SMOOTH MUSCLE CONTRACTION AND RELAXATION

R. Clinton Webb

Department of Physiology, Medical College of Georgia, Augusta, Georgia 30912

This brief review serves as a refresher on smooth muscle physiology for those educators who teach in medical and graduate courses of physiology. Additionally, those professionals who are in need of an update on smooth muscle physiology may find this review to be useful. Smooth muscle lacks the striations characteristic of cardiac and skeletal muscle. Layers of smooth muscle cells line the walls of various organs and tubes in the body, and the contractile function of smooth muscle is not under voluntary control. Contractile activity in smooth muscle is initiated by a Ca²⁺-calmodulin interaction to stimulate phosphorylation of the light chain of myosin. Ca²⁺ sensitization of the contractile proteins is signaled by the RhoA/Rho kinase pathway to inhibit the dephosphorylation of the light chain by myosin phosphatase, thereby maintaining force generation. Removal of Ca²⁺ from the cytosol and stimulation of myosin phosphatase initiate the process of smooth muscle relaxation.


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Sheets or layers of smooth muscle cells are contained in the walls of various organs and tubes in the body, including the blood vessels, stomach, intestines, bladder, airways, uterus, and the penile and clitoral cavernosal sinuses. When made to contract, the smooth muscle cells shorten, thereby propelling the luminal contents of the organ, or the cell shortening varies the diameter of a tube to regulate the flow of its contents. There are also bundles of smooth muscle cells attached to the hairs of the skin and to the iris and lens of the eye. When these bundles contract, the hairs become erect and the lens of the eye changes shape to focus light on the retina.

Smooth muscle cells lack the striated banding pattern found in cardiac and skeletal muscle, and they receive neural innervation from the autonomic nervous system. In addition, the contractile state of smooth muscle is controlled by hormones, autocrine/paracrine agents, and other local chemical signals. Smooth muscle cells also develop tonic and phasic contractions in response to changes in load or length. Regardless of the stimulus, smooth muscle cells use cross-bridge cycling between actin and myosin to develop force, and calcium ions (Ca²⁺) serve to initiate contraction.

This brief review will serve as a refresher for those educators who teach in medical and graduate courses of physiology. Additionally, those professionals who are in need of an update on smooth muscle physiology may find this review to be useful. New concepts about regulatory mechanisms are presented to add depth to the understanding of the integrated responses of contraction and relaxation in smooth muscle. For those individuals desiring a more in-depth treatment of the subject, several recent reviews are recommended (1, 3, 5, 7, 9, 10, 18).

THE CONTRACTILE MECHANISM

In the intact body, the process of smooth muscle cell contraction is regulated principally by receptor and mechanical (stretch) activation of the contractile pro-
PKC has contraction-promoting effects such as phosphorylation of L-type $\mathrm{Ca}^{2+}$ channels or other proteins that regulate cross-bridge cycling. Phorbol esters, a group of synthetic compounds known to activate PKC, mimic the action of DG and cause contraction of smooth muscle. Finally, L-type $\mathrm{Ca}^{2+}$ channels (voltage-operated $\mathrm{Ca}^{2+}$ channels) in the membrane also open in response to membrane depolarization brought on by stretch of the smooth muscle cell.

### Ca$^{2+}$ Sensitization Mechanism and Contraction of Smooth Muscle

In addition to the Ca$^{2+}$-dependent activation of MLC kinase, the state of myosin light chain phosphorylation is further regulated by MLC phosphatase [aka myosin phosphatase (1, 4, 9, 11–16)], which removes the high-energy phosphate from the light chain of myosin to promote smooth muscle relaxation (Fig. 1). There are three subunits of MLC phosphatase: a 37-kDa catalytic subunit, a 20-kDa variable subunit, and a 110- to 130-kDa myosin-binding subunit. The myosin-binding subunit, when phosphorylated, inhibits the enzymatic activity of MLC phosphatase, allowing the light chain of myosin to remain phosphorylated, thereby promoting contraction. The small G protein RhoA and its downstream target Rho kinase play an important role in the regulation of MLC phosphatase activity. Rho kinase, a serine/threonine kinase, phosphorylates the myosin-binding subunit of MLC phosphatase, inhibiting its activity and thus promoting the phosphorylated state of the myosin light chain (Fig. 1). Pharmacological inhibitors of Rho kinase, such as fasudil and Y-27632, block its activity by competing with the ATP-binding site on the enzyme. Rho kinase inhibition induces relaxation of isolated segments of smooth muscle contracted to many different agonists. In the intact animal, the pharmacological inhibitors of Rho kinase have been shown to cause relaxation of smooth muscle in arteries, resulting in a blood pressure-lowering effect (2, 17).

