3. Muscle

There are three kinds of muscle in the body. classified according to their structure and function. *Skeletal muscles* are characterized by the presence of thin light and dark bands (striations) that are seen to lie across fibres when viewed through a microscope. These muscles form some 40% of the fat-free body weight, they are under voluntary control, and they are the only tissue through which man can directly influence his environment. *Smooth muscles* (which ar also called involuntary or visceral muscles) lack traverse striations and are not under conscious control; smooth muscles are found in viscera and blood vessels. *Cardiac muscle,* like skeletal muscle, is striated but unlike skeletal muscle is spontaneously active; it generates the pressures required to drive blood around the vascular system.

3.1 Skeletal Muscle

Skeletal muscles have two major functions: to exert force and to produce heat. The level of non-shivering heat production is regulated by hormones whilst shivering and the heat it produces are under direct nervous control.

The maximal force that muscles develop is proportional to their cross-sectional area (up to 40 N/cm), so the 'strength' of a muscle is dependent on the number of muscle fibres and on their diameters. In general a pennate arrangement of fibres gives rise to contractions that are more powerful than a simple parallel arrangement. As the contractions of muscles depend on the shortening of a large number of subcellular units (sarcomeres) arranged in series, the speed with which a muscle shortens depends on the number of units in the series and on the rate of their shortening.

Cellular Structure of Skeletal Muscle

Muscle fibres are long multinucleate cells 50 to 60 microm in diameter and ranging in length from a few millimetres to many centimetres. Each fibre usually runs from tendon to tendon and terminates at each end in the connective tissue of the tendons but in large muscles two or more fibres may be arranged in series. The force developed by the muscle fibres is generated by intracellular contractile proteins which are arranged into *myofilaments*. The myofilaments are in bundles, called *myofibrils,* which run the whole length of the fibre. Each myofibril is surrounded by the *sarcoplasmic reticulum,* and between the lateral cisternae of the sarcoplasmic reticulum are fine *transverse (T) tubules* opening out on the surface membrane (the *sarcolemma*). The complex of a T-tubule and two adjacent portions of cisterna is known as a *triad* and in human muscles these are located at the junction of the A and I bands.

The myofilaments are arranged into *sarcomeres* which are the contractile units of muscle fibres. Each sarcomere is approximately 2 mmicrom in length and its limits are defined by a Z line at each end. From the Z line *thin* (approximately 5 x 1000 nanom) *actin* myofilaments project toward the middle of each sarcomere and in the central region of each sarcomere the filaments interdigitate with *thick* (approximately 12 x 1600 nanom) *myosin* filaments. Each thick filament is surrounded by an hexagonal array of thin filaments and from each thick filament helically arranged crossbridges extend towards the thin filaments.

As polarizing light is not transmitted through the myosin-containing region (i.e., it is anisotropic) this region is called the A band. But light is transmitted through the actin-containing region (i.e., it is isotropic) and so it is referred to as the I band. In the middle of the A band where the myosin and actin filaments do not overlap, there is a lighter H band which marks the region devoid of crossbridges and in the middle of this a finer dark M line. The Z zone lies in the middle of each I band.

Contractile Process

The sliding theory developed by Hansen and Huxley in the 1950s states that the thin and thick filaments remain the same length and that the change in length is achieved as a result of the filaments sliding over each other. The forces generated during contractile activity arise in the regions where the actin filaments overlap the crossbridges. A rod-like light meromyosin component of myosin molecules forms the backbone of the thick filament while a heavy meromyosin component forms the crossbridges. During contractions the myosin crossbridges attach to adjacent actin filaments and flex toward the centre of the sarcomere. As this occurs at both ends of the myosin filament the actin filaments are drawn in toward the centre, the Z lines are pulled closer and the muscle fibre shortens.

The actin filaments are composed mainly of globular actin molecules in aa helical arrangement and it has been shown that purified actin molecules combine with the crossbridge component of myosin molecules. This interaction is inhibited in normal resting cells by the presence of a troponin-tropomyosin complex. Early X-ray diffraction studies of muscles at rest and in rigor mortis, showed that the crossbridges could have two stable positions, the resting position and the flexed position.

