Excitable Tissue: Muscle

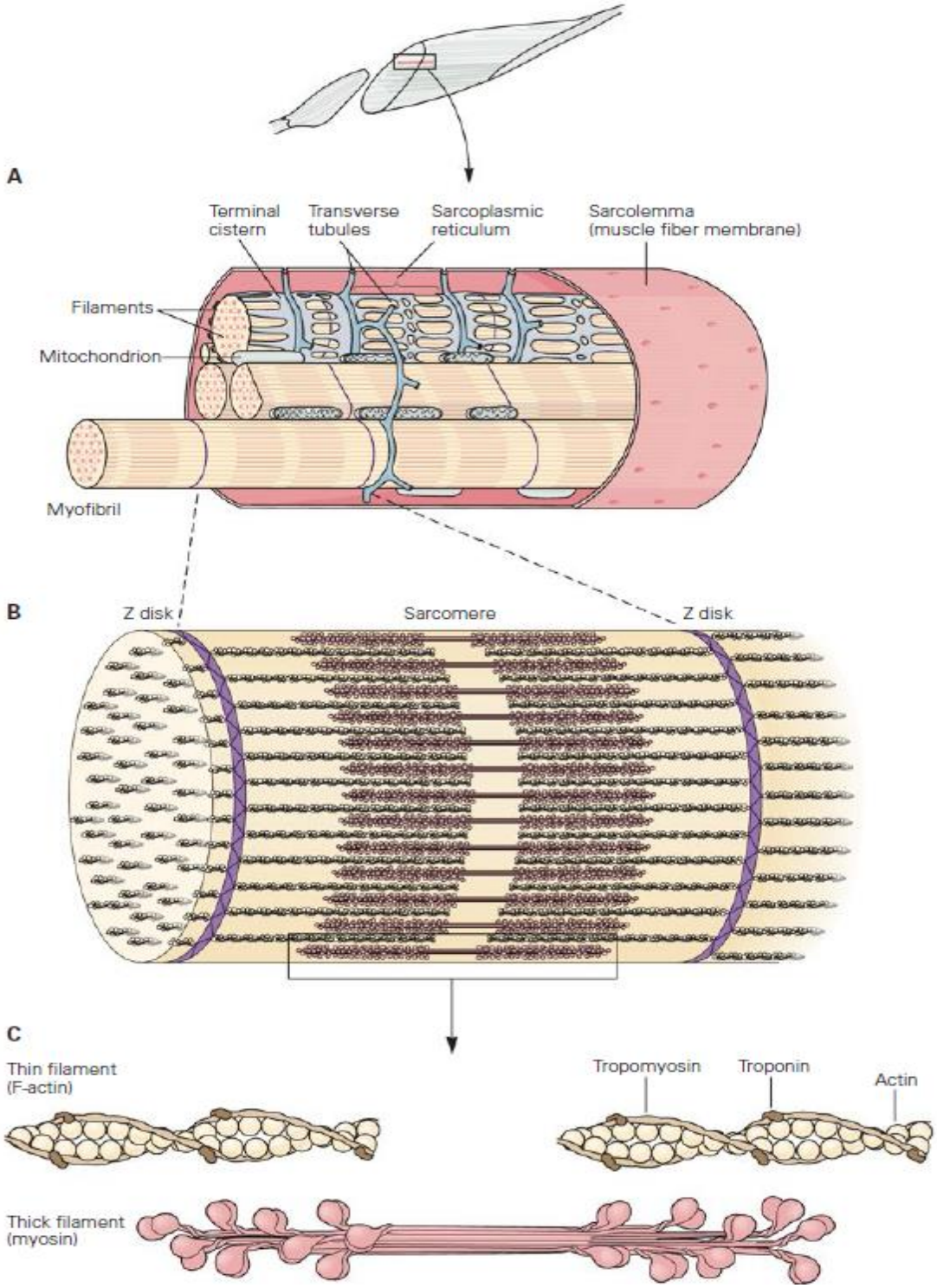
Muscle cells, like neurons, can be excited chemically, electrically, and mechanically to produce an action potential that is transmitted along their cell membranes. Unlike neurons, they respond to stimuli by activating a contractile mechanism. The contractile protein myosin and the cytoskeletal protein actin are abundant in muscle, where they are the primary structural components that bring about contraction.

