General physiology
Second semester 2023/2024
Lecture 28 and L 29

Excitation and Contraction in smooth muscle and properties of smooth muscle contraction

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Lecture objectives

- Explain the contraction process in smooth muscle and compare it to those of skeletal and cardiac muscle.
- Describe how smooth muscle can be activated to induce a contraction or to change the strength of a contraction.
- Explain the relationship between vascular smooth muscle membrane
- potential, voltage-gated calcium channels, and strength of contraction.
- Describe the difference between multiunit and unitary smooth muscle.
- Explain the following terms and their role in smooth muscle function:
- calmodulin, myosin light chain kinase, and myosin light chain phosphatase
- Define the Stress relaxation and latch state and describe their physiological importance.

Smooth Muscle Anatomical features

- Spindle shape
- Cells are not striated
- Fibers smaller than those in skeletal muscle 1 to 5 micrometers in diameter and only 20 to 500 micrometers in length.
- single, centrally-placed nucleus
- More actin than myosin
- No sarcomeres
  - Not arranged as symmetrically as in skeletal muscle, thus no striations.
- Dense bodies instead of Z disks
- Contraction is non-voluntary
- Contraction is modulated in a neuroendocrine (neurotransmitter and hormones)
- Types of smooth muscles
  - Unitary (single) smooth muscles
  - Multiunit unit smooth muscles

Multiunit Smooth Muscles

- Composed of discrete, separate smooth muscle fibers
- Each fiber operates and contract independently of the others, and often is innervated by a single nerve ending, as occurs for skeletal muscle fibers thus independent motor units
- 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
- Important characteristics of multi-unit smooth muscle fibers are that each fiber can contract independently of the others, and their control is exerted mainly by nerve signal
- No coupling, no gap junctions.

Multiunit Smooth Muscles

- Muscle fibers are heavily innervated by postganglionic fibers of the parasympathetic and sympathetic nervous systems, and it is these innervations that initiates their contraction and relaxation
- Contract only in response to its innervation and their control is exerted mainly by nerve autonomic signals
- Examples of multi-unit smooth muscle
  - are the ciliary muscle of the eye, the iris muscle of the eye
  - Piloerector muscles that cause erection of the hairs when stimulated by the sympathetic nervous system

Unitary or Single unit Smooth Muscles
(*Syncytial Smooth Muscle, Visceral Smooth Muscle)*

- Single units 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.
- **Gap junctions :** Impulse (action potentials) spreads through gap junctions
- Often muscle cells are autorhythmic and exhibit spontaneous pacemaker activity, or slow waves depolarization
- The frequency of slow waves sets the pattern of action potentials within an organ, which then determines the frequency of contractions

Unitary or Single unit Smooth Muscles (*Syncytial Smooth Muscle, Visceral Smooth Muscle)*

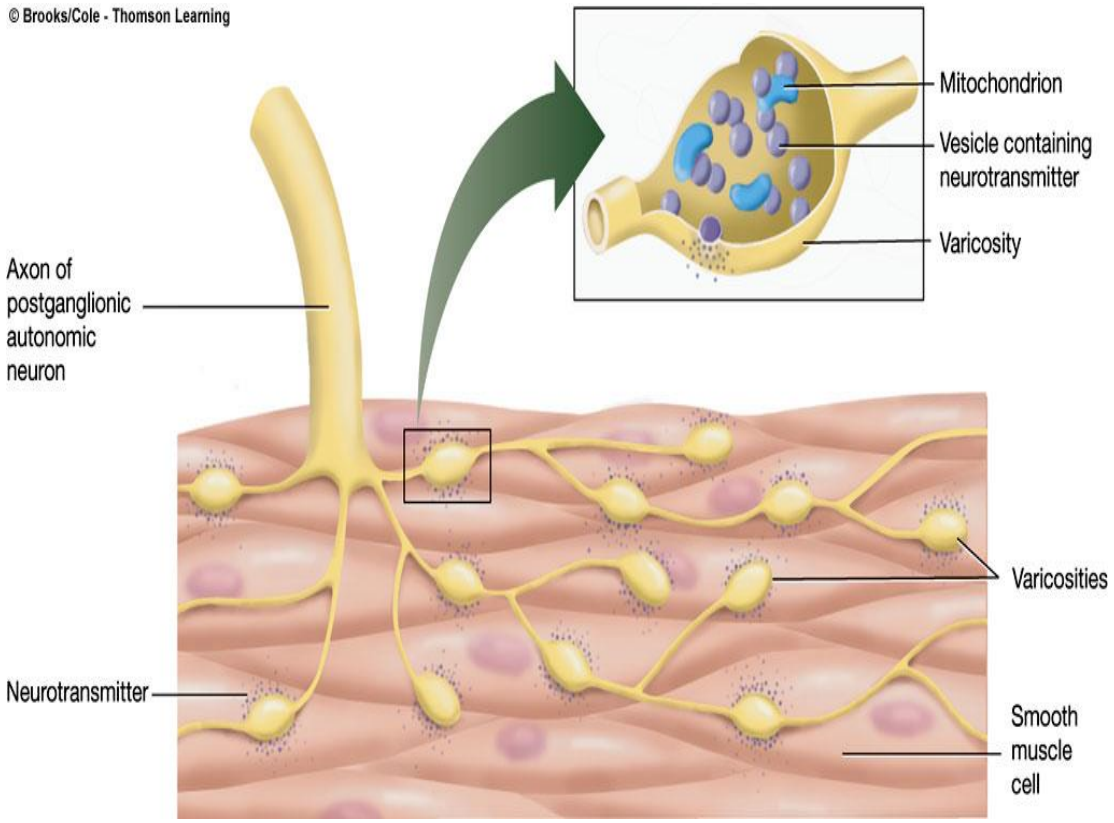
- Is innervated by autonomic nervous system (ANS).
- Muscle cells activity is modulated by ANS or hormones
- This type of smooth muscle is also known as syncytial smooth muscle because of its syncytial interconnections among fibers.
- Also called visceral smooth muscle because it is found in the walls of most viscera of the body, including the gastrointestinal tract, bile ducts, ureters, uterus, and many blood vessels , air ways and bladder.

Nervous and Hormonal Control of Smooth Muscle Contraction

- Unlike skeletal muscle which are excited by motor neurons signals, smooth muscle can be stimulated to contract by nervous signals, hormonal stimulation, stretch of the muscle.
- The principal reason for the difference is that the smooth membrane contains many types of receptor proteins that can initiate the contractile process. Still other receptor proteins inhibit smooth muscle contraction, which is another difference from skeletal muscle.

