Smooth Muscle

- Spindle-shaped
- Small (2-5 μm wide, 50-300 μm long)
- 1 centrally placed nucleus per cell
- Usually organized in small to moderate sized clusters of cells
- Lack sarcomeres
- No T-tubules or terminal cisternae
- Possess caveoli
- Poorly developed SR; contraction requires extracellular Ca²⁺
- Innervated by autonomic nervous system
- Thin filaments arranged in bundles attached to “dense bodies” (α-actinin) either on the sarcolemma or bound to the cytoskeleton.
- Thick filaments interdigitate among the thin filaments, but there is no regular alignment, hence the absence of striations.
- 10:1 ratio of actin:myosin, vs 2:1 ratio in skeletal muscle
Each fiber can contract independently and is usually innervated by a single nerve ending.

Fibers insulated from each other by covering of collagen and glycoprotein fibrillae.

Seldom exhibit spontaneous contraction.

Examples: ciliary muscle of eye, iris, piloerector muscles.
Types of Smooth Muscle

- Aggregates (bundles or sheets) of hundreds or thousands of fibers act as a single unit.

- Membranes are adherent to one another at numerous points so that force generated in one fiber can be transmitted to the next.

- Fibers are connected by gap junctions which allow ion flow from one fiber to another such that action potentials and contractions are simultaneous.

- Examples: walls of viscera: gut, bile ducts, ureters, uterus and many blood vessels
Multi-unit vs. Unitary Smooth Muscle

- Multiunit
  - Autonomic or intrinsic nerve
  - Vascularly with neurotransmitter vesicles
  - Neurotransmitter release and diffusion
  - Smooth muscle cells
  - $\uparrow$ [Ca$^{++}$]
  - Response

- Capillary
  - Circulating hormones and diffusion

- Single unit
  - Gap junction
  - Receptor for neurotransmitter
  - Receptor for hormone
  - $\uparrow$ [Ca$^{++}$]

Microscopic images of smooth muscle cells showing gap junctions, myofilaments, dense bodies, sarcoplasmic reticulum, and caveoli.
Smooth Muscle Contractile Properties

- Capable of prolonged tonic contraction – the pace of cross-bridge cycling in smooth muscle is about 1/10 to 1/300 that of skeletal muscle. However, the fraction of time that cross-bridges remain intact is greatly increased in smooth muscle. Myosin heads probably have greatly reduced ATPase activity, so the ATP hydrolysis that rotates the head is slower.

- Hence, the rate of ATP use is 1/10 to 1/300 that of skeletal muscle. This efficiency is beneficial to long-term tonicity of most viscera.

- The onset and relaxation of smooth muscle contraction is also slow. Contraction begins 50-100 milliseconds after excitation, peaking after about 1 second, then declines for a period of about 2 seconds – giving a total contraction time of around 3 seconds, and in some tissues up to 30 seconds.

- The maximum stress generation by smooth muscle (4-6 kg/cm²) exceeds that of skeletal muscle (3-4 kg/cm²)

Action Potentials in Smooth Muscle

- At rest, the smooth muscle action potential is -60 to -40 mV, which is 30 mV less negative than skeletal muscle.

- Action potentials occur in single-unit smooth muscle much like in skeletal muscle, but are rare in most types of multi-unit smooth muscle.

- The action potentials of single-unit smooth muscle occur as spike potentials or action potentials with plateaus. Spike potentials can be elicited by electrical stimulation, hormones, neurotransmitters, stretch, or spontaneously. The plateau can last as long as a second and can account for prolonged contraction.
Spontaneous Action Potentials in Smooth Muscle: Slow Waves

✓ Some smooth muscle is self-excitatory, generating action potentials without external stimulus. This is usually associated with a slow wave rhythm of depolarization. The slow wave itself is not the action potential, but is an intrinsic property of the smooth muscle mass. At a threshold membrane potential (near -35 mV), an action potential is induced. Mechanism of slow wave generation is still under question, but probably involve oscillations of Na⁺/K⁺ pumping activity.

Depolarization of Multi-unit Smooth Muscle Without an Action Potential

✓ When multi-unit smooth muscle is depolarized and contracts by the action of a neurotransmitter, an action potential does not develop because the single fiber is too small generate a self-propagating action potential as seen in a population of single-unit smooth muscle cells. Instead the depolarization is caused by the rapid spread of the neurotransmitter itself over the surface of the smooth muscle cell, which change the activity of ion channels on the cell membrane and SR.
**Pharmacomechanical Coupling**

✓ Contraction (or relaxation) in the absence of any change in $E_m$. Caused by a pharmacological agent’s ability to increase the concentration of intracellular IP$_3$, cGMP, or cAMP.

![Diagram of pharmacomechanical coupling](attachment:image.png)

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**Regulation of Smooth Muscle Activity**

✓ The big picture: smooth muscles can be stimulated to contract by several types of signals including nervous signals, hormones, stretch and other means. The smooth muscle membrane possesses many receptor proteins that can initiate contraction as well as other membrane receptors that can inhibit smooth muscle contraction.

✓ Neural control: No NMJs as per skeletal muscle. Instead, autonomic nerve fibers innervate smooth muscle by branching diffusely over the top of a sheet of smooth muscle fibers. Transmitters are released from the nerve fibers at points called varicosities. Varicosities of some fibers release ACh, while others release norepinephrine or other neurotransmitters.

✓ In multi-unit smooth muscle, varicosities lie very near the muscle fibers, essentially the same distance as a synaptic cleft in skeletal muscle. In this case, each muscle fiber is in contact with a varicosity, unlike the case for unitary smooth muscle.

