a small number of powerful contractions a few times a day, which in the case of a broken limb must of course not impose stress on the healing bone.

Strength training involves lifting weights which must be at least 50% of the muscle's maximum capacity or straining to an equivalent muscle tension against an immovable object (an isometric contraction; see p. 100). These exercises need only be performed a remarkably few times to achieve significant improvements in strength. Programmes involving 10 repetitions three times per week are not uncommon. If more than 10 repetitions can be performed, the muscle is not loaded sufficiently to obtain maximum effect; and if the set of 10 contractions is repeated more than three times per week, there is insufficient time for the muscle to recover from the injury which is almost inevitable in this type of training. The remarkable specificity of this type of exercise to the muscle being trained extends to the type and range of movement which is used. The muscle will be strongest over the range of movement for which it has been trained and, if trained by slow movements, will show significant improvements in strength at those speeds only.

Strength training results in muscle fibre hypertrophy; the fibres become thicker and stronger by laying down more protein in the form of the contractile mechanism in each fibre. The contractile mechanism of the muscle does not become stronger at the molecular level, there are just more contractile proteins in each fibre, and strength bears a very close relationship to the cross-sectional area of a muscle. As is the case with endurance training, specific muscle fibre types, the fast

fibres, are trained in strength training. Adult muscle fibres do not normally divide and so training does not occur by producing more fast fibres, although there is some evidence that intermediate or even slow fibres begin to take on the properties of fast fibres with strength training. Testosterone, the male sex hormone, improves the response to strength training, and so men respond better to this type of training than do women. It is debatable whether this is a direct effect on the response of fast fibres to exercise, an improvement in their ability to repair, or the individual's increased ability to tolerate damage resulting from excess loads as well as a psychological effect improving motivation (see Recent Advances: Anabolic steroids – bottled muscle, p. 27). Activities associated with strength training include weightlifting, wrestling, shot-putting and isometric exercises where the load does not move against the muscle effort and there is consequently no muscle shortening.

A moderated form of strength training is of particular interest to a specific group of patients – postmenopausal women. Many of these women lose bone mass because of the decline in female hormones. It has been demonstrated that applying loads to the skeleton, as in exercise, slows down this loss.

These two types of exercise training for strength or endurance represent the extremes of the range on which most sports lie. They have different effects on the different physiological systems of the body, and the effects on the cardiovascular system are a good example of this.

The cardiovascular system

Together with the skeletal muscle system, the cardiovascular system shows the most dramatic changes in response to exercise training, and, of the two types, endurance training has the more profound effects. We have already remarked on the increase in capillary density that takes place in trained skeletal muscle, but training also affects cardiac muscle. In a similar way to skeletal muscle, cardiac muscle responds to increased levels of exercise by hypertrophy and the ability to contract more strongly, emptying the ventricle more quickly and completely during systole. The response to endurance training is, however, very different from the response to strength training.

Endurance training results in an increased filling pressure of the venous return, as a result of the pumping action of the muscles and the imposed increased cardiac output, so the heart is *preloaded* (see p. 100) and the left ventricle increases in size without much increase in wall thickness (Fig. 2.4.1). In strength training just the opposite occurs with the left ventricle remaining the same volume but the wall

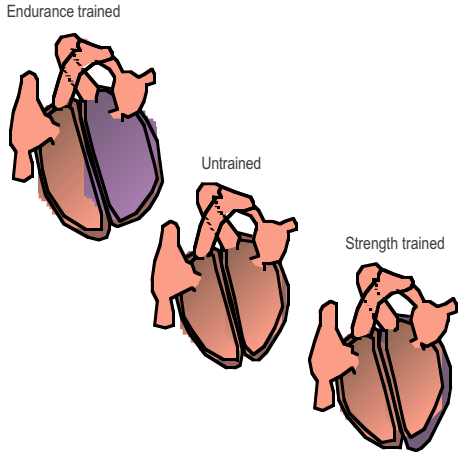

Fig. 2.4.1 Ventricular hypertrophy. Endurance training develops the size of the left ventricle without increasing the thickness of the wall. Strength training produces a thick-walled ventricle without any increase in size of the ventricle.

increasing in thickness. There is a suggestion that this increase in wall thickness increases the risk of heart disease by increasing the distances for diffusion of oxygen to the centre of the wall. Endurance-trained hearts on the other hand are enlarged to produce an increased stroke volume which means a slower rate is required to produce any given cardiac output. The resting heart rate of some endurance athletes falls below 40 per minute, some sustaining 'ventricular pauses' between beats of more than 2 s. These people are at risk of block of the cardiac conducting system, 'heart block'(see p. 100) and in several cases pacemakers have been implanted to relieve this life-threatening condition.