Endings of postganglionic autonomic neurons on smooth muscle

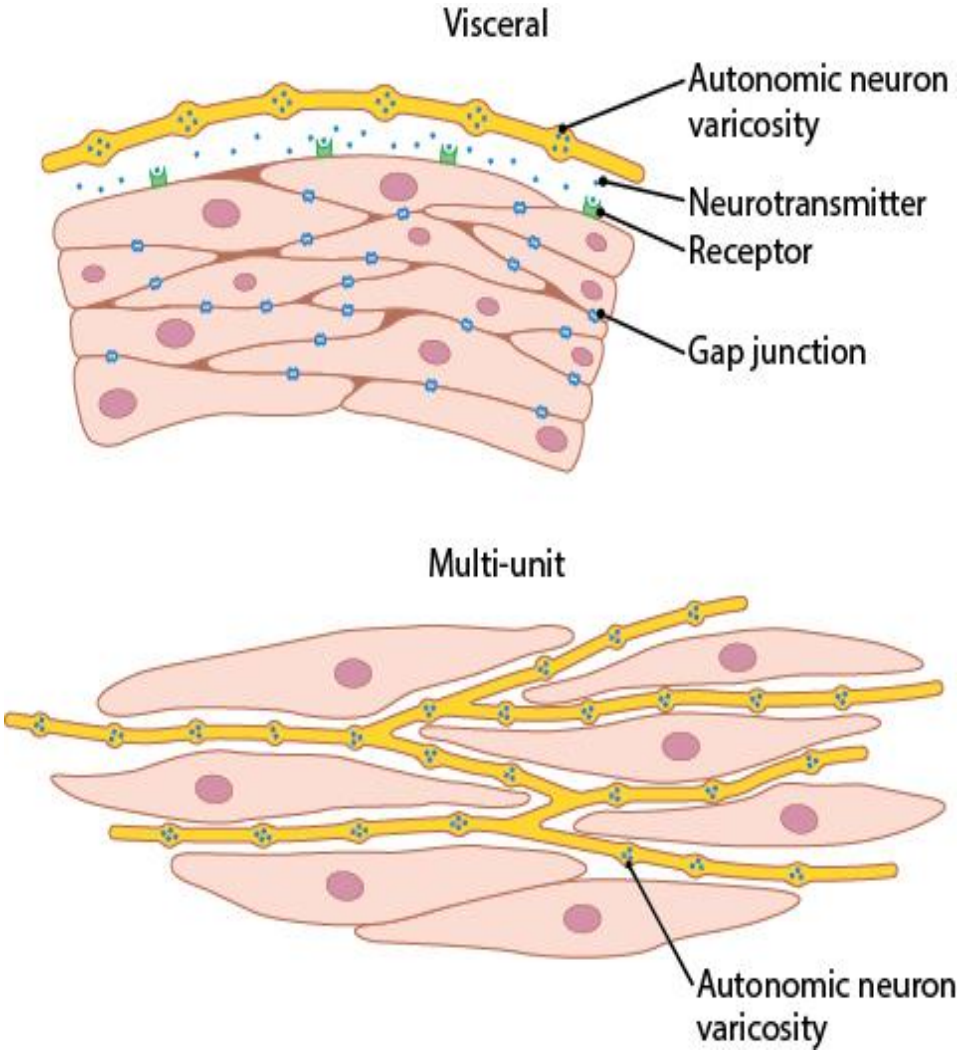
The nerve fibers run along the membranes of the smooth muscle cells and sometimes groove their surfaces. The multiple branches of postganglionic neurons are beaded with enlargements (varicosities) and contain synaptic vesicles. Neurotransmitter is released from the varicosities and diffuses to receptors on smooth muscle cell plasma membranes



Neuromuscular Junction at smooth muscles

Major points

- Less complex and less well understood compared to Skeletal muscles
- Autonomic nerve fibers branch and form “diffuse junctions” with underlying smooth muscle fibers.
- **Varicosities** in the terminal axons contain neurotransmitter
- Neurotransmitter is secreted into the matrix coating and diffuses to the muscle cells
- Acetylcholine and NE are the neurotransmitters



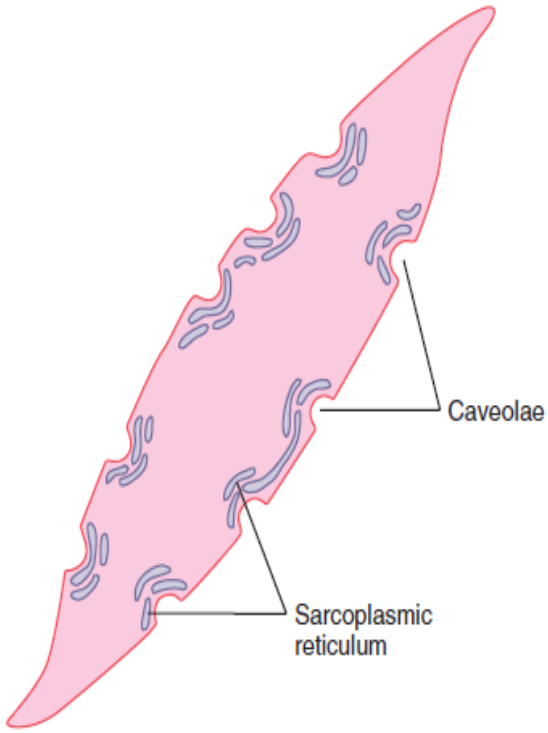
Contact junctions of in multiunit smooth muscles

- In multi-unit type of smooth muscle, the varicosities are separated from the muscle cell membrane by as little as 20 to 30 nanometers—the same width as the synaptic cleft that is found in the skeletal muscle junction.
- These are called contact junctions, and they function in much the same way as the skeletal muscle neuromuscular junction.
- The rapidity of contraction of these smooth muscle fibers is considerably faster than that of fibers stimulated by the diffuse junctions

Smooth Muscle Sarcoplasmic Reticulum

- A few slightly developed sarcoplasmic tubules that lie near the cell membrane in some larger smooth muscle cells.
- No T tubule
- Caveolae : Small invaginations of the cell membrane, called *caveolae .*

- The caveolae suggest a rudimentary analog of the transverse tubule system of skeletal muscle.
- When an action potential is transmitted into the caveolae, is believed to excite calcium ion release from the adjacent sarcoplasmic

