CASE 7

An 8-year-old boy is brought to the emergency room after being stung by a bee. His mother noticed that he was playing in the backyard when he suffered the sting, and within minutes he began having trouble in breathing. She also noticed that he had a “hive” rash over most of his body, along with increased difficulty breathing. When the emergency medical service (EMS) arrived, they administered epinephrine subcutaneously, which seemed to relieve most of the symptoms. In the emergency center, the boy was diagnosed with an anaphylactic reaction from the bee sting.

◆ What type of smooth muscle (unitary versus multiunit) is present in the bronchi of the lungs?

◆ Why does smooth muscle not appear striated?

◆ What is the molecular basis for contraction in a smooth muscle?
ANSWERS TO CASE 7: SMOOTH MUSCLE

Summary: An 8-year-old boy with bronchial constriction and an anaphylactic reaction from a bee sting is treated with epinephrine.

◆ Type of muscle unit: Multiunit smooth muscle.

◆ Appearance of smooth muscle: Thick and thin filaments are present but are not arranged in sarcomeres.

◆ Molecular basis for contraction: Calcium binds to calmodulin, which activates myosin light-chain kinase.

CLINICAL CORRELATION

Anaphylaxis is a life-threatening response of a sensitized human being to a specific antigen. Symptoms occur within minutes of the exposure. Some examples of common antigens are medications (penicillin), food (peanuts), pollen (ragweed), insect bites (honeybee, wasp), chemicals (ethylene oxide), and occupational exposure (latex). Symptoms of respiratory distress, angioedema, urticaria, vascular collapse, and possibly shock may ensue. The clinical symptoms are all a result of immune-mediated responses in different organs that lead to altered smooth muscle function. The offending antigen causes the release of various cytokines that affect various smooth muscles throughout the body. The patient may develop respiratory distress from bronchial constriction; cardiovascular changes from arteriolar dilation and increased capillary permeability; cutaneous manifestations of urticaria, pruritis, and angioedema; and gastrointestinal symptoms of nausea, vomiting, diarrhea, and crampy abdominal pain. Treatment with epinephrine provides both β- and α-adrenergic effects, causing bronchial dilation and vasoconstriction and thus relieving the symptoms of anaphylaxis. If the patient develops acute airway edema, control of the airway is paramount.

APPROACH TO SMOOTH MUSCLE PHYSIOLOGY

Objectives

1. Know the types of smooth muscles and their locations in the body.
2. Understand the arrangement of smooth muscle filaments.
3. List the steps in the excitation-contraction of muscle.

Definitions

Unitary smooth muscle: Muscle that contracts and relaxes as a unit.

Multiunit smooth muscle: Muscle that, like skeletal muscle, acts independently in contraction and relaxation.
DISCUSSION

Smooth muscle can be subclassified on the basis of location and contractile behavior. Smooth muscle is found in most organ systems and can be classified as, for example, airway, arterial, venous, intestinal, uterine among others. Although the muscle in each of these tissues is classified histologically as smooth muscle, there are many differences in the contractile activities and the regulation of contraction among the various smooth muscles. Some smooth muscles maintain a level of contraction most of the time and are called tonic smooth muscles; others contract and relax periodically and are called phasic smooth muscles. Part of this difference in behavior is because of the fact that in some smooth muscles the membranes of adjacent smooth muscle cells are coupled to one another through low-resistance electrical pathways (gap junctions) in their membranes. Thus, excitation of one cell will spread quickly, and a group of cells will contract in unison. This type of muscle also is called unitary smooth muscle. Other smooth muscles are arranged more like skeletal muscle, in which each muscle cell can act independently when stimulated. This type of muscle is called multiunit smooth muscle.

As in striated muscle, actin and myosin are the major contractile proteins in all smooth muscles. As in striated muscle, these proteins are arranged in two sets of filaments: actin in thin filaments and myosin in thick filaments. Myosin molecules are thought to be arranged in the thick filaments in the same way as are those in skeletal muscle, with cross-bridges extending to make contact with the actin filaments. Although there are thick and thin filaments in smooth muscle, they are not organized into sarcomeres and thus give a homogeneous smooth appearance under the light microscope. There are many more thin filaments than there are thick filaments, with the ratio being closer to 10:1 than to the 2:1 seen in skeletal muscle. Also, not every thin filament is in close proximity to a thick filament. In fact, there may be two or more populations of thin filaments: those associated with thick filaments and those associated with other actin-binding proteins and the cytoskeleton. Thin filaments are attached to elements of the cytoskeleton, but these attachments bear little anatomic resemblance to the Z disks found in striated muscle. Most common are thin filaments anchored to protein structures, which are called dense bodies.