Regular endurance training reduces resting blood pressure. In normal individuals, systolic blood pressure rises during exercise while diastolic pressure is unchanged or may even fall slightly. Because moderate hypertensives have no greater increases in blood pressure on exercise than normals they may use the beneficial effects of training to improve their condition.

With endurance training comes a change to the blood which seem to have a protective effect on the results of sustained exercise – plasma volume increases by up to 15%. This is accompanied by a smaller increase in the number of red corpuscles and so the blood appears to be slightly anaemic, which one would assume to be a bad thing. However this 'thin' blood is less viscous than normal and therefore easier for the heart to pump. Also, when athletes lose water during sweating, the blood becomes more concentrated, returning viscosity to normal values; so reduced viscosity and increased plasma volume before sustained exercise begins assists trained athletes in maintaining the high cardiac output they require during exercise.

Training for strength presents an entirely different cardiovascular picture where brief intervals of intense activity are interposed between long periods of rest. There is never the overall high rate of oxygen consumption required to provide training of the cardiovascular system. Even worse, the brief intense increases in blood pressure produced by maximal muscle contraction produces hypertrophy of the left ventricle, which does not increase in size as in endurance training. The ventricle wall can become thickened to such an extent that its stroke volume is reduced below that of an untrained individual.

The respiratory system

At rest, an individual might take a breath of 500 ml every 5 seconds, a minute ventilation of 6 litres per minute. During exercise, each breath may increase to more than 3 litres at an interval of less than 2 seconds. Thus the respiratory system can increase its performance 25 times compared to the heart's more modest fivefold increase in cardiac output on exercise.

The energy cost of breathing is very low, even during heavy exercise, less than half that used by the heart. It seems that breathing or the transfer of oxygen from the air into the blood does not limit even the most extreme forms of exercise in healthy individuals. There appears to be plenty of reserve in the performance of the respiratory system and perhaps because of this it has not been possible to prove that training improves the functions of the lungs. Other systems limit our exercise before we can reach the limits of our respiratory system. However, recent experiments in which subjects train their respiratory muscles by breathing against resistances show that these muscles can improve their performance as measured by such dynamic tests as FEV_1 (see p. 100). This training is probably of most use to individuals suffering from lung diseases such as asthma rather than athletes and normal individuals. This form of training must be highly specific to the muscles concerned

because, although people who have had the respiratory disadvantage of living at high altitude for many generations have lung volumes 30% greater than those living at sea level, a sojourn of a mere lifetime at altitude does not improve respiratory performance.

Water and salts and heat

Homiothermy, maintenance of a constant internal temperature, confers the advantage of stabilizing the rate of the chemical reactions which make up metabolism. To maintain a constant internal temperature we must strike a balance between the heat produced and lost by our bodies.

When we exercise hard we produce more than 10 times more heat than at rest and we visibly sweat; this is most obvious in hot surroundings. Sweating is a most efficient way of losing heat and depends on the high latent heat of vaporization of water (2300 kilojoules per litre). Theoretically we could lose all the heat produced by our resting metabolism by evaporating 4 litres of sweat per day. This is clearly not feasible, particularly during exercise, and we also lose heat by convection, conduction and, to a lesser extent, radiation.

The passive mechanisms of losing heat come into play first during exercise. Flow of blood to the skin increases and therefore skin temperature. Heat is more readily lost to the environment. However, as skin temperature rises there is less transfer of heat from blood to skin and the blood is not cooled so efficiently. The temperature of the skin must therefore be controlled by increasing convective and evaporative losses. The excess heat produced by hard physical work of the type that could be sustained for about 30 minutes is nicely balanced by the heat removed by evaporation at the maximum rate of sweating of the average individual of about 1 litre per hour.