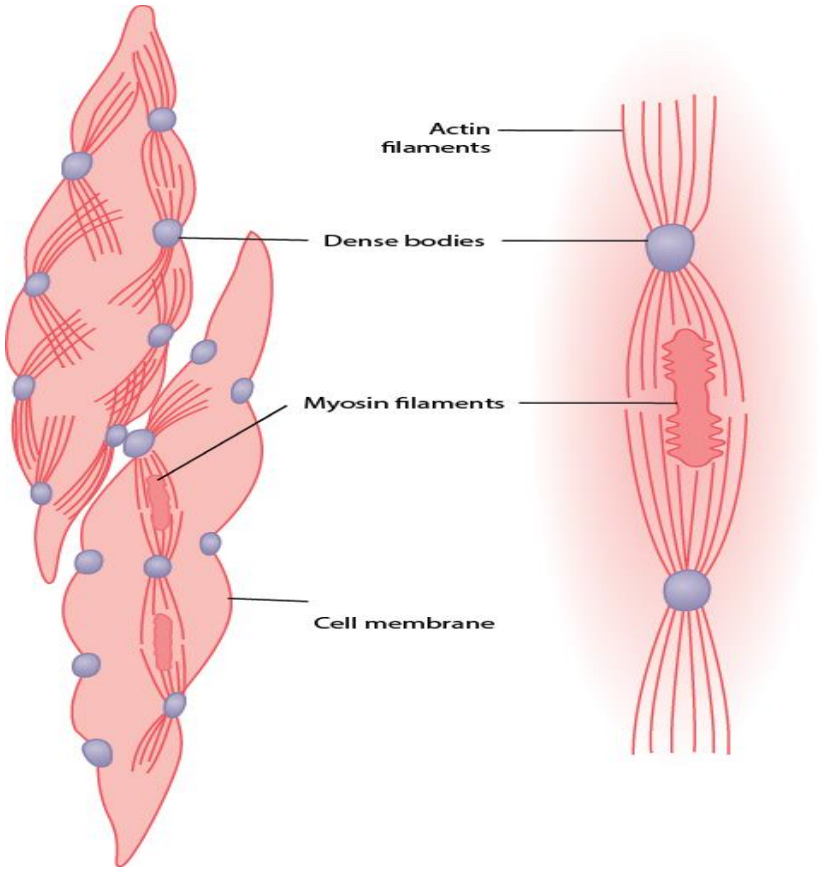


DEPOLARIZATION OF MULTI-UNIT SMOOTH MUSCLE WITHOUT ACTION POTENTIALS

- Multi-unit smooth muscle (examples smooth muscle of iris such as the muscle of the iris of the eye or the piloerector muscle of each hair)
- Normally contract in response to nerve stimuli.
- Autonomic nerve endings secrete acetylcholine smooth muscles and norepinephrine in the case of others.
- Neurotransmitter depolarization of the smooth muscle membrane, and this depolarization in turn elicits contraction.
- Action potentials usually do not develop because the fibers are too small to generate an action potential.
- Thus local depolarization (called the *junctional potential*) caused by neurotransmitter substance itself spreads “electrotonically” over the entire fiber causing muscle.

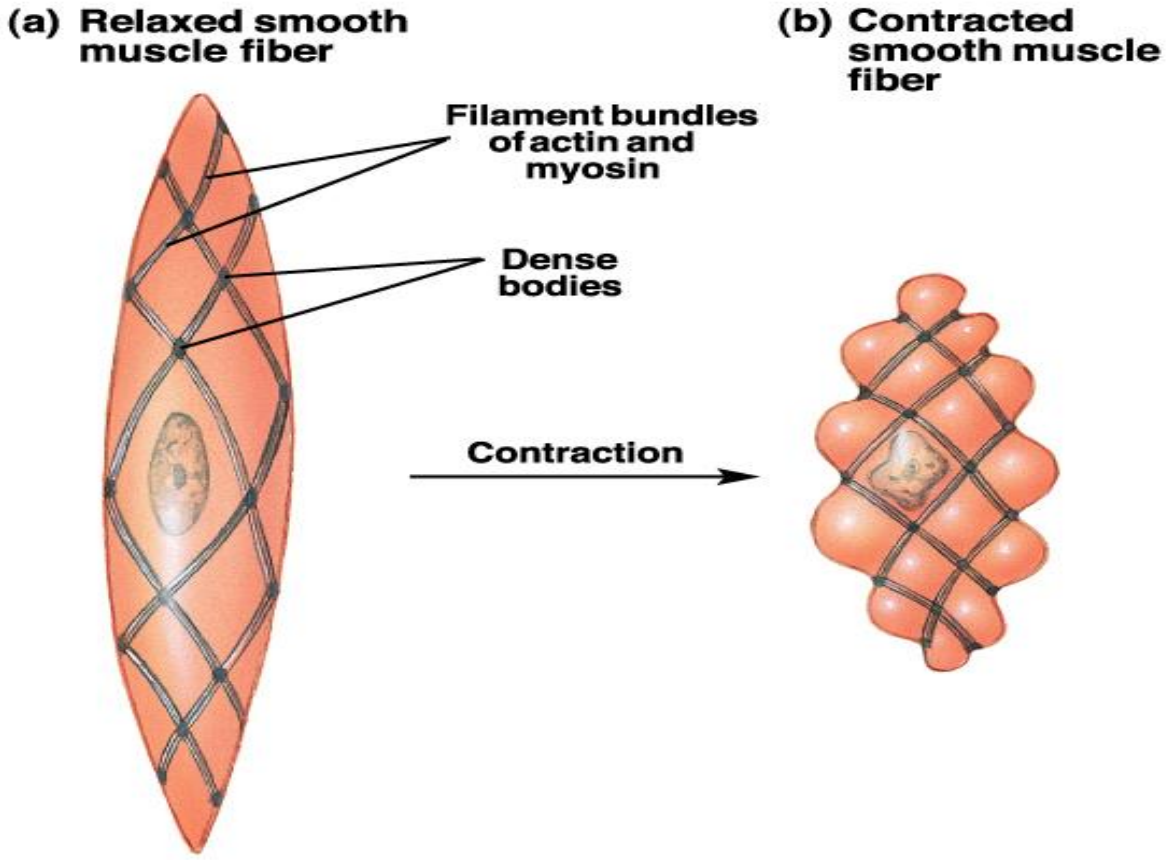
Contractile elements of smooth muscle

- Contains both *actin* and *myosin filaments,* similar to those of the actin and myosin filaments in skeletal muscle
- Interspersed among the actin filaments in the muscle fiber are myosin filaments. These filaments have a diameter more than twice that of the actin filament
- 5 to 10 times as many actin filaments as myosin filaments are usually found
- No regulatory arrangements in skeletal muscle
- No striation
- No troponin