Muscle is divided into three types: **skeletal, cardiac,** and **smooth,** although smooth muscle is not a homogeneous single category. Skeletal muscle makes up the great mass of the somatic musculature. It has well-developed cross-striations, does not normally contract in the absence of nervous stimulation, lacks anatomic and functional connections between individual muscle fibers, and is generally under voluntary control. Cardiac muscle also has cross-striations, but it is functionally syncytial and, although it can be modulated via the autonomic nervous system, it can contract rhythmically in the absence of external innervation owing to the presence in the myocardium of pacemaker cells that discharge spontaneously.

Smooth muscle lacks cross-striations and can be further subdivided into two broad types: unitary (or visceral) smooth muscle and multiunit smooth muscle. The type found in most hollow viscera is functionally syncytial and contains pacemakers that discharge irregularly. The multiunit type found in the eye and in some other locations.

SKELETAL MUSCLE ORGANIZATION

Skeletal muscle is made up of individual muscle fibers that are the “building blocks” of the muscular system in the same sense that the neurons are the building blocks of the nervous system. Most skeletal muscles begin and end in tendons, and the muscle fibers are arranged in parallel between the tendinous ends, so that the force of contraction of the units is additive. Each muscle fiber is a single cell that is multinucleated, long, cylindrical, and surrounded by a cell membrane, the sarcolemma. There are no syncytial bridges between cells. The muscle fibers are made up of myofibrils, which are divisible into individual filaments. These myofilaments contain several proteins that together make up the contractile machinery of the skeletal muscle.

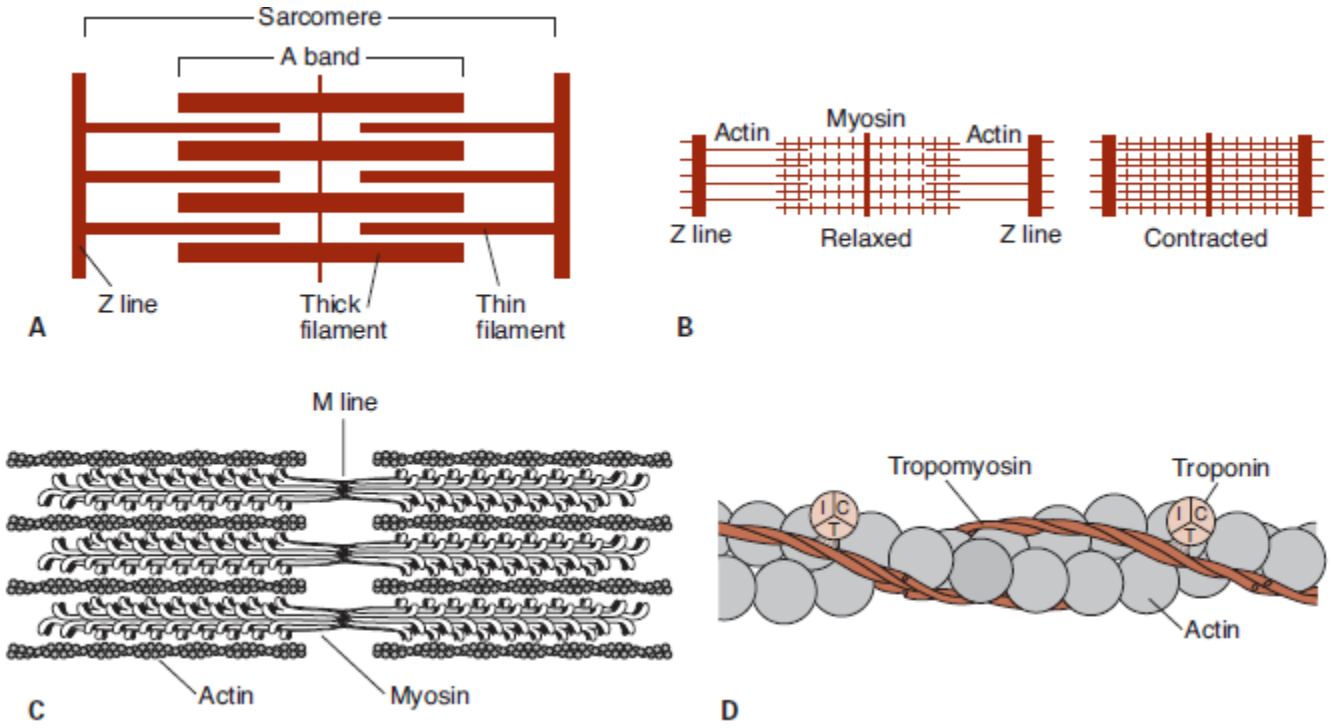


The contractile mechanism in skeletal muscle largely depends on the proteins **myosin-II, actin, tropomyosin ,**and **troponin.** Troponin is made up of three subunits: **troponin I, troponin T,** and **troponin C.** Other important proteins in muscle are involved in maintaining the proteins that participate in contraction in appropriate structural relation to one another and to the extracellular matrix.

