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Cont. with the excitable tissue …

Smooth Muscle

Two characteristics are common to all smooth muscles. They lack the cross-striated banding pattern found in skeletal and cardiac fibers (which makes them "smooth"), and the nerves to them are part of the autonomic division of the nervous system rather than the somatic division. Thus, smooth muscle is not normally under direct voluntary control.

Smooth muscle, like skeletal muscle, uses cross-bridge movements between actin and myosin filaments to generate force, and calcium ions to control cross-bridge activity. Smooth muscle can generally be divided into two major types:

1- *Multi-unit smooth muscle* and
2- *Unitary* (or *single-unit*) *smooth muscle.*

Multi-Unit Smooth Muscle

This type of smooth muscle is composed of discrete, separate smooth muscle fibers. Each fiber operates independently of the others and often is innervated by a single nerve ending, as occurs for skeletal muscle fibers. Furthermore, the outer surfaces of these fibers, like those of skeletal muscle fibers, are covered by a thin layer of basement membrane-like substance, a mixture of fine *collagen* and *glycoprotein* that helps insulate the separate fibers from one another.

The most important characteristic of **multi-unit smooth muscle** fibers is that each fiber can contract independently of the others, and their control is exerted mainly by nerve signals. In contrast, a major share of control of

unitary smooth muscle is exerted by non-nervous stimuli.

Some examples of multi- unit smooth muscle are the ciliary muscle of the eye and the iris muscle of the eye

Unitary Smooth Muscle

This type is also called *syncytial smooth muscle* or *visceral smooth muscle.* The term "unitary" is confusing because it does not mean single muscle fibers. Instead, it means a mass of hundreds to thousands of smooth muscle fibers that contract together as a single unit. The fibers usually are arranged in sheets or bundles, and their cell membranes are adherent to one another at multiple points so that force generated in one muscle fiber can be transmitted to the next. In addition, the cell membranes are joined by many *gap junctions* through which ions can flow freely from one muscle cell to the next so that action potentials or simple ion flow without action potentials can travel from one fiber to the next and cause the muscle fibers to contract together. This type of smooth muscle is also known as *syncytial smooth muscle* because of its syncytial interconnections among fibers. It is also called *visceral smooth muscle* because it is found in the walls of most viscera of the body, including the gastrointestinal tract, bile ducts, ureters, uterus, and many blood vessels.

One additional characteristic of single-unit smooth muscles is that a contractile response can often be induced by stretching the muscle. In several hollow organs—the stomach, for example—stretching the smooth muscles in the walls of the organ as a result of increases in the volume of material in the lumen initiates a contractile response.

Smooth muscle contains both *actin* and *myosin filaments*, having chemical characteristics similar to those of the actin and myosin filaments in skeletal muscle. It does not contain the normal troponin complex that is required in the control of skeletal muscle contraction, so the mechanism for control of contraction is different. The thin filaments are anchored either to the plasma membrane or to cytoplasmic structures known as **dense bodies,** which are functionally similar to the Z lines in skeletal muscle fibers.