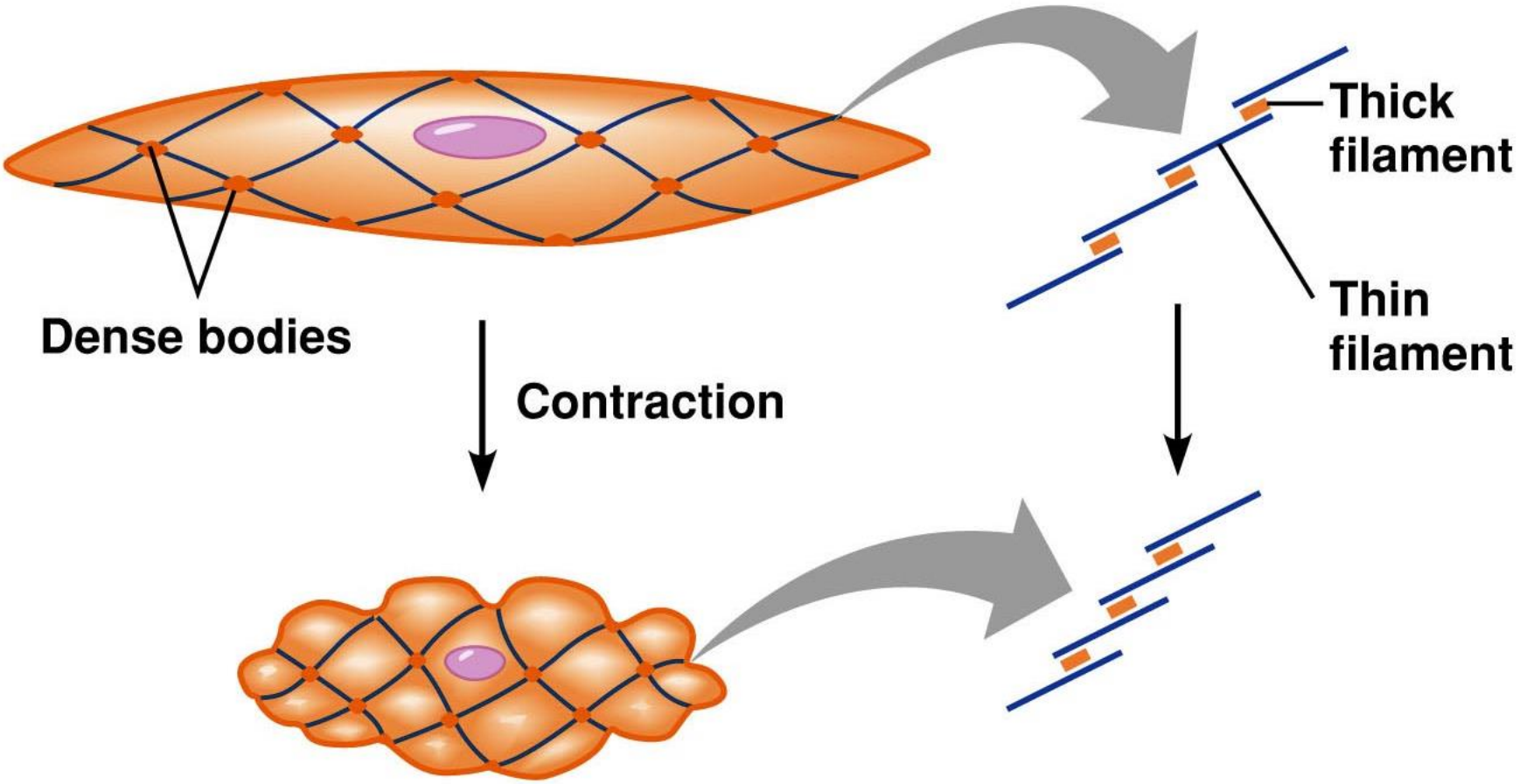


- **Dense bodies in smooth muscles**
- Membrane associated and cytoplasmic dense bodies containing α actinin (similar to Z lines in skeletal muscles)
- . Some of these bodies are attached to the cell membrane, and others are dispersed inside the cell.
- Some of the membrane-dense bodies of adjacent cells are bonded together by intercellular protein bridges. It is mainly through these bonds that the force of contraction is transmitted from one cell to the next.
- Contractile process
- The contractile process is activated by calcium ions, and adenosine triphosphate (ATP) is degraded to adenosine diphosphate (ADP) to provide the energy for contraction
- Different mechanism of contraction , however contraction involve interaction of actin and myosin

Contractile fibers are arranged in oblique bundles rather than in parallel sarcomeres



Smooth Muscle Cell



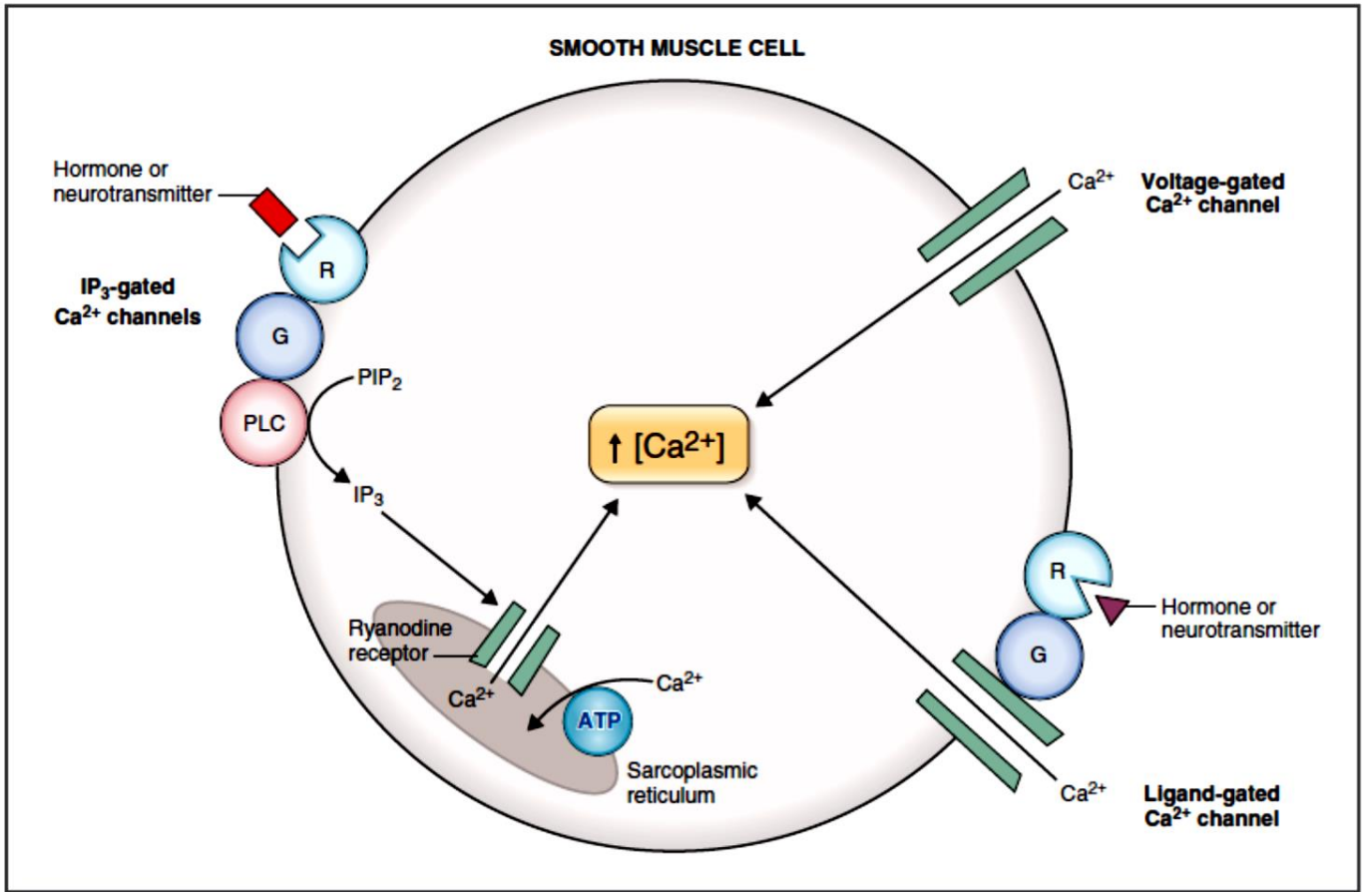
Myosin of Smooth Muscle contractile elements

- Different isoform than that found in skeletal muscle
- Smooth muscle myosin ATPase activity is much slower, contraction is longer
- Myosin light chain in the myosin head regulates contraction and relaxation

Regulation of Contraction of smooth muscles by Calcium Ions

- Initiating stimulus for most smooth muscle contraction is an increase in intracellular calcium ions.
- This increase can be caused in different types of smooth muscle by nerve stimulation of the smooth muscle fiber, hormonal stimulation, stretch of the fiber, or even changes in the chemical environment of the fiber (Local factors)
- Smooth muscle does not contain troponin,. Instead, smooth muscle contraction is activated by an entirely different mechanism
- Calcium Ions Combine with Calmodulin to Cause Activation of Myosin Kinase and Phosphorylation of the Myosin Head
- Calmodulin initiates contraction by activating the myosin cross-bridges

Mechanisms for increasing intracellular [Ca2+] in smooth muscle.