STRIATIONS

The parts of the cross-striations are frequently identified by letters. The light I band is divided by the dark Z line, and the dark A band has the lighter H band in its center. A transverse M line is seen in the middle of the H band, and this line plus the narrow light

areas on either side of it are sometimes called the pseudo-H zone. The area between two adjacent Z lines is called a **sarcomere.**



The thick filaments, which are about twice the diameter of the thin filaments, are made up of myosin; the thin filaments are made up of actin, tropomyosin, and troponin. The thick filaments are lined up to form the A bands, whereas the array of thin filaments extends out of the A band and into the less dense staining I bands. The lighter H bands in the center of the A bands are the regions where, when the muscle is relaxed, the thin filaments do not overlap the thick filaments. The Z lines allow for anchoring of the thin filaments. If a transverse section through the A band is examined under the electron microscope, each thick filament is seen to be surrounded by six thin filaments in a regular hexagonal pattern.

SARCOTUBULAR SYSTEM

The muscle fibrils are surrounded by structures made up of membranes that appear in electron photomicrographs as vesicles and tubules. These structures form the **sarcotubular system,** which is made up of a **T system** and a **Sarcoplasmic reticulum.** The T system of transverse tubules, which is continuous with the sarcolemma of the muscle fiber, forms a grid perforated by the individual muscle fibrils (Figure 5‑1). The space between the two layers of the T system is an extension of the extracellular space. The sarcoplasmic reticulum, which forms an irregular curtain around each of the fibrils, has enlarged **terminal cisterns** in close contact with the T system at the junctions between the A and I bands. At these points of contact, the arrangement of the central T system with a cistern of the sarcoplasmic reticulum on either side has led to the use of the term **triads** to describe the system. The T system, which is continuous with the sarcolemma, provides a path for the rapid transmission of the action potential from the cell membrane to all the fibrils in the muscle. The sarcoplasmic reticulum is an important store of Ca^{2+} and also participates in muscle

metabolism. As in nerves, depolarization is largely a manifestation of Na+ influx, and repolarization is largely a manifestation of K+ efflux.

THE MUSCLE TWITCH

A single action potential causes a brief contraction followed by relaxation. This response is called a **muscle twitch**, the action potential and the twitch are plotted on the same time scale. The twitch starts about 2 ms after the start of depolarization of the membrane, before repolarization is complete. The duration of the twitch varies with the type of muscle being tested. "Fast" muscle fibers, primarily those concerned with fine, rapid, precise movement, have twitch durations as short as 7.5 ms. "Slow" muscle fibers, principally those involved in strong, gross, sustained movements, have twitch durations up to 100 ms.

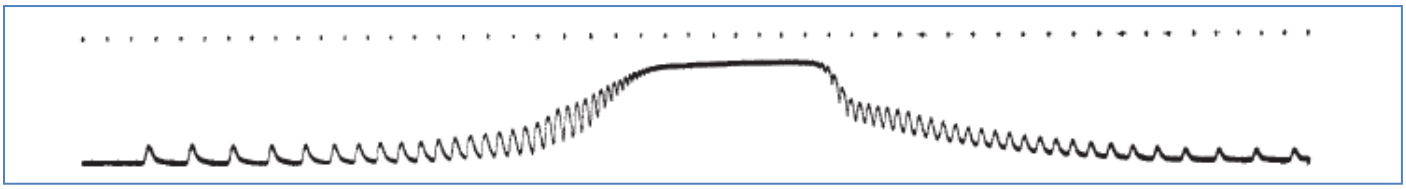
In resting muscle, troponin I is bound to actin and tropomyosin and covers the sites where myosin heads interact with actin. Also at rest, the myosin head contains tightly bound ADP. Following an action potential cytosolic Ca2+ is increased and free Ca2+ binds to troponin C. This binding results in a weakening of the troponin I interaction with actin and exposes the actin binding site for myosin to allow for formation of myosin/actin cross-bridges. Upon formation of the cross-bridge, ADP is released, causing a conformational change in the myosin head that moves the thin filament relative to the thick filament, comprising the cross bridge "power stroke." ATP quickly binds to the free site on the myosin, which leads to a detachment of the myosin head from the thin filament. ATP is hydrolyzed and inorganic phosphate (Pi) released, causing a "re-cocking" of the myosin head and completing the cycle. As long as Ca2+ remains elevated and sufficient ATP is available, this cycle repeats.