ATP is the fuel used to operate the contractile machinery and the other sources of energy, i.e., creatine phosphate, carbohydrates and fatty acids, are used to produce ATP. Myosin crossbridges contain an ATPase and the rate of contraction of the sarcomeres appears to depend on the speed with which this enzyme can hydrolyse ATP. When muscles are depleted of ATP the actin and myosin can no longer dissociate and *rigor mortis* occurs, that is, the muscles become stiff and inextensible.

Significant muscle shortening requires that the myosin crossbridges undergo repetitive cycles. When the muscle is unable to shorten, the elastic properties of the muscle fibres allow the crossbridge mechanism to operate and force to be generated.

Excitation-Contraction Coupling

Myosin ATPase activity and the contraction of muscle depend on both cytoplasmic MG^{2+} and Ca^{2+}, but ions have completely different roles. Whereas the Mg is necessary for myosin ATPase activity and is in adequate supply, Ca controls the interaction between the actin and myosin filaments and its supply is regulated. At rest the intracellular Ca concentration is so low (10^{-8} mol/L) that little interaction occurs. However during activity the concentration rises sharply, thus the development of tension within a muscle fibre is regulated by the free cytoplasmic Ca.

The interaction between actin and myosin (and the ATPase activity) is inhibited by the *troponin-tropomyosin* complex. The troponin component is a complex molecule spaced regularly along the actin filament and has specific tropomyosin-binding (T), calcium-binding (C) and inhibitory (I) subunits. The inhibitory effect of the complex on actin-myosin binding is removed when Ca binds to the C subunit. The change is thought to be associated with movement of the tropomyosin strands which lie in the grooves between the strands of actin molecules. Calcium concentrations of 10^{-5} mol/L cause maximal inhibition of the troponin-tropomyosin influence; lowering the calcium concentration allows the complex again to exert its influence.

In resting muscle the intracellular Ca concentration is low because the sarcoplasmic reticulum contains a membrane-bound pump that avidly collects Ca and then transports it to the lateral cisternae. However this Ca can be released by depolarization of T-tubule membranes that come into close apposition with the lateral cisternae. An action potential propagating along the muscle and down the T-tubules causes Ca release and and an elevation in the free intracellular Ca concentration; the propagation of the action potential down the T-tubule ensures that the contractile activity in adjacent myofibrils is synchronized.

Energy Balance

Very little ATP is stored in a muscle, and it must constantly be renewed because of its consumption in both the contractile process and the Ca transporting mechanism of the sarcoplasmic reticulum. The short-term reserve for replacement is creatine phosphate (PC), which forms a dynamic balance with free ATP, and the enzyme creatine phosphokinase (CPK) ensures that this equilibration is reached rapidly.

Depending on the type of muscle the major portion of the ATP may derive from either anaerobic or aerobic metabolism.

Under aerobic conditions the breakdown of muscle glycogen proceeds via the glycolytic pathway to lactic acid. The end-product is lactic acid rather than pyruvic acid and the oxidized nicotinamide dinucleotide (NAD^+) generated by the conversion of pyruvic acid to lactic acid is used in an earlier step. During aerobic conditions both fatty acids and pyruvate can enter the citric acid cycle via acetylcoenzyme A and thus a far greater amount of ADP is converted to ATP. For example, *3 mol of ATP is generated per mol of glucose-6-phosphate formed from glycogen during anaerobic metabolism (that is, 2 mol of ATP is generated per mol of glucose). In contrast, aerobic catabolism through the citric acid cycle of the 2 mol of pyruvate produced per mol of a 6-carbon sugar generates 36 mol of ATP, and oxidation of a mole of 6-carbon fatty acid generates 44 mol of ATP.*

The whole process, that is contraction and relaxation, operates with an *efficiency* of conversion of metabolic energy into external work of the order of 20%; the remainder is dissipated as heat.

Contraction of Muscle

When the length remains constant (*isometric contractions*), we measure the force (tension) generated by the contractile machinery. When the load remains constant (*isotonic contractions*), we measure the shortening of the muscle.

Isometric studies of muscle show that shortly after a muscle is stimulated by a *single* stimulus there is an increase in muscle tension which then decays. The time taken for the development of peak tension varies from 10 to 100 ms. Its rate of decline also varies and both depend on the type of muscle being studied. A single contraction of this type is called a *twitch.* If the muscle is stimulated a second time, before it has had time to relax completely, the second response adds to the first and a greater peak tension is developed. This is referred to as *mechanical summation.* If the stimulation of the muscle is prolonged it fails to relax completely and during the period of stimulation the tension fluctuates. With increasing frequency of stimulation the maximum tension is increased, the oscillation become smaller, and eventually, at *fusion frequency* a smooth *tetanic* contraction is produced. The tension produced in a tetanus may be two to three times as great as that produced in a twitch.