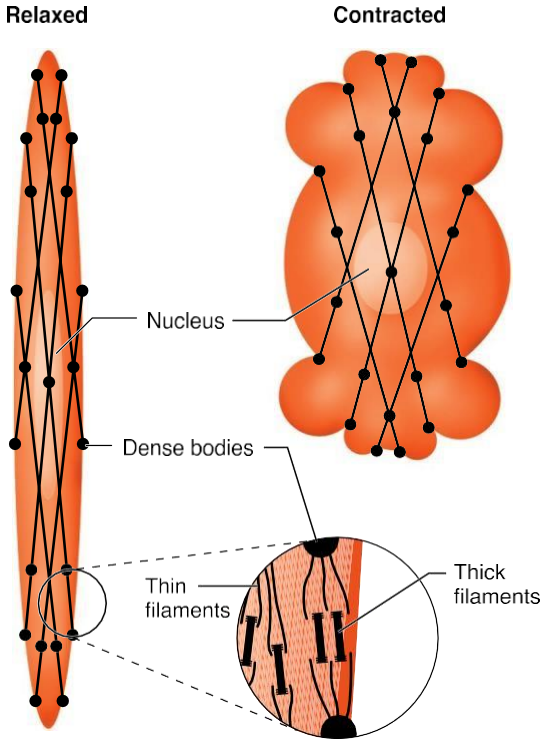
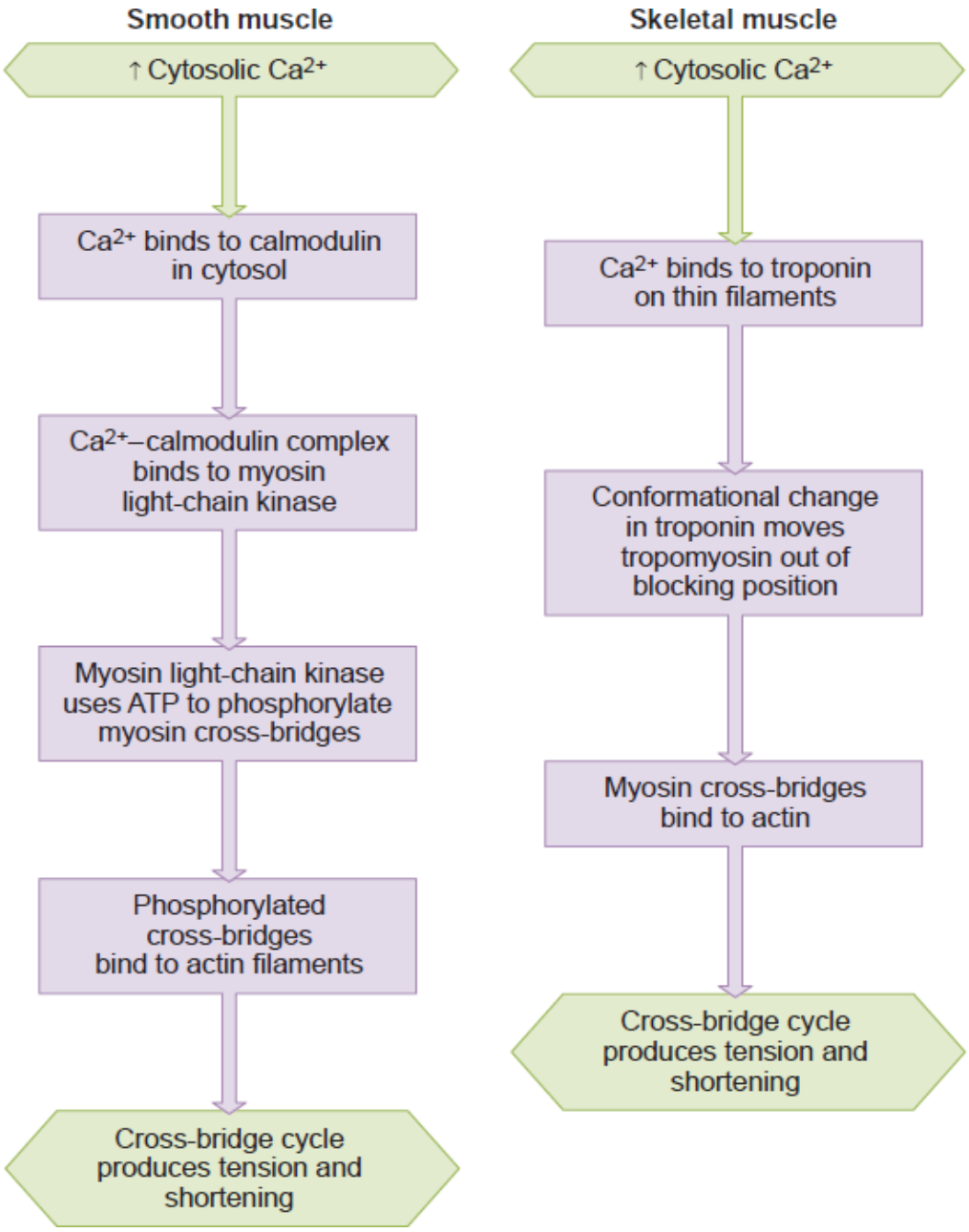


Figure 1: *Thick and thin filaments in smooth muscle are arranged in diagonal chains that are anchored to the plasma membrane or to dense bodies within the cytoplasm. When activated, the thick and thin filaments slide past each other, causing the smooth muscle fiber to shorten and thicken.*



Chemical studies have shown that actin and myosin filaments derived from smooth muscle interact with each other in much the same way that they do in skeletal muscle. Further, the contractile process is activated by calcium ions, and adenosine triphosphate (ATP) is degraded to adenosine diphosphate (ADP) to provide the energy for contraction.