Blood flow to the skin and the production of sweat is under the control of the hypothalamus and modification of this control is the basis of most acclimatization to exercise under hot conditions. Acclimatization improves the cooling mechanisms of the body and improves the individual's tolerance of raised body temperature. The maximum flow of blood to the skin is increased, but this is limited by the demands of other tissues for blood, and sweat production is modified. The acclimatized individual begins to sweat sooner after the start of exercise, produces more sweat by having more active sweat glands which are more sensitive than normal and produces sweat with a lower salt content, thus conserving salt and volume of the blood.

Conservation of volume is an important issue in sustained exercise such as the marathon. Water for sweat is initially extracted from the plasma, which in turn draws water from interstitial fluid, so 1 litre of sweat is made up of about equal amounts of water from plasma and water from the interstitial fluid (with of course the salt lost in sweat). An important part of the conservation of body water is carried out by the kidney producing concentrated urine by reabsorbing water under the stimulation of antidiuretic hormone (ADH; see p. 100). Exercise stimulates the release of this hormone and thus the retention of water. Loss of about 2 litres of plasma volume as sweat or otherwise will result in cardiovascular collapse (shock). This does not occur during exercise because when plasma volume drops sufficiently to affect cardiac output the ability to exercise drops as well, a natural brake preventing damage. If the athlete is sufficiently foolish, sometimes called 'well motivated', he will continue to exercise despite this dehydration; the body now diverts blood from the skin to maintain cardiac output and of course there is an explosive temperature rise which terminates his efforts. Rehydration normally takes place by absorption of water from the gut.

The gut

Energy for exercise and water and salt to replace sweat come from food and drink processed by the gut. As far as water replacement is concerned, the position is simple; water is absorbed best from dilute solutions. This issue has been clouded by manufacturers of 'isotonic' drinks which are claimed to enhance performance. If these drinks do as they claim, and some seem to at least in part, it is by the addition of carbohydrate in the form of large sugar polymers which provide carbohydrate but do not exert much osmotic effect to prevent the absorption of water. In this context, endurance athletes should beware of consuming sugar immediately before competing as this will promote the secretion of insulin which depresses blood glucose; however, exercise itself has the opposite effect (see below). Exercise imposes increased demands on almost all components of the diet and requires that the gut is able to absorb them in adequate amounts. To support strength training one should have about 1 g of protein per kg of body weight per day. Most European diets contain about 90 g per day, which is adequate, but in poor countries development of strength is limited by dietary factors.

The nervous and endocrine systems

All the systems that have been mentioned in relation to exercise are influenced by the nervous system:

- the central nervous system in terms of motor performance
- the autonomic nervous system in terms of control of the cardiovascular system and increasing levels of circulating catecholamines (adrenaline and noradrenaline) and cortisol.

An immediate increase in blood levels of catecholamines is seen at the beginning of exercise. This is due to sympathetic nervous system activity. This and the activity of the sympathetic system on the liver mobilize stored lipid and glycogen. Noradrenaline stimulates glycogen breakdown in muscles.

Within a few minutes of the start of exercise, ACTH-controlled levels of cortisol begin to rise. Cortisol increases the resistance to physical stress and has a permissive role on the effects of adrenaline and noradrenaline, its presence being required for them to be fully effective. Increased sympathetic activity to the pancreas during exercise stimulates glucagon secretion, which aids adrenaline and cortisol in releasing energy, and inhibits insulin release. This reduction in insulin means that the permeability of muscle fibres to glucose would be reduced just when they need glucose most. Evolution has dealt with this problem by causing exercise to increase the number of insulin receptors present on muscle fibres, to 'make the most' of the insulin molecules available. This effect of exercise can be used by diabetics to reduce the amount of insulin they have to inject.

In training for specific exercises, like training to play the piano, movements are learned by the motor systems of our brain and become more fluent. An interesting effect of exercise is the increased production of endorphins by the brain. The release of these '*end*ogenous m*orphines*' within the brain is enhanced by exercise and they produce morphine-like euphoria as well as reducing the awareness of pain. They may be responsible for 'runner's high', a pleasant state of mind that occurs about half an hour into quite strenuous exercise and lasts for several hours. Unfortunately this state is followed a few days after the exercise by withdrawal symptoms in which the 'addict' feels anxious and depressed and has to take another bout of exercise.