The substantial difference between the maximal tensions reached in a twitch and in a tetanus has been attributed to the physical properties of the muscle and to change in the cytoplasmic Ca concentration. First, muscles are not rigid and the forces generated by the contractile machinery are transferred to limbs by elastic structures (the tendons and myofilaments). These are embedded in a visco-elastic medium (the cytoplasm, sarcolemma, sarcolemmal connective tissue and the connective tissue around fibre bundles) and many of these elements are arranged parallel to the contractile machinery. Thus much of the energy consumed in a twitch is used in overcoming the damping action of these elements. With continued activation as in a tetanus, the elastic elements are stretched, the movement of filaments is minimal and the maximum muscle tension is attained. Secondly, there is evidence from invertebrate striated muscle that a higher level of cytoplasmic Ca, and hence muscle activation, is reached during a tetanus, but this has not been shown to occur in mammalian muscle.

Length-Tension Relationship

The tension generated by a muscle contracting isometrically depends on the initial length. In humans maximal muscle tension can be generated when the muscle is approximately at its maximal natural length in the body. The relationship between the length of a muscle and the contractile (active) force that it develops can be examined by measuring the forces generated by a muscle at different lengths. Two forces can be measured: the *passive force* and the *total force.*

When a relaxed (unstimulated) muscle held between a moveable clamp and a force transducer is progressively stretched, an increasing force (tension), derived from an increasing resistance to stretch, can be measured. As the contractile machinery is not active this force is passive and is due to the resistance exerted by elastic elements in the muscle. The force generated is not directly proportional to the increase in length (the elastic modulus increases with length) and elasticity varies greatly amongst muscles.

The curve of *total tension* is constructed by stimulating the muscle at various lengths and measuring the forces generated. Each of these forces will be the sum of both the passive force and the *active force* developed by the contractile machinery. The amplitude of the active force at the various lengths is obtained by arithmetically subtracting the passive force from the total force. The maximal active force is seen to occur near the natural resting length and to decrease with changes in length.

The most elegant way to relate these changes to the contractile machinery is to do this experiment with a single living muscle fibre. Then the force generated is seen to be related to the degree of overlap of the actin and myosin filaments. It can also be seen that at long lengths, when there is no overlap of the actin and myosin filaments, the fibre is incapable of generating a force. In the intermediate range when overlap of filaments is optimal the force generated is maximal. At shorter lengths the actin filaments overlap and interfere with each other and the force decreases. Eventually at very short lengths (60 to 70% of the maximal natural length) the Z bands will be pulled against the myosin filaments and the external force will again fall to zero. At this point the contractile machinery may still be active but the energy is used to distort the myosin filaments.

Force-Velocity Relationship

The length-tension curve has described the ability of muscles to develop tension when the muscle is held at fixed lengths (isometric contractions). The movement of limbs may be associated with the shortening of muscles under a constant load (isotonic contractions). The lighter the load the more rapidly it can be lifted. In fact both the rate and the degree of muscle shortening depend on the load. The relationship between the rate of shortening and the load carried by a muscle is illustrated by the force (load) - velocity curve.

This relationship is determined by measuring the rate of shortening of a muscle as it lifts a variety of loads. The muscles is not initially subject to each load as this would alter the starting length of the muscle. However before it can shorten the muscle must obviously first lift each load. Such an event is called an *after-loaded* contraction.

When stimulated tetanically an after-loaded muscle stars to contract. Initially and until the tension exceeds the load the contraction is isometric. After this the muscle shortens isotonically and continues to shorten until it reaches the length at which (according to the length-tension curve) the maximal force it can develop is equal to the load. It is clear that with zero load the time required initially to shorten (the latency) will be minimal and the velocity of contraction maximal. As the load is increased the latency is increased and the velocity decreases. Finally when the load is too heavy the velocity of shortening is zero and the muscle is contracting isometrically. It can be seen from the force-velocity curve that the *power* (force x velocity) which a muscle develops is not constant. The power output of a muscle is in fact optimal when both the load and the velocity are moderate - hence the advantage of ten-speed bicycles.