Smooth Muscle Contraction and Its Control

Because smooth muscle lacks the Ca^{++}-binding protein troponin, tropomyosin is never held in a position that blocks cross-bridge access to actin. Thus, the thin filament is not the main switch that regulates cross-bridge cycling. *Instead, cross-bridge cycling in smooth muscle is controlled by a Ca^{++}-regulated enzyme that phosphorylates myosin.* Only the phosphorylated form of smooth muscle myosin can bind to actin and undergo cross-bridge cycling.

The following sequence of events occurs after an increase in cytosolic Ca^{++} in a smooth muscle fiber:

(1) Ca^{++} binds to calmodulin, a Ca^{++}-binding protein that is present in the cytosol of most cells and whose structure is related to that of troponin.

(2) The Ca^{++}–calmodulin complex binds to another cytosolic protein, **myosin light-chain kinase,** thereby activating the enzyme.

(3) Active myosin light-chain kinase then uses ATP to phosphorylate myosin light chains in the globular head of myosin.

(4) Phosphorylation of myosin drives the cross-bridge away from the thick filament backbone, allowing it to bind to actin.

(5) Cross-bridges go through repeated cycles of force generation as long as myosin light chains are phosphorylated.

A key difference here is that Ca^{++}-mediated changes in the thick filaments turn on cross-bridge activity in smooth muscle, whereas in striated muscle, Ca^{++} mediates changes in the thin filaments.

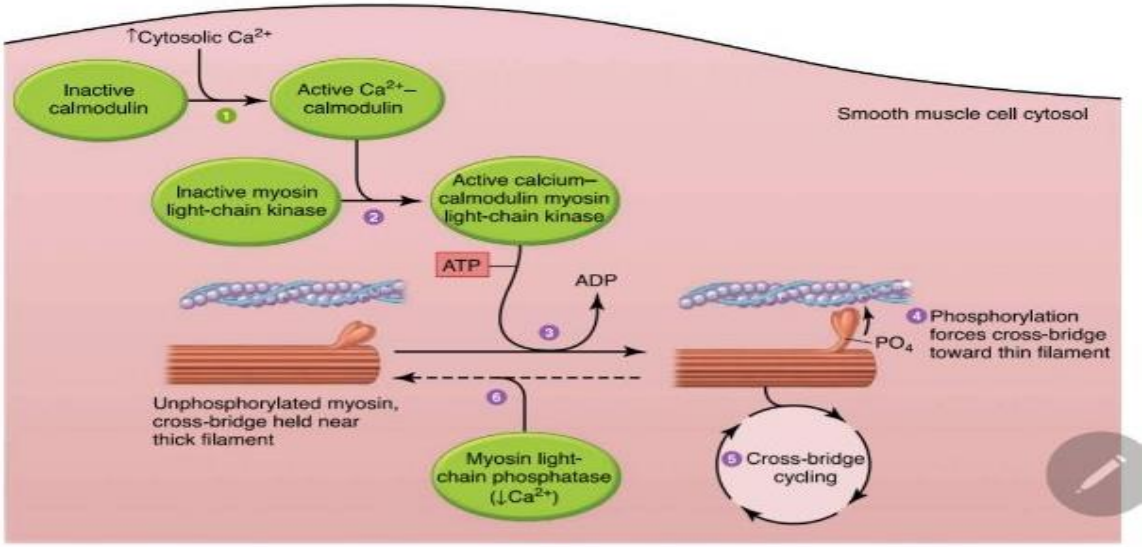


Figure : *Activation of smooth muscle contraction by Ca^{++}*

The smooth muscle form of myosin has a very low rate of ATPase activity, on the order of 10 to 100 times less than that of skeletal muscle myosin. Because the rate of ATP hydrolysis determines the rate of cross-bridge cycling and shortening velocity, smooth muscle shortening is much slower than that of skeletal muscle. Due to this slow rate of energy usage, smooth muscle does not undergo fatigue during prolonged periods of activity.

To relax a contracted smooth muscle, myosin must be dephosphorylated because dephosphorylated myosin is unable to bind to actin. This

dephosphorylation is mediated by the enzyme **myosin light-chain phosphatase,** which is continuously active in smooth muscle during periods of rest and contraction. When cytosolic Ca^{++} concentration increases, the rate of myosin phosphorylation by the activated kinase exceeds the rate of dephosphorylation by the phosphatase and the amount of phosphorylated myosin in the cell increases, producing an increase in tension. When the cytosolic Ca^{++} concentration decreases, the rate of phosphorylation decreases below that of dephosphorylation and the amount of phosphorylated myosin decreases, producing relaxation.