Exercise, by the endorphin mechanism or some other, has been shown to improve mood; and exercise has been successfully prescribed for

mildly depressed patients and found to be as effective as some drug treatments. Endorphins released during exercise suppress the sensation of pain and modulate the effects of other hormones. Endorphin effects are so powerful that they can obliterate the warning signs during prolonged exercise and allow marathon runners, for example, to continue until they collapse. This is obviously a dangerous situation which leads us to ask again if exercise is in fact a good thing.

Is exercise a good thing?

We have seen that pure strength training restricts its effects very largely to the muscles being trained. It is difficult to identify any benefit in this type of training other than a cosmetic one and perhaps a reduction in the incidence of damage due to overload of the muscles and joints.

Endurance training on the other hand has a wider spectrum of effects, particularly on the cardiovascular system. Experiments with animals have shown that exercise makes hearts more vascular, with the number and diameter of their coronary arteries increased. Exercise also reduces blood cholesterol and low-density lipoprotein, important components of atherosclerotic plaque. If atherosclerosis does occur and one artery becomes blocked in the trained heart, there are more than normal 'in reserve' to supply the affected region. More and more patients are being given exercise as therapy after a heart attack and many become fitter than they were before their attack. However, any such programme, for patients or used prophylactically, should be initiated with caution. It is well known that endurance athletes of all ages do die of heart attacks. A heroic fitness programme intemperately entered into, particularly by the middle-aged, may cause the heart attack it was intended to prevent.

High blood pressure (hypertension) is frequently used to identify those at risk from cardiovascular disease. The association is well proven in populations, but it is still difficult to identify which individual members of a population will develop pathology as a result of their high blood pressure. The problem facing the heart of the hypertensive patient is easy to visualize, with the heart pumping against a 'brick wall' of increased peripheral resistance. Increasing systolic pressure, as in exercise, would seem to be the last thing to do. However, it is quite clear now that the systolic pressure of mild to moderate hypertensives increases to values equivalent to those found in exercising normal subjects and they too enjoy the benefits of the reduced diastolic pressure of exercise. After exercise, blood pressure is reduced for several hours in these patients, giving their hearts a period of respite.

Whatever the mechanism is, many studies have shown that people who remain fit have prolonged lives. Mortality of fit people between 60 and 70 is one-third of that of the unfit. This figure should not be simply attributed to exercise. People who take exercise are usually interested in their diet and lifestyle and make conscious efforts to improve the possibility of extending their active life. It may be that by exercise these people provide themselves with a functional reserve in the systems trained by exercise which they can call upon if they do become ill. There seems no doubt therefore that a *judicious* exercise regimen can improve the chances of an extended active life.

Further reading

Bagshaw C R 1993 *Muscle contraction*, 2nd edn. Chapman & Hall, London.

A clearly written little book by a biochemist who brings together information from many disciplines at a level between general textbooks and specialist reviews. Sufficiently modern for the sections on technical development and molecular genetics to still be relevant. Useful for students undertaking an honours degree in physiology.

Bülbring E (ed) 1981 *Smooth muscle: an assessment of current knowledge*. Edward Arnold, London.

Although the material in this compilation is no longer 'current', it is a fascinating presentation of the work of the great names in muscle physiology at that time, edited by one of the leaders in the field. Of interest to the advanced student.

Jones D A, Round J M 1990 *Skeletal muscle in health and disease*. Manchester University Press, Manchester.

A very readable and concise book for undergraduates covering the physiology of skeletal muscle, then training and the problems of fatigue, pain, damage and muscle disease. A breadth of subjects not usually found between the same covers.

Katz B 1970 *Nerve, muscle, and synapse*. McGraw-Hill, London.

One of the best undergraduate textbooks on this subject at its time. Still most readable and fascinating to have one of the leaders of the field 'chatting' to you about what they had been doing about the subject.

Kingston B 1996 *Understanding muscle*. Stanley Thornes, Cheltenham.

A novel book of tasks to encourage the interactive learning of the functional anatomy of the major muscles. Great fun and an excellent book for undergraduate medical students and others who are encouraged to carry out the tasks (and perhaps drawings) on themselves and their friends.

Mottram D R (ed) 1988 *Drugs in sport*. Spon, London.