The reasons for the shape of the force-velocity curve are not known. One suggestion is that the myosin crossbridges move continually as a result of thermal agitation and there is only a limited space within which a crossbridge and an actin site can interact. If this is correct and the actin filament is moving, the probability of successful union will decrease as the

velocity of movement increases. Thus at high velocities few crossbridges will be formed and, as the force generated is dependent on the number of crossbridges, it will be low at high velocities. Accordingly the velocity of shortening will increase until the force generated by the muscle equals the load. This idea is supported by the observation that the velocity of shortening in isotonic contractions is relatively constant.

Muscle Fibre Types

The position of our body and the complex pattern of movements it performs are the result of the pulling actions of muscles. However, the diversity of these actions requires that the muscles used to perform them have different properties. The postural soleus muscle reaches a peak tension in 80 to 200 ms and the extraocular eye muscles develop their peak tension in 7 to 8 ms. The slow fibres have a low myosin ATPase activity and a high capacity to produce ATP by oxidative phosphorylation which is aided by a well-developed blood capillary network and high levels of intracellular *myoglobin.* The latter is an oxygen-binding protein which both facilitates the diffusion of O_2 into these muscle cells and stores a small quantity of O_2 in the cells. The combined effect of these characteristics is slow, fatigue-resistant contractions as the rate of production of ATP is sufficiently rapid to replace that split by the myosin ATPase. The high concentration and capillary density in these muscles has led to the use of the term 'red muscle'.

There are two distinct groups of fast-contracting fibres. Both are wider in diameter and a have a higher myosin ATPase activity than the slow fibres but their resistance to fatigue differ; the resistance to fatigue is correlated with a high oxidative capacity and those fibres with a high resistance are often referred to as *intermediate fibres.* The largest and fastest contracting type II fibres (the so-called *fast* fibres) have a poorly developed oxidative metabolism and depend largely on glycolysis for the production of ATP. Although ATP production by glycolysis is rapid, the high rate of consumption of these fibres during powerful contractions results in their rapid fatigue.

Regulation of Contraction

The total force generated by a muscle depends on the number of active fibres and the level of activity in each fibre. Each motor axon entering a muscle makes contact with a number of muscle fibres; each of these fibres is innervated by a single terminal branch of that axon. Thus groups of muscle fibres are activated synchronously.

Motor Units

A motor unit is comprised of a motor neurone and the group of muscle fibres innervated by the branches of its axon. Motor units vary greatly in size, ranging from one or two muscle fibres in the smallest units of muscles controlling fine movements of fingers or eyes to more than 2000 in the largest units in limb muscles. All the muscle fibres in a motor unit are of the same type, and they tend to be very homogenous in their properties and so the terms type I and type II are used for both motor units and muscle fibres. In general the type I units of slow muscle are rater similar in size although they are not particularly large; type II units, in contrast, supply fast muscles and are often large. The larger a motor unit is, the larger the axon and the nerve cell body of the motor neurone supplying it. This probably

reflects the need for production by the cell of all the materials needed to keep every one of its nerve terminals functioning.

Gradation of Tension

Increments in tension can result from an increase in the force generated by individual motor units or by the bringing into action (*recruitment*) of additional units. The initial development of muscle tension is thought to be largely due to recruitment of units. There is, in addition, an increase in firing frequency but the contribution of this to increments in tension is thought to be important mainly in the generation of larger forces.

The recruitment of motor units is not random but occurs in an orderly fashion from small to large. Low tensions are produced and precisely controlled by the selective mobilization of a number of small units. In fact under most circumstances a small proportion - paradoxically, the smallest ones - do most of the work. The largest units are activated only when a maximal effort is required and even then their activity is often brief.

Recruitment of Motor Neurones

The ordered recruitment from the *pool* of neurones supplying a muscle arises because the smallest cells are the most easily excited. The smaller surface area of the small motor neurones results in these cells having a higher input resistance. When similar excitatory synaptic currents are generated in the small and larger motor neurones the small ones reach threshold first. In contrast, inhibitory synaptic currents generated in neurones within an activated pool appear to be more effective on the larger neurones as these are the cells closest to their threshold. As the intensity of excitatory synaptic activity in a motor neuronal pool increases, larger and larger motor units are recruited and at the same time the frequency of discharges increases. However there are also neural mechanisms that limit the discharge frequency of individual motor neurones to a frequency appropriate to the type of muscle fibres they innervate.