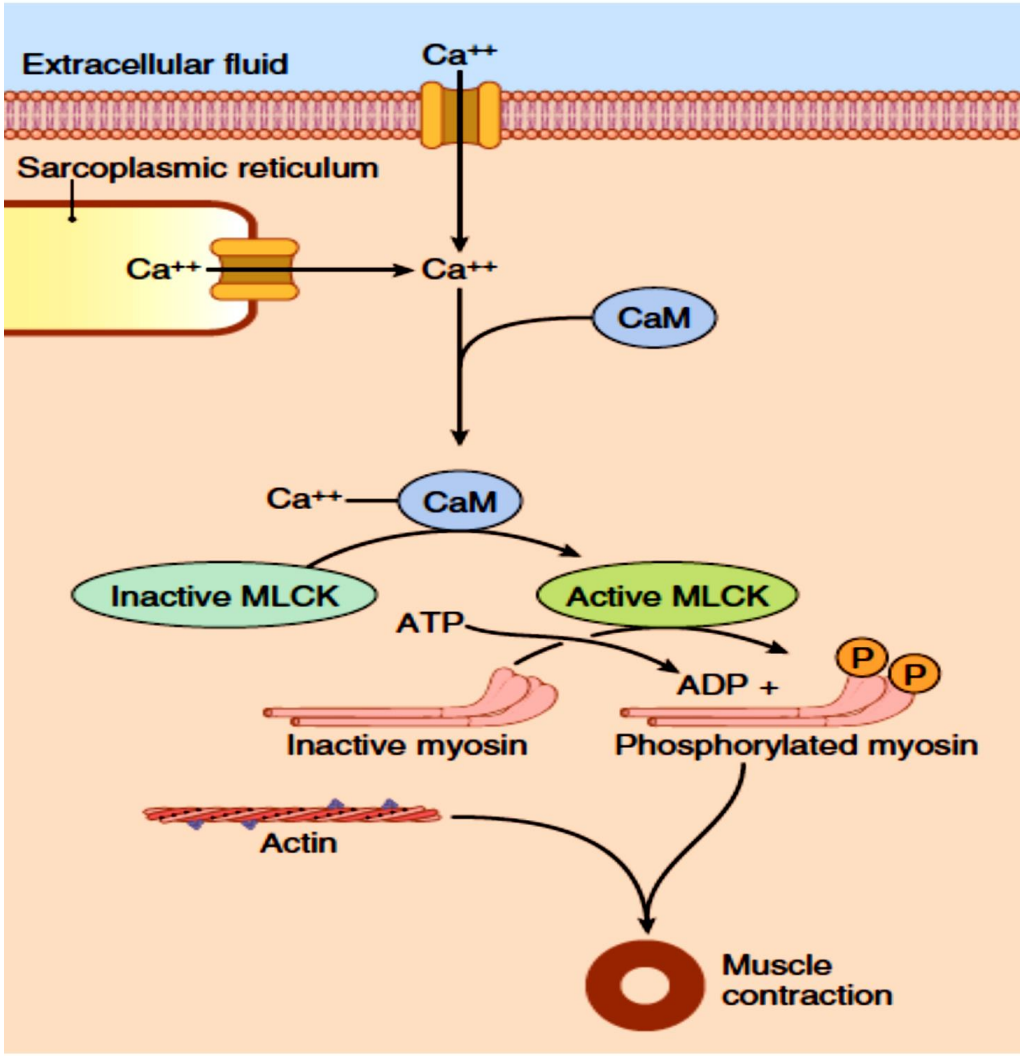
ATP, Adenosine triphosphate; G, GTP-binding protein (G protein); IP3, inositol 1,4,5-triphosphate; PIP2, phosphatidylinositol 4,5-diphosphate; PLC, phospholipase C; R, receptor for hormone or neurotransmitter

Contraction of smooth muscles

Intracellular calcium ion *(Ca++)* concentration increases when Ca++ enters the cell through calcium channels in the cell membrane or is released form the sarcoplasmic reticulum.

The Ca++ binds to calmodulin *(CaM)* to form a Ca++-CaM complex, which then activates myosin light chain kinase *(MLCK)*.

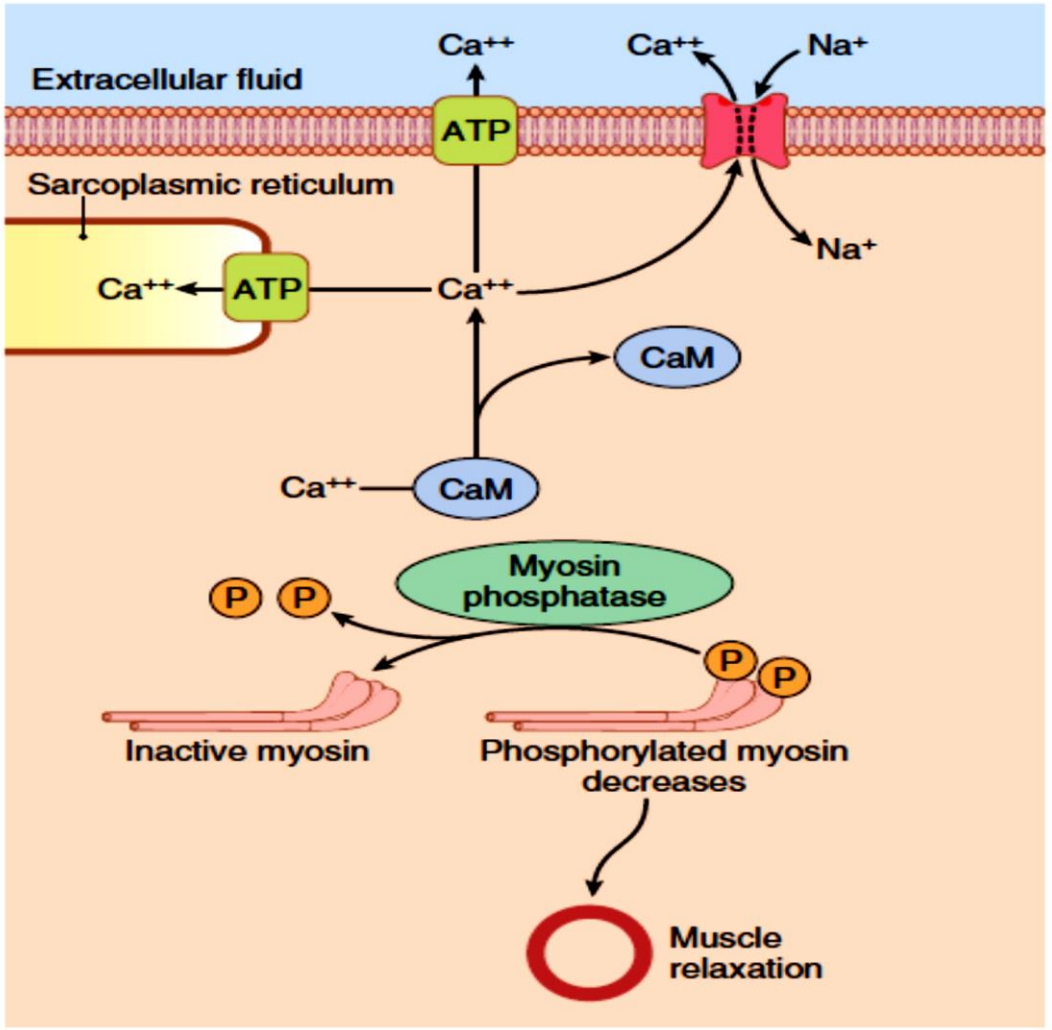
The active MLCK phosphorylates the myosin light chain leading to attachment of the myosin head with the actin filament and contraction of the smooth muscle.