For contraction to occur without an appreciable decrease in the length of the whole muscle. Such a contraction is called **isometric** ("same measure" or length). Contraction against a constant load with a decrease in muscle length is **isotonic** ("same tension"). Note that because work is the product of force times distance, isotonic contractions do work, whereas isometric contractions do not. In other situations, muscle can do negative work while lengthening against a constant weight.

SUMMATION OF CONTRACTIONS

The electrical response of a muscle fiber to repeated stimulation is like that of nerve. The fiber is electrically refractory only during the rising phase and part of the falling phase of the spike potential. At this time, the contraction initiated by the first stimulus is just beginning. However, because the contractile mechanism does not have a refractory period, repeated stimulation before relaxation has occurred produces additional activation of the contractile elements and a response that is added to the contraction already present. This phenomenon is known as **summation of contractions.** The tension developed during summation is considerably greater than that during the single muscle twitch. With rapidly repeated stimulation, activation of the contractile mechanism occurs repeatedly before any relaxation has occurred, and the individual responses fuse into one continuous contraction. Such a

response is called a **tetanus (tetanic contraction).** It is a **complete tetanus** when no relaxation occurs between stimuli and an **incomplete tetanus** when periods of incomplete relaxation take place between the summated stimuli. During a complete tetanus, the tension developed is about four times that developed by the individual twitch contractions.



FIBER TYPES

Although skeletal muscle fibers resemble one another in a general way, skeletal muscle is a heterogeneous tissue made up of fibers that vary in myosin ATPase activity, contractile speed, and other properties. Muscles are frequently classified into two types, "slow" and "fast."

ENERGY SOURCES & METABOLISM

Muscle contraction requires energy, and muscle has been called "a machine for converting chemical energy into mechanical work." The immediate source of this energy is ATP, and this is formed by the metabolism of carbohydrates and lipids. ATP is resynthesized from ADP by the addition of a phosphate group, some of the energy for this endothermic reaction is supplied by the breakdown of glucose to CO2 and H2O, but there also exists in muscle another energy-rich phosphate compound that can supply this energy for short periods. This compound is **phosphorylcreatine,** which is hydrolyzed to creatine and phosphate groups with the release of considerable energy. At rest, some ATP in the mitochondria transfers its phosphate to creatine, so that a phosphorylcreatine store is built up. During exercise, the phosphorylcreatine is hydrolyzed at the junction between the myosin heads and actin, forming ATP from ADP and thus permitting contraction to continue.

CARBOHYDRATE & LIPID BREAKDOWN

At rest and during light exercise, muscles utilize lipids in the form of free fatty acids as their energy source. As the intensity of exercise increases, lipids alone cannot supply energy fast enough and so use of carbohydrate becomes the predominant component in the muscle fuel mixture. Thus, during exercise, much of the energy for phosphorylcreatine and ATP resynthesis comes from the breakdown of glucose to CO2 and H2O. Glucose in the bloodstream enters cells, where it is degraded through a series of chemical reactions to pyruvate. Another source of intracellular glucose, and consequently of pyruvate, is glycogen, the carbohydrate polymer that is especially abundant in liver and skeletal muscle. When adequate O2 is present, pyruvate enters the citric acid cycle and is metabolized—through this cycle and the so-called respiratory enzyme pathway—to CO2 and H2O. This process is called **aerobic glycolysis.** The metabolism of glucose or glycogen to CO2 and H2O forms large

quantities of ATP from ADP. If O2 supplies are insufficient, the pyruvate formed from glucose does not enter the tricarboxylic acid cycle but is reduced to lactate. This process of **anaerobic glycolysis** is associated with the net production of much smaller quantities of energy-rich phosphate bonds, but it does not require the presence of O2.