It should be noted that the contractions of skeletal muscles that move objects, maintain posture and adapt to changes in load and fatigue, are not solely the result of motor units. These activities also make use of sensory information including that from the muscles and limbs involved.

Development and Maintenance of Skeletal Muscles

The speed with which muscles can contract and their ability to do work are not constant throughout life, but change as a person grows. Their performance is also influenced by exercise. The development, growth and maintenance of muscles are all dependent on the presence of an intact motor nerve supply.

Development of Muscles

The number of fibres in skeletal muscles appears to be genetically determined but the expression of the full genetic capacity is dependent on the normal development of the nerve supply to the muscles. If during early development the motor nerves fail to maintain contact,

for example as a result of physical or drug-induced damage, the muscles will be smaller than normal due to a decrease in the number of their fibres.

As well as influencing the number of fibres in a muscle the nerves also appear to determine the type of fibre that will develop. The properties of the muscle fibres within each motor unit are determined by the nerve controlling that unit. The muscles fibres within the one unit are homogeneous with respect to such things as contraction time, resistance to fatigue, enzymes of anaerobic and aerobic metabolism and myosin-ATPase.

These properties are determined early in development but they are not irreversible and changes can be seen in both developing and adult muscles, for example after denervation. The ability of nerves to regulate the properties of muscles is referred to as a *neurotrophic influence* but it is not known precisely how this influence is exerted. There is good evidence that nerve-induced muscle activity at the appropriate frequency (tonic low frequency for slow muscles and phasic high frequency for fast muscles) is important. There is also evidence suggesting that specific messengers, *neurotrophic factors,* are released by motor nerves to influence the muscle fibres they innervate.

Effects of Training

Type I fibres make up about 30 to 40% of the cells in human muscles and they are approximately the same size in men and women (the mean diameter being approximately 60 microm). Type II fibres are larger in men (average diameter 69 microm) than in women (550 microm). Two distinct responses to regularly performed strenuous exercise can be seen in muscle: hypertrophy of he fibres with an increase in strength (i.e., weight-lifters) and an increased capacity for aerobic metabolism (i.e., long-distance runners, cross-country skiers, swimmers).

Endurance exercise training gives rise to an increased capacity for oxidation of pyruvate and long-chain fatty acids. This is due to an increase in the absolute amount of enzymes, for example, those of the tricarboxylic acid cycle and those involved in the activation, transport and oxidation of long-chain fatty acids. There is an increase in myoglobin, which speeds the rate of diffusion of O_2 from cell membrane to mitochondria. Trained individuals have increased intramuscular stores of triglyceride and lowered concentrations of serum triglycerides and their muscle can utilize lipids directly from blood.

The consequences of these changes are that during submaximal exercise trained individuals derive more energy from fat and less from carbohydrate than do untrained individuals. Furthermore in the trained individual liver and muscle glycogen stores are better maintained during exercise and a greater proportion of oxygen is extracted from the blood supply to muscles. Fatigue is thought to be associated with depletion of muscle glycogen stores, accumulation of a high concentration of lactate and hypoglycaemia due to depletion of liver glycogen. All these changes are minimized by training, so that endurance is enhanced.

Effects of Aging

The total number of fibres in a muscle decreases with age, and it has been suggested that the average number of fibres per motor unit gets larger. It is a generally held opinion that

the units lost are the smaller ones and that the progressive loss of muscle fibres is due to a loss of nerve cells that supplied them. The potency of synaptic transmission also declines with age, possibly as a result of the observed decrease in the synthesizing ability of aged nerve cells.

Effects of Damage to Nerve or Muscle

After the nerve to a muscle is sectioned there are changes in both the muscle and the axons. The loss of the neural trophic influence results in pronounced changes in the muscle fibres. The earliest changes, such as the partial decrease in resting membrane potential and the increase in sensitivity to applied acetylcholine (which results from the addition of acetylcholine receptors to all of the sarcolemma), can be seen in a few days. But other changes, such as a pronounced decrease in the ability to develop tension, the change in enzymic composition, and the decrease in fibre diameter (*atrophy*), may take longer to develop. In man the fibres may shrink down to some 10 microm and remain so for months or until they are reinnervated. Reinnervated fibres grow and develop according to the characteristics of the motor neurone. If muscle fibres remain denervated for prolonged periods (months to years) they will gradually be replaced by connective tissue and fat.