Relaxation of smooth muscle

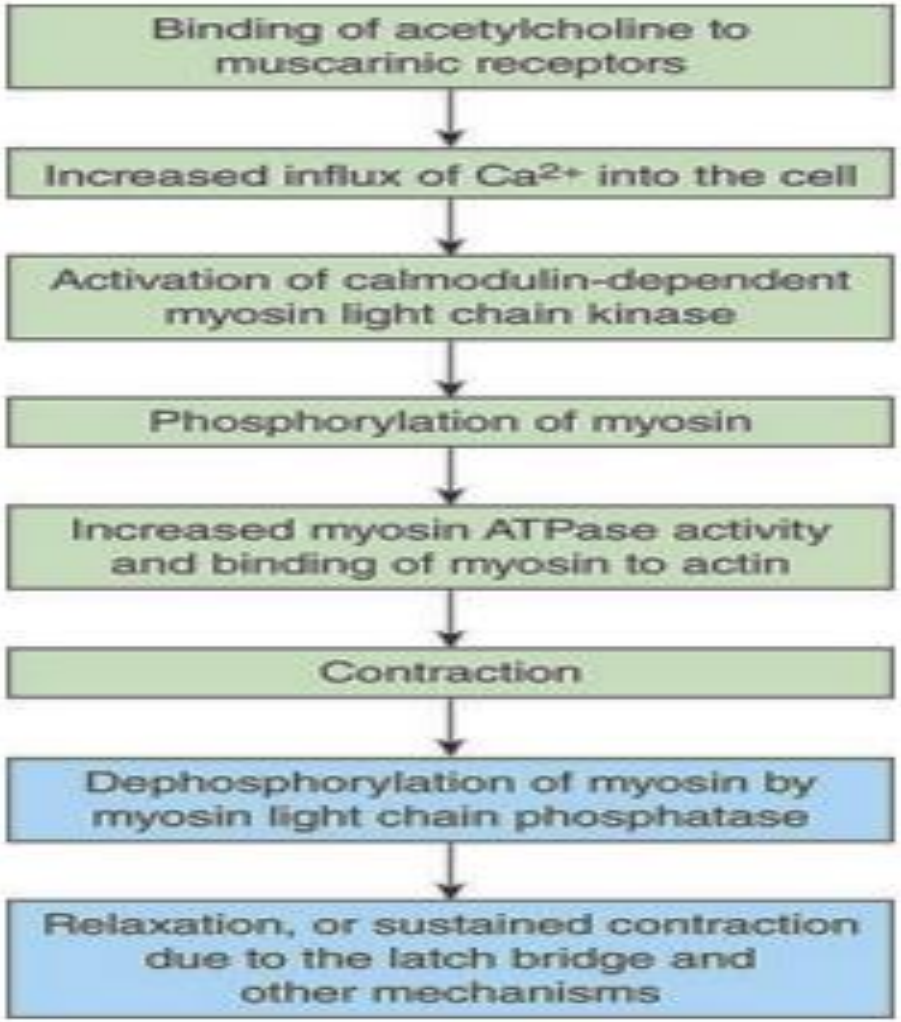
Relaxation occurs when calcium ion *(Ca++)* concentration decreases below a critical level Ca++ is pumped out of the cell or into the sarcoplasmic reticulum.

Ca++ is then released from calmodulin *(CaM)* and myosin phosphatase removes phosphate from the myosin light chain, causing detachment of the myosin head from the actin filament and relaxation of the smooth muscle.



Sequence of events in contraction and relaxation of smooth muscle.

Acetylcholine is given as a sources of stimulus in this example



Properties of smooth muscle contraction

- Low Energy Requirement to sustain smooth muscle Contraction and low O2 consumption
- Can operate over large range of lengths *(60 - 75% shortening possible)*
- *length tension relation ship is over a wide range*
- Can be **myogenic** (spontaneously active)
- Has **Ca^{2+} action potentials**. Ca entering through channels is a very important source of calcium for contraction
- Smooth muscles exhibits sustained prolonged tonic contraction which may last for hours or even days
- Grading of muscle contraction

  Depends on intracellular Ca Ions concentration ,

  No recruitment, specially in visceral smooth muscles

Characteristics of smooth muscle contraction

Slow muscle contraction

- Slow contraction due to slow cycling of cross bridges
- Degradation of the ATP that energizes the movements of the cross-bridge heads is greatly reduced, with corresponding slowing of the rate of cycling.
- longer latency to respond to stimulus
- Latency : begins to contract 50 to 100 milliseconds after it is excited
- initiation of contraction in response to calcium ions is much slower than in skeletal muscle
- Reaches full contraction about 0.5 second later, and then declines in contractile force in another 1 to 2 seconds
- Total contraction time of 1 to 3 seconds.
- This is about 30 times as long as a single contraction of an average skeletal muscle fiber.
- Other types of muscle contraction could be as short as (O.2 sec - 30 sec)