An important question facing the smooth-muscle physiologist is: what is the link between receptor occupation and activation of the Ca$^{2+}$-sensitizing activity of the RhoA/Rho kinase-signaling cascade? Currently, it is thought that receptors activate a heterotrimeric G protein that is coupled to RhoA/Rho kinase signaling via guanine nucleotide exchange factors.
(RhoGEFs; Fig. 1). Because RhoGEFs facilitate activation of RhoA, they regulate the duration and intensity of signaling via heterotrimeric G protein receptor coupling. There are ~70 RhoGEFs in the human genome, and three RhoGEFs have been identified in smooth muscle: PDZ-RhoGEF, LARG (leukemia-associated RhoGEF), and p115-RhoGEF. Increased expression and/or activity of RhoGEF proteins could augment contractile activation of smooth muscle and therefore play a role in diseases where an augmented response contributes to the pathophysiology (hypertension, asthma, etc.).

Several recent studies suggest a role for additional regulators of MLC kinase and MLC phosphatase (13–16). Calmodulin-dependent protein kinase II promotes smooth muscle relaxation by decreasing the sensitivity of MLC kinase for Ca2+. Additionally, MLC...
phosphatase activity is stimulated by the 16-kDa protein telokin in phasic smooth muscle and is inhibited by a downstream mediator of DG/protein kinase C, CPI-17.

**SMOOTH MUSCLE RELAXATION**

Smooth muscle relaxation occurs either as a result of removal of the contractile stimulus or by the direct action of a substance that stimulates inhibition of the contractile mechanism (e.g., atrial natriuretic factor is a vasodilator). Regardless, the process of relaxation requires a decreased intracellular Ca²⁺ concentration and increased MLC phosphatase activity. The sarcoplasmic reticulum and the plasma membrane contain Ca,Mg-ATPases that remove Ca²⁺ from the cytosol. Na⁺/Ca²⁺ exchangers are also located on the plasma membrane and aid in decreasing intracellular Ca²⁺. During relaxation, receptor- and voltage-operated Ca²⁺ channels in the plasma membrane close resulting in a reduced Ca²⁺ entry into the cell.

A decrease in the intracellular concentration of activator Ca²⁺ elicits smooth muscle cell relaxation. Several mechanisms are implicated in the removal of cytosolic Ca²⁺ and involve the sarcoplasmic reticulum and the plasma membrane. Ca²⁺ uptake into the sarcoplasmic reticulum is dependent on ATP hydrolysis. This sarcoplasmic reticular Ca₃Mg-ATPase, when phosphorylated, binds two Ca²⁺ ions, which are then translocated to the luminal side of the sarcoplasmic reticulum and released. Mg²⁺ is necessary for the activity of the enzyme; it binds to the catalytic site of the ATPase to mediate the reaction. The sarcoplasmic

![Diagram of smooth muscle relaxation](image-url)
The plasma membrane also contains Ca,Mg-ATPases, providing an additional mechanism for reducing the concentration of activator Ca\(^{2+}\) in the cell. This enzyme differs from the sarcoplasmic reticular protein in that it has an autoinhibitory domain that can be bound by calmodulin, causing stimulation of the plasma membrane Ca\(^{2+}\) pump.

\(\text{Na}^+ / \text{Ca}^{2+}\) exchangers are also located on the plasma membrane and aid in decreasing intracellular Ca\(^{2+}\). This low-affinity antiporter is closely coupled to intracellular Ca\(^{2+}\) levels and can be inhibited by amiloride and quinidine.

Receptor-operated and voltage-operated Ca\(^{2+}\) channels located in the plasma membrane are important in Ca\(^{2+}\) influx and smooth muscle contraction, as previously mentioned. Inhibition of these channels can elicit relaxation. Channel antagonists such as dihydropyridine, phenylalkylamines, and benzothiazepines bind to distinct receptors on the channel protein and inhibit Ca\(^{2+}\) entry in smooth muscle.

**SUMMARY**

Smooth muscle derives its name from the fact that it lacks the striations characteristic of cardiac and skeletal muscle. Layers of smooth muscle cells line the walls of various organs and tubes, and the contractile function of smooth muscle is not under voluntary control. Contractile activity in smooth muscle is initiated by a Ca\(^{2+}\)-calmodulin interaction to stimulate phosphorylation of the light chain of myosin. A Ca\(^{2+}\) sensitization of the contractile proteins is signaled by the RhoA/Rho kinase pathway to inhibit the dephosphorylation of the light chain by myosin phosphatase, maintaining force generation. Removal of Ca\(^{2+}\) from the cytosol and stimulation of myosin phosphatase initiate the process of smooth muscle relaxation.

**DISCLOSURES**

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Address for reprint requests and other correspondence: R. C. Webb, Dept. of Physiology, Medical College of Georgia, 1120 Fifteenth St., Augusta, GA 30912-3000 (E-mail: cwebb@mcg.edu).

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