When the nerve to a muscle is sectioned, some of the motor neurones die, but others regenerate their axons. However, in higher vertebrates there is little or no specificity in the re-establishment of nerve-muscle connections. Regrowth of the axons is aided and directed by the presence of the old nerve sheaths (hence the accurate suturing together of the cut ends of a nerve is important). Normal muscles have fibres within individual motor units well scattered across the muscle, but following regeneration of a cut nerve, muscle fibres of a single motor unit now occur as a clump of cells, as if the ingrowing nerve made connections with all the muscle fibres in its immediate vicinity. However reinnervation may not always be successful and when a whole limb is denervated there is very little evidence of orderliness in nerve regeneration to muscles and normal coordination of movement is never fully restored.

Damaged muscle fibres do not possess an intrinsic capacity for regeneration. However, damage is repaired very efficiently by the activation of small mononuclear cells (satellite cells) that normally lie beneath the basal lamina of muscle fibres. The cells undergo mitosis, increase in numbers, and ultimately fuse to repair the damaged fibres or to make new multinucleate muscle cells. In animals it is actually possible to remove a muscle, mince it, pour the mince back into the appropriate place in the animal, sew up the skin, and produce a new but smaller functional muscle. Regeneration of the muscle in such cases is critically dependent on the presence of the nerve.

3.2 Smooth Muscle

Smooth muscle has a wide range of functions and all muscular force not generated by skeletal or cardiac muscle are generated by smooth muscle. Thus smooth muscles control the movement of material through most hollow organs.

Smooth muscles vary in their level of activity, from those that show more or less continuous activity to those that are quiescent for prolonged periods. In some, only localized contractions occur (i.e., intestinal sphincters) whilst in other the whole organ may be involved

(i.e., bladder). Activity in smooth muscles may depend on a number of factors including the character of the smooth muscle cells, their environment, neural input and hormones. All neural influences are exerted by the autonomic nervous system. Some tissues are innervated by only one division, while others are innervated by both the parasympathetic and sympathetic divisions.

Smooth Muscle Structure

A connective tissue sheath, the *epimysium*, surrounds the smooth muscle of each organ. Thin septa extend inward from the epimysium to form the *perimysium,* which contains fibroblasts, capillaries, nerves and collagenous elastic fibres. The collagen fibres are synthesized by the muscle cell and form the major component of the extracellular space. The perimysium divides smooth muscle into discrete *bundles* of fibres. These bundles range from 20 to 200 microm in width, and anastomose with one another. These anastomoses can be seen at roughly 1 mm intervals along a given fibre bundle. An exception is found in arteriole walls which my be only a few cell diameters in thickness and the smooth muscle of which is not organized in bundles.

The individual smooth muscle cells within a bundle are 2 to 10 microm in diameter, and vary in length from about 50 microm in arterioles to 400 microm in most other organs. The smooth muscle cells within each bundle are fusiform, or irregular elongate cells that interweave and overlap with each other to form a network interlaced with collagen.

Individual smooth muscle cells come into close contact with ten or so neighbouring cells. At these points they may be connected by specialized intercellular junctions of relatively low electrical resistance called *gap junctions (nexuses).* At these junctions the sarcolemma of the cells is separated by 3.5 nm but the gap is bridged by structures which allow small ions to pass from cell to cell. The relatively low electrical resistance of these junctions allows current, which may have either an excitatory or an inhibitory effect, to pass from cell to cell. Where bundles exist the direct coupling of cells within each bundle may result in the bundles being the functional (contractile) unit.

Pronounced differences between the structure of smooth muscles and striated muscles are seen at he ultrastructural level. For instance, smooth muscle cells possess few mitochondria, the sarcoplasmic reticulum is poorly developed and located close to the sarcolemma, there is no post-junctional thickening or specialization at the neuromuscular junction and the myofilaments of actin and myosin are irregularly arranged. The actin filaments appear to be inserted into specialized structures in the sarcolemma, so-called dense bodies, and radiate out in a longitudinal direction from these, but a detailed knowledge of these filaments and myosin filaments is lacking.