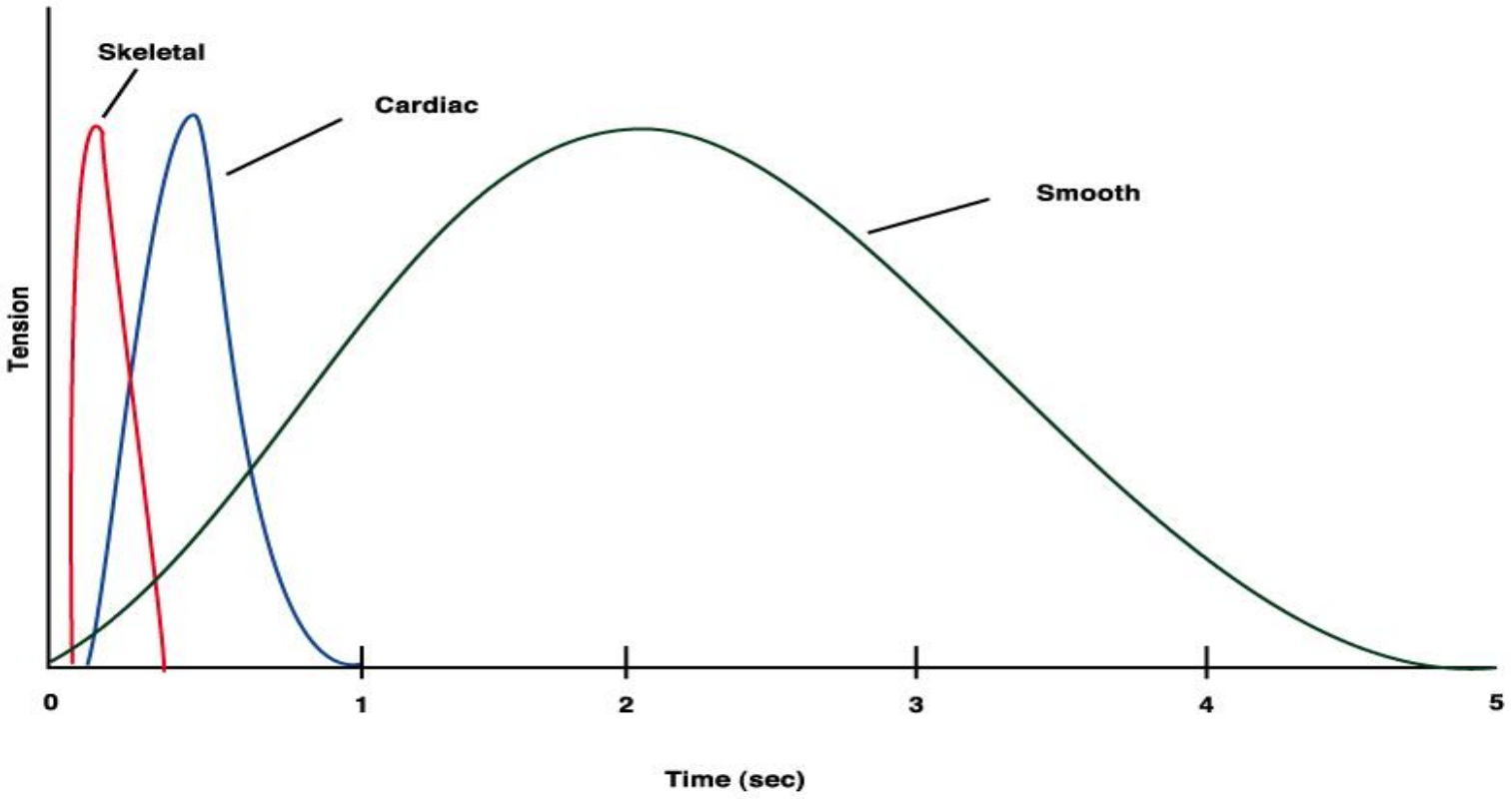
Properties of smooth muscle contraction

- **Slow Cycling of the Myosin Cross-Bridge**
- attachment to actin, then release from the actin, and reattachment for the next cycle—is much slower than in skeletal muscle
- The fraction of time that the cross-bridges remain attached to the actin filaments, which is a major factor that determines the force of contraction, is believed to be greatly increased in smooth muscle.
- A possible reason for the slow cycling is that the cross-bridge heads have far less ATPase activity than in skeletal muscle; thus, degradation of the ATP that energizes the movements of the cross-bridge heads is greatly reduced, with corresponding slowing of the rate of cycling

- **Low Energy Requirement to Sustain Smooth Muscle Contraction**
- Only 1/10 to 1/300 as much energy is required to sustain the same tension of contraction in smooth muscle as in skeletal muscle. This, too, is believed to result from the slow attachment and detachment cycling of the cross-bridges, and because only one molecule of ATP is required for each cycle, regardless of its duration
- This low energy utilization by smooth muscle is important to the overall energy economy of the body because organs such as the intestines, urinary bladder, gallbladder, and other viscera organs

- **Slowness of Onset of Contraction and Relaxation of the Total Smooth Muscle Tissue**
- Longer latency than that of skeletal muscle after it is excited, reaches full contraction about 0.5 second later, and then declines in contractile force in another 1 to 2 seconds, giving a total contraction time of 1 to 3 seconds.
- This is about 30 times as long as a single contraction of an average skeletal muscle fiber. However, because there are so many types of smooth muscle, contraction of some types can be as short as 0.2 second or as long as 30 seconds.
- The slow onset of contraction of smooth muscle, as well as its prolonged contraction, is caused by the slowness of attachment and detachment of the cross-bridges with the actin filaments. In addition, the initiation of contraction in response to calcium ions is much slower than in skeletal muscle,

Comparison of muscle twitch in different types of muscle



- **Maximum Force of Contraction Is Often Greater in Smooth Muscle Than in Skeletal Muscle**.
- Despite the relatively few myosin filaments in smooth muscle, and despite the slow cycling time of the cross-bridges, the maximum force of contraction of smooth muscle is often greater than that of skeletal muscle, as much as 4 to 6 kg/ cm2 cross-sectional area for smooth muscle in comparison with 3 to 4 kilograms for skeletal muscle.
- This great force of smooth muscle contraction results from the prolonged period of attachment of the myosin cross-bridges to the actin filaments.

Latch Mechanism Facilitates Prolonged Holding of Contractions of Smooth Muscle

- Smooth muscle can maintain tension for long periods (Tonic contraction)
- The latch state seems to occur because the cross bridges do not dissociate very rapidly in spite of the fact that the myosin light chain is dephosphorylated ;
- Accordingly energy expenditure is minimal
- This is thought to be important in sphincter muscles where tension development must occur for long periods of time.

Stress-Relaxation and reverse Relaxation in Smooth Muscle

- Mainly occurs in visceral unitary type of smooth muscle of many hollow organs
- Stress relaxation
- is its ability to return to nearly its original *force* of contraction seconds or minutes after it has been elongated or shortened.
- Response to stretch briefly, then return to their normal state of tension and adapt to new length
- For example, a sudden increase in fluid volume in the urinary bladder, thus stretching the smooth muscle in the bladder wall, causes an immediate large increase in pressure in the bladder.
- However, during the next 15 seconds to a minute or so, despite continued stretch of the bladder wall, the pressure returns almost exactly back to the original level Then, when the volume is increased by another step, the same effect occurs again.

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Stress-Relaxation and reverse Relaxation in Smooth Muscle

- Reverse stress-relaxation
- When the volume is suddenly decreased, the pressure falls drastically at first but then rises in another few seconds or minutes to or near the original level.
- These phenomena are called stress-relaxation and and reverse stretch relaxation , they allow a hollow organ to maintain about the same amount of pressure inside its lumen despite sustained large changes in volume.

Effects of Local Tissue Factors on smooth muscle contraction

- Lack of oxygen in the local tissues causes smooth muscle relaxation and, therefore, vasodilation.
- Excess carbon dioxide causes vasodilation. 3. Increased hygen ion concentration causes vasodilation.
- Adenosine, lactic acid, increased potassium ions, nitric oxide, and increased body temperature can all cause local vasodilation.
- Decreased blood pressure, by causing decreased stretch of the vascular smooth muscle, also causes these small blood vessels to dilate.

Effects of Hormones on Smooth Muscle Contraction

- Many circulating hormones in the blood affect smooth muscle contraction to some degree, and some have profound effects.
- Among the more important of these hormones are norepinephrine, epinephrine, angiotensin II, endothelin, vasopressin, oxytocin, serotonin, and histamine.
- A hormone causes contraction of a smooth muscle when the muscle cell membrane contains hormone-gated excitatory receptors for the respective hormone. Conversely, the hormone causes inhibition if the membrane contains inhibitory receptors for the hormone rather than excitatory receptors.