In some smooth muscles, when stimulation is persistent and the cytosolic Ca^{++} concentration remains elevated, the rate of ATP hydrolysis by the cross-bridges declines even though isometric tension is maintained. This condition is known as the **latch state** and a smooth muscle in this state can maintain tension in an almost rigor like state without movement. Dissociation of cross-bridges from actin does occur in the latch state, but at a much slower rate. The net result is the ability to maintain tension for long periods of time with a very low rate of ATP consumption. A good example of the usefulness of this mechanism is seen in sphincter muscles of the gastrointestinal tract, where smooth muscle must maintain contraction for prolonged periods.

Removal of Ca^{++} from the cytosol to bring about relaxation is achieved by the active transport of Ca^{++} back into the sarcoplasmic reticulum as well as out of the cell across the plasma membrane. The rate of Ca^{++} removal in smooth muscle is much slower than in skeletal muscle.

The degree of activation also differs between muscle types. In skeletal muscle, a single action potential releases sufficient Ca^{++} to saturate all troponin sites on the thin filaments, whereas only a portion of the cross-bridges are activated in a smooth muscle fiber in response to most stimuli. Therefore, the tension generated by a smooth muscle cell can be *graded* by varying cytosolic Ca^{++} concentration. The greater the increase in Ca^{++} concentration, the greater the number of cross-bridges activated and the greater the tension.

Membrane Activation

Many inputs to a smooth muscle plasma membrane can alter the contractile activity of the muscle. This contrasts with skeletal muscle, in which membrane activation depends only upon synaptic inputs from somatic neurons. Some inputs to smooth muscle increase contraction, and others inhibit it. Moreover, at any one time, the smooth muscle plasma membrane may be receiving multiple inputs, with the contractile state of the muscle dependent on the relative intensity of the various inhibitory and excitatory stimuli. All these inputs influence contractile activity by altering cytosolic Ca^{++} concentration.

Smooth muscle is different from skeletal muscle in another important way with regard to electrical activity and cytosolic Ca^{++} concentration. Smooth muscle cytosolic Ca^{++} concentration can be increased (or decreased) by graded depolarizations (or hyperpolarizations) in membrane potential, which increase or decrease the number of open Ca^{++} channels.

Whereas some neurotransmitters enhance contractile activity, others decrease contractile activity. This is different than in skeletal muscle, which receives only excitatory input from its motor neurons; smooth muscle tension can be either increased or decreased by neural activity.

Moreover, a given neurotransmitter may produce opposite effects in different smooth muscle tissues. For example, norepinephrine, the neurotransmitter released from most postganglionic sympathetic neurons, enhances contraction of most vascular smooth muscle by acting on α adrenergic receptors. By contrast, the same neurotransmitter produces relaxation of airway (bronchiolar) smooth muscle by acting on B2 - adrenergic receptors. Thus, the type of response (excitatory or inhibitory) depends not on the chemical messenger, but on the receptors the chemical messenger binds to in the membrane and on the intracellular signaling mechanisms those receptors activate.

In addition to receptors for neurotransmitters, smooth muscle plasma membranes contain receptors for a variety of hormones. Binding of a hormone to its receptor may lead to either increased or decreased contractile activity.

Local Factors

Local factors, including paracrine signals, acidity, oxygen and carbon dioxide concentration, osmolarity, and the ionic composition of the extracellular fluid, can also alter smooth muscle tension. Responses to local factors provide a means for altering smooth muscle contraction in response to changes in the muscle's immediate internal environment, which can lead to regulation that is independent of long-distance signals from nerves and hormones.

Many of local factors induce smooth muscle relaxation. Nitric oxide (NO) is one of the most commonly encountered paracrine compounds that produce smooth muscle relaxation. NO is released from some axon terminals as well as from a variety of epithelial and endothelial cells. Because of the short life span of this reactive molecule, it acts in a paracrine manner, influencing only those cells that are very near its release site. Some smooth muscles can also respond by contracting when they are stretched. Stretching opens mechanically gated ion channels, leading to membrane depolarization. The resulting contraction opposes the forces acting to stretch the muscle.

Table 1: *Inputs Influencing Smooth Muscle Contractile Activity*

Spontaneous electrical activity in the plasma membrane of the muscle cell
Neurotransmitters released by autonomic neurons
Hormones
Locally induced changes in the chemical composition (paracrine factors, acidity, oxygen, osmolarity, and ion concentrations) of the extracellular fluid surrounding the cell
Stretch