The bad news for anyone contemplating enhancing his or her sporting performance with drugs.

Perry S V 1996 *Molecular mechanisms in striated muscle*. Cambridge University Press, Cambridge.

An excellent, readable book on the molecular basis of muscle contraction suitable for honours degree students.

Walsh E G 1992 *Muscles, masses and motion*. Blackwell, Oxford.

A most interesting book which is at the same time scholarly and readable and concentrates on the control of movement. Can be read by all levels for information and entertainment.

Questions

Answer true or false to the following statements:

2.1

Skeletal and smooth muscle:

A. Are controlled by different types of nerve.
B. Differ in that only skeletal muscle contains Z-disks.
C. Both make use of troponin to regulate contraction.
D. Both rely on nerves to initiate contraction.
E. Can both produce sustained contraction at low energy cost.

2.2

In skeletal muscle:

A. Individual muscle fibres are covered by a connective tissue sheet known as the epimysium.
B. Muscle fibres are usually arranged in series.
C. Muscle fibres are multinucleate.
D. Each motor unit is innervated by several motoneurones.
E. Muscle fibres are made up of myofibrils which contain the myofilaments.

2.3

In striated muscle:

A. The thick myofilaments are attached to the Z-disks.
B. The T-tubules act as a Ca^{2+} store.
C. A sarcomere extends from one Z-disk to the next.
D. The length of the thin myofilaments can be calculated from the width of the I-band.
E. The length of the thick myofilaments can be calculated from the width of the A-band.

2.4

During contraction of striated muscle:

A. The length of both A- and I-bands decreases.
B. The force generated depends on the initial sarcomere length.
C. ATP is broken down by the myosin ATPase during the power stroke, i.e. as the myosin crossbridge is pulling on the actin.
D. ATP binding by myosin causes it to detach from actin.
E. Crossbridge formation is promoted by an elevation of sarcoplasmic [Ca^{2+}].

2.5

Excitation–contraction coupling:

A. Depends on Ca^{2+} binding to tropomyosin in skeletal muscle.
B. Depends on Ca^{2+} binding to calmodulin in smooth muscle.
C. Links changes in membrane potential to changes in mechanical state.
D. Can lead to fused tetany in skeletal muscle because the sarcoplasmic [Ca^{2+}] stays elevated for some time after the repolarization of the action potential.
E. Produces shorter twitches in Type I than in Type II skeletal muscle fibres.

2.6

Skeletal muscle metabolism:

A. Uses glucose as its main energy source under resting conditions.
B. Produces large reductions in ATP levels during contractile activity.
C. Is mainly aerobic in Type I (slow-twitch) fibres.
D. Produces lactic acid at high workloads.
E. Is likely to be mainly aerobic in fibres which contain a high density of mitochondria.

2.7

Skeletal muscle contraction in humans:

A. Is usually isometric during normal activity.
B. Usually involves a mixture of fast- and slow-twitch fibres.
C. Is an important source of heat in the body.
D. Promotes hypertrophy of the contracting fibres.
E. Can lead to an oxygen debt, part of which is due to anaerobic production of lactic acid.

2.8

Smooth muscle:

A. Of the visceral type, functions as an electrical syncytium because of the presence of gap junctions.
B. Has a lower myosin content than skeletal muscle and so can contract less forcefully.
C. Contains dense bodies which are attached to myosin molecules.
D. Can transmit force from one cell to the other via dense bands on the cell membrane.
E. Is made up of mononucleate fibres.

2.9

Smooth muscle contraction:

A. May be stimulated by muscle stretch.
B. Requires a much slower rate of ATP breakdown than striated muscle contraction.
C. Can be stimulated by humoral agents which activate phospholipase C.
D. Can be regulated by sympathetic and parasympathetic nerves.
E. Is rapid in comparison with striated muscle.

2.10

Excitation–contraction coupling in smooth muscle:

A. Is always dependent on Ca^{2+} release from intracellular stores.
B. Depends on phosphorylation of actin.
C. Is terminated by a phosphatase enzyme.
D. Following a rise in sarcoplasmic Ca^{2+} can lead to a maintained contraction even after sarcoplasmic Ca^{2+} levels have fallen again.
E. Requires tropomyosin.