Mechanisms of Smooth Muscle Excitation or Inhibition by Hormones or Local Tissue Factor

- Excitation
- Some hormone receptors in the smooth muscle membrane open sodium or calcium ion channels and depolarize the membrane, the same as after nerve stimulation.
- Depolarization allows for calcium ion entry into the cell, which promotes the contraction.
- Inhibition
- Occurs when the hormone (or other tissue factor) closes the sodium and calcium channels to prevent entry of these positive ions; inhibition also occurs if the normally closed potassium channels are opened, allowing positive potassium ions to diffuse out of the cell. Both these actions increase the degree of negativity inside the muscle cell, a state called hyperpolarization, which strongly inhibits muscle contraction

Other mechanism of hormones affecting smooth muscle contraction : Role of cAMP and cGMP

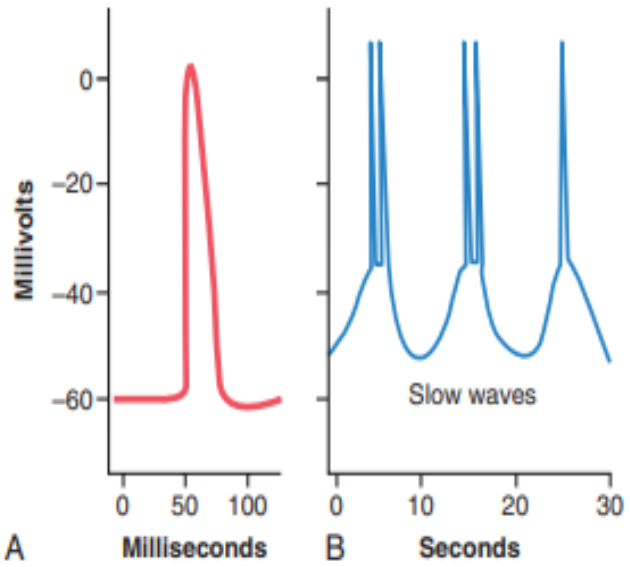
- To inhibit contraction, other receptor mechanisms are known to activate the enzyme adenylate cyclase or guanylate cyclase in the cell membrane. The portions of the receptors that protrude to the interior of the cells are coupled to these enzymes, causing the formation of cyclic adenosine monophosphate (cAMP) or cyclic guanosine monophosphate (cGMP), so-called second messengers.
- cAMP or cGMP has many effects, one of which is to change the degree of phosphorylation of several enzymes that indirectly inhibit contraction. The pump that moves calcium ions from the sarcoplasm into the sarcoplasmic reticulum is activated, as well as the cell membrane pump that moves calcium ions out of the cell; these effects reduce the calcium ion concentration in the sarcoplasm, thereby inhibiting contraction.

MEMBRANE POTENTIALS AND ACTION POTENTIALS IN VISCERAL SMOOTH MUSCLE

- In the normal resting state, the intracellular potential is usually about −50 to −60 millivolts
- The action potentials of visceral smooth muscle occur in one of two forms
  - spike potentials
  - action potentials with plateau
- Such action potentials can be elicited in many ways
  - Electrical stimulation.
  - Spontaneous generation in the muscle fiber
  - Hormones
  - transmitter substances from nerve fibers
  - Stretch

Spike potentials

- Typical smooth muscle action potential (spike potential) elicited by an external stimulus.
- Observed in GT and in most types of unitary smooth muscle.
- The duration of this type of action potential is 10 to 50 milliseconds,
- Such action potentials can be elicited in many ways—for example, by electrical stimulation, by the action of hormones on the smooth muscle, by the action of transmitter substances from nerve fibers, by stretch, or slow waves depolarization
- Sodium participates little in the generation of the action potential in most smooth muscle.
- Instead, flow of calcium ions to the interior of the fiber is mainly responsible for the action potential
- Depolarization phase is mainly due to activation of L type Ca channel
- Receptive spike potentials generated by slow wave depolarization

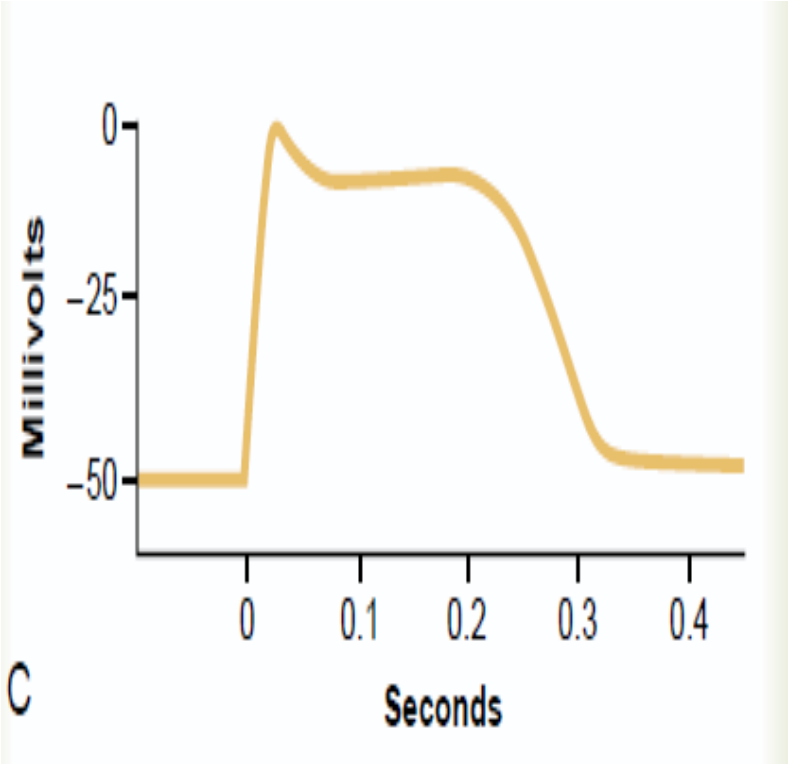


Action potential with a plateau, recorded from a smooth muscle fiber of the uterus

The onset of this action potential is similar to that of the typical spike potential.

However, instead of rapid repolarization of the muscle fiber membrane, the repolarization is delayed for several hundred to as much as 1000 milliseconds (1 second).

The importance of the plateau is that it can account for the prolonged contraction that occurs in some types of smooth muscle, such as the ureter, the uterus under some conditions, and certain types of vascular smooth muscle.



Slow Wave Potentials
(*pacemaker waves) in* Unitary Smooth Muscle Can

- action potentials arise within the smooth muscle cells without an extrinsic stimulus
- action potentials arise within the smooth muscle cells without an extrinsic stimulus
- Slow wave depolarization Leads to Spontaneous Generation of Action Potentials.
- the slow waves are caused by waxing and waning of the pumping of Na pump. Another suggestion is that the conductances of the ion channels increase and decrease rhythmically
- This type of pacemaker activity for example in the gut
- Controls the rhythmical contractions of the gut.
- Slope of depolarization is influenced by ANS

Slow wave and spikes potentials in visceral smooth muscles
Effects of sympathetic and parasympathetic stimulation