Contractile Activity of Smooth Muscle

The contractions of smooth muscles are in general much slower than those of skeletal muscle. When excited by a single stimulus there is often long latency, a slow rise to peak tension (> 1 s) and then a slow decline to the resting state. In many tissues this single contraction may take several seconds. With repetitive stimulation the forces generated by smooth muscles increase and can reach levels similar to those found in skeletal muscles (30-

40 N/cm^2). However unlike many skeletal muscles, smooth muscles can maintain their tension at a high level for long periods and over a wide range of muscle lengths. It seems probable that the low activity of the myosin-ATPase may account for both the slow development of force and the relatively low oxygen consumption during contractions (< 1/100 that of skeletal muscle). The ability to contract over a wide range of lengths (up to four times the resting length) may be a result of the irregular arrangement of the myofilaments.

As with skeletal muscle, the force generated by smooth muscle is controlled by the level of intracellular Ca. At rest the cytoplasm contains approximately 10^{-8} mol/L Ca but this my rise to approximately 10^{-5} mol/L Ca during the development of maximal tension. This Ca may come from the interstitial fluid as a result of a change in membrane permeability to Ca or be released internally from bound stores. The incoming Ca appears to contribute substantially to the rising phase of the smooth muscle action potential.

Resting Membrane Potential and Action Potentials

The resting membrane potential of many smooth muscles is in the range of -60 to -70 mV and the basis of this membrane potential is similar to that found in other excitable cells. However, the resting membrane potential is some 20 mV below the equilibrium potential for K and this may be the result of a relatively large resting permeability to Na.

Not all smooth muscles exhibit action potentials, but in those that do they are usually spike-like, but somewhat slower than in skeletal muscle. Plateau-type action potentials are seen in some tissues (i.e., in the ureter). A depolarization of some 20 mV is required to reach threshold and initiate an action potential. The action potentials reach a peak potential of some + 10 mV and if the stimulus is maintained repetitive firing may occur, the frequency depending on the degree of depolarization.

The inward current responsible for the action potential in nerves and skeletal muscles is carried by sodium ions. This can be shown by the fact that the magnitude of the overshoot of the action potential is directly proportional to E_{Na}, and that action potentials fail in solutions depleted of E_{Na}. This is not true for some smooth muscles, where removing Na from the bathing fluid actually makes the action potential larger. On the other hand, removing Ca ions from the bathing fluid does abolish action potentials, while increasing Ca produces larger action potentials. Mn, which blocks Ca-mediated action potentials in other tissues, blocks the smooth muscle action potential.

Types of Smooth Muscle

The activity of smooth muscles may be rhythmical and in these tissues dependent on spontaneous myogenic mechanisms. Other tissues are quiescent until stimulated by an incoming signal. The former have often been referred to as 'unitary' (cells acting together) and the latter as 'multiunit' (cells acting independently) smooth muscles respectively, but these divisions are now of little use as they represent extremes. Smooth muscles are now conveniently divided into three groups according to their membrane properties.

Spontaneously Active Smooth Muscle

Many organs containing smooth muscle contract rhythmically (i.e., stomach, small intestine, ureter, parturient uterus). As this coordinated activity is seen in the presence of neurotoxins or local anaesthetics it is concluded that it is initiated by the smooth muscle cells, i.e., it is *myogenic* (as in the hear). Such activity usually depends on the spontaneous generation of action potentials, and the presence of a conducting system (the gap junctions). Two types of mechanism are responsible for the spontaneous generation of action potentials, *pacemaker* potentials and *slow waves.*

In some smooth muscle (i.e., uterus and taenia coli) it appears that focal pacemaker regions slowly depolarize a group of cells to threshold. The subsequent action potentials are then conducted through the tissue. The pacemaker regions are not constant in location, and it is thought that all regions within these tissues have the capacity to assume the role of pacemaker.

The rhythmic activity of the stomach and intestine result from depolarizations called slow waves. These ar discrete plateau-type depolarizations, lasting 2 to 8 s, that can be recorded from all regions of the external muscle layer. As slow waves can be initiated by depolarizing current they are propagated and their frequency is determined by the cells having the highest rate. In the intestine, where they are about 20 mV in amplitude, and in the antrum of the stomach, where they are about 40 mV in amplitude, the slow waves initiate action potentials or spikes. In these tissues the amplitude of contractions depends on the number of action potentials. The situation is less certain in the fundus and body of the stomach where the slow waves are larger but no spikes are seen.