(Answers overleaf →)

Answers

2.1

A. True. Somatic nerves control skeletal muscle, whereas autonomic nerves control smooth muscle.
B. True.
C. False. Troponin is central to excitation–contraction coupling in skeletal muscle but is absent from smooth muscle.
D. False. Skeletal muscle relies on nervous stimulation but many smooth muscles are spontaneously active, with the nerves modulating contraction.
E. False. This is a feature of smooth rather than skeletal muscle.

2.2

A. False. Endomysium surrounds individual muscle fibres; epimysium covers an entire muscle.
B. False. Muscle fibres are in parallel in most skeletal muscles.
C. True.
D. False. A motor unit consists of a single motoneurone and the fibres it innervates.
E. True.

2.3

A. False. Thick myofilaments are connected by the M-line or disk, thin myofilaments connect to the Z-disk.
B. False. The sarcoplasmic reticulum is the Ca^{2+} store.
C. True. This is the contractile subunit of the muscle fibres.
D. False. Thin myofilaments extend beyond the I-band because they interdigitate with the thick myofilaments in the A-band region.
E. True. The A-band is caused by the thick myofilaments.

2.4

A. False. Only I-band decreases in length.
B. True. This is reflected in the length–tension relationship for the whole muscle and relates to changes in the amount of myofilament overlap with changing length.
C. False. ATP breakdown is linked with repositioning of the detached myosin head prior to attachment at a new position on the actin; this stores energy within the myosin molecule. The power stroke, which pulls the actin along, is associated with release of ADP and phosphate from the myosin.
D. True. ATP depletion after death prevents this, causing rigor mortis.
E. True. This is a crucial step in excitation–contraction coupling.

2.5

A. False. Ca^{2+} binds to troponin, which in turn moves the tropomyosin to allow myosin and actin to bind.
B. True. There is no troponin in smooth muscle.
C. True. This is what the term means.
D. True. This results in a contraction which is longer than the electrical event which stimulated it, so further action potentials can be fired before the fibre has had time to relax.
E. False. Type I fibres are slow-twitch fibres.

2.6

A. False. Fatty acids are mainly used at rest, but use of glucose is greatly increased during exercise.
B. False. ATP levels only drop a little because creatine phosphate is used to rapidly replenish the ATP levels.
C. True. Anaerobic metabolism is more a feature of Type II, particularly Type IIb, fast-twitch fibres.
D. True. Lactic acid is produced as a result of anaerobic glycolysis.
E. True. Mitochondria are the site of oxidative phosphorylation during aerobic metabolism.

2.7

A. False. Normal contractions are usually neither isometric nor isotonic, since both muscle length and tension change.
B. True. Most human muscles contain both types of fibre.
C. True. This is used to maintain body temperature in cold conditions, e.g. through shivering.
D. True. This explains the exercise-induced increase in muscle size; the number of fibres does not increase.
E. True. Oxygen is used to manufacture glucose from lactic acid in the liver via the Cori cycle; this is probably only one cause of the oxygen debt, however.

2.8

A. True. Gap junctions in single-unit or visceral smooth muscle allow electrical signals to spread from cell to cell.
B. False. The myosin content is reduced in smooth muscle, but the contractile force per unit cross-section is similar to or greater than that in skeletal muscle.
C. False. They are attached to the actin.
D. True. Dense bands are connected to extracellular connective tissue by microfibrils.
E. True. This is unlike skeletal muscle, which is multinucleate.

2.9

A. True. This is possibly due to opening of stretch-activated membrane channels.
B. True. This allows contraction to be maintained at lower energy cost.
C. True. Phospholipase C leads to production of inositol 1,4,5-trisphosphate (IP_3) which release Ca^{2+} from intracellular stores in smooth muscle.
D. True. The response depends on the tissue and the receptors present.
E. False. It tends to be slow because of the slow rate of ATP breakdown.

2.10

A. False. Ca^{2+} entry across the sarcolemma from the extracellular space can be important too.
B. False. It is myosin which is phosphorylated by the MLCK (myosin light-chain kinase) enzyme, which is activated by Ca^{2+}-calmodulin.
C. True. This myosin (light-chain) phosphatase reverses the effect of MLCK.
D. True. This is referred to as the latch state.
E. False. The troponin–tropomyosin system does not play a role in smooth muscle.