✓ ACh excites smooth muscle in some organs but is inhibitory in others. Same is true for norepinephrine, which acts oppositely of ACh. The membrane bound receptors determine the activity of each.
Like skeletal muscle, contraction in smooth muscle is initiated by an increase in intracellular Ca^{2+}. This increase can be caused by nerve stimulation, hormonal stimulation, stretch of the fiber or intrinsic changes in the chemical and electrical environment of the cell.

Smooth muscle does not contain troponin, so the action by which Ca^{2+} allows binding of actin by the myosin heavy chains is completely different than in skeletal muscle.

Intracellular Ca^{2+} instead binds with calmodulin.

The Ca^{2+}-calmodulin complex (CaCM) binds with another protein called caldesmon (Cald) – the CaCM-Cald complex moves tropomyosin off of the myosin binding sites on the actin filament.
Excitation-Contraction Coupling in Smooth Muscle (cont.)

- CaCM also binds to an enzyme called Myosin Light Chain Kinase (MLCK), which phosphorylates the myosin regulatory light chain of each myosin head. This activation allows the head to bind the myosin binding site of the actin filament and proceed through the cross-bridge cycle.

- When CaCM is not present, MLCK cannot phosphorylate the myosin regulatory light chain, which in turn prevents the myosin head from binding the actin filament. Furthermore, the CaCM-Cald complex will not be present and tropomyosin will occlude the myosin binding sites of the actin filament.

- During the cessation of smooth muscle contraction, myosin phosphatase removes the phosphate from the myosin regulatory light chain.
Smooth Muscle Cross-Bridge Cycle

Once smooth muscle has developed full contraction, the degree of activation and ATP use can be reduced to levels far below those at the initiation of contraction.

Helps maintain prolonged tonic contraction for hours with little energy use or excitatory signals (neurotransmitters, hormones, etc.)
“Latch Mechanism” results from slowing of cross-bridge cycles.
Stress-Relaxation of Smooth Muscle

✓ Smooth muscle, especially that lining visceral organs (unitary), has the ability to return nearly to its original force of contraction seconds or minutes after it has been elongated or shortened.

✓ Allows hollow organs to maintain the same internal pressure despite wide variation in volume

✓ Underlying this phenomenon is a constant number of cross-bridge attachments, but at different positions along actin filaments

Local Tissue Factors and Hormones Can Cause Smooth Muscle Contraction without Action Potentials

✓ Much smooth muscle contraction is initiated by stimulatory factors acting directly on the contractile machinery, without action potentials. Such local chemical factors include hypoxia (relaxation), hypercapnia (relaxation), proton concentration (relaxation), temperature, lactic acid, increased K⁺, low Ca²⁺, etc.

✓ Hormones and neurotransmitters affecting smooth muscle include norepinephrine, epinephrine, ACh, angiotensin, vasopressin, oxytocin, serotonin, and histamine. They act via hormone-gated excitatory or inhibitory receptors.

✓ Hormones may or may not initiate/inhibit contraction by affecting membrane potential. They may initiate contraction by causing a release of Ca²⁺ from the SR. Alternatively, they may inhibit contraction via initiation of the second messenger pathways of cAMP and cGMP.

✓ cGMP and cAMP initiate a cascade that activates Ca²⁺ pumps that remove sarcoplasmic Ca²⁺ to SR or the outside of the cell.
ENDOTHELIA and SMOOTH MUSCLES

- Smooth muscle in blood vessels - notably arterioles - work in close association with the overlying epithelial cells. Action of hormones, neurotransmitters (ACh) or deformation of the epithelial cell by flow of blood can trigger reactions which can stimulate or inhibit associated smooth muscle beds.

- These effects may operate via second messenger systems such as phospholipase A2 (PLA2) which may in turn activate cyclo-oxygenase (COX) / prostacyclin synthase (PCS) enzyme systems to produce prostaglandins (PGI2) which diffuse readily through the tissue fluids to act on the smooth muscle cells.

- Alternatively activation of nitric oxide synthase (L-arginase) (NOS) may result in production of the highly diffusible gaseous "neurotransmitter" NO. These paracrine agents act on the smooth muscle cells either through G-protein systems or directly on ion channels.
**NITRIC OXIDE (NO)**

![Diagram of NO production and effects]

**Better Blood Flow**
Nitric oxide increases the diameter of blood vessels. Drugs that stimulate its release are used to treat hypertension and could help treat hypertension.

**VIAGRA**
*(sildenafil citrate) tablets*

*Uh, huh. That's right. I'm all over it, so move along...punk.*

*Wow Elizabeth, you're looking great!*

*Why thank you!*
**How does it work?**

Sexual stimulation initiates the release of NO from nerve endings and cells inside the penis.

Nitric Oxide then activates specific enzymes which result in increased levels of cGMP.

It's actually cGMP that causes the smooth muscle around the penile arteries to relax, allowing these arteries to dilate...allowing for increased blood flow...and ultimately the development of the Bob Dole's "other" salute.

Phosphodiesterase-V (PDE-5) is an enzyme that binds to and digests cGMP. If cGMP is digested too quickly, its "relaxing" affect on penile smooth muscle tissue will be reversed, causing the erection to weaken (in many cases this will happen so rapidly, it will appear as if no erection was ever present).

Sildenafil citrate (VIAGRA®) is a PDE-5 inhibitor, slowing the breakdown of cGMP and allowing cGMP to remain active in artery dilation, thus prolonging erection.