The spontaneous contractile activity can be altered by nervous activity which may be either excitatory or inhibitory. For example in the intestine acetylcholine, the transmitter released from parasympathetic nerves, causes the smooth muscle to depolarize. As a consequence the number and frequency of action potentials on each slow waves is increased and the contractions are more forceful. In contrast, the inhibitory action of noradrenaline, the transmitter released from sympathetic neurones to the detrusor muscle, and the inhibitory actions of non-adrenergic, non-cholinergic autonomic neurones to the gut are due to hyperpolarization and movement of the membrane potential away from threshold. This may result in complete cessation of contractile activity while the spontaneous fluctuations in membrane potentials continue at a sub-threshold level. Hormones may have similar actions.

Electrically Inexcitable Smooth Muscle

This term applies to an extreme, but not unimportant, group of smooth muscles that do not generate action potentials (i.e., bronchial, tracheal and specific arterial smooth muscles of some species). In these tissues the membrane potential remains stable until the tissue is stimulated. Stimulation may be the result of neurotransmitter release or the activity of local or blood-borne agents (i.e., histamine and bradykinin). Stimulation is accompanied by depolarization and subsequent contractions. In tissues with a sparse innervation, excitation can spread because of the presence of gap junctions. The physiological advantage of these muscles may reside in their generally slow and sustained response to nerve stimulation.

Intermediate Smooth Muscle

This category is the most widely distributed (i.e., iris, pilo-erector, blood vessels, vas deferens, seminal vesicles). These have a stable resting potentials. The cells are linked by gap junctions but conduction is decremental and so the contractions fail to spread throughout the tissue. The force of contraction is proportional to the frequency of the action potentials and is usually under neural control.

Activation of Smooth Muscle

Contraction of all smooth muscles is dependent on changes in the intracellular Ca level. This can occur as a result of inherent myogenic mechanisms which regularly depolarize the muscle fibres or from neural or hormonal action. Contractions may also be induced by other means. For instance, some smooth muscles are relatively plastic when slowly stretched but rapid stretching results in a stretch-induced depolarization and contraction. Such behaviour may be important in *autoregulation* of blood vessels. In other tissues local agents modify the force of contraction (i.e., the actions of O_2 and CO_2 on blood vessels of the lungs, and histamine on bronchial smooth muscle).

In many tissues the dominant influence is exerted by the nerves. Excitation is usually the result of a depolarization (an *excitatory junction potential*) which is caused mainly by an increased conductance to Na and to lesser extent K. In the case of inhibition the hyperpolarization of the smooth muscle membrane (the *inhibitory junction potential*) may be due to an increased conductance to K (and possibly Cl).

In both cases the increase in conductance arises as a result of the neurotransmitter interacting with specific surface receptors on the muscle fibres. If the neuromuscular junction has a relatively small junctional cleft (20 nm) then the junctional potential is distinct with a fast rate of rise and may last 0.5 s. It seems that wider (400-500 nm) neuromuscular junctions may not exhibit the same rapid junctional potentials and the response to nerve stimulations is relatively slow. In fact in some tissues (i.e., the tunica media of blood vessels) many of the muscle fibres may not be directly innervated. They may, however, be under some neural influence, current spreading from neighbouring innervated regions (through gap junctions).

The contractile activity of many smooth muscles is also influenced by circulatory hormones and parahormones. It can be seen that the action of many hormones are limited to particular smooth muscles. Thus the stimulatory actions of the GIT hormone, gastrin, on smooth muscle, are largely limited to the stomach and gall-bladder; and the stimulatory actions of oxytocin are limited to the uterus. The specificity of these interactions is demonstrated by the inability of hormones with similar structures (i.e., gastrin and cholecystokinin, and oxytocin and vasopressin) to have the same effects. This presumably reflects the highly specific nature of the receptors on the plasma membrane.

Other hormones have widespread activities, thus adrenaline can change the contractile activity of many tissues (i.e., blood vessels, bronchioles and the intestines). Similarly, the highly potent prostaglandins (PG) and thromboxanes have pronounced effects on a number of smooth muscles. Thus PGF_2 is a potent stimulator of uterine contractility (and is used to

induce labour at term), of intestinal smooth muscle and of bronchial smooth muscle. However, thee physiological roles of the latter compounds are less certain.