Even though thick and thin filaments are not arranged in sarcomeres, the basic contractile model given for striated muscle—the sliding of one filament over the other as a result of cross-bridge cycling (see Case 6)—is thought to hold true for smooth muscle. The lack of a rigid structure may account for some of the quantitative differences seen in contractions of smooth muscle compared with those of striated muscle.

Smooth muscle myosin is an adenosine triphosphatase (ATPase), and its splitting of adenosine triphosphate (ATP) provides the energy required for muscle contraction. Although it is an ATPase, pure smooth muscle myosin exhibits low ATPase activity. Furthermore, myosin ATPase activity is not increased upon the addition of actin alone, unless myosin is phosphorylated. This indicates that the regulation of smooth muscle contraction is mediated via the
thick filaments rather than via the thin filaments as in striated muscle. The main mechanism for the initiation of contraction appears to involve phosphorylation of the 20,000-d light chains of myosin. In resting smooth muscle, phosphorylation is low. Myosin light chain kinase is the enzyme that, on stimulation, is activated and quickly catalyzes the phosphorylation of the myosin light chains. This results in actin-activated ATPase activity and contraction. When the stimulus to contract ceases, kinase activity decreases, myosin light chains are dephosphorylated by phosphatases, and the muscle relaxes.

Although the regulatory proteins are different in smooth muscle, the sequence of events leading to contraction is caused by the actions of calcium. In relaxed muscle, the levels of “free” cytosolic calcium—calcium that is not bound to other structures, such as sarcoplasmic reticulum (SR), mitochondria, and nuclei—is low (<10⁻⁷ M). Upon stimulation of the muscle, the calcium level increases into the micromolar, or higher, range to initiate contraction. Calcium binds with calmodulin (one of the calcium-binding proteins found in many tissues), and then the calcium–calmodulin complex binds to and activates the myosin light chain kinase. Once the stimulus for muscle contraction ceases, free calcium levels decrease, and calcium dissociates from the regulatory proteins. The muscle then relaxes. In addition to calcium levels regulating contraction, changes in the activities of myosin light chain kinase and phosphatases also influence contractions by altering levels of light chain phosphorylation in response to calcium.

The sources and sinks for calcium and, therefore, excitation–contraction coupling vary markedly from one smooth muscle to another. Some have an abundant SR. When these cells are excited, events initiated at the cell membrane cause the release of calcium from the SR. In some cells, the event is a depolarization, either sustained or phasic, of the cell membrane. Additionally, receptor activation by ligands may stimulate the intracellular production of second messengers, such as inositol triphosphate, that in turn cause the release of SR calcium. Other smooth muscle cells have almost no SR. These cells must rely on the entry of enough calcium through membrane calcium channels to activate their contractile proteins.

As in striated muscle, cytoplasmic free calcium must be decreased to allow for relaxation. In cells with abundant SR, most of this calcium is pumped back into the SR via a calcium ATPase. However, in these cells, and especially in cells with little SR, calcium also must be expelled from the cell across the cell membrane. Presumably, this is accomplished by a sodium–calcium exchange mechanism and perhaps by a membrane-bound calcium ATPase.

Smooth muscle cells vary in the manner in which they are excited. Many have membrane potentials that fluctuate rhythmically to reach threshold levels periodically. Others have stable resting potentials. In addition to this inherent activity, most smooth muscles are multiply innervated. Many have membrane receptors for circulating hormones and locally released paracrine and autacoids. In addition, many smooth muscles respond directly to stretching of their membranes. Also, in contradistinction to what occurs in striated muscle, certain ligand–receptor interactions in smooth muscle lead to inhibition of contraction rather than excitation. Thus, at any one time, a specific smooth muscle cell will
be receiving multiple inputs, some excitatory and some inhibitory. In this particular clinical case, the airway smooth muscle is contracting in response to the cytokine and paracrine mediators released by the allergic response. This increases the resistance to airflow, making breathing difficult. Smooth muscle of the gastrointestinal tract also is stimulated by mediators released by the allergic response, resulting in the gastrointestinal symptoms. However, smooth muscle in some blood vessels is relaxed, and capillary permeability is increased by some of the same mediators. This can result in hypotension and edema. Epinephrine is able to counteract these actions because it can interact with β-adrenergic receptors on airway smooth muscle and gastrointestinal smooth muscle to elicit relaxation; it also can interact with α-adrenergic receptors on vascular smooth muscle to cause contraction, thus maintaining blood pressure.