RIGOR

When muscle fibers are completely depleted of ATP and phosphorylcreatine, they develop a state of rigidity called **rigor.** When this occurs after death, the condition is called **rigor mortis**. In rigor, almost all of the myosin heads attach to actin but in an abnormal, fixed, and resistant way.

THE MOTOR UNIT

Each single motor neuron and the muscle fibers it innervates constitute a **motor unit.** The number of muscle fibers in a motor unit varies. In muscles such as those of the hand and those concerned with motion of the eye (ie, muscles concerned with fine, graded, precise movement), each motor unit innervates very few (on the order of three to six) muscle fibers. On the other hand, values of 600 muscle fibers per motor unit can occur in human leg muscles. The group of muscle fibers that contribute to a motor unit can be intermixed within a muscle. That is, although they contract as a unit, they are not necessarily "neighboring" fibers within the muscle.

ELECTROMYOGRAPHY

Activation of motor units can be studied by electromyography, the process of recording the electrical activity of muscle on an oscilloscope. This may be done in unanaesthetized humans by using small metal disks on the skin overlying the muscle as the pick-up electrodes or by using hypodermic needle electrodes. The record obtained with such electrodes is the **electromyogram (EMG).** With needle electrodes, it is usually possible to pick up the activity of single muscle fibers. It has been shown by electromyography that little if any spontaneous activity occurs in the skeletal muscles of normal individuals at rest. With minimal voluntary activity a few motor units discharge, and with increasing voluntary effort, more and more are brought into play to monitor the **recruitment of motor units.** Gradation of muscle response is therefore in part a function of the number of motor units activated. In summary, EMGs can be used to quickly (and roughly) monitor abnormal electrical activity associated with muscle responses.

CARDIAC MUSCLE

The striations in cardiac muscle are similar to those in skeletal muscle, and Z lines are present. Large numbers of elongated mitochondria are in close contact with the muscle fibrils. The muscle fibers branch and interdigitate, but each is a complete unit surrounded by a cell membrane. Where the end of one muscle fiber abuts on another, the membranes of both fibers parallel each other through an extensive series of folds. These areas, which

always occur at Z lines, are called **intercalated disks**. They provide a strong union between fibers, maintaining cell-to-cell cohesion, so that the pull of one contractile cell can be transmitted along its axis to the next. Along the sides of the muscle fibers next to the disks, the cell membranes of adjacent fibers fuse for considerable distances, forming gap junctions. These junctions provide low-resistance bridges for the spread of excitation from one fiber to another. They permit cardiac muscle to function as if it were a syncytium, even though no protoplasmic bridges are present between cells. The T system in cardiac muscle is located at the Z lines rather than at the A‑I junction, where it is located in mammalian skeletal muscle.

The role of Ca^{2+} in excitation‑contraction coupling is similar to its role in skeletal muscle However, it is the influx of extracellular Ca^{2+} through the voltage-sensitive ion channels in the T system that triggers calcium-induced calcium release at the sarcoplasmic reticulum. Because there is a net influx of Ca^{2+} during activation, there is also a more prominent role for plasma membrane Ca^{2+} ATPases and the Na^{+}/Ca^{2+} exchanger in recovery of intracellular Ca^{2+} concentrations. Cardiac muscle is generally slow and has relatively low ATPase activity. Its fibers are dependent on oxidative metabolism and hence on a continuous supply of O_2.

The relation between initial fiber length and total tension in cardiac muscle is similar to that in skeletal muscle; there is a resting length at which the tension developed on stimulation is maximal. In the body, the initial length of the fibers is determined by the degree of diastolic filling of the heart, and the pressure developed in the ventricle is proportionate to the volume of the ventricle at the end of the filling phase **(Starling's law of the heart).**

Mammalian hearts have an abundant blood supply, numerous mitochondria, and a high content of myoglobin, a muscle pigment that can function as an O_2 storage mechanism. Normally, less than 1% of the total energy liberated is provided by anaerobic metabolism.