All smooth muscles exhibit length–force (tension) relationships similar to those seen in striated muscle, even though sarcomeres are absent in smooth muscle. However, there are some quantitative differences compared with striated muscle. Smooth muscle cells can develop active force over greater variations in muscle length, and many can generate greater force than skeletal muscle can. All smooth muscles also exhibit force–velocity relationships that are similar to those seen in striated muscle. A major quantitative difference is that $V_{max}$ is much lower. Finally, many smooth muscles resemble cardiac muscle in that changes in contractility occur. This probably is because of the varying amounts of calcium that enter and/or are released with a single action potential or another excitation event.

**COMPREHENSION QUESTIONS**

[7.1] A patient is given a drug that causes inhibition of myosin light-chain kinase. Which of the following is the most likely clinical effect?

A. Arterial hypertension  
B. Decreased airway resistance  
C. Decreased force of contraction of the heart  
D. Decreased tone of postural muscles  
E. Diarrhea

[7.2] A 55-year-old man has been taking a β-adrenergic receptor antagonist for treatment of a cardiac arrhythmia. Lately, he has noticed that he is experiencing some difficulty breathing, especially shortly after taking his medication. Which of the following is the most likely mechanism of the patient’s respiratory difficulty?

A. Decreased levels of ATP in airways smooth muscle  
B. Decreased levels of cytoplasmic “free” calcium in airways smooth muscle  
C. Less phosphorylation of myosin in airway smooth muscle  
D. Less production of inositol triphosphate in airway smooth muscle  
E. The effect of endogenous relaxants on airway smooth muscle
A bundle of muscle cells is found to contract rhythmically and in unison even when its nerve supply is disrupted. Although muscle contractions are dependent on the presence of extracellular calcium, the cells have poorly developed T tubules. Which of the following most likely describes the muscle type?

A. Cardiac muscle  
B. Fast-twitch skeletal muscle  
C. Multiunit smooth muscle  
D. Slow-twitch skeletal muscle  
E. Unitary smooth muscle

**Answers**

B. Inhibition of myosin light chain kinase mainly affects smooth muscle, and so there would be minimal to no effect on cardiac or skeletal muscle. Because smooth muscle contraction would be inhibited, not stimulated, by the drug, arterial and intestinal smooth muscle would relax to produce hypotension and constipation. However, relaxation of airway smooth muscle would decrease resistance to airflow.

E. Airway smooth muscle has β-adrenergic receptors that when stimulated by endogenous catecholamines (mainly epinephrine) causes muscle relaxation. Blocking these receptors will prevent relaxation and allow endogenous contractile agents to predominate. Decreasing levels of ATP (smooth muscle does not undergo rigor), cytoplasmic "free" calcium, phosphorylation of myosin, and production of inositol triphosphate all would result in relaxation, not contraction, of smooth muscle.

E. Although all muscles can contract rhythmically and in unison under the right conditions, skeletal muscle can do so only by being activated by its motor nerves. Skeletal muscle also does not require extracellular calcium. Cardiac muscle does not need innervation to contract rhythmically in unison and does require extracellular calcium; however, it has highly developed T tubules. Among the smooth muscles, only unitary smooth muscle can contract rhythmically and in unison without extrinsic innervation.
PHYSIOLOGY PEARLS
❖ Smooth muscle is present in most organ systems, where it constitutes in part the walls of many structures.
❖ The pattern of contraction of smooth muscle varies from organ to organ and can be tonic and/or phasic.
❖ As in striated muscle, contraction is initiated by an increase in intracellular “free” calcium.
❖ Calcium initiates contraction by binding with calmodulin, which in turn activates a kinase that phosphorylates smooth muscle myosin, which then can interact with actin.
❖ Many endogenous chemicals and administered drugs act on receptors on smooth muscle membranes to cause contraction or relaxation. The state of contraction of a specific smooth muscle results from the interaction of these stimulatory and inhibitory mediators.
❖ Not all smooth muscles react the same way to any particular mediator.

REFERENCES