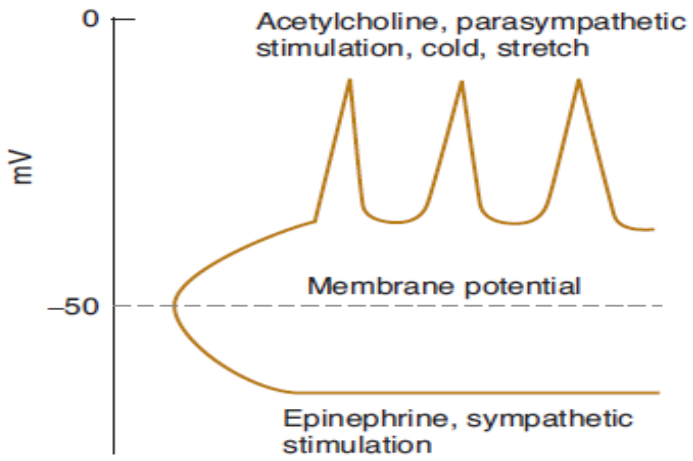
SMOOTH MUSCLE MORPHOLOGY

They lack visible cross-striations. Actin and myosin-II are present, and they slide on each other to produce contraction. However, they are not arranged in regular arrays, as in skeletal and cardiac muscle, and so the striations are absent. Instead of Z lines, there are **dense bodies** in the cytoplasm and attached to the cell membrane, and these are bound by α-actinin to actin filaments. Smooth muscle also contains tropomyosin, but troponin appears to be absent. In general, smooth muscles contain few mitochondria and depend, to a large extent, on glycolysis for their metabolic needs. In general, smooth muscle can be divided into **unitary** (or **visceral**) **smooth muscle** and **multiunit smooth muscle.** Unitary smooth muscle occurs in large sheets, is found primarily in the walls of hollow viscera. The musculature of the intestine, the uterus, and the ureters are examples. Multiunit smooth muscle is made up of individual units, it is found in structures such as the iris of the eye, in which fine, graded contractions occur. It is not under voluntary control, but it has many functional similarities to

skeletal muscle. In addition, these cells respond to hormones and other circulating substances. Blood vessels have both unitary and multiunit smooth muscle in their walls. Unitary smooth muscle is characterized by the instability of its membrane potential and by the fact that it shows continuous, irregular contractions that are independent of its nerve supply. This maintained state of partial contraction is called **tonus,** or **tone.** The membrane potential has no true "resting" value, being relatively low when the tissue is active and higher when it is inhibited, but in periods of relative quiescence values for resting potential are on the order of −20 to −65 mV.

Myosin is dephosphorylated by **myosin light chain phosphatase** in the cell. However, dephosphorylation of myosin light chain kinase does not necessarily lead to relaxation of the smooth muscle. Various mechanisms are involved. One appears to be a latch bridge mechanism by which myosin cross-bridges remain attached to actin for some time after the cytoplasmic Ca2+ concentration falls**.** This produces sustained contraction with little expenditure of energy, which is especially important in vascular smooth muscle. Unitary smooth muscle is unique in that, unlike other types of muscle, it contracts when stretched in the absence of any extrinsic innervation. Stretch is followed by a decline in membrane potential, an increase in the frequency of spikes, and a general increase in tone.

If epinephrine or norepinephrine is added to a preparation of intestinal smooth muscle arranged for recording of intracellular potentials in vitro, the membrane potential usually becomes larger, the spikes decrease in frequency, and the muscle relaxes. Norepinephrine is the chemical mediator released at noradrenergic nerve endings, and stimulation of the noradrenergic nerves to the preparation produces inhibitory potentials. Acetylcholine has an effect opposite to that of norepinephrine on the membrane potential and contractile activity of intestinal smooth muscle. If acetylcholine is added to the fluid bathing a smooth muscle preparation in vitro, the membrane potential decreases and the spikes become more frequent. The muscle becomes more active, with an increase in tonic tension and the number of rhythmic contractions.



The effects of acetylcholine and norepinephrine on unitary smooth muscle serve to emphasize two of its important properties: (1) its spontaneous activity in the absence of nervous stimulation, and (2) its sensitivity to chemical agents released from nerves locally or

brought to it in the circulation. In mammals, unitary muscle usually has a dual nerve supply from the two divisions of the autonomic nervous system. The function of the nerve supply is not to initiate activity in the muscle but rather to modify it. Stimulation of one division of the autonomic nervous system usually increases smooth muscle activity, whereas stimulation of the other decreases it. However, in some organs, noradrenergic stimulation increases and cholinergic stimulation decreases smooth muscle activity; in others, the reverse is true.